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International Union of Basic and Clinical Pharmacology. LXXXIV: Leukotriene Receptor Nomenclature, Distribution, and Pathophysiological Functions

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***Abstract*——The seven-transmembrane G protein-coupled receptors activated by leukotrienes are divided into two subclasses based on their ligand specificity for either leukotriene B_4 or the cysteinyl leukotrienes (LTC_4, LTD_4, and LTE_4). These receptors have been designated BLT and CysLT receptors, respectively, and a subdivision into BLT_1 and BLT_2 receptors and $CysLT_1$ and $CysLT_2$ receptors has been established. However, recent findings have also indicated the existence of putative additional leukotriene receptor subtypes. Furthermore, other ligands interact with the leukotriene receptors. Finally, leukotrienes may also activate other receptor classes, such as purinergic receptors. The aim of this review is to provide an update on the pharmacology, expression patterns, and pathophysiological roles of the leukotriene receptors as well as the therapeutic developments in this area of research.**

I. Introduction: Leukotriene Receptors

The seven-transmembrane G protein-coupled receptors (GPCRs[1]) activated by leukotrienes are divided into two subclasses based on their ligand specificity for either leukotriene B_4 (LTB_4) or the cysteinyl leukotrienes (LTC_4, LTD_4, and LTE_4). The leukotriene receptors belong to the A5 subfamily of the rhodopsin receptor-like GPCRs (Joost and Methner, 2002). According to the

previous report from the International Union of Basic and Clinical Pharmacology's (IUPHAR) Nomenclature Committee for Leukotriene Receptors, these receptors have been designated BLT and CysLT receptors, respectively (Brink et al., 2003). Furthermore, a subdivision into BLT_1 and BLT_2 receptors and $CysLT_1$ and $CysLT_2$ receptors has been established, as indicated in Table 1 (Brink et al., 2003).

However, several reports have also indicated the existence of additional leukotriene receptor subtypes (Rovati et al., 1997; Bäck, 2002; Norel and Brink, 2004; Rovati and Capra, 2007; Austen et al., 2009). In addition, evidence has emerged that ligands other than leukotrienes interact with the leukotriene receptors and that leukotrienes may also signal through receptors preferentially activated by other endogenous ligands. For example, lipid mediators that are structurally different from leukotrienes have been reported to signal through BLT receptors (Arita et al., 2007; Okuno et al., 2008). As described later, 12(*S*)-hydroxyheptadeca-5*Z*,8*E*,10*E*-trienoic acid (12-HHT) was identified as a more potent ligand for BLT_2R than for LTB_4 (Okuno et al., 2008). Furthermore, although evidence that LTE_4 signals through the $P2Y_{12}$ receptor was demonstrated (Nonaka et al., 2005; Paruchuri et al., 2009; Fredman et al., 2010), one of the orphan GPCRs, GPR17, has been postulated to be activated by both cysteinyl leukotrienes and nucleotides (Ciana et al., 2006). Finally, both the $CysLT_1$ receptor ($CysLT_1R$) antagonists in clinical use as antiasthmatic drugs have been demonstrated to inhibit the effects of nucleotides acting at different P2Y receptors. These observations demonstrate that these classic leukotriene receptor antagonists (LTRAs) can inhibit non-$CysLT_1$-mediated proinflammatory reactions, suggesting activities potentially relevant for interpatient variability in response to treatment. The aim of the present review is to provide an extensive update on the pharmacology, expression patterns, and pathophysiological roles of the leukotriene receptors. Furthermore, a comment on the potential therapeutic developments in this area of research will be presented.

A. Brief Historical Background of Leukotrienes and Their Receptors

Ever since the identification of the biochemical structure of the leukotrienes and their association with inflammation (Samuelsson, 1983), the pathophysiological role of these lipid mediators has been explored in many experimental approaches (Brink et al., 2003). Initially, LTB_4 was appreciated for its potent chemotactic effects on neutrophil granulocytes (Ford-Hutchinson et al., 1980; Malmsten et al., 1980; Palmblad et al., 1981) and its ability to serve as a complete secretagog for human peripheral blood neutrophils (Serhan et al., 1982). In contrast, initial studies of cysteinyl leukotrienes were mainly focused on their potent bronchoconstrictive effects (Dahlén et al., 1980). However, subsequent studies have extended these findings and associated leukotriene receptor signaling with several pathophysiological processes.

The first leukotriene receptor to be cloned was the human BLT_1, and the molecular structure was reported in 1997 (Yokomizo et al., 1997). This molecular identification of the BLT_1 receptor (BLT_1R) permitted the characterization of functional BLT_1R in several leukocyte populations (Kim and Luster, 2007) and also in nonmyeloid cells, such as vascular smooth muscle and endothelial cells (Bäck et al., 2005). Although the LTB_4-induced interaction with BLT_1R corresponded with several effects observed in those target cells, initial studies had revealed both high- and lower-affinity binding sites for LTB_4 specifically in human granulocytes (Goldman and Goetzl, 1984). The molecular

[1]Abbreviations: β_2AR, β_2-adrenoreceptor(s); aa, amino acids; AD, atopic dermatitis; AIA, aspirin-induced asthma; AML1, acute myeloid leukemia 1; AP-1, activator protein-1; AR, allergic rhinitis; ATA, aspirin-tolerant asthma; BAL, broncho-alveolar lavage; BAY U9773, 6(*R*)-(4-carboxyphenylthio)-5(*S*)-hydroxy-7(*E*),9(*E*),11(*Z*),14(*Z*)-eicosatetraenoic acid; BLTR, BLT receptor(s); BLT_1R, BLT_1 receptor(s); BLT_2R, BLT_2 receptor(s); BMDC, bone marrow-derived dendritic cell; BMMC, bone marrow-derived mast cell; CF, cystic fibrosis; CHO, Chinese hamster ovary; COPD, chronic obstructive pulmonary disease; COX, cyclooxygenase; CP-105,696, 1-[3-(4-phenyl-benzyl)-4-hydroxy-chroman-7-yl] cyclopentane carboxylic acid; CU, chronic urticaria; CVD, cardiovascular disease; CysLTR, cysteinyl leukotriene receptor(s); $CysLT_1R$, $CysLT_1$ receptor(s); $CysLT_2R$, $CysLT_2$ receptor(s); DC, dendritic cell; DSS, dextran sodium sulfate; EAE, allergic encephalomyelitis; EC, endothelial cell; ECP, eosinophil cationic protein; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinases; FcR, Fc receptor; FLAP, 5-lipoxygenase activating protein; GPCR, G protein-coupled receptor; GRK, GPCR kinases; h, human; HEK, human embryonic kidney; HETE, hydroxyeicosatetraenoic acid; HHT, hydroxyheptadecatrienoic acid; HpETE, hydroperoxyeicosatetraenoic acid; HUVEC, human umbilical cord endothelial cell; IBD, inflammatory bowel disease; IFN, interferon; IGF, insulin growth factor; IL, interleukin; IUPHAR, International Union of Basic and Clinical Pharmacology; JNK, c-Jun NH_2-terminal kinase; 5-LO, 5-lipoxygenase; LPS, lipopolysaccharide; LT, leukotriene; LTC4S, LTC_4 synthase; LTRA, leukotriene receptor antagonist; LY255283, 1-[5-ethyl-2-hydroxy-4-[[6-methyl-6-(1*H*-tetrazol-5-yl)heptyl]oxy]phenyl]ethanone; LY293111, 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]-propoxy]phenoxyl]benzoic acid; m, murine; MAPK, mitogen-activated protein kinase; MC, mast cell; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; MK0571, 3-[[3-[2-(7-chloroquinolin-2-yl)vinyl]phenyl]-(2-dimethylcarbamoylethylsulfanyl)methylsulfanyl] propionic acid; MMP, matrix metalloproteinases; MNC, mononuclear cell; MRS 2395, 2,2-dimethyl-propionic acid 3-(2-chloro-6-methylaminopurin-9-yl)-2-(2,2-dimethyl-propionyloxymethyl)-propyl ester; MS, multiple sclerosis; NCBI, National Center for Biotechnology Information; NF-κB, nuclear factor κB; NO, nitric oxide; NSAID, nonsteroidal anti-inflammatory drug; OVA, ovalbumin; P2Y, pyrimidinergic nucleotide; PAF, platelet-activating factor; PGE_2, prostaglandin E_2; PI, phosphatidylinositol; PI3K, phosphatidylinositol 3-kinase; PK, protein kinase; PPAR, peroxisome proliferator-activated receptor; PTX, pertussis toxin; QL, quality of life; RANTES, regulated on activation normal T cell expressed and secreted; RT-PCR, reverse transcriptase-polymerase chain reaction; Rv, resolvin; SKF 104353, 2(*S*)-hydroxyl-3(*R*)-carboxyethylthio)-3-[2-(8-phenyloctyl) phenyl] propanoic acid; SMC, smooth muscle cell; SNP, single nucleotide polymorphism; STAT, signal transducer and activator of transcription; Th, T helper; TM, transmembrane domain; TNF, tumor necrosis factor; TRP, transient receptor potential; U75302, -[6-(3-hydroxy-1*E*,5*Z*-undecadienyl)-2-pyridinyl]-1,5-hexanediol; VEGF, vascular endothelial growth factor; WT, wild type.

TABLE 1
Leukotriene receptors
For full details, see http://www.iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=270&familyId=35.

Receptor	BLT_1	BLT_2	$CysLT_1$	$CysLT_2$
Amino acids				
Hs	352	389	337	346
Mm	351	360	339	309
Rn	351	358	352	309
NCBI sequence no.				
Hs	NP_858043	NP_062813	NP_006630	NP_065110
Mm	NP_032545	NP_065236	NP_067451	NP_598481
Rn	NP_067688	NP_446092	NP_446093	NP_596904
Gene name				
Hs	*LTB4R*	*LTB4R2*	*CYSLTR1*	*CYSLTR2*
Mm	*Ltb4r1*	*Ltb4r2*	*Cysltr1*	*Cysltr2*
Rn	*Ltb4r*	*Ltb4r2*	*Cysltr1*	*Cysltr2*
Chromosomal location				
Hs	14q11.2-q12	14q11.2-q12	Xq13.2-21.1	13q14.12-q21.1
Mm	14 C2	14 C1	X D	14 D2
Rn	15p 13	15p 13	Xq 31	15p 11
Selective ligands	—[a]	—[a]	—[a]	—[a]
Nonselective ligands	LTB_4	LTB_4; 12-HHT	LTC_4; LTD_4; LTE_4	LTC_4; LTD_4; LTE_4
Selective antagonists	U75302; CP-105,696	LY-255,283	Montelukast; zafirlukast; pranlukast	CysLT2cpd
Nonselective antagonists	ONO-4057	ONO-4057	BAY U9773	BAY U9773

Hs, *Homo sapiens*; Mm, *Mus muscularis*; Rn, *Rattus norvegicus*; ONO-4057, (5-[2-(2-carboxyethyl)-3-[6-(4-methoxyphenyl)-5*E*-hexenyl]oxyphenoxy]valeric acid.
[a] No ligands identified.

explanation for the latter finding was provided in 2000, when a gene with high sequence similarity to BLT_1R was identified and encoded a low-affinity LTB_4 receptor, which has subsequently been denoted BLT_2R (Yokomizo et al., 2000; Brink et al., 2003). Transgenic overexpression of the human BLT_1R in mice increased the inflammatory response to LTB_4 (Chiang et al., 1999), whereas genetic BLT_1R disruption decreased leukocyte chemotaxis and protected against disease development in response to several different proinflammatory stimuli (Haribabu et al., 2000; Tager et al., 2000; Brink et al., 2003) (see section II.E).

The classification of the CysLT receptors was initially based on the differential profiles of guinea pig trachea contractions induced by either LTC_4 or LTD_4 (Brink et al., 2003). Because a classification based on agonist selectivity is not generally applicable, the names $CysLT_1$ and $CysLT_2$ were introduced when referring to responses being sensitive and resistant (Labat et al., 1992) to the class of CysLT receptor antagonists, which had been developed for the treatment of asthma (Brink et al., 2003). The subsequent cloning of these receptors in 1999 and 2000 (Lynch et al., 1999; Sarau et al., 1999; Heise et al., 2000; Nothacker et al., 2000; Takasaki et al., 2000) largely confirmed these pharmacological characteristics of the $CysLT_1$ and $CysLT_2$ receptors.

B. Chemical Structure of Endogenous Leukotriene Receptor Agonist

Most endogenous ligands for the leukotriene receptors are derived from lipoxygenase metabolism of arachidonic acid and are shown in Fig. 1. The formation of leukotrienes by 5-lipoxygenase (5-LO) involves the oxygenation at carbon number 5 of arachidonic acid to form 5-hydroperoxyeicosatetraenoic acid (HpETE). Subsequently, removal of hydrogen at carbon 10 from 5-HpETE leads to formation of the epoxide intermediate LTA_4, which serves as precursor for LT synthesis (Shimizu et al., 1984; Rådmark and Samuelsson, 2009) (Fig. 1). Although detected in the cytosolic or nucleosolic fraction of resting cells, cellular activation leads to 5-LO translocation to the nuclear envelope in a calcium-dependent manner, where colocalization with the 5-LO-activating protein (FLAP) is a prerequisite for LT synthesis (Evans et al., 2008).

The enzyme LTA_4 hydrolase is located in the cytosol and stereospecifically adds water to carbon 12 of LTA_4, leading to formation of LTB_4 (Haeggström, 2004). Several inactivating pathways for LTB_4 are known, of which ω-oxidation has been most extensively studied in human leukocytes (for review, see Yokomizo et al., 2001b). In this pathway, LTB_4 is converted to 20-hydroxy-LTB_4 by LTB_4 ω-hydroxylase and then to 20-carboxy-LTB_4 as indicated in Fig. 1 (Yokomizo et al., 2001b). The latter metabolites may also act as ligands at the BLT receptors, which will be discussed below.

The other metabolic pathway of LTA_4 involves the enzyme LTC_4 synthase (LTC_4S), a microsomal glutathione transferase, which conjugates LTA_4 with glutathione to form LTC_4 (Fig. 1) (Austen, 2007). After transportation to the extracellular space by an ATP-dependent transporter (multidrug resistance-associated protein) that recognizes its glutathione moiety, LTC_4 is metabolized by γ-glutamyl transpeptidase into LTD_4. Subsequently, a serum dipeptidase, which cleaves the peptide bond between the cysteinyl and glycyl residues in the LTD_4 side chain, leads to the formation of LTE_4 (Fig. 1). Because LTC_4, D_4, and E_4 all contain a cysteinyl group at carbon number 6 (Fig. 1), these LTs are referred to as the cysteinyl leukotrienes. Thus, the receptors for these LTs are termed CysLT receptors (Brink et al., 2003).

In addition to 5-LO metabolites, products of the 12- and 15-lipoxygenase metabolism of arachidonic acid metabo-

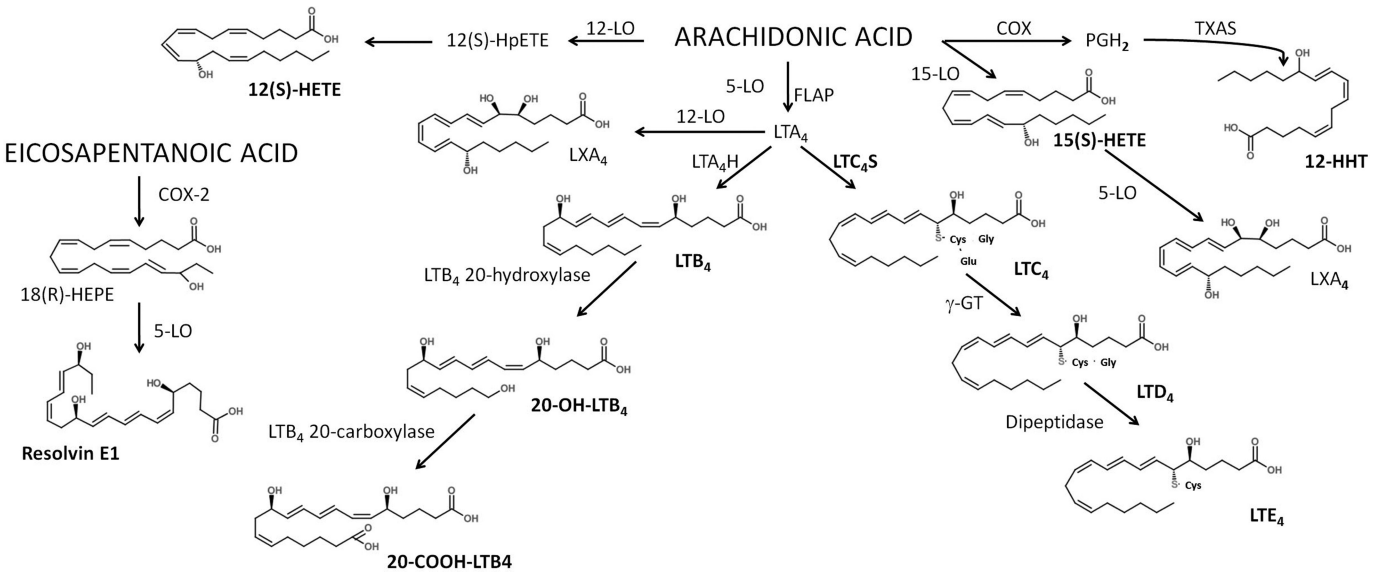

FIG. 1. Biosynthesis and chemical structures of endogenous leukotriene receptor agonists, derived from arachidonic acid. Lipoxin (LX) biosynthesis pathways in humans via 15-LO and 5-LO interaction or 12-LO via 5-LO derived LTA_4 are also depicted. In addition, resolvin E1, derived from eicosapentaenoic acid (EPA), may act as a partial BLT_1R agonist. GT, glutamyl transferase; HEPE, hydroxyeicosapentaenoic acid; LTA_4H, LTA_4 hydrolase; TXAS, thromboxane synthase.

lism can act as ligands for the LT receptors (Fig. 1). For example, 12(*R*)-hydroxyeicosatetraenoic acid (HETE) competes with LTB_4 binding at BLT_1R (Yokomizo et al., 1997, 2001c), whereas 12(*S*)-HETE, 12(*S*)-HpETE, and 15(*S*)-HETE activate BLT_2R (Yokomizo et al., 2001c). The orphan receptor GPR31 has been suggested as a high-affinity receptor for 12(*S*)-HETE (Guo et al., 2011). Finally, 12-HHT (Fig. 1), which is formed through the cyclooxygenase pathway of arachidonic acid metabolism is a high-affinity BLT_2R agonist (Okuno et al., 2008).

II. BLT Receptors

A. BLT Receptor Subtypes

1. BLT_1 Receptor. The open reading frame of the human *LTB4R* gene encodes the BLT_1R. The BLT_1R protein consists of 352 aa (NCBI Reference Sequence: NP_858043) (Fig. 2). The BLT_1R has also been isolated in other species, with a homology similar to that of the human protein in mice (78%; Huang et al., 1998), in guinea pigs (78%; Masuda et al., 1999), and in rats (80%; Toda et al., 1999).

Although LTB_4 seems to be the sole full agonist at BLT_1R, binding studies in membrane fractions of BLT_1R-transfected cells have shown significant competitions for 20-OH-LTB_4, 12-oxo-LTB_4 and 12-epi-LTB_4, 20-COOH-LTB_4, and 12(*R*)-HETE (Yokomizo et al., 1997, 2001c). However, not all of these ligands seem to induce similar intracellular signaling. For example, studies of the recombinant guinea pig BLT_1R have shown that although 20-OH-LTB_4 was less potent than LTB_4 in the mobilization of intracellular Ca^{2+} ($[Ca^{2+}]_i$),

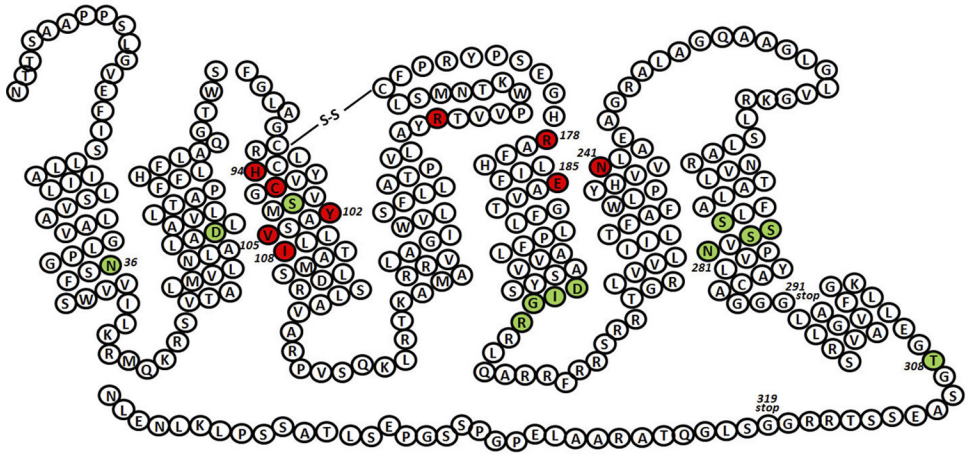

FIG. 2. Schematic representation of the human BLT_1 receptor with the boundaries of each transmembrane, extracellular, and intracellular domain derived from the molecular modeled structure described previously (Basu et al., 2007; Kuniyeda et al., 2007). The amino acid residues involved in the ligand binding are shown in red, whereas residues implicated in receptor signaling are shown in green. The C-tail truncations in the described mutants (see text) are indicated by "stop".

these agonists were equally potent in inhibiting cAMP formation (Masuda et al., 1999). In addition, the eicosapentaenoic acid metabolite resolvin (Rv) E1 was identified as a partial BLT_1R agonist. In particular, RvE1 selectively inhibited adenylate cyclase and attenuated LTB_4-induced nuclear factor κB (NF-κB) activation in BLT_1- but not in BLT_2-transfected cells, whereas in human peripheral blood mononuclear cells RvE1 partially induced calcium mobilization and blocked subsequent stimulation by LTB_4 (Arita et al., 2007). These data thus suggest that this mediator, besides activating the receptor ChemR23, could act through inhibition of LTB_4-induced signaling. More information on this new genus of specialized proresolving mediators has been published recently (Bannenberg and Serhan, 2010).

Initially, BLT_1R expression was reported to be restricted to phagocytic leukocytes (Yokomizo et al., 1997), and subsequent studies identified BLT_1R expression in granulocytes, monocytes, and dendritic cells. In addition, lymphocytes also express BLT_1R (see section II.D), and functional BLT_1R are now known to be expressed in nonmyeloid cells, such as vascular smooth muscle cells (SMCs) (Bäck et al., 2005), as well as endothelial cells (ECs) (Qiu et al., 2006), skeletal muscle satellite cells (Sun et al., 2009), and neural stem cells (Wada et al., 2006).

2. BLT_2 Receptor. In the analysis of human and mouse *LTB4R* genes, an open reading frame encoding a putative seven-transmembrane-type receptor with sequence similarities to BLT_1R was identified (Yokomizo et al., 2000). This gene was shown to encode a receptor protein that exhibited LTB_4 binding with a 20-fold higher K_d, and calcium signaling with a 30-fold higher EC_{50} value compared with BLT_1R (Yokomizo et al., 2000). The gene has been designated *LTB4R2*, and the receptor has been classified as the BLT_2 receptor (BLT_2R) (Brink et al., 2003). The BLT_2R protein consists of 358 aa (NCBI Reference Sequence: NP_062813) and exhibits a 36 to 45% aa identity with the human BLT_1R (Kamohara et al., 2000; Tryselius et al., 2000; Yokomizo et al., 2000). The murine BLT_2R has a 92% aa homology with the human receptor protein, which is a higher homology compared with that of BLT_1R (78% aa identity between murine and human proteins; Iizuka et al., 2005). These data suggest that the BLT_2R has been conserved during evolution.

In contrast to the relatively specific binding of LTB_4 at BLT_1R, several lipoxygenase products in addition to LTB_4 have been identified as ligands for BLT_2R. These include 12(*S*)-HETE, 12(*S*)-HpETE, and 15(*S*)-HETE (Fig. 1) (Yokomizo et al., 2001c). Furthermore, the thromboxane synthase product 12-HHT formed in activated blood platelets and macrophages from prostaglandin H_2 (Fig. 1) is also a natural ligand for BLT_2R (Okuno et al., 2008). In the latter study, the EC_{50} values of 12-HHT and LTB_4 for $[Ca^{2+}]_i$ mobilization in CHO-BLT_2R cells were 19 and 142 nM, respectively, whereas 12-HHT failed to induce calcium mobilization in CHO-BLT_1R cells (Okuno et al., 2008). Several binding studies further demonstrated that BLT_2R is a high-affinity receptor for 12-HHT and that 12-HHT and LTB_4 occupy the same binding site on BLT_2R (Okuno et al., 2008). A synthetic selective BLT_2R agonist has also been reported and termed compound A (Iizuka et al., 2005).

In CHO cells expressing the human BLT_2R, maximal chemotaxis was observed at LTB_4 concentrations greater than 1 μM, compared with 10 nM for CHO cells expressing human BLT_1R (Yokomizo et al., 2001a; Okuno et al., 2008). Data suggest that coexpression of both human BLT_1 and BLT_2 receptors makes CHO cells migrate toward both very low and high LTB_4 concentrations (Yokomizo et al., 2001a). Other hydroxyeicosanoids acting as BLT_2R agonists, such as 12(*S*)-HETE, 12(*R*)-HETE, and 12-epi-LTB_4, require even higher concentrations (approximately 10 μM) to induce a maximal chemotactic response (Yokomizo et al., 2001c). In contrast, maximal chemotaxis for 12-HHT in CHO cells expressing the human BLT_2R is observed at 30 nM, suggesting that this high-affinity BLT_2R ligand is coupled to chemotaxis (Okuno et al., 2008). In line with findings in CHO cells, murine BLT_2R-expressing 300.19 cells exhibit higher affinity for 12-HHT than for LTB_4. 12-HHT-induced intracellular calcium flux with the same efficacy as LTB_4 (Mathis et al., 2010). However, in the latter cells, 12-HHT was only a weak agonist for chemotaxis with 3% activity relative to LTB_4 (Mathis et al., 2010), suggesting a ligand-specific coupling to chemotaxis. Studies of primary cells have generated variable results as to the role of BLT_2R in LTB_4-induced chemotaxis (see section II.D).

The most abundant BLT_2R expression is found in the spleen, followed by liver, ovary, and leukocytes, and BLT_2R expression is also detected in several other organs, suggesting a ubiquitous expression pattern, at least in human tissues (Yokomizo et al., 2000). The tissue distribution of BLT_2R is different in mouse tissues, with the highest expression in small intestine followed by colon and skin (Iizuka et al., 2005). Physiological and pathophysiological responses associated with BLT_2R signaling include macrophage and mast cell (MC) chemotaxis (Subbarao et al., 2004; Lundeen et al., 2006; Okuno et al., 2008), guinea pig lung parenchyma contraction (Sakata et al., 2004), and mouse models of angiogenesis (Kim et al., 2009), itch-associated scratching (Kim et al., 2008), colitis (Iizuka et al., 2010), and arthritis (Mathis et al., 2010).

3. Genomic Organization and Transcriptional Regulation. The genes encoding BLT_1R and BLT_2R are designated *LTB4R* and *LTB4R2*, respectively (Table 1), and are located within 10 kilobase pairs of each other in both the human and murine genome (Yokomizo et al., 2000). The genes encoding the BLT receptors form a gene cluster on human chromosome 14q11.2-q12 with the open reading frame of the *LTB4R2* gene overlapping one of

the promoter regions of the human *LTB4R* gene (Kato et al., 2000; Yokomizo et al., 2000; Brink et al., 2003). The *LTB4R* gene consists of three exons, and, in line with other receptors for chemoattractants such as fMet-Leu-Phe and interleukin (IL)-8, the open reading frame is intronless (Kato et al., 2000). One of the *LTB4R* promoters has been shown to contain consensus sequence for NF-κB and Sp1 binding (Kato et al., 2000). Spontaneous mutations around the *LTB4R* and *LTB4R2* genes have been reported to be associated with cerebrovascular disease (Bevan et al., 2008), but the close proximity of the genes encoding those receptors suggests that those polymorphisms cannot be ascribed to either of the genes alone.

In THP-1 cells, the deletion of a Sp1 binding site in the *LTB4R* promoter decreases transcriptional activity (Kato et al., 2000). In human monocytes, BLT_1R mRNA expression is down-regulated by proinflammatory stimuli, such as lipopolysaccharide (LPS), interferon (IFN)-γ, and tumor necrosis factor (TNF)-α, whereas the anti-inflammatory cytokine IL-10 and dexamethasone up-regulate BLT_1R mRNA in these cells (Pettersson et al., 2005). Likewise, in human neutrophil granulocytes, BLT_1R mRNA is up-regulated by dexamethasone (Stankova et al., 2002), and BLT_1R protein and LTB_4 binding are decreased by TNF-α and LPS (O'Flaherty et al., 1991; Pettersson et al., 2003). The latter findings support earlier studies demonstrating decreased LTB_4 binding and LTB_4-induced chemotaxis in neutrophils derived from endotoxemic rabbits (Hartiala et al., 1985; Goldman et al., 1986). Of interest, the transcriptional regulation of the *LTB4R* gene may vary between cells of hematopoietic and nonhematopoietic origin (Kato et al., 2000). In contrast to findings in leukocytes, BLT_1R expression is up-regulated by LPS, IL-1β, and IFN-γ in vascular SMCs, as demonstrated by studies of cells derived from human, rat, or mouse vessels (Bäck et al., 2005; Heller et al., 2005). Furthermore, vascular injury in vivo significantly up-regulates BLT_1R mRNA through NF-κB signaling (Bäck et al., 2005). Likewise, whereas BLT_1R is expressed at low levels in human umbilical cord endothelial cells (HUVECs) under resting conditions, either LPS or IL-1β induces BLT_1R mRNA and protein levels and renders HUVECs responsive to LTB_4 (Qiu et al., 2006). This cell-specific expression of BLT_1R may be dependent on epigenetic regulation, for example, through methylation of the promoter region, which has been shown to regulate BLT_1R transcription in vitro (Kato et al., 2000). In a recent study, the enhancer in the human *LTB4R*, termed *AE-BLex*, was discovered at the intron I-exon-II boundary (Hashidate et al., 2010). *AE-BLex* possesses two acute myeloid leukemia 1 (AML1, also known as Runx1) recognition sites. The AML1/*AE-BLex* complex was confirmed in several BLT_1R-expressing leukemia cell lines and human peripheral leukocytes. Thus, AML1 enhances BLT_1R expression by binding to AE-BLex, which is accessible in leukocytes. The enhancement of the BLT_1R expression in leukocytes is due to a loosening of the chromatin structure around AE-BLex, leading to the incremental binding of AML1 (Hashidate et al., 2010).

B. Structure-Function Relationships for BLT Receptors

LTB_4 binds near the extracellular surface of BLT_1R, and although polar residues within transmembrane domains (TMs) III, V, and VI and extracellular loop 2 are critical for ligand binding, polar residues in TMs II, III, and VII play a central role in transducing the ligand-induced conformational change to activation (Sabirsh et al., 2006; Basu et al., 2007) (Fig. 2). Furthermore, a conformational change of TM IV takes place during ligand binding (Baneres et al., 2003).

Site-directed mutagenesis has revealed several of the residues involved in LTB_4 binding to BLT_1R (Fig. 2). Although initial studies had suggested that mutating all receptor cysteines (except Cys^{90} and Cys^{168}) to serine did not alter ligand binding, selective replacement of Cys^{97} in the TM III domain to serine leads to a 100-fold decrease in the affinity for the agonist (Mesnier and Banères, 2004). Furthermore, residues His^{94}, Tyr^{102}, Val^{105}, and Ile^{108} in TM III, Asn^{241} in TM IV, and Arg^{178} and Glu^{185} in TM IV have been shown to be necessary for ligand binding (Sabirsh et al., 2006; Basu et al., 2007) (Fig. 2). In addition to the TM domains, the second extracellular loop of BLT_1R may play an even more critical role for LTB_4 binding as suggested by the complete loss of ligand binding after mutation of Arg^{156} to alanine (Basu et al., 2007) (Fig. 2). In line with the homology between the BLT_1 and BLT_2 receptors (see section II.A), most of the binding site residues described above suggest a common binding mode for LTB_4 at the two BLT receptor subtypes (Basu et al., 2007). However, the presence of Tyr^{94} in BLT_2R at the place of His^{94} within BLT_1R has been suggested to account for some of the differences in the binding affinities and agonist selectivity between these receptors (Basu et al., 2007).

Structural models for the ligand-free and ligand-bound states of BLT_1R have revealed an activation core formed around Asp^{64}, and mutagenesis toward Asn^{36}, Ser^{100}, and Asn^{281} and a triad of serines, Ser^{277}, Ser^{278}, and Ser^{279} (Fig. 2), resulted in loss of signaling capacity, whereas mutant receptors retained normal LTB_4 binding (Basu et al., 2007). Furthermore, mutating the third intracellular loop, which consists of the cytoplasmic end of TM V (Fig. 2), reduced G_i-dependent signaling associated with a loss of the high-affinity LTB_4 binding state (Kuniyeda et al., 2007).

The C-tail containing a putative cytoplasmic helical domain, helix 8, of the BLT receptors has recently received attention. For example, BLT_1R with a mutated helix 8 exhibit increased LTB_4 binding as well as prolonged $[Ca^{2+}]_i$ mobilization and cellular metabolic activation compared with the WT receptor, suggesting that helix 8 might work as a scaffold for G proteins, changing

BLT_1R to a low-affinity state leading to release of the ligand and signal shutdown (Okuno et al., 2003). In contrast, helix 8 may not be critical for either ligand binding or activation of BLT_2R (Yasuda et al., 2009). However, human BLT_2Rs lacking helix 8 accumulate in the endoplasmic reticulum, suggesting that helix 8 may be required for BLT_2R protein folding and passage through the endoplasmic reticulum to the cell membrane (Yasuda et al., 2009).

Whereas cells expressing a complete C-tail-truncated BLT_1R (G291stop, Fig. 2) exhibit increased numbers of binding sites and increased signal transduction compared with wild-type BLT_1R (Gaudreau et al., 2004), a partially C-tail-truncated BLT_1R mutant (G319stop, Fig. 2) has shown binding characteristics similar to WT BLT_1R (Gaudreau et al., 2002). Furthermore, mutating a dileucine motif (Leu^{304}-Leu^{305}), suggested to be involved in a hydrophobic core (Fig. 2), mimicked the increased binding and signaling associated with the complete C-tail truncated receptor (Gaudreau et al., 2004). In addition, this latter mutation prevented LTB_4-induced BLT_1R internalization (Gaudreau et al., 2004), which corroborated the findings that the complete C-tail-truncated BLT_1R lost the capacity to internalize through the involvement of GPCR kinases (GRK) 2 and 6 (Gaudreau et al., 2002; Chen et al., 2004). In addition, substitution of Thr^{308} within a putative casein kinase 2 site in the full-length BLT_1R (Fig. 2) prevented most of GRK6-mediated inhibition of LTB_4-induced inositol phosphate production while only partially affecting the LTB_4-induced BLT_1R phosphorylation (Gaudreau et al., 2002). Through the substitution of all Ser and Thr residues in the C-terminal tail with Ala (to generate a phosphorylation-defective mutant) or with Asp/Glu (to mimic constitutive phosphorylation), it has been shown that BLT_1R phosphorylation may be an important mediator of G protein activation, whereas β-arrestin-associated BLT_1R internalization seems to be independent of phosphorylation (Jala et al., 2005). For the murine BLT_1R, a PKC consensus phosphorylation site has been reported to be located on the second intracellular loop, and a Ser^{127} substitution within this site prevented $mBLT_1R$ desensitization (Mollerup et al., 2007).

C. Intracellular Signaling Pathways and Second-Messenger Systems

The downstream intracellular signaling pathways after BLT_1 and BLT_2 receptor activation involve increased $[Ca^{2+}]_i$ and inhibition of adenylyl cyclase (Brink et al., 2003). The G protein coupling for the BLT receptors may depend on the type of G proteins expressed in the different cells studied. In several cell types expressing endogenous BLT receptors, pertussis toxin (PTX) inhibits the increased $[Ca^{2+}]_i$ in response to LTB_4, suggesting coupling to G_i proteins (Brink et al., 2003). However, in BLT_1R-transfected cells, a significant portion of the LTB_4-induced $[Ca^{2+}]_i$ response is resistant to PTX, suggesting also the involvement of G_q-protein coupling (Yokomizo et al., 1997; Haribabu et al., 1999; Brink et al., 2003; Sabirsh et al., 2004). These different profiles of PTX sensitivity suggest that BLT_1R and BLT_2R signal through different subtypes of G_i proteins (Yokomizo et al., 2000).

BLT receptor transduction also activates a number of kinases that phosphorylate downstream signal transduction proteins (Brink et al., 2003). For example, phosphorylation of mitogen-activated protein kinases (MAPKs) is involved in the LTB_4-induced proliferation of RAW 264.7 macrophages and bronchial SMCs (Nieves and Moreno, 2006; Watanabe et al., 2009). In addition, extracellular signal-regulated kinases (ERKs) may also be involved in LTB_4-induced proliferation, as demonstrated in vascular SMCs (Heller et al., 2005) and in signaling associated with delayed neutrophil apoptosis (Pétrin et al., 2006). The reported effects of different kinase inhibitors may also depend on which LTB_4-induced response is studied. For example, wortmannin, a phosphatidylinositol 3-kinase (PI3K) inhibitor has been reported to block LTB_4-induced chemotaxis, whereas calcium mobilization remains intact (Haribabu et al., 1999; Sabirsh et al., 2004). Tyrosine kinases have been implicated in LTB_4-signaling in neutrophil granulocytes (Dryden et al., 1992) and BLT_1-transfected HeLa cells (Sabirsh et al., 2004).

Effects on transcription have been implicated in BLT receptor intracellular signaling. For example, treatment of monocytes with LTB_4 increased the transcriptional activation of the IL-6 gene (Brach et al., 1992). In this study, a reporter gene assay identified two restricted regions within the IL-6 promoter. These binding sites for NF-IL-6 and NF-κB conferred inducibility by LTB_4. Exogenous addition of LTB_4 increased the DNA binding of these transcription factors in monocytes (Brach et al., 1992; Huang et al., 2004) and induced nuclear translocation of NF-κB p65 in murine bone marrow-derived dendritic cells (Toda et al., 2010). The LTB_4-induced NF-κB DNA binding activity was abolished by the BLT_1R antagonist 1-[3-(4-phenyl-benzyl)-4-hydroxy-chroman-7-yl] cyclopentane carboxylic acid (CP-105,696) (Huang et al., 2004), suggesting that transcriptional alterations by LTB_4 may be through BLT_1R. One possible mechanism for this transcriptional activation by LTB_4 could be through LTB_4-induced intracellular H_2O_2 formation (Gagnon et al., 1989), because the oxidant scavenger *N*-acetyl-L-cysteine completely blocks LTB_4-mediated transcription factor binding in monocytes (Brach et al., 1992). However, another study failed to observe any effects of other antioxidants on IL-6 protein secretion (Rola-Pleszczynski and Stanková, 1992). In the latter study, the partial inhibition of LTB_4-induced IL-6 secretion by genistein suggested the involvement of tyrosine phosphorylation events during this process.

D. Receptor Distribution and Cellular Targets

1. Neutrophil Granulocytes. The expression of both BLT_1 and BLT_2 receptor proteins in neutrophil granulocytes has, for example, been demonstrated by immunohistochemical analysis of surgical specimens derived from human abdominal aortic aneurysms (Houard et al., 2009). The potent neutrophil chemotactic activity of LTB_4 through BLT_1R signaling has been well established (Ford-Hutchinson et al., 1980; Malmsten et al., 1980; Palmblad et al., 1981). In neutrophils derived from the synovial fluid of patients with rheumatoid arthritis, BLT_1 receptor antagonism inhibits LTB_4-induced calcium mobilization and produces a rightward shift of the peak chemotactic response. In contrast, the BLT_2R antagonist 1-[5-ethyl-2-hydroxy-4-[[6-methyl-6-(1*H*-tetrazol-5-yl) heptyl]oxy]phenyl]ethanone (LY255283) only inhibits $[Ca^{2+}]_i$ and the chemotactic response to LTB_4 at high concentrations, at which this compound may also act as an antagonist at BLT_1R (Mathis et al., 2010). Studies in knockout mouse models have also shown that the LTB_4-induced chemotaxis and calcium mobilization in zymosan-elicited murine peritoneal neutrophils derived from either WT or BLT_2 knockout mice display similar LTB_4 dose-response relations, whereas neutrophils from BLT_1R knockout and BLT_1R-BLT_2R knockout mice lack both chemotaxis and alterations of $[Ca^{2+}]_i$ in response to LTB_4 (Haribabu et al., 2000; Tager et al., 2000; Terawaki et al., 2005; Mathis et al., 2010).

In addition to chemotaxis, LTB_4 stimulates neutrophil release of lysozyme (Hafstrom et al., 1981), matrix metalloproteinases (MMP) (Kjeldsen et al., 1992), myeloperoxidase (Terawaki et al., 2005), elastase, α-defensins (Flamand et al., 2007), and azurocidin (Di Gennaro et al., 2009). Initial characterization of the binding of $[^3H]LTB_4$ in relation to the functional effects of LTB_4 on human neutrophils suggested that whereas high-affinity binding sites mediated chemotaxis, this lysosomal degranulation occurred by LTB_4 binding to low-affinity sites (Goldman and Goetzl, 1984). Subsequent results demonstrated that both subsets of LTB_4 binding sites contributed to increases in $[Ca^{2+}]_i$ induced by LTB_4 (Goldman et al., 1985). In line with those findings, the neutrophil secretagog activity of LTB_4 has consistently been observed at higher LTB_4 concentrations compared with those needed to induce chemotaxis (Serhan et al., 1982). For example, maximal release of α-defensins from neutrophils was observed at 100 nM LTB_4 (Flamand et al., 2007), and the release of azurocidin was gradually increased at LTB_4 concentrations ranging from 10 nM to 1 μM (Di Gennaro et al., 2009). The latter apparent low-affinity response, however, was inhibited by the selective BLT_1R antagonist CP-105,696, but not by the selective BLT_2R antagonist LY255238. Despite the low-affinity profile, further support for lysosomal enzyme release being mediated through BLT_1R rather than BLT_2R signaling has emerged from studies of knockout mice. Although a low-affinity binding site for LTB_4 has been characterized in neutrophils derived from BLT_1R knockout mice, the myeloperoxidase release in response to LTB_4 is also abolished in those cells (Terawaki et al., 2005), hence challenging the concept of lysosomal enzyme release through BLT_2R signaling.

In addition to being a major neutrophil chemoattractant and promoting the release of lysosomal enzymes (Hafstrom et al., 1981; Serhan et al., 1982), prolonged exposure of neutrophils to LTB_4 delays their constitutive apoptosis in a time- and concentration-dependent manner (Hébert et al., 1996). Furthermore, threshold levels of LTB_4 (0.01 nM) induce surface expression of adhesion molecules, such as the β2-integrin CD11b and Mac-1, which have been implicated in LTB_4-induced neutrophil adhesion to endothelial cells (Gimbrone et al., 1984; Showell et al., 1998). The antimicrobial neutrophil response may also be facilitated by LTB_4 through increased surface expression of Toll-like receptors 7, 8, and 9 (Gaudreault and Gosselin, 2009) and stimulated secretion of the cathelicidin LL-37 (Flamand et al., 2007; Wan et al., 2007).

2. Eosinophil Granulocytes. Western blot analysis has demonstrated BLT_1R expression in eosinophils of both murine and human origin, with up-regulated expression levels in IL-5 transgenic mice and after inhalation of mold allergen (Huang et al., 1998). Consistent with findings in neutrophils, eosinophils derived from mice (Huang et al., 1998) and guinea pigs (Ng et al., 1991; Sun et al., 1991) also display a dose-dependent bell-shaped chemotactic response to LTB_4 with an optimum concentration of 1 to 10 nM. However, species differences may exist in terms of LTB_4-induced responses in eosinophils, because human cells may be less responsive to LTB_4 when chemotaxis is monitored (Sun et al., 1991). Nevertheless, human blood-derived eosinophils and eosinophil-differentiated HL-60 cells exhibit an increase in intracellular calcium concentration upon stimulation with LTB_4 (Patry et al., 1996; Murray et al., 2003). Furthermore, in line with findings in IL-5 transgenic mice (Huang et al., 1998), human eosinophils primed with IL-5 exhibit enhanced LTB_4-induced chemotaxis (Sehmi et al., 1992). Priming with cytokines, such as IL-5, may therefore be a prerequisite for regulating the expression and responsiveness of BLT receptors on human eosinophils. In guinea pigs, LTB_4 induced eosinophil superoxide generation in vitro (Ng et al., 1991). However, in contrast to findings in neutrophils, human eosinophil apoptosis was not altered by LTB_4 (Murray et al., 2003).

There are also animal studies that support a role of LTB_4 in regulating the recruitment of eosinophils into tissues in vivo. In guinea pigs, cutaneous LTB_4 injection induces an accumulation of ^{111}In-marked eosinophils (Faccioli et al., 1991) and oral treatment of sensitized guinea pigs with the selective BLT_1R antagonist -[6-(3-hydroxy-1*E*,5*Z*-undecadienyl)-2-pyridinyl]-1,5-hexane-

diol (U75302) decreased eosinophil influx to the lung and BAL after antigen challenge (Richards et al., 1989). However, the studies of OVA sensitization and challenge in BLT_1R-deficient mice have generated contradictory results, with both decreased eosinophil accumulation (Terawaki et al., 2005) and no alterations compared with results in WT mice (Miyahara et al., 2005a). In support of a pathophysiological role of LTB_4-induced eosinophil activation, BLT_1R-deficient mice exhibit decreased leukocyte content in peritoneal exudates compared with those in WT mice in response to thioglycollate-induced acute peritonitis (Tager et al., 2000). Furthermore, oral treatment with the BLT_1R antagonist CP-105,696 blocked the recruitment of eosinophils into the spinal cord and completely inhibited the development of paralysis in experimental allergic encephalomyelitis (EAE), a murine model of multiple sclerosis (MS) (Gladue et al., 1996). The potential in vivo effects of either pharmacological or genetic BLT_1R targeting also reflect indirect eosinophil activation, for example, through T lymphocyte-dependent responses and Th2 cytokines, such as IL-5 and IL-13 (Miyahara et al., 2005a,b; Terawaki et al., 2005). Finally, findings that blood eosinophil counts are unaltered in BLT_1R knockout mice compared with those in WT mice have suggested that BLT_1R is not necessary for granulocytopoiesis (Terawaki et al., 2005).

3. Basophil Granulocytes. There is presently a paucity of information regarding the expression of BLT receptors on basophil granulocytes. In human blood-derived basophils, LTB_4 induces a slight chemotactic response, which is more pronounced than that observed for PAF but less than that observed with C5a (Tanimoto et al., 1992). The receptor involved in the latter response, however, is presently unknown.

4. Monocytes/Macrophages. In human blood-derived monocytes, LTB_4 induces a dose-dependent increase in $[Ca^{2+}]_i$ with an ED_{50} of approximately 1.0 nM, which is inhibited by PTX (Rediske et al., 1993). Furthermore, BLT_1R protein has been demonstrated on human blood-derived monocytes by fluorescence-activated cell sorting (Friedrich et al., 2003; Pettersson et al., 2003). An analysis of monocyte subpopulations suggested that BLT_1R protein is more abundantly expressed in monocytes with high CD14 expression compared with $CD16^+$ monocytes (Pettersson et al., 2005).

In addition to chemotaxis, BLT_1R signaling in human monocytes also induced an up-regulation of integrin expression, involved in monocyte adhesion to endothelial cells in vitro and in vivo (Vaddi and Newton, 1994; Friedrich et al., 2003). Furthermore, LTB_4-induced activation of human monocytes has been associated with the release of IL-1β (Rola-Pleszczynski and Lemaire, 1985), IL-6 (Brach et al., 1992; Rola-Pleszczynski and Stanková, 1992), and monocyte chemoattractant protein 1 (MCP-1) (Huang et al., 2004).

BLT_1R expression has also been demonstrated on peritoneal and alveolar macrophages and in RAW 264.7 cells (Huang et al., 1998; Toda et al., 1999). In the latter macrophage cell line, LTB_4 induces increased proliferation and $[^3H]$thymidine uptake, suggesting that LTB_4 may also have mitogenic effects on macrophages (Nieves and Moreno, 2006).

Early studies had shown that LTB_4 enhanced macrophage bacterial phagocytosis in vitro (Demitsu et al., 1989). Subsequent results have demonstrated that this effect required the cells to be opsonized with IgG and that LTB_4 enhanced only Fc receptor (FcR)-mediated phagocytosis (Mancuso and Peters-Golden, 2000), whereas the phagocytosis of apoptotic cells (efferocytosis) was not affected by LTB_4 (Canetti et al., 2003). The signaling pathways involved in LTB_4-enhanced FcR-dependent phagocytosis include $G\alpha_{i3}$ protein (Peres et al., 2007), PKC activation (Mancuso and Peters-Golden, 2000), and the tyrosine kinase Syk (Canetti et al., 2003). It is noteworthy that a recent report demonstrated that FcR engagement results in tyrosine phosphorylation of BLT_1R by the Src family of kinases, which leads to a molecular complex within plasma membrane lipid rafts comprising the FcR, BLT_1R, $G\alpha_{i3}$ protein, and Src (Serezani et al., 2009). Because disruption of lipid rafts abolished the LTB_4-enhanced phagocytosis in the latter study, the formation of a complex between BLT_1R and immunoreceptors may represent a major mechanism in macrophage phagocytosis.

Several of the LTB_4-induced responses in monocytes/macrophages, such as MCP-1 secretion, intregrin-dependent monocyte arrest, and macrophage phagocytosis enhancement, are blocked by selective BLT_1R antagonists (Friedrich et al., 2003; Huang et al., 2004). However, BLT_2 receptor mRNA has also been detected in human monocytes (Yokomizo et al., 2001a). Furthermore, BLT_1 and BLT_2 receptor expression has been demonstrated immunohistochemically in macrophage-rich areas within human atherosclerotic lesions (Bäck et al., 2005) and abdominal aortic aneurysms (Houard et al., 2009), as well as by in situ hybridization of macrophages in synovial tissues from patients with rheumatoid arthritis (Hashimoto et al., 2003). Although an initial study demonstrated that macrophages derived from BLT_1R knockout mice did not alter $[Ca]_i$ after LTB_4 stimulation (Tager et al., 2003), a subsequent study reported that these cells display chemotaxis toward LTB_4 albeit at 100-fold higher concentrations than that in WT macrophages (Subbarao et al., 2004). The latter observation suggests that the low-affinity BLT_2 receptor may be involved in LTB_4-induced monocyte/macrophage chemotaxis. Based on results obtained in transfected CHO cells, in which expression of one BLT receptor leads to chemotaxis toward a narrow range of LTB_4 concentrations, coexpression of human BLT_1 and BLT_2 receptors makes cells migrate toward a wider range of LTB_4 concentrations (Yokomizo et al., 2001a).

5. Dendritic Cells. Dendritic cells (DCs) are antigen-presenting cells that control adaptive immunity through

direct interaction with T lymphocytes. Initially, human monocyte-derived DCs were reported to express mRNA for BLT_2R but not BLT_1R and the LTB_4-induced DC chemotaxis was reported to be inhibited by the BLT_2R antagonist LY255283 (Shin et al., 2006). However, a subsequent study revealed BLT_1R protein expression by flow cytometric analysis of human DCs (Toda et al., 2010). The latter finding was in line with the demonstration of BLT_1R but not BLT_2R mRNA in murine bone marrow-derived DCs (BMDCs) (Toda et al., 2010). The latter cells exhibit functional responses to LTB_4, such as increased $[Ca^{2+}]_i$ and chemotaxis (Del Prete et al., 2007; Toda et al., 2010), not observed in BMDCs derived from either BLT_1R or BLT_1R and BLT_2R knockout mice (Del Prete et al., 2007; Toda et al., 2010). Other responses associated with LTB_4 stimulation of murine DCs include induction of the chemokine receptor CCR7 (Del Prete et al., 2007), IL-12 secretion, and NF-κB translocation (Toda et al., 2010). Furthermore, murine DCs lacking both BLT_1R and BLT_2R exhibited decreased in vivo migration to draining lymph nodes after either paw injection (Del Prete et al., 2007) or intratracheal instillation (Miyahara et al., 2008). In vivo models have also implicated a pathophysiological role for DC BLT receptors by demonstrating decreased airway hyperreactivity after transfer of OVA-pulsed BLT_1R-deficient BMDCs compared with wild-type BMDCs (Miyahara et al., 2008) and decreased skin contact hypersensitivity in BLT_1R and BLT_2R knockout mice (Del Prete et al., 2007). Finally, the OVA-dependent cytokine production in mouse splenocytes after adoptive transfer of BLT_1R-deficient BMDCs exhibited decreased production of the Th1 cytokine IFN-γ and elevated levels of the Th2 cytokines IL-4 and IL-5 (Toda et al., 2010).

6. T Lymphocytes. The chemotactic response of human blood-derived human T lymphocytes was initially reported to exhibit a peak concentration of LTB_4 at 10^{-8} M (i.e., a lower potency compared with granulocytes) (Leppert et al., 1995). The latter observation was supported by the binding of radioactive LTB_4 to the $CD4^+8^+3^{low}$ Tsup-1 cell line, which was characterized by a K_d of approximately 200 nM and a rank order of competitive potencies of 20-OH-LTB_4, 6-*trans*-LTB_4, which were both similar to that of the low-affinity subset of human neutrophil LTB_4-binding sites (Leppert et al., 1995). Subsequent studies of peripheral blood cells have supported those initial observations by the identification of dominant levels of BLT_2R mRNA compared with BLT_1R mRNA (Yokomizo et al., 2001a). Moreover, in peripheral blood, LTB_4 bound only to 11% of T lymphocytes, representing mainly cells of the $CD8^+$ subset (Payan et al., 1984). The latter observation was subsequently supported by a flow cytometric demonstration of BLT_1 and CD8 coexpression in a small fraction of peripheral blood cells, whereas $CD4^+$ lymphocytes were BLT_1R-negative (Pettersson et al., 2003). However, decreased BLT_2R expression has been observed after T-lymphocyte stimulation (Yokomizo et al., 2001a), and animal studies indicate that BLT_1R activation may be the major signaling pathway mediating LTB_4-induced T lymphocyte recruitment in vivo (Goodarzi et al., 2003; Tager et al., 2003; Miyahara et al., 2005a). Furthermore, morphological analyses have associated adventitial vascular inflammation with an accumulation of BLT_1R-expressing T lymphocytes (Houard et al., 2009).

BLT_1R mRNA expression is induced in antigen-exposed murine $CD8^+$ T-effector cells, associated with an increased chemotactic response; effects inhibited either by the BLT_1R antagonist CP-105,696 or in cells derived from BLT_1R knockout mice (Goodarzi et al., 2003; Ott et al., 2003). These findings suggest that the ability to use BLT_1R for migration into inflamed tissues is a feature specific to fully differentiated $CD8^+$ effector cells (Goodarzi et al., 2003). Likewise, BLT_1R mRNA is induced in $CD4^+$ murine lymphocytes during either Th1 or Th2 polarization (Tager et al., 2003). A subsequent study of human blood-derived T lymphocytes demonstrated that the small fraction of BLT_1R-positive cells also were enriched for the activation markers CD38 and HLA-DR and expressed the effector cytokines IFN-γ and IL-4 (Islam et al., 2006). Furthermore, in vitro activation of human T lymphocytes by alloactivated DCs increased BLT_1R surface expression and enhanced LTB_4-induced chemotaxis (Islam et al., 2006). In further support of an up-regulation of BLT_1R in activated T lymphocytes, the number of circulating $CD8^+$ cells positive for BLT_1R was increased during acute Epstein-Barr virus infection (Islam et al., 2006). Finally, bronchoalveolar lavage derived from patients with lung transplant graft dysfunction (Medoff et al., 2005) and asthma (Islam et al., 2006) contained an increased proportion of BLT_1R-positive T lymphocytes.

LTB_4 stimulation also enhanced the production of IL-1, IL-2, IL-5, and IFN-γ in human blood-derived T lymphocytes in vitro (Rola-Pleszczynski et al., 1986; Yamaoka and Kolb, 1993) and the production of MMP-2, -3, and -9 in $CD4^+8^+3^{low}$ Tsup-1 cells (Leppert et al., 1995). Furthermore, LTB_4 inhibited the differentiation of murine naive $CD4^+$ T lymphocytes into $CD25^+$ $Foxp3^+$ T regulatory cells and increased IL-17 expression (Chen et al., 2009a), providing the first suggestion that LTB_4 may counteract the generation of immunosuppressive T regulatory cells and promote the differentiation into Th17 cells. In support of a role for LTB_4 in the development of Th17 immune responses, lymph node cells derived from BLT_1R knockout mice after EAE induction exhibit decreased IL-17 production (Kihara et al., 2010).

The role of BLTR signaling in T lymphocyte recruitment has also received support from in vivo studies. The pulmonary inflammation and airway hyperresponsiveness after OVA sensitization and challenge are reduced in BLT_1R knockout mice and restored after reconstitution with BLT_1R-expressing T lymphocytes (Tager et al.,

2003; Miyahara et al., 2005a). In addition, mice lacking $CD8^+$ T lymphocytes are protected from airway hyperresponsiveness induced by allergen sensitization and challenge (Miyahara et al., 2005b). Whereas reinstallation of $CD8^+$ cells restored airway hyperresponsiveness in the latter mice, adoptive transfer of BLT_1R-deficient $CD8^+$ cells maintained the protective effect (Miyahara et al., 2005b). In other models, such as complete Freund's adjuvant-induced peritonitis, adoptive transfer of fluorescence-marked T lymphocytes derived from both BLT_1R-deficient and WT mice resulted in an accumulation of 1.6- to 1.9-fold higher numbers of WT cells in peritoneal exudates (Goodarzi et al., 2003).

7. B Lymphocytes. BLT_1R protein and BLT_1R and BLT_2R mRNA have been detected in $CD19^+$ human B lymphocytes (Yokomizo et al., 2001a; Pettersson et al., 2003; Runarsson et al., 2005). In cells derived from either blood or tonsillectomy tissues, LTB_4 enhances the effects of other stimulating factors on CD23 expression, proliferation, and differentiation of resting, but not activated, B lymphocytes (Yamaoka et al., 1989, 1994; Dugas et al., 1990). The latter findings were subsequently supported by the demonstration that Epstein-Barr virus infection of B lymphocytes is associated with a loss of BLT_1R expression and a lack of LTB_4-induced effects on the proliferation of infected cells (Liu et al., 2008). BLT_1R protein expression has also been demonstrated in B lymphocytes derived from patients with B-cell chronic lymphocytic leukemia (Runarsson et al., 2005). In this study, LT synthesis inhibitors decreased DNA synthesis and antigen expression in B-cell chronic lymphocytic leukemia lymphocytes, an effect that was reversed by exogenously added LTB_4 (Runarsson et al., 2005).

8. Mast Cells. Experiments in human umbilical cord blood-derived mast cells have demonstrated that LTB_4 is a chemoattractant for the immature c-kit^+ MC populations, whereas the mature c-kit^{high} MCs are unresponsive (Weller et al., 2005). The chemotactic effects induced by LTB_4 on murine bone marrow-derived mast cells (BMMCs) cultured in the presence of IL-3 may also depend on the maturity of the MC, because cells cultured for 2 to 6 weeks migrate in response to LTB_4 (Kitaura et al., 2005; Weller et al., 2005; Lundeen et al., 2006), whereas after 10 weeks of culture, the cells are unresponsive to this agonist (Weller et al., 2005). The latter finding correlated with a decrease in BLT_1R mRNA. For example, 2-week-old BMMCs expressed 4-fold higher levels than 6-week-old cells and 10-fold more than 10-week-old cells (Weller et al., 2005). A subsequent study also described BLT_2R mRNA in BMMC after 4 weeks of culture and indicated that either the BLT_1R antagonist U75302 or the BLT_2 receptor antagonist LY255283 inhibited LTB_4-induced BMMC chemotaxis, although no additive effect was observed after combination of the two receptor antagonists (Lundeen et al., 2006). In addition, antigen stimulation increased BLT_2R expression in murine BMMCs (Cho et al., 2010a). In support of a functional murine MC BLT_2 receptor, the BLT_2 receptor agonists 12-HHT and 12(*S*)-HETE have also been reported to induce BMMC migration (Lundeen et al., 2006; Okuno et al., 2008). The $[Ca^{2+}]_i$ induced by 12-HHT was abolished in BMMCs derived from BLT_2R knockout mice, whereas BMMCs from both WT and BLT_1R knockout mice responded to LTB_4 (Mathis et al., 2010). However, LTB_4-induced migration was abolished in BMMCs derived from BLT_1R-deficient mice, whereas 12-HHT-induced migration was abolished in BMMCs derived from BLT_2R-deficient mice (Okuno et al., 2008). Finally, a human MC line, HMC-1, has been reported to express both BLT_1 and BLT_2 receptor mRNA and migrate in response to LTB_4 (Lundeen et al., 2006). An unexpected finding was that flow cytometry and immunostaining suggested an intracellular localization of BLT_1R protein in these cells (Lundeen et al., 2006), but the functional significance of this receptor localization remains to be established.

9. Vascular Smooth Muscle Cells. The LTB_4-induced vasoconstriction, demonstrated in human pulmonary artery (Sakata et al., 2004), in guinea pig pulmonary artery and aorta (Bäck et al., 2004; Sakata et al., 2004), and in rat basilar artery (Trandafir et al., 2005), has led to the hypothesis that nonmyeloid cells, such as SMCs, also express BLT receptors. Immunohistochemical analysis of human arteries has revealed BLT_1R expression in the muscular layers of carotid atherosclerotic endarterectomies, as well as in human nonatherosclerotic mammary arteries (Bäck et al., 2005). Moreover, in human coronary artery SMCs, 8-fold higher BLT_1R mRNA levels compared with BLT_2R mRNA has been demonstrated by RT-PCR (Heller et al., 2005), supporting the observation that the BLT_1R subtype may be the dominant BLT receptor subtype in vascular SMCs. The expression of BLT_1R proteins on human coronary artery SMCs has also been demonstrated by Western blot (Bäck et al., 2005) and flow cytometry (Heller et al., 2005). In contrast to this apparent constitutive BLT_1R expression in human coronary artery SMCs, murine aortic SMCs express BLT_1R mRNA only after 24 h of treatment with TNF-α and IFN-γ (Heller et al., 2005).

In human coronary artery SMCs, LTB_4 induced an approximately 4-fold increase in whole-cell currents measured by patch clamp, and the activation of SMC by LTB_4 induces migration and proliferation (Bäck et al., 2005). Furthermore, LTB_4 stimulated the release of MMP-2 (Hlawaty et al., 2009; Seo et al., 2010) and activation of integrin signaling pathways in vascular SMCs (Moraes et al., 2010). The pathophysiological importance of LTB_4-induced activation of SMCs in the context of atherosclerosis has been reinforced by the inhibitory effects of BLT receptor antagonists on the development of intimal hyperplasia after vascular injury (Kondo et al., 1998; Bäck et al., 2005; Hlawaty et al., 2009). Furthermore, atherosclerotic lesions of apoE(−/−) mice

display reduced SMC content after BLT_1R gene disruption (Heller et al., 2005).

10. Bronchial Smooth Muscle Cells. In line with findings in human vessels, immunohistochemical staining of human bronchi revealed colocalization of both BLT_1R and BLT_2R protein with smooth muscle α-actin-positive airway SMCs (Watanabe et al., 2009). Furthermore, both receptors were also identified on human airway SMCs in culture by RT-PCR, Western blot analysis, and flow cytometry. In the latter cells, LTB_4 induced proliferation and migration, which was inhibited by the selective BLT_1R antagonist U75302 (Watanabe et al., 2009).

11. Endothelial Cells. In human vessels, endothelial expression of BLT_1R has been demonstrated by immunohistochemical analysis and was only observed in atherosclerotic and not in healthy arteries, suggesting an induction during vascular inflammation (Bäck et al., 2005). The latter notion of BLT_1R immunoregulation has received support from studies in HUVECs demonstrating BLT_1R up-regulation by LPS and IL-1β (Table 2), whereas BLT_2R was induced by TNF-α (Qiu et al., 2006).

LTB_4-induced endothelial activation has also been implicated in increased leukocyte adherence (Hoover et al., 1984). However, the in vitro neutrophil adherence observed after LTB_4 stimulation of HUVECs is weak (Lindström et al., 1990; Palmblad et al., 1994), and the role of endothelial BLT receptors in leukocyte adhesion is today not fully characterized. Papayianni et al. (1996) demonstrated that LTB_4 had no effect on P-selectin expression in HUVECs. Another study reported no effect on monocyte arrest under physiological flow conditions after EC stimulation with LTB_4 (Friedrich et al., 2003). These observations provided evidence for a direct effect of LTB_4 on leukocytes rather than on ECs. However, other investigators demonstrated that the endothelium released vasoactive factors via BLT receptor activation (Bäck et al., 2004; Qiu et al., 2006). These reports provide evidence for a role of LTB_4 in regulating endothelial function. In addition, vascular endothelial growth factor (VEGF) up-regulated the expression of BLT_1R and BLT_2R mRNA and protein in HUVECs (Kim et al., 2009). It is noteworthy that VEGF also increased the release of 12(*S*)-HETE, and the VEGF-induced blood vessel formation in vivo and in vitro was inhibited by either the BLT_2R antagonist LY255283 or BLT_2R knock down by small interfering RNA (Kim et al., 2009). These findings suggest a role for 12(*S*)-HETE signaling through endothelial BLT_2R in angiogenesis. Taken together, the data indicate that the ligands for the BLT receptors affect ECs but that the interaction between the ligands and the endothelium in adhesion experiments is presently difficult to observe, possibly being masked by the LTB_4-induced effects on leukocytes.

E. BLT Receptor Functional Analysis through Altered Gene Expression

1. BLT Receptor Transgenic Models. Transgenic mice expressing the human BLT_1R under the CD11b promoter to obtain leukocyte specific expression exhibit an increased granulocyte infiltration in response to topical LTB_4 application and ischemia reperfusion (Chiang et al., 1999; Brink et al., 2003). In addition, transgenic BLT_2R overexpressed in mice have been studied in a model of angiogenesis and shown to exhibit increased blood vessel formation in response to LTB_4 and 12(*S*)-HETE (Kim et al., 2009).

2. BLT_1 Receptor Knockout. Mice lacking BLT_1R were generated in 2000 (Haribabu et al., 2000; Tager et al., 2000; Brink et al., 2003). Although these mice developed normally and had no apparent hematopoietic abnormalities, decreased leukocyte chemotaxis (Haribabu et al., 2000; Tager et al., 2003) and integrin-mediated leukocyte arrest in postcapillary venules (Tager et al., 2003) in response to LTB_4 compared with WT mice were reported. In addition, BLT_1R deficiency conferred protection against inflammatory responses in different disease models.

After induction of acute peritonitis, BLT_1R-deficient mice exhibit decreased leukocyte content in peritoneal exudates compared with that in WT mice (Haribabu et al., 2000; Tager et al., 2000; Goodarzi et al., 2003) Other in vivo studies of endotoxin provocation have demonstrated decreased portal venule leukocyte adherence in response to systemic LPS in BLT_1R knockout mice compared with that in WT mice (Ito et al., 2008), whereas the leukocyte infiltration after local intraocular LPS injection was not altered by BLT_1R disruption (Smith et

TABLE 2
Immunoregulation of human BLT_1R expression

Receptor	Cytokine	Cell	Effect[a]	Reference
BLT_1	IFN-γ	Monocytes	$\downarrow$ mRNA; $\downarrow$ protein; $\downarrow$ chemotaxis	Pettersson et al., 2005
	TNF-α	Monocytes	$\downarrow$ mRNA; $\downarrow$ protein	Pettersson et al., 2005
		Granulocytes	$\downarrow$ protein	Pettersson et al., 2003
	IL-1β	Vascular SMCs	$\uparrow$ mRNA	Bäck et al., 2005
		HUVECs	$\uparrow$ mRNA; $\uparrow$ protein	Qiu et al., 2006
	IL-10	Monocytes	$\uparrow$ mRNA; $\uparrow$ protein	Pettersson et al., 2005
	LPS	Monocytes	$\downarrow$ mRNA	Pettersson et al., 2005
		Granulocytes	$\downarrow$ protein	Pettersson et al., 2003
		Vascular SMCs	$\uparrow$ mRNA	Bäck et al., 2005
		HUVECs	$\uparrow$ mRNA; $\uparrow$ protein; $\uparrow$ $[Ca^{2+}]_i$	Qiu et al., 2006
	IL-5	Eosinophils	$\uparrow$ chemotaxis	Sehmi et al., 1992; Thivierge et al., 2000

[a] $\uparrow$, up-regulation; $\downarrow$, down-regulation; specified are the effects (at mRNA, protein, and functional level).

al., 2004). In addition to models of acute inflammation, BLT_1R knockout mice have also revealed decreased inflammation in more chronic inflammatory responses. For example, in contrast to the lack of effects on endotoxin-induced uveitis, BLT_1R-deficient mice were protected from experimental autoimmune uveitis induced by immunization of interphotoreceptor retinoid-binding protein (Liao et al., 2006).

Mice lacking apolipoprotein E exhibit hyperlipidemia and develop spontaneous atherosclerosis. Apolipoprotein E and BLT_1R double knockout mice display smaller lesions compared with their apoE(−/−) littermates (Subbarao et al., 2004; Heller et al., 2005; Bäck, 2008b). The latter double knockout mice are also protected from abdominal aortic aneurysm development induced by angiotensin II infusion (Ahluwalia et al., 2007).

After OVA sensitization, BLT_1R knockout mice exhibit decreased airway responsiveness associated with a decreased leukocyte accumulation (Tager et al., 2003; Miyahara et al., 2005a; Terawaki et al., 2005), which is restored after adoptive transfer of BLT_1R-expressing T lymphocytes (Miyahara et al., 2005a; Tager et al., 2003) (see section II.D). In the EAE model, BLT_1R-deficient mice develop less severe clinical signs of disease and a significantly delayed onset of disease than WT mice, associated with decreased inflammatory infiltration in the spinal cord (Kihara et al., 2010). Finally, BLT_1R knockout mice are protected in models of both collagen- and K/BxN serum-induced arthritis (Kim et al., 2006a; Shao et al., 2006; Mathis et al., 2010), discussed in detail below. In this context, BLT_1R knockout mice displayed a decrease in bone resorption induced by either LPS or ovariectomy (Hikiji et al., 2009).

3. BLT_2 Receptor Knockout. In recent studies, BLT_2R knockout mice were generated (Iizuka et al., 2010; Mathis et al., 2010). Because of to the close proximity of the BLT_1R gene promoter, the BLT_2R gene disruption was generated through insertion into the open reading frame of the BLT_2 gene to avoid alterations of BLT_1R expression (Iizuka et al., 2010; Mathis et al., 2010). The BLT_2R-deficient mice were viable, developed normally, and displayed no overt behavioral or morphological defects (Mathis et al., 2010). An unexpected finding was that opposing phenotypic changes were observed in two different mouse models of disease. BLT_2R knockout mice displayed attenuated inflammatory arthritis in response to K/BxN serum transfer (Mathis et al., 2010). The latter effect was associated with decreased inflammatory cell influx and could be reproduced by bone marrow transplantation, suggesting that leukocyte BLT_2R is necessary for full arthritis development (Mathis et al., 2010). However, the protection against K/BxN serum-induced arthritis conferred by the lack of BLT_1R is more pronounced compared with that observed in BLT_2R-deficient mice (Kim et al., 2006a; Mathis et al., 2010). Nevertheless, the transfer of WT neutrophils into BLT_1R knockout mice promoted the entry of endogenous BLT_1R-deficient neutrophils into the joints of these mice (Kim et al., 2006a) through the production of IL-1 (Chou et al., 2010). Taken together, these data suggested that although the BLT_1R may be necessary for the initiation of autoantibody-induced arthritis, BLT_2R may play a possible role at later stages of disease, when local LTB_4 concentrations are higher in the joint (Mathis et al., 2010). In contrast to the findings of decreased arthritis in BLT_2R knockout mice, another study demonstrated that this gene disruption induced more severe colitis in response to dextran sodium sulfate (DSS) compared with that in either WT or BLT_1R knockout mice, which was accompanied by increased expression of inflammatory cytokines, chemokines, and MMPs (Iizuka et al., 2010). However, in the latter study, BLT_2R deficiency was associated with a dysfunctional barrier function in colonic epithelial cells rather than direct effects on leukocytes (Iizuka et al., 2010). Although the effects of DSS-induced colitis have not been fully explored in BLT_1R knockout mice, those mice exhibit weight loss similar to that in WT mice, suggesting no protective effects. The notion that BLT_2R agonists other than LTB_4 may be involved in the exacerbated colitis observed after BLT_2R knockout (Iizuka et al., 2010) is supported by the fact that HHT is produced at 5- to 6-fold higher levels compared with LTB_4 in inflamed colonic biopsy specimens (Zijlstra et al., 1992, 1993) (see section II.E).

4. BLT_1 and BLT_2 Receptor Double Knockout. Double knockout of BLT_1R and BLT_2R has been generated through direct targeting of the genes encoding both receptors (Shao et al., 2006). In line with findings after disruption of any of the BLT receptor subtypes alone (see above), these mice were also viable, developed normally, and displayed no overt behavioral or morphological defects and no alterations of leukocyte subpopulation counts (Shao et al., 2006). After collagen-induced arthritis, both BLT_1R knockout and BLT_1R-BLT_2R knockout mice respond in a similar fashion with less clinical and histological signs of arthritis, as well as smaller synovial inflammatory cell infiltration compared with WT mice, without altering the antibody response (Shao et al., 2006).

F. Potential Therapeutic Applications

The cell-type specific BLTR signaling discussed above (see section II.D) may imply differential effects of LTB_4 in the development of different diseases. For example, LTB_4 may mainly exert its effects on neutrophil granulocytes in models of arthritis (Kim et al., 2006a) abdominal aortic aneurysms (Houard et al., 2009), and cerebral ischemia/reperfusion (Barone et al., 1992), whereas models of MS have implicated a major role of LTB_4-induced effects on eosinophil granulocytes (Gladue et al., 1996). In contrast, T lymphocytes may be the main effector cells in LTB_4-induced airway hyperresponsiveness (Miyahara et al., 2005a). Furthermore, in other

disease models, LTB_4 signaling may affect several cell types, such as in atherosclerosis, in which macrophages, vascular SMCs, and ECs express BLT_1 receptors (Bäck et al., 2005). The roles of LTs and related lipid mediators in various diseases have been extensively reviewed (Shimizu, 2009).

1. Atherosclerosis. The uptake and modification of lipids in the vascular wall induce a local inflammatory reaction, eventually developing into an atherosclerotic lesion. Generation of LTB_4 has been described in ex vivo stimulated atherosclerotic vessels, and intraluminal LT formation has been demonstrated during coronary balloon angioplasty (Brezinski et al., 1992; Bäck, 2008b). In addition, several of the BLT receptor-expressing immune cells discussed above are present in the atherosclerotic lesion (Bäck, 2008b). Although studies of targeted 5-LO have generated contradictory results, BLT_1R knock out (Subbarao et al., 2004; Heller et al., 2005) and the BLT_1R antagonist CP-105,696 (Aiello et al., 2002) reduces atherosclerosis in hyperlipidemic mice (Bäck, 2008b). In addition to effects on the inflammatory response, LTB_4 signaling through BLT_1R expressed in vascular SMCs may also be involved in the development of atherosclerosis and intimal hyperplasia after vascular interventions (Bäck et al., 2005; Heller et al., 2005; Hlawaty et al., 2009). Clinical trials have been initiated to evaluate the effects of anti-LTs on biomarkers and atherosclerosis morphology in patients with coronary heart disease (Bäck, 2009a).

2. Aortic Abdominal Aneurysms. Circulating neutrophils derived from patients undergoing surgery for abdominal aortic aneurysms produce increased levels of LTB_4 (Gadaleta et al., 1994), and the expression levels of LTB_4 synthesizing enzymes has in addition been demonstrated in neutrophils infiltrating the intraluminal thrombus covering the aneurysm (Houard et al., 2009). This local LTB_4 production has also been demonstrated to transduce the major part of the chemotactic activity derived from the intraluminal thrombus (Houard et al., 2009). In addition to neutrophils, BLTR-positive macrophages and T lymphocytes may be involved in the adventitial inflammation, which is part of the pathogenesis of abdominal aortic aneurysms (Houard et al., 2009). The importance of BLT_1R signaling has also received support from animal studies. Either genetic or pharmacological targeting of BLT_1R signaling reduces the incidence of experimental abdominal aortic aneurysms induced by angiotensin infusion in apoE knockout mice (Ahluwalia et al., 2007; Kristo et al., 2010).

3. Cerebrovascular Disease. Leukotrienes are produced during cerebral ischemia, and LT synthesis inhibitors limit the damage after experimental cerebral ischemia and reperfusion (Bäck, 2009b). Although most studies on the receptors involved in this protective effect have focused on CysLTRs and more recently GPR17 (see section III.H), there are also studies supporting a role for BLTR signaling in cerebrovascular disease. In a study in rats, temporary middle cerebral artery occlusion followed by reperfusion time dependently increased LTB4 binding in the cerebral cortex, which was paralleled by increases in myeloperoxidase activity (Barone et al., 1992). The results of the latter study suggested increased LTB_4 binding to receptors located on accumulating neutrophils in ischemic brain tissue (Barone et al., 1992).

In human cerebrovascular disease, macrophage 5-LO expression and LTB_4 production have been reported to correlate with either clinical or radiological signs of cerebral ischemia in patients undergoing vascular surgery for carotid artery stenosis (Cipollone et al., 2005). Furthermore, BLT_1R and BLT_2R are expressed within carotid artery atherosclerotic lesions (Bäck et al., 2005). Finally, and as stated above (see section II.A), haplotypes within the *LTB4R* and *LTB4R2* gene complex conferred a 2.3-fold increased risk for ischemic stroke in two case-control studies (Bevan et al., 2008).

4. Multiple Sclerosis. MS is an inflammatory disorder of the central nervous system associated with blood-brain barrier breakdown, inflammatory cell accumulation, and myelin degradation (Mirshafiey and Jadidi-Niaragh, 2010). As discussed above (see section II.D), the beneficial effects on EAE after either genetic or pharmacological BLT_1R targeting (Fretland et al., 1991; Gladue et al., 1996; Kihara et al., 2010) suggest that that BLT_1R signaling may potentially affect both the onset and severity of MS. In support of this, increased levels of LTB_4 have been detected in cerebrospinal fluid from patients with MS (Neu et al., 1992, 2002). Of interest, 5-LO was identified as one of the most up-regulated genes by microarray analysis in both human MS lesions and in brains from mice after EAE induction (Whitney et al., 2001). In the brain parenchyma around MS lesions, 5-LO expression colocalized with macrophages (Whitney et al., 2001). However, in contrast to findings in BLT_1R knockout mice (Kihara et al., 2010), 5-LO-deficient mice exhibit an exacerbated EAE compared with WT mice (Emerson and LeVine, 2004). These opposing effects of targeting either LT synthesis or LT receptors are in line with findings in atherosclerosis (see above) and point to the fact that targeting 5-LO will inhibit both proinflammatory mediators (i.e., LTs) and anti-inflammatory mediators (i.e., lipoxins), as has been demonstrated in 5-LO-deficient mice (Bafica et al., 2005). This, in turn, suggests that endogenous anti-inflammatory mediators derived from 5-LO metabolism may be involved in regulating these disease models. In addition, studies in mice lacking 12/15-LO have also shown exacerbated EAE (Emerson and LeVine, 2004) or a defect in both corneal reepithelization and neutrophil recruitment that correlates with a reduction in endogenous lipoxin formation (Gronert et al., 2005), raising the notion that lipoxins, for which the biosynthesis involves both 5-LO and 12/15-LO (Serhan et al., 2008), may be beneficial in MS. These findings suggest that BLT receptor antago-

nism may represent an advantage compared with 5-LO inhibition in MS.

5. Arthritis. BLTR expression has been demonstrated in synovial tissues derived from patients with rheumatoid arthritis (Hashimoto et al., 2003). The beneficial effects in models of rheumatoid arthritis after genetic disruption of BLT_1R and/or BLT_2R in C57BL6 mice (Kim et al., 2006a; Shao et al., 2006; Mathis et al., 2010) were discussed above (see section II.E. Pharmacological treatment with the BLT_1R antagonist CP-105,696 reduced the histological signs of collagen-induced arthritis in the more arthritis-prone DBA/1J mice (Griffiths et al., 1995). In humans, oral administration of the BLT receptor antagonist amebulant (Birke et al., 2001) inhibits Mac-1 expression on neutrophils (Alten et al., 2004), but clinical trials in patients with arthritis have not shown any statistically significant beneficial effects (Díaz-González et al., 2007).

6. Pulmonary Inflammation. Although most studies of LTs in asthma have focused on CysLT receptor signaling (see section III.A), several studies point to a participation of LTB_4 in chronic airway inflammation. For example, whereas $CysLT_1R$ antagonists generally have small effects on the increased bronchial responsiveness in asthma, clinical trials of either 5-LO inhibitors or FLAP antagonists have been more effective, supporting an involvement of LTB_4 (Dahlén, 2006). In addition, neutrophil recruitment to the airway is thought to be a major component of continuing inflammation and progression of chronic obstructive pulmonary disease (COPD), and the 46% of the neutrophil chemotactic activity in sputum derived from patients with COPD is inhibited by a BLT receptor antagonist (Woolhouse et al., 2002). Increased concentrations of LTB_4 have also been reported in BAL (Wenzel et al., 1995) and exhaled breath condensates from patients with asthma (Csoma et al., 2002). In further support of a role of BLT_1R signaling in asthma, the BLT_1R antagonist CP-105,696 decreased airway hyperresponsiveness in a primate model of asthma (Turner et al., 1996). As discussed above (section II.E), BLT_1R knockout mice exhibited decreased airway responsiveness after OVA sensitization and challenge, associated with decreased pulmonary inflammation and mucus secretion compared with that in WT mice (Miyahara et al., 2005a; Terawaki et al., 2005). In addition, BLT_2R signaling may be involved in the response to OVA sensitization and challenge, as suggested by the reduced airway inflammation and reduced airway hyperresponsiveness after BLT_2R targeting through in vivo administration of either the BLT_2R antagonist LY255283 or an antisense BLT_2R (Cho et al., 2010b).

In a crossover study of 12 atopic asthmatic individuals, the BLT receptor antagonist LY293111, 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]-propoxy]phenoxyl]benzoic acid (LY293111) did not alter either lung function or airway reactivity after allergen challenge but significantly reduced the number of neutrophils in BAL derived from treated patients compared with placebo (Evans et al., 1996).

7. Inflammatory Bowel Disease. Colonic mucosa derived from patients with inflammatory bowel disease (IBD) exhibit increased mRNA levels of LT-forming enzymes and enhanced LTB_4 production (Sharon and Stenson, 1984; Jupp et al., 2007). However, studies performed with ex vivo stimulated human colonic mucosa have revealed that lower amounts of LTB_4 are released compared with other arachidonic acid metabolites (Zijlstra et al., 1992, 1993). For example, 15-HETE is the dominant product formed after addition of exogenous arachidonic acid to human biopsy specimens obtained at coloscopy (Zijlstra et al., 1992, 1993). Furthermore, HHT, which may act as a high-affinity BLT_2R ligand (see section II.A and Fig. 1), is produced at 5- to 6-fold higher concentration compared with LTB_4 (Zijlstra et al., 1992, 1993). Nevertheless, the exact role of these ligands and the two BLTR subtypes in IBD remains to be established. Whereas different BLTR antagonists inhibit colonic inflammation and neutrophil infiltration in animal models of IBD (Fretland et al., 1990, 1991), BLT_2R-deficient mice exhibit exacerbated colonic inflammation (Iizuka et al., 2010).

8. Cancer. LTB_4 levels are increased in different human cancer tissues, such as prostate (Larré et al., 2008) and oral (el-Hakim et al., 1990) cancers. Furthermore, immunohistochemical analysis has revealed expression of BLT receptors in human pancreatic and colon cancers (Hennig et al., 2002; Ihara et al., 2007). As outlined above, LTB_4 signals through pathways associated with cell proliferation, such as MAPK, ERK, and PI3K, which has also been implicated in tumor growth (Tong et al., 2005; Ihara et al., 2007). In support of the latter suggestion, in vitro studies have shown that LTB_4 promotes and that BLT_1R antagonists inhibit the proliferation of cultured human cancer cell lines (Earashi et al., 1995; Bortuzzo et al., 1996; Ihara et al., 2007). In addition to direct effects on tumor cells, the BLT_2 receptor-associated angiogenesis discussed above (see section II.A) (Kim et al., 2009) may potentially also be involved in LTB_4-induced cancer growth (Wang and Dubois, 2010a).

Administration of the BLT_1R antagonist LY293111 after transplantation of human cancer cells to athymic mice resulted in reduced tumor growth and reduced incidence of metastases (Hennig et al., 2004, 2005). However, results from clinical trials using the latter antagonist in combination with gemcitabine did not improve the prognosis for patients with either pancreatic or lung cancer (Wang and Dubois, 2010a).

G. Other Receptors Involved in BLT Receptor Signaling

1. Peroxisome Proliferator-Activated Receptors. Peroxisome proliferator-activated receptors (PPARs) are li-

gand-activated transcription factors that belong to the nuclear hormone receptor superfamily (Michalik et al., 2006). PPARs activate gene transcription associated with metabolism and inflammation, in response to synthetic PPAR ligands developed for the treatment of diabetes and dyslipidemia (Michalik et al., 2006). In addition, LTB_4 has been identified among the endogenous ligands for PPARα. In transfected HeLa cells, LTB_4 activated PPARα reporter gene transcription in the micromolar range and bound a fusion protein containing the ligand-binding domain of PPARα, with a K_d of 90 nM (Devchand et al., 1996). Subsequent studies using different methods have confirmed LTB_4 binding to and activation of PPARα (Krey et al., 1997; Lin et al., 1999; Narala et al., 2010), although negative results have also been reported (Forman et al., 1997). In addition to results obtained in vitro, a recent study has also demonstrated that mice lacking LTB_4 biosynthesis through 5-LO knockout exhibited reduced PPARα activation in response to LPS administration in vivo (Narala et al., 2010). The latter results therefore support the observation that endogenous intracellular LTB_4 formation can reach sufficient concentrations for PPARα activation under inflammatory conditions (Narala et al., 2010).

2. Vanilloid Transient Receptor Potential V1 Receptor. The TRPV1 receptor is a ligand-gated, nonselective cation channel, which belongs to a family of TRP channels present exclusively in small sensory neurons and associated with pain. Although capsaicin and other vanilloids are the classic agonists, endogenous ligands derived from lipoxygenase metabolism of arachidonic acid and anandamide have also been reported to activate TRPV1 receptors (Hwang et al., 2000; McHugh et al., 2006). In inside-out patches of cultured dorsal root ganglion, TRPV1 receptors are activated by lipoxygenase products such as 12(*S*)-HpETE, 15(*S*)-HpETE, 5(*S*)-HETE, and LTB_4, whereas LTC_4 is without effect (Hwang et al., 2000). The EC_{50} for LTB_4-induced TRPV1 activation was 11 μM, which was 10-fold higher than that obtained for capsaicin in the latter study (Hwang et al., 2000) and substantially lower compared with BLT_1R-mediated LTB_4-induced signaling. In line with these findings, LTB_4 also increased $[Ca^{2+}]_i$ in TRPV1-transfected CHO cells, albeit with significantly lower E_{max} and a longer exposure time required to achieve maximum effects compared with capsaicin (McHugh et al., 2006). Indeed, very recently it has also been demonstrated in vivo that both peripheral and spinal administration of RvE1 or RvD1 in mice potently reduces inflammatory pain behaviors, without affecting basal pain perception. These actions are transduced through RvE1-mediated inhibition of TRPV- and TNF-α-induced excitatory postsynaptic current increases in spinal dorsal horn neurons (Xu et al., 2010).

III. CysLT Receptors

A. CysLT Receptor Subtypes

1. From Cloning CysLT Receptors to Recent Molecular Advances. The CysLTRs eluded gene cloning with conventional approaches for many years. Eventually, in 1999 two separate groups cloned the first CysLTR (Lynch et al., 1999; Sarau et al., 1999), and in the following year the second receptor subtype was cloned by three different groups (Heise et al., 2000; Nothacker et al., 2000; Takasaki et al., 2000). Hydrophobicity analysis of the deduced primary amino acid sequences demonstrated that both receptors possess seven TM helices organized in a serpentine topology, confirming early studies that provided evidence that cysteinyl LTs were acting through a GPCRs and confirmed pharmacological evidence for CysLTR heterogeneity based on the functional as well as on ligand-binding data (for review of early reports, see Capra, 2004; Capra et al., 2007; Evans, 2003). To date well documented results have been obtained, establishing the existence of two receptor subtypes referred to as $CysLT_1$ and $CysLT_2$ (see section III.G). This nomenclature was based on the observations that the $CysLT_1$ receptor was sensitive to inhibition by classic antagonists, whereas the effects mediated by the $CysLT_2$ receptor were not inhibited by these antagonists (Labat et al., 1992; Brink et al., 2003). These receptors belong to the rhodopsin family of the GPCR gene superfamily and, in particular, to the purine receptor cluster (within the δ group) of phylogenetically related receptors. In addition to a number of orphan receptors, this group includes receptors that respond to purinergic or pyrimidinergic nucleotides, proteases, and PAF (Fredriksson et al., 2003; Kroeze et al., 2003). Unlike the monoamine or neuropeptide receptors, the receptors belonging to the purine cluster have no clear homologs in invertebrates, suggesting a relatively recent evolutionary origin (Adams et al., 2000). Human $CysLT_1$ and $CysLT_2$ receptors share only 38% aa identity, with very low homology in the extreme carboxyl termini. Of interest, human CysLTRs have higher homology with the purinoceptor P2Y1/2/6 (32–30% aa identity) or GPR17 (34–32% aa identity) than with the other known LT receptors, the $BLT_{1/2}$ receptors ($\leq$27% aa identity).

The human $CysLT_1$ gene/chromosome location has been mapped on the long arms of chromosome X (Xq13-Xq21), a region lacking asthmatic disease markers (Lynch et al., 1999), whereas $CysLT_2$ on human chromosome 13 (13q14) (Heise et al., 2000; Takasaki et al., 2000) is near a marker that has been associated with atopic asthma (Cookson, 1999; Kimura et al., 1999).

a. $CysLT_1$ Receptor. The open reading frame of the human $CysLT_1$ encodes a protein of 337 aa (NCBI Reference Sequence: NP_006630) with a calculated molecular mass of 38 kDa, observed to migrate at a molecular mass of approximately 42 kDa as a monomeric form (Bautz et al., 2001; Figueroa et al., 2001; Ohd et al.,

2003; Hasegawa et al., 2010), although oligomers were often observed (see section III.G). However, other authors observed monomeric migration at different molecular masses, possibly reflecting differences in the cell type, protein/cell maturation, or experimental conditions: 30 to 36 kDa (Sjöström et al., 2001, 2002) and 38 to 40 kDa (Capra et al., 2004). Human $CysLT_1R$ possesses four potential N-glycosylation sites, one in the extracellular N-tail, two in the second extracellular loop, and one in the third extracellular loop, besides many potential protein kinase A and C phosphorylation sites (see section III.D), mostly located in the third intracellular loop and carboxyl terminal (Lynch et al., 1999). The rank order of potency for the cysteinyl LTs is $LTD_4 > LTC_4$ when tested in different functional assays, such as stimulation of calcium-activated chloride conductance in *Xenopus laevis* oocytes or fluorescence calcium imaging in COS-7, HEK-293, or CHO human $CysLT_1$-transfected cells. LTE_4 is the less potent agonist acting as a partial agonist. As expected, the LTD_4 functional response is potently inhibited by the selective $CysLT_1R$ antagonists, 3-[[3-[2-(7-chloroquinolin-2-yl)vinyl]phenyl]-(2-dimethylcarbamoylethylsulfanyl) methylsulfanyl] propionic acid (MK-571), zafirlukast, pranlukast, montelukast, and pobilukast (Brink et al., 2003; Evans, 2003; Capra, 2004). Saturation radioligand binding experiments on membranes from COS-7 cells expressing the human $CysLT_1R$ and using [^{3}H]LTD_4 as a labeled ligand demonstrated a single K_d of 0.3 nM (Lynch et al., 1999) or high- and low-affinity binding sites with K_d values of 0.06 and 6.2 nM (Capra et al., 2005). B_{max} has been reported to be approximately 50 fmol/mg membrane protein in both reports.

The genomic organization of the human *CYSLTR1* gene has been obtained by 5′- and 3′-rapid amplification of cDNA ends method, modified to ensure the amplification of only full-length transcripts (Woszczek et al., 2005). The gene consists of five exons that are variably spliced and a single promoter region TATA-less with multiple transcription start sites. Four different $CysLT_1R$ transcripts were identified with a dominant and wide expression of the transcript I, containing exons 1, 4, and 5, with the strongest presence in blood leukocytes, spleen, thymus, lung, and heart (Woszczek et al., 2005). Successive articles reported that *CYSLTR1* contains three exons with the entire open reading frame located in exon 3 and that five splice variants were detected in human leukocytes (Zhang et al., 2006), whereas in human airway SMCs and peripheral blood mononuclear cells (MNCs) three transcripts and, possibly, two putative promoters were found (Duroudier et al., 2007). In summary, multiple splice variants of $CysLT_1R$ exist, and the transcript expression patterns seem to differ from tissues and cell types. At present, the role of alternative splice variants of $CysLT_1R$ is not known. Woszczek et al. (2005) also reported in their study that the promoter region contains several binding sites for transcription factors, such as activator protein-1 (AP-1) and GATA and that $CysLT_1R$ expression is functionally regulated at the transcriptional level by IL-4 through a signal transducer and activator of transcription (STAT)-6 response element localized to the proximal promoter region, confirming former studies by Thivierge et al. (2001) (see section III.B).

b. $CysLT_2$ Receptor. The open reading frame of human $CysLT_2R$ encodes a protein of 346 aa (NCBI Reference Sequence: NP_065110), which seems to migrate at a molecular mass of 58 kDa in basophil lysates (Gauvreau et al., 2005) and approximately 50 kDa in platelet (Hasegawa et al., 2010) or at approximately 40 to 42 kDa in HUVECs and COS-7 cells transfected with human $CysLT_2$ cDNA (Carnini et al., 2011). Human $CysLT_2R$ possesses four potential N-glycosylation sites, three of which in the extracellular N-tail, as well as many potential protein kinase A and C phosphorylation sites mostly located in the third intracellular loop and carboxyl terminal (Heise et al., 2000). Ca^{2+} mobilization assay in HUVECs confirmed early observation in recombinant systems that LTD_4 and LTC_4 are equipotent agonists with an identical EC_{50} of ~35 nM, and lack of sensitivity of the response to the classic $CysLT_1R$ antagonists, montelukast, zafirlukast, and pranlukast, whereas LTE_4 and 6(*R*)-(4-carboxyphenylthio)-5(*S*)-hydroxy-7(*E*),9(*E*), 11(*Z*),14(*Z*)-eicosatetraenoic acid (BAY U9773 behave as partial agonists (Lötzer et al., 2003). Equilibrium binding studies in intact HUVECs using [^{3}H]LTC_4 as labeled ligand revealed the presence of a high-affinity binding site with K_d of 29 pM and B_{max} of 32 fmol/10^8 cells (Carnini et al., 2011). In $CysLT_2$-transfected COS-7 cell membranes high- and low-affinity binding sites with K_d values of 0.4 and 50 nM or a single site of 4.8 nM were obtained in two independent saturation experiments using [^{3}H]LTD_4 as labeled ligand (Heise et al., 2000).

The genomic organization of the human *CYSLTR2* has also been published recently. Similarly to *CYSLTR1*, the gene has a TATA-less promoter with multiple transcription start sites. Six variably spliced exons have been identified and eight different $CysLT_2R$ transcripts were also identified in endothelial and monocytic cells (Woszczek et al., 2007). It is noteworthy that IFN-γ increased $CysLT_2R$ mRNA expression and calcium signaling in ECs. However, there were no significant changes in gene reporter and mRNA $t_{1/2}$ assays in response to this cytokine, suggesting transcriptional control of $CysLT_2R$ mRNA up-regulation by IFN-γ response motifs localized outside of the cloned $CysLT_2R$ promoter region. Stimulation of ECs by cysteinyl LTs induced mRNA and protein expression of early growth response genes 1, 2, and 3 and cycloxygenase-2 (COX-2) (Woszczek et al., 2007).

2. Receptor Expression Patterns with Functional Significance. The pathophysiological role of cysteinyl LTs in asthma is well documented (Drazen, 2003; Holgate et al., 2003; Sampson et al., 2003; Arm, 2004; Capra et al., 2007; Hallstrand and Henderson, 2010), and results ob-

tained from localization studies are consistent with the antibronchoconstrictive and anti-inflammatory activities of $CysLT_1R$ antagonists (Kemp, 2003; Riccioni et al., 2004; Currie et al., 2005; Capra et al., 2006; Dahlén, 2006; Ducharme et al., 2006; Montuschi et al., 2007; del Giudice et al., 2009). However, the finding of CysLTR expression in other tissues will certainly encourage the discovery of new functions for cysteinyl LTs in other physiological and pathological conditions (Capra et al., 2007).

a. $CysLT_1$ Receptor. Initial immunohistochemical analysis confirmed the presence of $CysLT_1R$ protein in a series of cells of particular relevance to asthma and atopy such as monocytes and eosinophils but also in pregranulocytic $CD34^+$ cells and in subsets of B lymphocytes (Figueroa et al., 2001). Monocytes/macrophages isolated from peripheral blood MNCs express $CysLT_1R$ mRNA either in large excess compared with $CysLT_2R$ transcript levels (Lötzer et al., 2003) or, exclusively, such as in U937 (Capra et al., 2005), a human leukemic monocyte/macrophage cell line. This correlates with the finding that cysteinyl LTs contribute to inflammatory reactions by induction of MCP-1 via the CCR2B receptor in THP-1 cells (Ichiyama et al., 2005; Woszczek et al., 2005; Hashimoto et al., 2009). This reported induction by MCP-1 was also observed in another monocytic leukemia cell line and was further supported by the enhanced activation of chemotactic activity observed in human monocytes (Woszczek et al., 2008a). Likewise, in THP-1 cells, montelukast and zafirlukast significantly down-regulated the chemotaxis induced by MCP-1 and p38 MAPK expression (Hung et al., 2006). These data suggest a dominant functional pathway for the interaction between cysteinyl LTs and MCP-1 in a variety of MNCs, including human monocytes. In animal models, inhibition of MCP-1 produces antiatherogenic effects in vivo in a rabbit carotid balloon injury model (Ge et al., 2009).

The expression of CysLTRs in eosinophils was not unexpected (Bandeira-Melo and Weller, 2003), because the contribution of cysteinyl LTs to their accumulation within asthmatic airways has been well documented (Gauvreau et al., 2001; Ohshima et al., 2002; Nagata and Saito, 2003; Saito et al., 2004). In a recent study, the $CysLT_1R$ has been associated with cytokine transduction signals for the up-regulation of eosinophilopoiesis by IL-13 and eotaxin in murine bone marrow (Queto et al., 2010). These data support early reports demonstrating the inhibitory action of $CysLT_1R$ antagonists on eosinophil activation and migration (Virchow et al., 2001; Fregonese et al., 2002; Suzuki et al., 2003; Ueda et al., 2003; Saito et al., 2004; Nagata et al., 2005), as well as on adhesion (Fregonese et al., 2002; Nagata et al., 2002; Kushiya et al., 2006; Meliton et al., 2007; Profita et al., 2008). There is considerable information available to demonstrate the ability of CysLTR antagonists to reduce airway eosinophilia and eosinophil cationic protein (ECP) in animals (Underwood et al., 1996; Ihaku et al., 1999) and in humans (Pizzichini et al., 1999; Obase et al., 2002; Steinke et al., 2003; Strauch et al., 2003; Laitinen et al., 2005; Kopriva et al., 2006).

$CysLT_1Rs$ are also found to be expressed in B lymphocytes and $CD34^+$ hematopoietic progenitor cells (Figueroa et al., 2001). Indeed, early observations demonstrated that LTD_4-stimulate chemotaxis and transendothelial migration of $CD34^+$ hematopoietic progenitor cells (Bautz et al., 2001; Mohle et al., 2003) as well as their proliferation (Braccioni et al., 2002; Parameswaran et al., 2004; Boehmler et al., 2009) and that these activities were suppressed by different $CysLT_1$ receptor antagonists. Altogether these data indicate a physiological role for cysteinyl LTs as autocrine regulators of hematopoiesis corroborated by the expression of LTC_4S in immature myeloid cells (Tornhamre et al., 2003).

Basophils have also been shown to accumulate in the airways of subjects with atopic asthma (Gauvreau et al., 2001), and these authors documented that human basophils express variable levels of functional $CysLT_1R$. Of interest, they found that prolonged stimulation of cell cultures with LTD_4 reduced the frequency of CD95 Fas receptor expression, an effect that, albeit modest, was reversed by the $CysLT_1R$ antagonist zafirlukast (Gauvreau et al., 2005). These results seem to suggest that the cysteinyl LT/$CysLT_1R$ system might have a direct effect on basophil accumulation in allergic tissues.

MCs are a primary source of cysteinyl LTs (Austen, 2005) after allergic or nonallergic stimulation and, accordingly to their classification as autacoids, CysLTRs are widely expressed in these cells (Mellor et al., 2001; Sjöström et al., 2002) and are responsible for their proliferation and activation (Jiang et al., 2006, 2009; Kaneko et al., 2009). In agreement with this finding, montelukast has been found to significantly reduce the number of MCs in the inflamed paws of mice with collagen-induced arthritis (Shiota et al., 2006).

The expression of both $CysLT_1R$ and $CysLT_2R$ has also been reported in human platelets by RT-PCR, Western blotting, and flow cytometry (Hasegawa et al., 2010). In this report, the authors demonstrate that cysteinyl LTs induced a release of RANTES and that this effect was inhibited by pranlukast, suggesting a novel role for platelets in allergic inflammation (Hasegawa et al., 2010).

In agreement with a role of cysteinyl LTs in asthma, $CysLT_1Rs$ are expressed by a variety of airway mucosal inflammatory cells and the numbers of inflammatory $CysLT_1R$-expressing cells (eosinophils, neutrophils, MCs, macrophages, and B lymphocytes but not T lymphocytes) significantly increase in subjects with stable asthma and patients hospitalized for asthma exacerbation compared with control subjects (Zhu et al., 2005). Of interest, a strong positive correlation exists between this observation and the augmented numbers of $CD45^+$ progenitors (cells expressing the pan-leukocyte marker

CD45 antigen) (Zhu et al., 2005). In addition, human fibroblasts have been shown to express both $CysLT_1$ (James et al., 2006; Vannella et al., 2007) and $CysLT_2$ receptors (Vannella et al., 2007). These cells are also known to produce cysteinyl LTs, suggesting a regulation via an autocrine/paracrine secretion of these lipid mediators. Indeed, exogenous administration of LTD_4 but not of LTC_4 was also able to induce proliferation of both murine and human fibrocytes, and $CysLT_1R$ antagonists blocked this mitogenic effect (Vannella et al., 2007). In contrast, there are two reports that evaluated the contribution of cysteinyl LTs to fibroblast-mediated fibrosis and remodeling in chronic hyperplastic eosinophilic sinusitis (Steinke et al., 2004) or in healthy subjects (Yoshisue et al., 2007) and found that fibroblasts did not substantially express $CysLT_1R$ or $CysLT_2R$, even after priming with IL-4 or IL-13 (Steinke et al., 2004). However, cysteinyl LTs have a broader capability to synergize with epidermal growth factor receptor (EGFR) to increased thymidine incorporation and cell proliferation, effects that, in agreement with the absence of CysLTRs, are not inhibited by specific $CysLT_1R$ antagonists (MK-571 and montelukast) or by the dual antagonist BAY U9773, pointing to a different mechanism/receptor (Yoshisue et al., 2007).

In human nasal mucosa, increased expression of $CysLT_1R$ has been found both at gene and protein levels in blood vessels and in the interstitial vascular ECs, as well as in eosinophils, MCs, macrophages, and neutrophils (Shirasaki et al., 2002, 2006) and in nasal polyps (Chao et al., 2006; Pérez-Novo et al., 2006). Because subjects with aspirin-induced asthma (AIA) have greater airway hyperresponsiveness to the effects of inhaled cysteinyl LTs than those with aspirin-tolerant asthma (ATA) (Arm et al., 1989), Sousa and colleagues (Sousa et al., 2002; Corrigan et al., 2005) hypothesize that this could be due to the elevated expression of $CysLT_1R$ on inflammatory cells. Their study on nasal biopsy specimens from patients with chronic rhinosinusitis and nasal polyps revealed that aspirin-sensitive rhinosinusitis is indeed characterized by increased numbers of nasal inflammatory leukocytes expressing the $CysLT_1R$. These results have been confirmed (Ozen et al., 2007) and are consistent with two other reports in which the augmented receptor expression was observed for the majority of eosinophils and subsets of MNCs obtained by nasal lavage (Figueroa et al., 2003) or in sputum after allergen challenges in patients with seasonal allergic rhinitis (AR) (Boulay et al., 2010). Finally, $CysLT_1$ but not $CysLT_2$ mRNA has been demonstrated in nasal C-fiber neurons, where LTD_4 directly increased the excitability of capsaicin-sensitive guinea pig nasal trigeminal neurons. These observations suggest a novel mechanism for the actions of cysteinyl LTs and offer an explanation for the observed beneficial use of $CysLT_1R$ antagonists in treating nasal allergen-induced neuronal symptoms (Taylor-Clark et al., 2008).

RT-PCR has allowed the demonstration that human saphenous veins express both a functional $CysLT_1R$, which mediates contractile effects of cysteinyl LTs, but also a $CysLT_2R$, which, on the contrary, does not seem to be implicated in contraction (Mechiche et al., 2004) and whose functional role remains to be determined (Allen et al., 1992). Human pulmonary veins also express both receptors and although activation of the former induced the release of a contractile factor only partially blocked by $CysLT_1R$ antagonists, the activation of the $CysLT_2R$ released nitric oxide (NO) (Ortiz et al., 1995). In addition, human pulmonary artery vascular SMCs seem to express at least two different receptors, a $CysLT_1R$ and a novel CysLTR subtype, both responsible for vasoconstriction (Walch et al., 2002). Thus, the mechanical effects of LTD_4 on human pulmonary vasculature are complex and involve both direct and indirect mechanisms mediated via at least two, and possibly more, types of cysteinyl LT receptors (Walch et al., 2000).

In the gastrointestinal system, $CysLT_1R$ expression has been documented in the small intestine and colon (Lynch et al., 1999; Sarau et al., 1999). Subsequently, the presence of the $CysLT_1R$ subtype was reported in a nontransformed epithelial intestinal cell line (Ohd et al., 2003), corroborating previous findings for LTD_4-induced signaling in these cells (Grönroos et al., 1995; Thodeti et al., 2000, 2001). In addition, $CysLT_1R$ functions were characterized in colorectal carcinoma cells (Ohd et al., 2003), and low expression of $CysLT_1R$ and high expression of $CysLT_2R$ correlated with high differentiation and good prognosis (Magnusson et al., 2007, 2010). The same results have been also extended to breast cancer cells and patient survival (Magnusson et al., 2011).

b. $CysLT_2$ Receptor. Localization studies have identified a distinctive expression pattern for human $CysLT_2R$, despite some overlapping with $CysLT_1R$. Indeed, expression in heart, particularly in Purkinje fiber cells, myocytes, and fibroblasts derived from atrium and ventricle, brain, and adrenal glands is specific to $CysLT_2R$ (Heise et al., 2000; Nothacker et al., 2000; Takasaki et al., 2000).

Several authors indicated that HUVECs almost exclusively express $CysLT_2R$ (Mita et al., 2001b; Lötzer et al., 2003), which is responsible for the calcium mobilization and contraction evoked in these cells by cysteinyl LTs, as well as by the selective $CysLT_2R$ agonist BAY U9773 (Sjöström et al., 2003; Carnini et al., 2011), for which activation results in a proinflammatory EC phenotype (Uzonyi et al., 2006). ECs are strategically located at the interface with blood circulation where they become exposed to neutrophil- and platelet-derived LTs, a setting that has potential implications for cardiovascular diseases (CVDs). Moreover, previous studies demonstrated that cysteinyl LTs can trigger several functional responses in ECs, such as PAF accumulation and neutrophil adhesion (McIntyre et al., 1986) and secretion of von Willebrand factor and of P-selectin surface expression (Datta et al., 1995). In light of these expression data, the

responses data can be attributed to the $CysLT_2R$ and, accordingly, are not inhibited by selective $CysLT_1R$ antagonists (Pedersen et al., 1997).

Kamohara et al. (2001) were the first to report the presence of a functional $CysLT_2R$ on human coronary artery SMCs. These authors demonstrated that LTC_4 enhanced $[Ca^{2+}]_i$, an effect that was not blocked by $CysLT_1R$ antagonists but blocked by the calcium channel blocker nicardipine. Further significance of cysteinyl LTs involvement in atherosclerosis arises from the observation that cysteinyl LTs induce contractions of human atherosclerotic coronary arteries, whereas nonatherosclerotic arteries are unresponsive (Allen et al., 1998). Taken together, these results suggest that the activation of $CysLT_2R$ can induce profound effects in cardiac as well as in hemodynamic and microcirculatory pathophysiology and that this receptor subtype represents an interesting pharmacological target in the future for CVDs.

Although little expression for $CysLT_1R$ has been reported in brain (Lynch et al., 1999; Sarau et al., 1999), apparent localization has been documented by immunohistochemical analysis in human brains with traumatic injury or tumors (Zhang et al., 2004). In contrast, $CysLT_2R$ mRNA is highly expressed in the central nervous system, with particular concentration in hypothalamus, thalamus, putamen, pituitary, and medulla (Heise et al., 2000) and in small, but not large, vessels in mouse brain (Moos et al., 2008). A number of articles have reported the involvement of either $CysLT_1$ (Fang et al., 2006) or $CysLT_2$ (Fang et al., 2007) or both receptors (Sheng et al., 2006; Wang et al., 2006; Huang et al., 2008) in the inflammatory process subsequent to brain vascular insults (vascular ischemia or oxygen deprivation). Spatiotemporal expression of $CysLT_2R$ mRNA in rat brain was observed after focal cerebral ischemia induced by middle cerebral artery occlusion, suggesting that $CysLT_2R$ may be related to the acute neuronal injury and late astrocyte proliferation in the ischemic brain (Fang et al., 2007).

In the immune system, moderate expression of $CysLT_2$ mRNA was seen in spleen, lymph nodes, and peripheral blood leukocytes (Heise et al., 2000). A comparative study on the levels of CysLTR subtype expression in human peripheral blood leukocytes (eosinophils, neutrophils, monocytes, and T lymphocytes) indicated a significantly high expression for $CysLT_2$ mRNA in eosinophils (Mita et al., 2001b), suggesting unidentified roles for this receptor in these cells. Mellor et al. (2003) reported that human MCs constitutively express the $CysLT_2R$, whose proposed function seems to be the production of IL-8. $CysLT_2R$ expression was also reported in basophils (Gauvreau et al., 2005), but a functional role for this protein was not identified, despite flow cytometric analysis, which revealed an expression level equivalent to that of the $CysLT_1R$. No $CysLT_2R$ expression was found in either undifferentiated or differentiated promyelocytic HL-60 and U937 cells (Nothacker et al., 2000; Capra et al., 2005).

$CysLT_2R$ was expressed in the majority of eosinophils and in subsets of MCs and MNCs, but not in neutrophils, obtained by nasal lavage of patients with seasonal AR (Figueroa et al., 2003). Sousa et al. (2002) and Corrigan et al. (2005) extended a previous study on $CysLT_1R$ expression in the nasal mucosa of subjects with chronic rhinosinusitis, both AIA and ATA, and found that the distribution of $CysLT_2R$ differs from that of $CysLT_1$, with a predominance of $CysLT_2R$ on glands and epithelium. They also showed that nasal mucosal inflammatory leukocytes showed no evidence of up-regulation of $CysLT_2R$ in subjects with rhinosinusitis, whether AIA or ATA, compared with control subjects (Corrigan et al., 2005). However, $CysLT_2R$ up-regulation has been demonstrated in nasal polyp tissue and expression was correlated with eosinophilic inflammation (Pérez-Novo et al., 2006). In human lung, the $CysLT_2$ mRNA signal was high in interstitial macrophages and weak in SMCs (Heise et al., 2000), in which, on the contrary, $CysLT_1$ mRNA expression was elevated. Of interest, RT-PCR revealed that A549 cells, a human lung adenocarcinoma-derived line with alveolar epithelial cell properties, express mRNA for $CysLT_2R$ but not $CysLT_1R$ (Sloniewsky et al., 2004).

The adrenal gland may represent a novel tissue for future studies on cysteinyl LT functions and $CysLT_2R$ role in modulating the endocrine system because strong expression was detected in medullary pheochromocytes (Lynch et al., 1999; Nothacker et al., 2000).

3. Localization of CysLT Receptors. The mechanism of action of cysteinyl LTs is thought to be primarily dependent on their specific plasma membrane receptors that, as discussed above, belong to the superfamily of GPCRs. However, a few reports indicate that CysLTR could also be localized to a nuclear compartment, suggesting major unanticipated roles for these receptors in cell signaling and function. Bandeira-Melo et al. (2002b) provided the first evidence for an intracrine CysLTR-induced signaling of eosinophil vesicular transport-mediated IL-4 secretion, which is PTX-sensitive. Furthermore, $CysLT_1R$ was found to be located in the outer nuclear membrane in colon cancer cells and may apparently be translocated into the nucleus after prolonged exposure to the agonist in nontransformed intestinal epithelial cells (Nielsen et al., 2005a). These authors also demonstrated that a nuclear localization sequence (localized in the C tail) is essential for the receptor translocation to the nucleus, as already demonstrated for other GPCRs (Boivin et al., 2008) as well as for other proteins that normally target the nucleus, such as 5-LO (Hanaka et al., 2002). Finally, $CysLT_1R$ expression in myofibroblasts derived from human heart valves exhibits a perinuclear pattern, and LTC_4 increased nuclear $[Ca^{2+}]$ in those cells (Nagy et al., 2011).

Because other lipid mediators have been demonstrated to exert biological functions including transcrip-

tional regulation of COX-2 and inducible NO synthase through their nuclear GPCRs (Marrache et al., 2005), one can speculate that the roles for nuclear receptors may be different from those on plasma membrane and that intracellular GPCRs may constitute a distinctive mode of action for gene regulation (Boivin et al., 2008). A recent report has shown that $CysLT_1R$ and $CysLT_2R$, but also the purinergic $P2Y_{12}$ receptor, are expressed on eosinophil granule membranes and that cysteinyl LTs stimulated isolated eosinophil granules to secrete ECP. Of interest, although montelukast inhibited ECP release, the $P2Y_{12}$ receptor antagonist 2,2-dimethyl-propionic acid 3-(2-chloro-6-methylaminopurin-9-yl)-2-(2,2-dimethyl-propionyloxymethyl)-propyl ester (MRS 2395) also inhibited cysteinyl LT-induced ECP release, adding another piece of evidence to the CysLT-P2Y receptor interaction puzzle (Neves et al., 2010) (see sections III.D and III.H).

B. CysLT Receptor Expression and Immunoregulation

Human $CysLT_1R$ expression was up-regulated through augmented transcriptional activity by priming cells with Th2-like cytokines (i.e., IL-5 in eosinophil-differentiated HL-60 cells) (Thivierge et al., 2000) and IL-4 and IL-13 in human monocytes and monocyte-derived macrophages (Thivierge et al., 2001; Shirasaki et al., 2007). The regulation of human $CysLT_1R$ expression by IL-13 has also been reported in the literature for lung fibroblasts (Chibana et al., 2003) and airway SMCs together with TGF-β and IFN-γ, whereas, surprisingly, IL-4 was found to be ineffective (Espinosa et al., 2003). In the latter cells, up-regulation of $CysLT_1R$ by IFN-γ has been demonstrated, and this correlates with increases in LTD_4-induced responses (Amrani et al., 2001). HUVECs express $CysLT_1R$ at a very low level (Sjöström et al., 2001), unless they are subjected to prolonged treatment with IL-1β (Gronert et al., 2001). The up-regulation by IL-1β and IFN-γ seems intriguing because these cytokines are generally considered to be counterregulatory, inhibiting both the production and activities of the proallergic Th2-like cytokines. Use of IFN-γ is indeed one of the theoretical approaches to obtain IgE immunomodulation in asthma, albeit adverse effects suggest limited use (Stokes and Casale, 2004). However, there are also investigators who suggest that IFN-γ is likely to be proinflammatory in many aspects of chronic allergic inflammation, evolving our understanding of classic Th2 diseases (Liu, 2000).

Priming human MCs with IL-4 did not result in the up-regulation of $CysLT_1R$, either at the transcript or the protein level, but rather resulted in the appearance of an apparently new CysLTR also activated by the pyrimidinergic ligand UDP (Mellor et al., 2001). In a subsequent report, the same authors also demonstrated that human MCs primed with IL-4 responded to UDP, LTC_4, and LTD_4 by producing IL-5, TNF-α, and especially large quantities of macrophage inflammatory protein (MIP)-1β that were inhibited by the $CysLT_1R$ antagonist MK-571. Nevertheless, human MCs constitutively also express the $CysLT_2R$, and IL-4 consistently up-regulated surface expression on a fraction of cells (Mellor et al., 2003). Whether IL-4 priming up-regulates a known CysLTR or induces the expression of a new receptor subtype (see section III.G) remains to be established.

A 2- to 3-fold enhancement of $CysLT_1R$ expression was observed in B lymphocytes after exposure to a combination of activating anti-CD40 antibody and IL-4. This enhancement, in turn, induced an increase in responsiveness to LTD_4 in terms of Ca^{2+} flux and up-regulation of IgE and IgG production, which was totally prevented by the selective $CysLT_1R$ antagonist montelukast (Lamoureux et al., 2006). Therefore, Early et al. (2007) showed that IL-4, but not IL-13, was able to significantly induce mRNA and protein concentrations for $CysLT_1R$ from T and B lymphocytes.

CysLTRs can also be immunoregulated by cytokines that play an essential role in down-modulating adaptive and innate immune responses. IL-10, for example, down-regulated mRNA of $CysLT_1$ and $CysLT_2$ receptors in a time- and concentration-dependent fashion. In addition, cysteinyl LT-induced activation and chemotaxis of human monocytes and monocyte-derived immature DCs, measured by cytosolic Ca^{2+} flux and immediate-early gene expression, was potently decreased by IL-10 and by the $CysLT_1$ antagonist MK-571 (Woszczek et al., 2008b). Of interest, maturation of DCs with LPS (Thivierge et al., 2006), a classic Toll-like receptor 4 agonist, or zymosan (Thivierge et al., 2009), a Toll-like receptor 2 agonist, down-regulated $CysLT_1R$ mRNA levels and protein expression and reduced functional responsiveness to LTD_4. Indeed, the effect of zymosan was, at least partially, dependent on endogenous production of PGE_2 and IL-10 (Thivierge et al., 2009). Therefore, montelukast prevents the decrease of IL-10 and inhibits NF-κB activation in inflammatory airway of "asthmatic" guinea pigs (Wu et al., 2006).

Transcript levels of $CysLT_2R$ seem to be up-regulated by the Th2-like cytokine IL-4 in HUVECs (Lötzer et al., 2003) but suppressed by Th1-like (proinflammatory) cytokines, such as TNF-α (Lötzer et al., 2003; Sjöström et al., 2003), LPS, or IL-1β (Sjöström et al., 2003) in a rapid and partially reversible manner. However, IFN-γ has been found to induce $CysLT_2R$ expression and to enhance the responsiveness to cysteinyl LTs of human ECs (Woszczek et al., 2007), as well as of monocytes, T cells, and B lymphocytes (Early et al., 2007). These data confirm early observations by Fujii et al. (2005), who postulated that $CysLT_2R$ might modulate exacerbations of asthma, as they observed that $CysLT_2R$ expression on eosinophils was up-regulated by IFN-γ and increased during asthma exacerbation, especially in nonatopic subjects. In addition, another proinflammatory cytokine, IL-18, has also been recently postulated to up-regulate $CysT_2R$ expression in HUVECs at the early

stage of administration, accelerating cell apoptosis (Zhou et al., 2009).

Besides in HUVECs, $CysLT_2R$ expression was also significantly increased in monocytes and eosinophils after IL-4 priming (Early et al., 2007) or IL-13 treatment (Shirasaki et al., 2007). At variance with data reported previously for $CysLT_1R$, $CysLT_2R$ expression increased after DC maturation induced by LPS, suggesting that these cells may differentially respond to cysteinyl LTs, depending on their maturational stimuli (Thivierge et al., 2006).

These observations suggest that the expression of the CysLTRs may be functionally up-regulated, mainly by Th2-like cytokines (consistent with the classic view of the pathobiological mechanisms of asthma and other allergic diseases), but also by a classic Th1 cytokine (i.e., IFN-γ) at least in some cells (Table 3). This finding raises the possibility that constitutive and inducible receptors may or may not behave in a similar way, prompting a detailed pharmacological examination of receptors expressed before and after priming.

C. Intracellular Signaling Pathways and Second-Messenger Systems

1. $CysLT_1$ Receptor. In consideration of the crucial bronchoconstrictor activity of cysteinyl LTs (Hallstrand and Henderson, 2010) and their role in asthma (Capra et al., 2007), intracellular Ca^{2+} mobilization and phosphatidylinositol (PI) metabolism were the obvious signal transduction systems to investigate (for a review of early reports, see Brink et al., 2003; Rovati and Capra, 2007). Upon cloning, LTD_4-induced functional responses in oocytes (Lynch et al., 1999) or HEK-293 cells (Sarau et al., 1999) indicated that, at least in these systems, $CysLT_1R$ is very weakly, if not at all, coupled to a PTX-insensitive G protein ($G_{q/11}$).

However, an initial study demonstrated in circulating MNCs that cysteinyl LTs modulate Ca^{2+} responses

TABLE 3
Immunoregulation of human CysLTR expression

Receptor	Cytokine	Cell	Effect[a]	Reference
$CysLT_1$	IL-4	Monocytes and monocytes-derived macrophages	↑ mRNA; ↑; protein; ↑ $[Ca^{2+}]_i$	Thivierge et al., 2001
			↑ mRNA	Woszczek et al., 2005; Shirasaki et al., 2007
	+ Anti-CD40 antibody	B lymphocytes	↑ mRNA; ↑ protein ↑ $[Ca^{2+}]_i$; ↑ IgE/IgG production	Early et al., 2007 Lamoureux et al., 2006
		T lymphocytes	↑ mRNA; ↑ protein	Early et al., 2007
	IL-5	Eosinophil-differentiated HL60	↑ mRNA; ↑ protein; ↑ $[Ca^{2+}]_i$	Thivierge et al., 2000
	IL-13	Monocytes and monocyte-derived macrophages	↑ mRNA; ↑ protein; ↑ $[Ca^{2+}]_i$	Thivierge et al., 2001
			↑ mRNA	Thivierge et al., 2001; Shirasaki et al., 2007
		Lung fibroblasts	↑ mRNA; ↑, protein; ↑ eotaxin production	Chibana et al., 2003
		Airway SMCs	No effect on mRNA; ↑ protein; ↑ cell proliferation	Espinosa et al., 2003
	IFN-γ	Airway SMCs	↑ mRNA; ↑ protein; ↑ cell stiffness	Amrani et al., 2001
		Airway SMCs	↑ mRNA; ↑ protein; no effect on cell proliferation	Espinosa et al., 2003
	IL-1β	HUVECs	↑ mRNA	Gronert et al., 2001
	TGF-β	Airway SMCs	No effect on mRNA; ↓ protein; ↓ cell proliferation	Espinosa et al., 2003
	IL-10 (zymosan-induced)	Monocytes and monocyte-derived dendritic cells	↓ mRNA; ↓ $[Ca^{2+}]_I$ and chemotaxis	Woszczek et al., 2008b
			↓ mRNA; ↓ $[Ca^{2+}]_i$ and chemotaxis	Thivierge et al., 2009
	LPS	Monocyte-derived dendritic cell	↓ mRNA; ↓ protein; ↓ $[Ca^{2+}]_i$ and chemotaxis	Thivierge et al., 2006
$CysLT_2$	IL-4	HUVECs	↑ mRNA	Lötzer et al., 2003
		Mast cells	↑ protein	Mellor et al., 2003
		B and T lymphocytes, monocytes, eosinophils	↑ mRNA; ↑ protein	Early et al., 2007
	IL-13	Monocytes	↑ mRNA	Shirasaki et al., 2007
	IFN-γ	Eosinophils (asthmatics)	↑ mRNA; ↑ protein	Fujii et al., 2005
		ECs	↑ mRNA; ↑ $[Ca^{2+}]_i$	Woszczek et al., 2007
		Monocytes, T and B lymphocytes	↑ mRNA; ↑ protein	Early et al., 2007
	IL-18	HUVECs	↑ mRNA; ↑ protein (first 2 h)	Zhou et al., 2009
	TNF-α	HUVECs	↓ mRNA	Lötzer et al., 2003; Sjöström et al., 2003
	LPS	HUVECs	↓ mRNA	Sjöström et al., 2003
		Monocyte-derived dendritic cell	↑ mRNA; ↑ protein	Thivierge et al., 2006
	IL-1β	HUVECs	↓ mRNA	Sjöström et al., 2003
	IL-10	Monocytes and monocyte-derived dendritic cells	↓ mRNA	Woszczek et al., 2008b

[a] ↑, up-regulation; ↓, down-regulation; specified are the effects (at mRNA, protein, and functional level).

through a PTX-sensitive G protein ($G_{i/o}$) (Baud et al., 1987). In further reports, investigators have shown that the Ca^{2+} modulation may be through two distinct G proteins, one PTX-sensitive and one insensitive, in monocyte/macrophage U937 cells (Pollock and Creba, 1990; Capra et al., 2003) or in a human epithelial cell line (Sjölander et al., 1990; Adolfsson et al., 1996). Subsequently, $CysLT_1R$-dependent actin reorganization was shown to be coupled with a PTX-sensitive G protein and to Rho in an intestinal epithelial cell line (Grönroos et al., 1996; Massoumi and Sjölander, 1998; Massoumi et al., 2002) or in bronchial SMCs (Saegusa et al., 2001). Thus, these data confirm $CysLT_1R$ promiscuity in G protein coupling in constitutive systems, in good agreement with the finding that LTD_4 activates distinct signaling pathways differently coupled to G proteins in MNCs (Saussy et al., 1989; Skoglund and Claesson, 1991; Hoshino et al., 1998; Capra et al., 2003) or intestinal epithelial cells (Grönroos et al., 1998; Paruchuri and Sjölander, 2003; Nielsen et al., 2005b). Among these pathways several groups have demonstrated the activation of MAPK by $CysLT_1R$ in THP-1 cells (Hoshino et al., 1998), renal mesangial cells (McMahon et al., 2000), intestinal epithelial cells (Paruchuri et al., 2002), monocyte/macrophage U937 cells (Capra et al., 2004), astrocytes (Ciccarelli et al., 2004), colon cancer cells (Parhamifar et al., 2005), MCs (Jiang et al., 2006), and airway SMCs (Ravasi et al., 2006). Cysteinyl LTs have been shown to induce proliferation in a variety of cells, such as human hematopoietic cell lines (Snyder et al., 1989; Braccioni et al., 2002; Parameswaran et al., 2004), airway epithelial cells (Leikauf et al., 1990), vascular (Porreca et al., 1995, 1996; Kaetsu et al., 2007) and airway SMCs (Cohen et al., 1995; Panettieri et al., 1998; Espinosa et al., 2003; Bossé et al., 2008), glomerular mesangial cells (Kelefiotis et al., 1995), intestinal epithelial cells (Paruchuri and Sjölander, 2003), astrocytes (Fang et al., 2006; Huang et al., 2008) and fibrocytes (Vannella et al., 2007).

There are many possible pathways through which GPCRs may induce ERK1/2 activation, one of which requires the transactivation of a growth factor receptor. Indeed, a first report suggested that LTD_4 synergizes with the insulin growth factor axis to induce airway SMC proliferation (Cohen et al., 1995), involving proteolysis of airway SMC-produced inhibitory insulin growth factor-binding proteins by LTD_4-induced MMP-1 (Rajah et al., 1996). In the same cellular system, LTD_4 has been demonstrated to induce phosphorylation of apoptosis signal-regulating kinase 1 (Kumasawa et al., 2005), a kinase upstream of c-Jun NH_2-terminal kinase (JNK) and p38 MAPK, which in turn regulates transcription factor AP-1, an essential step for regulation of cell proliferation and differentiation. In renal mesangial cells, LTD_4-induced proliferation requires ERK1/2 and p38 activation and is dependent on PI3K and PKC (McMahon et al., 2000). LTD_4 also transactivates the platelet-derived growth factor receptor β, which is a process associated with c-Src recruitment and Ras activation, an effect insensitive to PTX and apparently related to $CysLT_1R$ activation (McMahon et al., 2002). LTD_4-induced airway SMC proliferation was also demonstrated to require transactivation of the EGFR through generation of reactive oxygen species (Ravasi et al., 2006). It is noteworthy that very recently LTD_4 has been demonstrated to transcriptionally activate VEGF production via $CysLT_1R$, with the involvement of JNK, ERK, the AP-1 complex, and Sp1 (Poulin et al., 2011). Taken together, these findings suggest that cysteinyl LTs may be important in the process of airway remodeling and potentially provide a previously unknown benefit of using LTRAs in the prevention or treatment of chronic asthma, albeit long-term studies aimed to determine its effects on airway remodeling are still lacking. Finally, in human MCs, LTD_4 enhanced proliferation in a $CysLT_1$- and ERK-dependent manner, which in turn required transactivation of c-kit (Jiang et al., 2006).

However, in THP-1 cells LTD_4 has been postulated to activate MAPK through a PKC-Raf-1-dependent pathway (Hoshino et al., 1998), whereas in differentiated U937 cells ERK1/2 activation involves a Ras-GTP-dependent pathway, phospholipase C, and Ca^{2+}-dependent tyrosine kinase(s) (Capra et al., 2004). In addition, LTD_4 has been shown to induce proliferation and migration of mouse embryonic stem cells via a mechanism involving STAT-3, PI3K, glycogen synthase kinase-3β/β-catenin phosphorylation and calcineurin expression (Kim et al., 2010).

In intestinal epithelial cells, LTD_4 has been shown to increase cell survival and proliferation (Ohd et al., 2000; Paruchuri and Sjölander, 2003), activating MAPK through a Ras-independent but PKCε-dependent pathway (Paruchuri et al., 2002), and to increase cell mobility via a PI3K/Rac signaling pathway (Paruchuri et al., 2005). Furthermore, the antiapoptotic effect involves the prevention of caspase 8 activation and Bid cleavage (Wikström et al., 2003a), as well as COX-2 transcription and Bcl-2 up-regulation mediated through a PTX-sensitive G protein and the ERK-1/2 pathway (Wikström et al., 2003b). Indeed, LTD_4 exposure, through PI3K-dependent phosphorylation of glycogen synthase kinase-3β induced a β-catenin translocation to the nucleus, where there is an elevation of the promoter activity of the TCF/LEF family of transcription factors, and to the mitochondria, where the action is associated with the cell survival protein Bcl-2 (Mezhybovska et al., 2006). $CysLT_1R$ involvement in colon cancer cell proliferation was also shown via endogenous production of cysteinyl LTs that, through cytosolic phospholipase A_2 activation (Parhamifar et al., 2005), mediates an autocrine survival and proliferation signal in nontumor- and tumor-derived epithelial cells (Paruchuri et al., 2006). To the best of our knowledge, there is only one report suggesting that cysteinyl LTs may, on the contrary, inhibit the

growth of a human cell line (i.e., the mammary cancer MCF-7 cells) (Przylipiak et al., 1998).

Proliferation is not the only effect induced by MAPK activation. For example, in monocytes, LTD_4 induced p38 phosphorylation (Woszczek et al., 2008a), a pathway involved in the regulation of immediate-early gene expression. In a human epithelial cell line, $CysLT_1R$ activation has been shown to lead to either STAT-1 phosphorylation through PKC and ERK1/2 activation, causing enhanced intercellular cell adhesion molecule-1 expression and eosinophil adhesion (Profita et al., 2008), or to up-regulate mucin gene *MUC2* transcription via a signaling pathway involving PKC and NF-κB (Suzuki et al., 2008). In this respect, NF-κB, a transcription factor largely involved in inflammation and in regulating the immune response, has been demonstrated to be involved in the $CysLT_1R$ transduction pathway by different groups. In isolated lung MNCs, for example, LTD_4 activated NF-κB and induced production of RANTES (Kawano et al., 2003), whereas in THP-1 and in human DCs $CysLT_1R$ engagement induced AP-1- and NF-κB-dependent IL-8 expression (Thompson et al., 2006), as well as increased MCP-1 (Hashimoto et al., 2009). In partial agreement with these data LTD_4 has been demonstrated to induce AP-1, but not NF-κB signaling in intestinal epithelial cells (Bengtsson et al., 2008). Therefore, montelukast inhibited NF-κB activation in THP-1 cells in a dose-related manner (Maeba et al., 2005), and TNF-α-stimulated IL-8 expression through changes in NF-κB p65-associated histone acetyltransferase activity in differentiated U937 cells (Tahan et al., 2008).

However, three distinct studies have reported that LTD_4 did not induce NF-κB nuclear translocation. In contrast, pranlukast inhibited NF-κB activation (Ichiyama et al., 2003), TNF-α production (Tomari et al., 2003), or *MUC2* gene transcription (Ishinaga et al., 2005), effects that were suggested to be independent from $CysLT_1R$ antagonism. A different study also reported that pranlukast inhibited IL-5 production in various cells irrespective of their $CysLT_1R$ mRNA expression (Fukushima et al., 2005), again suggesting that the compound may have other activities beyond $CysLT_1R$ antagonism. Furthermore, montelukast and zafirlukast have been demonstrated to inhibit the effects of nucleotides acting at different P2Y receptors ($P2Y_{1,2,4,6}$) (Mamedova et al., 2005), although in a noncompetitive manner. These observations have recently been confirmed by another report demonstrating that montelukast and zafirlukast, acting in a concentration-dependent manner, can inhibit non–$CysLT_1R$-mediated proinflammatory reactions in human monocytes while inhibiting UDP-induced Ca^{2+} mobilization (Woszczek et al., 2010). Taken together, these data demonstrate non-CysLTR-related activities for these classic LTRAs. Thus, the therapeutic effects of these compounds must be considered with some reserve.

Another interesting cellular function that emerged to be modulated by $CysLT_1R$ is the up-regulation of β integrins. Massoumi and Sjölander (2001) first demonstrated that in intestinal epithelial cells LTD_4 induced a Src-dependent rapid tyrosine phosphorylation of vinculin, as well as PKC-dependent up-regulation of active $\beta1$ integrins on the cell surface and a consequent enhanced adhesion of cells to collagen IV. Furthermore, in Caco-2 cells, LTD_4 controlled adhesive properties and migration by up-regulating COX-2 and stimulating PGE_2-induced expression of $\alpha2\beta1$ integrins (Massoumi et al., 2003). In another study, LTD_4 was demonstrated to rapidly induce focal adhesion kinase-related tyrosine kinase phosphorylation and significantly up-regulated $\alpha4\beta1$ and $\alpha5\beta1$ integrin-dependent adhesion of both primitive and committed hematopoietic stem and progenitor cell (Boehmler et al., 2009).

In some systems, $CysLT_1R$ activation can contribute to the propagation of the inflammatory reaction by the release of various inflammatory mediators and cytokines. Thus, although cytokines may regulate CysLTR expression, cysteinyl LTs may, in turn, induce their release in an amplifying circuit of inflammation. For example, in U937 cells, LTD_4 triggered a rapid release of arachidonic acid metabolites into the culture medium, an effect that was suppressed by the CysLTR antagonist 2(*S*)-hydroxyl-3(*R*)-carboxyethylthio)-3-[2-(8-phenyloctyl) phenyl] propanoic acid (SKF 104353), by the topoisomerase I inhibitor camptothecin, and by staurosporine (Mattern et al., 1990). Several different groups have reported $CysLT_1R$-induced release of Th2 cytokines, such as IL-4 from cord blood-derived eosinophils (Bandeira-Melo et al., 2002a,b), IL-5 from MNCs (Nabe et al., 2002; Frieri et al., 2003; Faith et al., 2008), chemokines, such as RANTES, from MNCs (Kawano et al., 2003) or platelets (Hasegawa et al., 2010), IL-8 from THP-1 cells (Thompson et al., 2006), and MIP-1α and MIP-1β (Ichiyama et al., 2009) or IL-11 (Lee et al., 2007a) from epithelial cells. Of interest, LTC_4 and LTD_4, but not LTE_4, enhanced TNF-α-induced MMP-9 production in human MNCs (Ichiyama et al., 2007), an effect that, although inhibited by montelukast, does not seem to be $CysLT_1R$-dependent in eosinophils (Langlois et al., 2006). Finally, a combination of LTD_4 and IL-5 or granulocyte macrophage–colony-stimulating factor synergistically induced TGF-$\beta1$ expression in eosinophils (Kato et al., 2005), whereas LTC_4 induced TGF-$\beta1$ production in airway epithelial cells (Perng et al., 2006) or in a time- and concentration-dependent manner in $CysLT_1R$-transfected HEK-293 cells (Bossé et al., 2008).

Thus, montelukast and/or pranlukast significantly reduced in OVA-treated mice the increased IL-4 and IL-13 (Henderson et al., 2002; Lee et al., 2007a) in BAL fluid, IL-11 and TGF-$\beta1$ in BAL and lung tissues (Lee et al., 2007a), IL-4, IL-5, IL-13, and eotaxin in BAL, and TGF-β gene expression in GATA-3-overexpressing mice (Kiwamoto et al., 2011), thereby preventing airway in-

flammation, bronchial hyperresponsiveness, and airway fibrosis. Of interest, LTD_4 in HEK-293 cells stably transfected with the $CysLT_1R$ can transcriptionally activate furin production with consequent maturation of furin, a proprotein convertase involved in the maturation/activation of several substrates implicated in the remodeling processes (Thompson et al., 2008b).

Treatment with montelukast decreased the amount of IL-4 but increased the amount of INF-γ mRNA expression in the lungs of IL-2-treated OVA-sensitized rats (Nag et al., 2002), decreased tissue inflammation, decreased total cell count and number of eosinophils and lymphocytes in BAL and inhibited the increase in endothelin-1 and INF-γ after intratracheal Sephadex provocation in rats (Finsnes et al., 2002). Furthermore, montelukast significantly inhibited LPS-induced IL-6, TNF-α, and MCP-1 production in the peripheral blood MNCs of control subjects and patients with asthma (Maeba et al., 2005), whereas pranlukast decreased the levels of many cytokines and chemokines (IL-4, IL-5, IL-1β, TNF-α, RANTES, and IL-8) in nasal mucosa, leading to improvement in patients with nasal symptoms (Ueda et al., 2003).

2. CysLT$_2$ Receptor. Obtaining detailed information about signal transduction systems involved in $CysLT_2R$ activation was hampered by the absence of selective antagonists, at least until a short time ago (Huang et al., 2008; Wunder et al., 2010). Thus, most of the data still rely on either recombinant systems or have been obtained in ECs that predominantly express $CysLT_2R$. As in the case of the $CysLT_1R$, the $CysLT_2R$ also seems to be mainly coupled to PI hydrolysis and intracellular Ca^{2+} mobilization through a PTX-insensitive G protein ($G_{q/11}$) in recombinant systems (Heise et al., 2000). $CysLT_2R$ activation in HUVECs causes an increase in $[Ca^{2+}]_i$ (Lötzer et al., 2003), confirming early reports in which LTC_4 and LTD_4 were demonstrated to induce a rapid $[Ca^{2+}]_i$ transient that was inhibited by the receptor antagonist pobilukast (Heimbürger and Palmblad, 1996), which, despite being considered a $CysLT_1R$ antagonist, is apparently a dual $CysLT_1$/$CysLT_2R$ antagonist (G. E. Rovati, unpublished observations). Furthermore, in the same cells cysteinyl LTs induce myosin light-chain kinase activation, stress fiber formation, and EC contraction that are totally PTX-insensitive (Carnini et al., 2011). In contrast, in human MCs under conditions in which $CysLT_1R$ is blocked by MK-571 pretreatment, $CysLT_2R$ stimulation elicited secretion of IL-8 through p38 activation, an effect completely inhibited by PTX (Mellor et al., 2003).

As mentioned previously, in ECs of human vasculature $CysLT_2R$ induced relaxation (Allen et al., 1992), an effect that was successively linked to the formation of NO, at least in human pulmonary arteries and veins (Ortiz et al., 1995). In addition to direct action on the vascular tone, cysteinyl LT-induced activation of ECs may also lead to changes in the transcriptional activity. In HUVECs, LTD_4 induces endothelial P-selectin expression (Pedersen et al., 1997), strongly stimulates expression of MIP-2 (Zhao et al., 2004), and together with thrombin up-regulates 37 early inducible genes, among which the most strongly induced are early growth response 1 (*EGR1*), nuclear receptor subfamily 4 group A transcription factors, E-selectin, CXC ligand 2, IL-8, a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif 1 (*ADAMTS1*), Down syndrome critical region gene 1 (*DSCR1*), tissue factor, and COX-2 (Uzonyi et al., 2006). IL-8 induction has been studied in more detail, demonstrating that in HEK-293 cells stably transfected with $CysLT_2R$ LTC_4 transcriptionally activates its production through induction of NF-κB and AP-1 transcription factors (Thompson et al., 2008a). However, at variance with the results in HUVECs, a recent article suggested that in EA.hy926 cells, a human EC line, LTD_4 induced the phosphorylation of ERK1/2, but not that of p38 or JNK and that these effects were blocked by the $CysLT_1R$ antagonist montelukast or by the dual antagonist BAY U9773, but not by a novel $CysLT_2R$ antagonist referred to as Bay $cysLT_2$ (Yuan et al., 2009).

D. Desensitization and Cross-Talk of CysLT Receptors

Early reports showed that in rat basophilic leukemia cells (Vegesna et al., 1988) and in differentiated U937 cells (Winkler et al., 1988; Pollock and Creba, 1990) treatment with phorbol 12-myristate 13-acetate reduced LTD_4-induced PI metabolism and $[Ca^{2+}]_i$ mobilization, whereas inhibitors of PKC selectively enhanced LTD_4-induced $[Ca^{2+}]_i$ transients (Winkler et al., 1990). These observations suggested for the first time that PKC might play a role in determining the responsiveness of $CysLT_1R$. Indeed, native human $CysLT_1R$ has been demonstrated to be the target for unidirectional extracellular nucleotide-mediated heterologous desensitization (Capra et al., 2005). In fact, ATP/UDP-induced $CysLT_1R$ desensitization, which was sensitive to PKC inhibition, did not cause receptor internalization and induced a faster recovery of $CysLT_1R$ functionality with respect to LTD_4-induced homologous desensitization. The latter, which was not sensitive to PKC activation by phorbol 12-myristate 13-acetate, induced a fast receptor trafficking and down-regulation, and has been shown to most likely depend on GRK2 activation. Of interest, activation of the $CysLT_1R$ by LTD_4 had no effect on P2Y receptor responses (Capra et al., 2005).

In addition, heterologous desensitization of $CysLT_1R$ is mediated not only by $G_{q/i}$-coupled receptors but also by G_s-coupled receptors [i.e., β_2-adrenoreceptors (β_2AR), histamine $H_{1/2}$ and prostaglandin $EP_{2/4}$ receptors] in differentiated U937 cells and human monocytes, this time through activation of PKA (Capra et al., 2010). Of interest, heterologous desensitization seems to affect mostly the G_i-mediated signaling of the $CysLT_1R$ (Capra et al., 2005, 2010).

However, Naik et al. (2005) reported that agonist-induced internalization of recombinant human $CysLT_1R$ expressed in HEK-293 cells is GRK/arrestin-independent and significantly PKC-dependent. They also demonstrated that mutation of putative PKC phosphorylation sites in the C-tail of the receptor reduced internalization and increased the signaling, significantly attenuating the effects of PKC inhibition. These findings may reflect the use of recombinant systems that produce varying results, depending on cell type and G protein availability, especially when dealing with GPCRs (Kenakin, 1997). In addition, both PKCα and PKCε have been shown to be activated and involved in the regulation of the LTD_4-induced Ca^{2+} signal in human SMCs (Accomazzo et al., 2001) and intestinal epithelial cells (Thodeti et al., 2001). Therefore, in human airway SMCs, PKC inhibition augmented LTD_4-stimulated contraction and increased PI hydrolysis and Ca^{2+} flux, confirming that PKC can regulate $CysLT_1R$ responses (Deshpande et al., 2007). Such an integrated network presumably tunes the strength and duration of the inflammatory signals, thereby leading to fine regulation of the physiological responses.

Although a phylogenetic relationship exists between P2YR and CysLTR on the basis of sequence alignment followed by evolutionary analyses (Fredriksson et al., 2003; Kroeze et al., 2003), functional relationships between cysteinyl LT/CysLTR and purine/P2YR systems are still a matter of debate. Mellor et al. (2001, 2002) first suggested that UDP is also able to activate CysLTRs and that UDP and LTD_4 mediated ERK activation and cytoprotection, implying a cysteinyl LT-mediated autocrine loop (Jiang et al., 2009). However, UDP was not able to compete for binding sites labeled by $[^3H]LTD_4$ in COS-7 cells transiently expressing $hCysLT_1R$. These data, together with the lack of cross-desensitization between $CysLT_1R$ and P2Y receptors, seem to exclude the involvement of a CysLTR/P2YR heterodimer (Capra et al., 2005). These observations have been recently confirmed by another group using receptor desensitization and small interfering RNA experiments in monocytes and $CysLT_1R$-transfected HEK-293 cells. These investigators reported that LTD_4 and UDP were acting on separate receptors (Woszczek et al., 2010). On the other hand, Nonaka et al. (2005) first reported that LTE_4 acts as an agonist at the $P2Y_{12}$ receptor, data recently confirmed by a different laboratory (Fredman et al., 2010), which seemed to corroborate the demonstration of LTE_4-induced pulmonary inflammation mediated through the $P2Y_{12}$ receptor (Paruchuri et al., 2009). In conclusion, a number of investigations demonstrated a close interplay between these two receptor systems, a topic that may have an impact on the development of therapeutic drugs (see section III.H).

The purinergic receptor, however, is not the only receptor system shown to interact with the CysLTRs. A number of studies have reported that LTRAs used as add-on therapy decrease the need for β_2-agonists (Nathan et al., 1998; Noonan et al., 1998; Jarvis and Markham, 2000; Virchow et al., 2000; Keam et al., 2003; Vaquerizo et al., 2003; Deykin et al., 2007; Borderias et al., 2007) and that a positive association exists between a CysLTR antagonist and a β_2-agonist in controlling asthma symptoms, particularly in patients homozygous for the glycine-16 β_2AR polymorphism, which predisposes them to agonist-induced down-regulation and desensitization of the β_2AR (Lipworth et al., 2000). The response to β_2-agonist agonists is reduced in asthmatic airways, and this desensitization has been postulated to be due in part to inflammatory mediators such as cysteinyl LTs (Song et al., 1998; Milanese et al., 2005). Indeed, LTD_4, through $CysLT_1R$ activation, induced β_2AR desensitization in human airway SMCs in vitro, an effect again mediated by the PKC pathway (Rovati et al., 2006). Another interesting aspect of CysLTR crosstalk is the growth factor receptor transactivation, an aspect already discussed in section III.C.

E. CysLT Receptor Functional Analysis through Altered Gene Expression

1. Gene Disruption. In 2001, a short isoform and a long isoform of $mCysLT_1R$ were identified in the mouse (Maekawa et al., 2001; Martin et al., 2001). Comparison of the human and the mouse $CysLT_1R$ cDNAs demonstrated that human transcript II contains sequences equivalent to the mouse short isoform (Woszczek et al., 2005). Both cDNAs, the human transcript II and the mouse short isoform, are less preferentially expressed (Woszczek et al., 2005). At the same time, the $mCysLT_2R$ was cloned and two 5′-untranslated region splice variants were identified, with the short form lacking exon 3 as the predominant transcript (Hui et al., 2001). A pharmacological difference was also noted between mouse and human $CysLT_2R$. Pranlukast, a specific inhibitor for $hCysLT_1R$, antagonized $mCysLT_2R$ responses at concentrations of 10 μM, as determined by $[Ca^{2+}]_i$ elevation and receptor-induced promoter activation (Ogasawara et al., 2002).

Soon thereafter, Maekawa et al. (2002) generated $CysLT_1R$-deficient mice by targeted gene disruption; this resulted in loss of both isoforms of the receptor. Peritoneal macrophages from wild-type mice, which expressed both $CysLT_1R$ and $CysLT_2R$, responded strongly to LTD_4 and slightly to LTC_4 in a Ca^{2+} mobilization assay, whereas those from mutant mice responded to neither ligand. Furthermore, the same authors observed that plasma protein extravasation, but not neutrophil infiltration, was significantly suppressed in $CysLT_1R$-null mice after zymosan-induced peritonitis or IgE-mediated passive cutaneous anaphylaxis, demonstrating that in acute inflammation the microvasculature responds through the $CysLT_1R$ to cysteinyl LTs generated in vivo by either monocytes/macrophages or MCs. The finding that $CysLT_1R$-null mice were not protected against chronic injury induced by bleomycin suggested a proinflammatory role for the $CysLT_2R$ in the

chronic response. This finding was corroborated by the observation that bleomycin-induced pulmonary inflammation with fibrosis is significantly attenuated in LTC_4S-null mice but markedly aggravated in $CysLT_1R$-null mice (Beller et al., 2004a). The same group of researchers examined this issue by generating $CysLT_2R$-deficient mice (Beller et al., 2004b) and found that $CysLT_2R$ is responsible for mediating the contribution of the cysteinyl LTs to bleomycin-induced chronic pulmonary inflammation and fibrosis. In conclusion, these authors unexpectedly found that $CysLT_1R$ does not mediate the signal for chronic inflammation and fibrosis. They propose that $CysLT_1R$ is responsible for bronchoconstriction, for microvasculature leakage in acute inflammation, and for a counteracting role in chronic inflammation, whereas the $CysLT_2R$ is the receptor providing the signal for chronic inflammation. Furthermore, $CysLT_2R$-targeted gene disruption revealed a significant reduction in vascular permeability (Beller et al., 2004b). These data have been further confirmed in transgenic mouse models (see below).

GPR17-deficient mice sensitized and challenged with dust mite exhibited markedly increased pulmonary inflammatory and serum IgE responses compared with those of wild-type mice. In contrast, a reduced response to this intervention was observed in mice lacking $CysLT_1R$. These findings reveal a constitutive negative regulation of $CysLT_1R$ functions by GPR17 in both the antigen presentation and downstream phases of allergic pulmonary inflammation (Maekawa et al., 2010), confirming the in vitro observation of an interplay between GPR17 and $CysLT_1R$ (Maekawa et al., 2009) (see section III.H).

2. CysLT Receptor Transgenic Models. A transgenic mouse specifically overexpressing the human $CysLT_1R$ in SMCs via the α-actin promoter was generated to explore the importance of increased cysteinyl LT signaling in airway function. This transgenic model overcame the problem of mice and isolated murine tracheal rings having a minimal bronchoconstrictor response to direct LT challenge compared with that of guinea pigs or humans (Dahlén et al., 1980; Ashida et al., 1987; Martin et al., 1988). Mice were sensitized by intraperitoneal injections with *Aspergillus fumigatus* to obtain a model of allergic airway inflammation. The authors observed that in transgenic mice allergen-induced airway hyperresponsiveness was significantly enhanced after LTD_4 challenge, thus indicating that overexpression of human $CysLT_1R$ on SMCs leads to smooth muscle hyperresponsiveness (Yang et al., 2004).

Hui et al. (2004) have generated mice in which the human $CysLT_2R$ is overexpressed in ECs and reported the effects on endothelial integrity and blood pressure regulation mediated by this receptor subtype in vivo. These researchers observed that, in $CysLT_2R$ transgenic mice, the permeability response to exogenous LTC_4 and to endogenous cysteinyl LTs evoked by passive cutaneous anaphylaxis was augmented and that this enhanced vascular permeability is controlled via Ca^{2+} signaling and takes place via a transendothelial vesicle transport mechanism as opposed to a paracellular route (Moos et al., 2008). Furthermore, the rapid, systemic pressor response to intravenous LTC_4 was diminished coincidentally with augmented production of NO (Hui et al., 2004). The same group also observed that overexpression of the $hCysLT_2R$ in mice aggravates myocardial ischemia-reperfusion injury by increasing endothelial permeability and exacerbating inflammatory gene expression, leading to accelerated left ventricular remodeling, induction of peri-infarct zone cellular apoptosis, and impaired cardiac performance (Jiang et al., 2008).

F. Pharmacogenetics of CysLT System

The characterization of the genes encoding the cysteinyl LT system, including the *CysLTR1* and *CysLTR2* genes, has advanced the study of CysLTR pharmacology and the GPCR pharmacogenomics of inflammatory disease (Thompson et al., 2005). Furthermore, many of the genes encoding proteins involved in the synthesis and signaling pathways of the cysteinyl LTs are polymorphic and are of interest in genetic studies of asthma (Silverman et al., 2001; Palmer et al., 2002; Israel, 2005).

1. $CysLT_1$ Receptor Pharmacogenetics. The $CysLT_1R$ is a candidate gene in atopic asthma because drugs that act as high-affinity antagonist ligands of the $CysLT_1R$, such as montelukast, zafirlukast, and pranlukast, have been shown to have a beneficial therapeutic effect in some cases of atopy that result in asthma (for reviews on LTRAs in therapy, see Bousquet et al., 2009; Diamant et al., 2009; Dunn and Goa, 2001; Keam et al., 2003; Wahn and Dass, 2008), allergic rhinitis (AR), or rhinosinusitis (Grayson and Korenblat, 2007) (see section III.I.1). Moreover, approximately 20% of patients report no change in symptoms during treatment with these agents (Drazen et al., 1999, 2000; Israel, 2005). This finding suggests that in some patients with asthma, the pathway regulating airway cysteinyl LT activity may not be activaed with the clinical symptoms of asthma resulting from the actions of other mediators, which would lead to the clinical phenotype of resistance to LTs modifiers (Asano et al., 2002; Lima et al., 2006; Telleria et al., 2008; Tantisira et al., 2009; Langmack and Martin, 2010).

Although the $CysLT_1R$ gene may harbor inactivating mutations in some populations, there are many more variants of the $CysLT_2R$ (Thompson et al., 2003). For example, in studies of the people living on the isolated south Atlantic island of Tristan da Cunha, two variants of the $CysTL_1R$ have been identified, an I206S variant and an activating G300S variant (Thompson et al., 2007). Although the G300S variant was found to be a mildly activating in response to LTD_4 in vitro, it was nonetheless associated with atopy in the Tristan da Cunha population.

Furthermore, a number of SNPs in the promoter region of the *CYSLTR1* gene have been found by different groups. Some SNPs were not associated with either the development of asthma/rhinitis (Choi et al., 2004; Zhang et al., 2006) or the response to treatment (Lee et al., 2007b), whereas others, in particular the −927T > C polymorphism (Arriba-Mendez et al., 2006; Hao et al., 2006; Sanz et al., 2006; Al-Shemari et al., 2008; Bizzintino et al., 2009), have been postulated to cause differences in transcriptional activity that may be predictors of disease risk (Duroudier et al., 2007; Hong et al., 2009), or treatment response (Kim et al., 2007b) or be associated with AIA (Kim et al., 2006b, 2007a).

As mentioned before, Lynch et al. (1999) mapped the $CysLT_1$ gene to the long arm of the human X chromosome. Therefore, Ohd et al. (2003) found a significantly higher frequency of $CysLT_1R$ staining in tissues from male patients affected by colorectal adenocarcinoma, suggesting the presence of allele-dependent dysregulation or sex-specific transcriptional subordination. Although there are four SNP variants in the promoter region of the *CYSLTR1* gene, two of the haplotypes, termed CAAC and TGGC, constitute more than 95% of the alleles noted in small population samples. There was no predisposition in patients with asthma or rhinitis to have one haplotype or the other. However, among women with asthma who were homozygous for the CAAC haplotype, there was a significantly higher expression of the $CysLT_1R$ transcript I than in women who had the CAAC/TCGC complex genotype; transcript II levels were also significantly lower than those in healthy women homozygous for the CAAC haplotype. These data are concordant with previous findings that TCG and CAA haplotypes in the promoter region are associated with different transcriptional activity (Zhang et al., 2006). Of interest, in a recent report of the British 1958 birth cohort, data suggested that the *CYSLTR1* gene promoter polymorphisms might influence the risk of atopy in the female white population with suggestive evidence of heterozygote vigor (Duroudier et al., 2009).

2. $CysLT_2$ Receptor Pharmacogenetics. The $CysLT_2R$ is also a candidate gene for asthma and atopy because it maps to a region of chromosome 13q14 that has been linked to asthma (Kimura et al., 1999) and atopy (Daniels et al., 1996). Specific $CysLT_2R$ antagonists have only recently been reported (Huang et al., 2008; Wunder et al., 2010), and thus the pharmacological importance of $CysLT_2R$ antagonism in asthma or atopy is yet to be established. However, the development of drugs that target the $CysLT_2R$ may be useful not only for asthma, given that approximately 20% of patients fail to respond to $CysLT_1R$ agents, particularly when the $CysLT_2R$ is also polymorphic, but also for cardiovascular diseases (Funk, 2005; Moos and Funk, 2008; Riccioni et al., 2008).

The Tristan da Cunha study has identified an atopy associated with the M201V variant, which, unlike the G300S $CysLT_1$ variant, is partially inactivating in terms of $[Ca^{2+}]_i$ signaling (Thompson et al., 2003) and has been demonstrated to have a reduced affinity for LTC_4 and particularly for LTD_4, an impairment of IL-8 transactivation as well as NF-κB and JNK phosphorylation (Brochu-Bourque et al., 2011). This association of the $CysLT_2R$ M201V variant with airway disease has been independently replicated in a large outbred population (Pillai et al., 2004). Transmission disequilibrium testing in 137 Japanese asthmatic families revealed that the −1220A>C polymorphism of the *CYSLTR2* gene is associated with the development of asthma (Fukai et al., 2004), whereas four other sequence variants (either in the 5′- or 3′-flanking region or downstream of the gene) are associated with AIA (Park et al., 2005) and have been linked to altered $CysLT_2R$ expression (Shin et al., 2009). It is noteworthy that two other *CYSLTR2* gene variants, in association with an *ALOX5* polymorphism, have been shown to increase the response to montelukast (Klotsman et al., 2007).

The fact that $CysLT_1R$ and $CysLT_2R$ are both polymorphic in some individuals suggests that if they are coexpressed on inflammatory cells, they may functionally alter cysteinyl LT signaling. If, like many GPCRs, the $CysLT_1R$ and $CysLT_2R$ form functional dimers with unique pharmacological properties (Jiang et al., 2007), the $CysLT_2R$ may also play a role in the $CysLT_1R$ pharmacology (see section III.G). Paradoxically, in the inbred Tristan da Cunha population the activating $CysLT_1R$ G300S variant and the inactivating $CysLT_2R$ M201V variant seem to interact to confer risk for atopy. In this sample, all double heterozygotes were atopic. General linear modeling indicated that the $CysLT_1R$ and $CysLT_2R$ genotypes were independently associated with atopy and asthma phenotypes. The gene-gene interaction, therefore, presents as being consistent with an additive effect that is highly associated with atopy (Thompson et al., 2007).

G. Homodimers or Heterodimers?

Some experimental evidence indicates the possibility that CysLTR might exist as homodimers and/or heterodimers, on the basis of the observation of dimeric and oligomeric forms of $CysLT_1R$ in Western blots and the punctate appearance of the immunohistochemical signal in peripheral blood leukocytes (Figueroa et al., 2001) or U937 cells (Capra et al., 2005). In human MCs, which can express both receptor subtypes, Mellor et al. (2003) observed that under conditions in which $CysLT_1R$ is blocked, IL-5 generation results only from stimulation with the selective $CysLT_2R$ agonist BAY U9773 and not with cysteinyl LTs, leading them to speculate that this could arise from stimulation of a $CysLT_1/CysLT_2$ heterodimer at a site inaccessible to interference from MK-571. Finally, Beller et al., (2004b) postulated, on the basis of the magnitude of the attenuation in IgE-dependent, MC-mediated passive cutaneous anaphylaxis in $CysLT_1R/CysLT_2R$-null mice, that the effect observed in

wild-type littermates was mediated through $CysLT_1$/$CysLT_2$ heterodimers. These speculations have been now confirmed by assessment of the formation of a $CysLT_1$/$CysLT_2$ heterodimer at the nuclear envelope of human MCs. Negative regulation of $CysLT_1R$-induced mitogenic signaling responses of MCs by $CysLT_2R$ demonstrates physiologically relevant functions for GPCR heterodimers on primary cells central to inflammation (Jiang et al., 2007). It is noteworthy that recently it has been demonstrated that $CysLT_1R$ formed heterodimers with its counter-receptor $CysLT_2R$ under basal conditions and that LTD_4 triggers reduced dimerization of CysLTRs in intestinal epithelial cells (Parhamifar et al., 2010).

These observations are of potential interest, considering that GPCR oligomerization influences CysLTR pharmacology and function and offers new horizons for the study of important aspects of cysteinyl LT biology and possibly for the development of new drugs (Dalrymple et al., 2008; Kenakin, 2002; Prinster et al., 2005) (see section III.H).

H. Other Receptors Related to CysLT Receptors

Over the years, data were reported in the literature to suggest the existence of additional CysLTR subtypes in human tissues (Brink et al., 2003). This proposal was based on classic pharmacodynamic observations on agonist and antagonist potencies and as well as on receptor pharmacological profiles (Rovati et al., 1997; Bäck, 2002; Norel and Brink, 2004; Rovati and Capra, 2007; Austen et al., 2009).

1. GPR17. In an intriguing report Mellor et al. (2001) suggested that in MCs both the $CysLT_1R$ and a yet-unidentified elusive receptor up-regulated by treatment with the proinflammatory cytokine IL-4 were responsive to both cysteinyl LTs and UDP. Pharmacological studies performed with classic $CysLT_1R$ or the dual $CysLT_1$/$CysLT_2R$ antagonists excluded the possibility that this additional receptor was the $CysLT_2R$ subtype. Subsequently, the hypothesis that the $hCysLT_1R$ was responding to UDP was also excluded (Capra et al., 2005; Woszczek et al., 2010), whereas different $CysLT_1R$ antagonists have been demonstrated to inhibit P2Y receptor signaling (Mamedova et al., 2005; Woszczek et al., 2010).

Screening for orphan GPCRs at an intermediate phylogenetic position between P2Y and CysLT receptor families revealed that the heterologous expression of GPR17 in 1321N1 cells resulted in the generation of an apparently specific and concentration-dependent response to both cysteinyl LTs and extracellular nucleotides (Ciana et al., 2006). In line with previous expression data (Bläsius et al., 1998), both human and rat GPR17 was highly present in brain and in other organs typically undergoing ischemic damage, such as kidney and heart. These data are consistent with the demonstration that both the $CysLT_1$ and $P2Y_{12/13}$ receptor antagonists (montelukast and cangrelor, respectively) or in vivo GPR17 receptor knockdown protected against brain damage in the permanent middle cerebral artery occlusion model of ischemic damage in the rat (Ciana et al., 2006). However, GPR17 has been demonstrated to colocalize and dimerize with $CysLT_1R$ on the cell surface of human peripheral blood monocytes and was a negative regulator of the $CysLT_1R$ both in vitro (Maekawa et al., 2009) and in vivo (Maekawa et al., 2010), without inducing a specific response, at least when expressed in a recombinant system. A recent article confirmed that GPR17 is indeed activated by uracil nucleotides (Benned-Jensen and Rosenkilde, 2010), although, at least in isolation, it may not respond to cysteinyl LTs (G. E. Rovati, unpublished observations). In addition, in a different native system (differentiated PC12 cells) knock down of GPR17 by small interfering RNA abolished LTD_4-induced effect on cell viability (Daniele et al., 2010). In this respect, it might be important to note that $P2Y_6$ receptors also require an intact cysteinyl LT synthesis and signaling system to induce survival and activation of MCs (Jiang et al., 2009). Thus, $CysLT_1R$ and $P2Y_6R$, which are coexpressed on many cell types of innate immunity, seem to reciprocally amplify one another's function through endogenous ligands. In conclusion, whether GPR17 is really a dualistic receptor (a single protomer responding to two different classes of ligands) or may form heterodimers with a P2Y receptor is a matter certainly deserving further investigation.

2. Leukotriene E_4 Receptor(s). Although LTE_4 is only a weak agonist for the defined $CysLT_1R$ and $CysLT_2R$, this ligand is the most stable and abundant cysteinyl LT in vivo. However, the literature on LTE_4-induced effects is conflicting, and there seems to be tissue- and model-related differences that remain to be defined. In addition, data from studies in the presence and absence of conversion inhibitors also produced different results (Brink et al., 2003). Early reports indicated greater potency for LTE_4 compared with that for the other cysteinyl LTs in constricting guinea pig trachea in vitro (Lewis et al., 1980; Lee et al., 1984) and comparable activity in eliciting a cutaneous wheal and flare response in humans (Soter et al., 1983). Furthermore, patients with AIA responded with enhanced bronchoconstriction to inhalation of LTE_4 relative to their responses to LTC_4 or histamine (Christie et al., 1993), and inhaled LTE_4 caused more tissue and airway eosinophilia than LTD_4 (Gauvreau et al., 2001). In contrast, LTE_4 failed to activate a CysLTR in human pulmonary vessels (Walch et al., 2002). In 2008, the first report that LTE_4 mediated prostaglandin D_2 production, which was sensitive to the $CysLT_1R$ antagonist MK-571 but resistant to knock down of this receptor, was published (Paruchuri et al., 2008). Furthermore, this effect, induced through COX-2 induction and ERK, p90RSK, and cAMP-regulated-binding protein phosphorylation, was not mediated by LTD_4 but was sensitive to PPAR-γ knockdown, suggesting the

presence of a LTE_4-selective receptor in human MCs (Paruchuri et al., 2008). Almost simultaneously it was demonstrated that intradermal injection of LTE_4 into the ear of mice deficient in both $CysLT_1R/CysLT_2R$ elicited a vascular leak that exceeded the response to intradermal injection of LTC_4 or LTD_4 and that this response was inhibited by pretreatment of the mice with PTX or a Rho kinase inhibitor (Maekawa et al., 2008). This putative mouse LTE_4-specific receptor, however, was not MK-571-sensitive, adding complexity to LTE_4 puzzle (Austen et al., 2009). One last piece of the puzzle has been revealed by the same group on the basis of a study in mice lacking both $CysLT_1R/CysLT_2R$: the ADP-reactive $P2Y_{12}$ receptor was required for LTE_4-mediated pulmonary inflammation. Platelet $P2Y_{12}$ receptor expression permitted LTE_4-induced activation of ERK in CHO cells and allowed chemokine and prostaglandin D_2 production by LAD2 cells, a human MC line. Of interest, competition experiments between radiolabeled ADP and unlabeled LTE_4 in this last system seemed to suggest that $P2Y_{12}$ must complex with another receptor to recognize LTE_4 (Paruchuri et al., 2009). Thus, in the light of the progress on heterodimer pharmacology of GPCRs and their possible physiological significance (Prinster et al., 2005; Gurevich and Gurevich, 2008; Milligan, 2009), the possibility that some of these additional CysLTR subtypes might be the result of the formation of heterodimers with a different pharmacological profile, rather than representing new distinct proteins, should always considered (see section III.H). In all previous cases, these data add complexity to the already established "cross-talk" between the purinergic and the LT receptor systems (Capra et al., 2005; Jiang et al., 2009), suggesting these as possible additional means by which these two receptor systems interact with each other.

I. New Potential Therapeutic Applications of Leukotriene Receptor Antagonists

1. Allergic Rhinitis. Many of the cells involved in the pathophysiology of AR produce and release cysteinyl LTs, and a connection between the upper airway disease, rhinitis, and lower airway disease, asthma, has been delineated with the aid of important studies indicating that they essentially represent components of a single inflammatory airway disease (Blaiss, 2005; Thomas, 2006). Molecular and clinical studies also substantiated a role for cysteinyl LTs and their receptors in AR (Peters-Golden and Henderson, 2005; Peters-Golden et al., 2006). Furthermore, beyond the existing connection between AR and asthma, AR and chronic rhinosinusitis seem to be related both epidemiologically and symptomatically. In fact, some studies have demonstrated possible involvement of the cysteinyl LT system in chronic rhinosinusitis also (Arango et al., 2002; Higashi et al., 2004), and both $CysLT_1$ and $CysLT_2$ receptors were expressed in various inflammatory cells of patients with active seasonal AR (Figueroa et al., 2003) or rhinosinusitis (Sousa et al., 2002) (see section III.A).

Given the shared pathophysiologies and the frequent coexistence, a common therapeutic approach would seem logical (Greenberger, 2003; Stelmach and Cukier, 2006). Indeed, evidence has begun to accumulate in support of the utility of LTRAs in AR (Wilson et al., 2004; Rodrigo and Yañez, 2006) or rhinosinusitis (Grayson and Korenblat, 2007; Scadding et al., 2008).

Montelukast, which significantly reduced daytime nasal, eye and throat symptoms, nighttime symptoms, and symptoms affecting quality of life (QL) in adult patients with seasonal AR (Grainger and Drake-Lee, 2006; Nayak and Langdon, 2007; Bousquet et al., 2009), has also been demonstrated to be safe in children (Bisgaard et al., 2009). Similar results have also been obtained with zafirlukast (Piatti et al., 2003) and pranlukast (Ueda et al., 2003; Okubo and Baba, 2008).

Other studies indicate that LTRAs can alleviate the signs and symptoms of AR when used either as monotherapy (van Adelsberg et al., 2003; Lee et al., 2004b; Ho and Tan, 2007; Wahn and Dass, 2008; Diamant et al., 2009; Cingi and Ozlugedik, 2010) or in combination with an antihistamine in adults (Meltzer et al., 2000; Nayak et al., 2002; Ciprandi et al., 2004; Kurowski et al., 2004; Ciebiada et al., 2006; Lagos and Marshall, 2007; Li et al., 2009), as well as in children (Phan et al., 2009). Results from meta-analyses indicate that antihistamines and LTRAs are equally effective in improving symptoms of AR and QL, but that both drugs are less effective than intranasal corticosteroids (Pullerits et al., 2002; Saengpanich et al., 2003; Di Lorenzo et al., 2004b; Wilson et al., 2004; Rodrigo and Yañez, 2006; Van Hoecke et al., 2007). However, in a retrospective observational study, addition of montelukast to current corticosteroid therapy improved long-term asthma control and resulted in substantial reductions in asthma-related resource use by patients with mild or moderate persistent asthma and concomitant seasonal AR (Borderias et al., 2007), confirming previous results on the efficacy of montelukast in patients with AR and asthma (Nayak, 2004; Philip et al., 2004; Price et al., 2006; Virchow and Bachert, 2006; Storms, 2007). Of interest, systemic medication such as montelukast, as expected, provided better relief for symptoms distant from the nasal cavity, whereas the antihistamine reduced rhinorrhea more than either montelukast or budesonide (Sardana et al., 2010). Both second-generation antihistamines and montelukast have been found to be relatively safe and effective in children also (Phan et al., 2009). Montelukast received approval from the U.S. Food and Drug Administration in January 2003 for the treatment of seasonal AR and in 2005 for the treatment of perennial AR.

2. Aspirin/Nonsteroidal Anti-Inflammatory Drug Intolerance. A variable percentage (2–20%) of adults with asthma exhibit an AIA phenotype (Jawien, 2002), which is the second most frequent untoward allergic reaction to

drugs (de Weck et al., 2006). AIA consists of the precipitation of asthma and rhinitis attacks in the airways or urticaria and angioedema in the skin in response to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit COX-1 (Szczeklik and Stevenson, 2003); selective inhibition of COX-2 does not provoke such responses (Stevenson and Simon, 2001; Gyllfors et al., 2003; Stevenson and Szczeklik, 2006). Within 3 h of ingestion of aspirin or NSAIDs, individuals with AIA develop bronchoconstriction, often accompanied by rhinorrhea, conjunctival irritation, and scarlet flush (Obase et al., 2005). Compared with normal individuals or subjects with aspirin-tolerant asthma, patients with AIA have increased baseline levels of cysteinyl LTs in urine (Christie et al., 1991; Higashi et al., 2004; Micheletto et al., 2006) exhaled air (Antczak et al., 2002), and in saliva and induced sputum (Gaber et al., 2008), levels that are further enhanced by aspirin challenge (Ortolani et al., 1987; Sladek and Szczeklik, 1993; Szczeklik et al., 1996) and that might be derived, at least in part, from MCs (Sladek and Szczeklik, 1993; O'Sullivan et al., 1996; Mita et al., 2001a). Although a definite explanation for this syndrome is not yet available, a large body of evidence supports the possibility that patients with AIA are particularly dependent on the bronchoprotective and anti-inflammatory properties of prostaglandin E_2 (Stevenson and Szczeklik, 2006) and that inhibition of COX-1 in these patients triggers MC activation and release of LTs as well as histamine and tryptase (Picado et al., 1992). In addition to the already discussed high levels of cysteinyl LTs and the localization of $CysLT_1R$ in nasal mucosa and leukocytes of patients with AIA (Sousa et al., 2002), the clinical relevance of the cysteinyl LTs in AIA has been supported by studies demonstrating that patients with AIA respond favorably to clinical treatment with LT modifiers (Dahlén et al., 1998, 2002; Israel, 2000; Mastalerz et al., 2002a,b Obase et al., 2002; Lee et al., 2004a; Micheletto et al., 2004; Park et al., 2010).

The possible association between *CysLTR1* and *CysLTR2* gene polymorphisms and AIA has already been discussed (see section III.F). *CysLTR1* gene polymorphism, which is often associated with increased $CysLT_1R$ expression, has been found to be associated with AIA in males (Kim et al., 2006b, 2007a). Considering that *CysLTR2* gene polymorphisms, which, on the contrary, seem to affect $CysLT_2R$ mRNA transcription and stability (Shin et al., 2009), have also been found to be associated with AIA, particularly when combined with the LTC_4S polymorphisms −444A>C (Park et al., 2005), one might envisage a protective role for $CysLT_2R$ in AIA. These data seem to support the finding that $CysLT_2R$, interacting with $CysLT_1R$, down-modulates cysteinyl LT-dependent responses in MCs (Jiang et al., 2007).

3. Other Atopic Diseases. Beyond asthma and rhinitis, there are other atopic diseases in which cysteinyl LTs are considered to play a role and that normally affect adults and children with relevant human and economic burden, such as atopic dermatitis (AD) and urticaria. Although the role of cysteinyl LTs in the inflammation of AD is unclear, several reports in the literature, but not all (Veien et al., 2005), detail improvements in patients (adult and children) with moderate to severe AD with the use of LTRAs at the doses generally recommended for asthma treatment (Capra et al., 2006; Leonardi et al., 2007; Broshtilova and Gantcheva, 2010). In support, there is also the evidence that elevated levels of LTE_4 have been found in the urine of patients with AD (Adamek-Guzik et al., 2002; Øymar and Aksnes, 2005). Chronic urticaria (CU) may manifest as an idiopathic reaction or as a reaction to a known cause, such as cold, pressure, food additives, or NSAIDs; however, this does not occur with selective COX-2 inhibitors (Zembowicz et al., 2003). Of interest, the prevalence of aspirin sensitivity among patients with CU is estimated to be between 20 and 30% (Grattan, 2003), and recently the LTC_4S −444A>C polymorphism has been suggested to be a risk factor for aspirin-induced urticaria (Sánchez-Borges et al., 2009). Thus, these patients may be more likely to respond to LTRA therapy (Asero, 2000; Pacor et al., 2001). Indeed, although some authors found LTRAs to be ineffective in CU (Reimers et al., 2002; Di Lorenzo et al., 2004a) or even to induce a paradoxical exacerbation (Minciullo et al., 2004; Tedeschi, 2009), montelukast has been demonstrated to be effective in patients for whom treatment with histamine H1-receptor antagonists had proved ineffective (Erbagci, 2002; Bagenstose et al., 2004). These data, therefore, suggest that LTRAs may have benefit for patients with conditions not sufficiently controlled with histamine H1-receptor antagonists (Sanada et al., 2005; Wan, 2009).

4. Cardiovascular Diseases. Biomedical research in the LT field has been markedly polarized to asthma and allergic disorders and has largely overlooked other diseases that are also based on the existence of an inflammatory process with increased vascular permeability and edema, such as CVD (Capra et al., 2007). Although blocking the inflammatory component of any human disease is a long-standing and established concept, the use of LT modifiers (LTRAs and LT synthesis inhibitors) in treating the inflammatory component of CVDs has, surprisingly, been seriously contemplated only in the past few years (Funk, 2005; Peters-Golden and Henderson, 2007; Bäck, 2008b). However, a growing body of evidence suggests a major role for the LTs generated by the 5-LO pathway in the pathogenesis and progression of CVDs (Lötzer et al., 2005; Bäck, 2009a), particularly atherosclerosis, myocardial infarct, stroke, aortic aneurysms, and intimal hyperplasia, as LT signaling is emerging as a crucial component in vascular inflammation (Bäck et al., 2007). Cysteinyl LTs have a unique pharmacological profile, characterized by potent constrictor actions on the microvasculature and thus regulation of blood pressure, enhanced permeability of the

postcapillary venules, reduced coronary blood flow, reduced myocardial contractility, and cardiac output without affecting the heart rate (for review, see Brink et al., 2003 and Capra et al., 2007).

Both CysLTR subtypes are expressed in diseased human arteries (Allen et al., 1998; Spanbroek et al., 2003). However, the role of $CysLT_1R$ in CVDs is rather controversial. Findings suggesting a role for cysteinyl LTs in the extension of ischemic damage and in cardiac dysfunction during reperfusion (Toki et al., 1988; Hock et al., 1992) are evenly balanced by results suggesting that these autacoids have no (Hahn et al., 1992) or little (Ito et al., 1989) contribution to the progression of myocardial ischemia-reperfusion injury. On the other hand, the LTRAs investigated in these studies belong to the first generation of molecules and may have not displayed enough potency to compete with the endogenous ligands, which are likely to be present with very high local bioavailability at sites where inflammatory cell accumulation and myocardial injury take place. In fact, the newer potent and commercially available $CysLT_1R$ antagonist, montelukast, has been found to inhibit atherosclerotic lesion size and intimal hyperplasia (Kaetsu et al., 2007; Jawien et al., 2008) and to reduce vascular reactive oxygen species production, to significantly improve EC function, and to ameliorate atherosclerotic plaque generation in a mouse model in vivo (Mueller et al., 2008). Furthermore, in a rabbit carotid balloon injury model, it significantly reduced the neointima, decreased macrophage content, increased SMC content, and inhibited expression of MCP-1 without having influence on plasma lipids, indicating antiatherogenic effects unrelated to plasma lipid modulation (Ge et al., 2009). A randomized controlled trial of placebo versus either montelukast or theophylline in asthmatic individuals reported significantly lower C-reactive protein in montelukast-treated patients (Allayee et al., 2007).

As regards a role for the $CysLT_2R$ in CVD, the early, endothelium-targeted overexpression of the human $CysLT_2R$ in mice aggravates myocardial ischemia-reperfusion injury (Hui et al., 2004), leading to accelerated left ventricular remodeling and impaired cardiac performance (Jiang et al., 2008). Despite expression data suggesting that $CysLT_2R$ is the main isoform of the receptor for cysteinyl LTs in the normal brain (see section III.A), selective $CysLT_1R$ antagonists might have a protective effect in focal cerebral ischemia (Yu et al., 2005a,b; Ciana et al., 2006; Qian et al., 2006), possibly decreasing blood-brain barrier permeability (Biber et al., 2009). However, the dual $CysLT_1/CysLT_2$ receptor antagonist BAY U9773 has been proved to be more potent and effective than a selective $CysLT_1R$ antagonist in preventing the brain permeability alteration induced by neutrophil activation (Di Gennaro et al., 2004).

The first report indicated that in vivo inhibition of GPR17 by either montelukast or antisense technology dramatically reduced ischemic damage in a rat model of focal cerebral ischemia (Ciana et al., 2006). Subsequently, it was suggested that GPR17 might orchestrate oligodendrocyte maturation after brain or spinal cord injury at a later stage, indicating a role in fostering brain repair (Lecca et al., 2008; Ceruti et al., 2009, 2011). The latter findings were supported by in vitro experiments showing that GPR17 activation stimulated the maturation of preoligodendrocytes (Lecca et al., 2008; Fumagalli et al., 2011). In contrast, GPR17 transgenic mice exhibited blocked differentiation of neural progenitor cells into oligodendrocytes and also inhibited terminal differentiation of primary oligodendrocyte precursor cells, supporting GPR17 as a negative regulator of oligodendrocyte differentiation and myelination (Chen et al., 2009b). Fumagalli et al. (2011) recently suggested that one possible explanation for the apparent differences between those studies may be that the overexpression of GPR17 occurred with the CNPase promoter in the latter study (Chen et al., 2009b), inducing GPR17 expression at a rather advanced maturation stage. Nevertheless, GPR17-deficient mice exhibit early onset of central nervous system myelination (Chen et al., 2009b), and the exact role of GPR17 signaling in oligodendrocyte maturation and function remains to be determined. Thus, whether GPR17 or indeed cysteinyl LTs are friends or foes in ischemic brain injury still needs to be established (Bäck, 2008a).

5. CysLT in Other Diseases. A number of observations document that 5-LO and its products may be relevant in different diseases either because of an increase in cysteinyl LT production/CysLTR expression or because the use of LTRAs has proved to be efficacious. For example, cysteinyl LTs have been found in the sputum and urine of patients with cystic fibrosis (CF) (Sampson et al., 1990; Spencer et al., 1992), a disease in which the inflammatory process contributes to progressive lung tissue damage, and their concentrations increase during disease exacerbations together with oxidative stress (Reid et al., 2007). Few studies have been conducted to test the hypothesis that LTRAs have the potential to ameliorate CF lung disease. A pilot study indicated that zafirlukast may benefit adult patients with CF (Conway et al., 2003), whereas montelukast treatment significantly decreased serum (Schmitt-Grohé et al., 2002) and sputum levels of eosinophil cationic protein, IL-8, myeloperoxidase, and increased serum and sputum levels of IL-10 in children (Stelmach et al., 2005). These observations suggest that LTRAs may have measurable anti-inflammatory properties and potential to ameliorate CF lung disease, particularly with long-term use (Schmitt-Grohé et al., 2007). Chronic inflammation also plays a crucial role also in COPD. However, pulmonary inflammation in COPD is, to some extent, different from that in asthma, because other inflammatory cells (i.e., neutrophils, macrophages, and $CD8^+$ T lymphocytes) are implicated (Gan et al., 2004). In addition, the profile of exhaled eicosanoids may be different from that previ-

ously reported in asthma: exhaled PGE_2 is selectively increased in COPD, whereas LTE_4 is increased in asthma (Montuschi et al., 2003), but not in COPD (Gaki et al., 2007). There are only a few studies of the clinical effects of LTRAs in COPD. For example, lung function improvement has been observed with zafirlukast in smokers with COPD (Cazzola et al., 2000; Nannini and Flores, 2003) Furthermore, a retrospective study of patients with moderate to severe COPD, reported that montelukast use improved patient's functional scores (shortness of breath, sputum production, wheezing, and nocturnal symptoms), use of drugs (oral and inhaled corticosteroids, inhaled bronchodilators, and supplemental oxygen), number of visits to the emergency department as well as the number and duration of hospitalizations for acute exacerbations (Rubinstein et al., 2004), and QL (Celik et al., 2005). However, further clinical studies are required to judge the real impact of LTRAs in COPD therapy or at least in a subset of patients with COPD (Usery et al., 2008). Given the significant neutrophilic inflammation in COPD, it is likely that LTB_4 has a role in the disease (see also section II.F), and thus BLT antagonists and/or 5-LO/FLAP inhibitors may have greater potential as additional therapy in COPD.

Cysteinyl LTs have been implicated in different liver diseases, such as cholestasis, hepatic inflammation, portal hypertension, and hepatorenal syndrome (Keppler et al., 1988; Farzaneh-Far and Moore, 2003), and their excretion is enhanced in patients with liver cirrhosis and hepatorenal syndrome (Huber et al., 1989). Furthermore, cysteinyl LTs are generated in the liver during the reperfusion period and may contribute to the development of hepatic edema and exert cytotoxicity (Takamatsu et al., 2004). Although inhibition of FLAP abrogated experimental liver injury (Titos et al., 2005) and decreased hepatic inflammation and fibrosis in mice (Horrillo et al., 2007), montelukast was also found to be effective in prevention of liver and intestine injury by reducing apoptosis and oxidative stress in a hepatic ischemia-reperfusion injury model (Daglar et al., 2009) and to improve hepatic fibrosis in cholestatic rats (El-Swefy and Hassanen, 2009).

Finally, the presence of receptors that respond to LTD_4 in human detrusor myocytes (Bouchelouche et al., 2001a) and evidence for increased urinary LTE_4 in patients with interstitial cystitis and detrusor mastocytosis (Bouchelouche et al., 2001b) may suggest a role for cysteinyl LTs as proinflammatory mediators in this disease. Montelukast treatment resulted in significant improvement in urinary frequency and pain (Bouchelouche et al., 2001c), as well in remission of an eosinophilic cystitis (Sterrett et al., 2006), suggesting a role for LTRAs in managing interstitial cystitis.

LTs are elevated in a number of cancers and some preclinical cancer models have shown efficacy of early LT synthesis inhibitors (Rioux and Castonguay, 1998; Steele et al., 1999). In addition, some reports have advanced the concept that GPCRs are mediators of cell growth by demonstrating their potential to activate MAPKs, particularly ERK1/2 (Marinissen and Gutkind, 2001). Several mitogenic pathways might link GPCRs to the nucleus, some of them requiring the capacity of GPCRs to transactivate a growth factor receptor, such as the EGFR (Daub et al., 1996). Indeed, as already discussed in section III.C.1, $CysLT_1R$ activation is able to induce MAPK phosphorylation as well as growth factor receptor transactivation, and, thus, to stimulate proliferation (Wang and Dubois, 2010b). Furthermore, consistent data linking $CysLT_1Rs$ directly to cancer and block of apoptosis are available for epithelial colon cancer cells (Ohd et al., 2003; Nielsen et al., 2005a; Parhamifar et al., 2005; Magnusson et al., 2007, 2010), whereas little information is available on $CysLT_1R$ expression in brain tumors, such as astrocytoma, ganglioglioma, and metastatic adenocarcinoma (Zhang et al., 2004), in prostate cancer (Matsuyama et al., 2007) or in breast cancer (Magnusson et al., 2011). Taken together, these findings encourage the study of pharmacological treatment of selected forms of cancer with the LTRAs already marketed for asthma.

IV. Nomenclature for Leukotriene Receptors

Based on the above-cited studies, the IUPHAR Nomenclature Committee for Leukotriene Receptors concludes that the previously established nomenclature for leukotriene receptors (Brink et al., 2003) remains pertinent. Nevertheless, the present nomenclature may present some limitations, which need to be taken into consideration.

Although 12-HHT is an endogenous ligand for BLT_2R with higher affinity than LTB_4, the classification of this receptor as the low-affinity receptor for LTB_4 can be motivated by the important amino acid identity with the high-affinity BLT_1R and the close genomic localization of the *LTB4R* and *LTB4R2* genes. However, considering that 12-HHT is produced in platelets more abundantly than LTB_4, the nomenclature of BLT_2R may be reconsidered in the future.

Second, the interaction between purinergic and leukotriene signaling represents an interesting cross-talk in which leukotrienes may activate purinergic receptors and nucleotides may signal through CysLT receptors. Although there is a phylogenetic relationship between purinergic receptors and leukotriene receptors, the exact interactions between these receptor classes remain to be established. Likewise, classifying the recently deorphanized GPR17 or the $P2Y_{12}$ receptor into the leukotriene receptor class seems to be premature at this time. Finally, although functional studies and in vivo experiments indicate that not all leukotriene-induced responses fit the current receptor classification, the molecular structure of the putative leukotriene receptor(s) is presently unknown.

In conclusion, there is no doubt that leukotriene signaling is complex and may involve several receptor classes. The majority of the known leukotriene-induced effects can be assigned to the currently identified receptor subtypes (Table 1). It is hoped that future studies will extend our current understanding of putative additional leukotriene receptors.

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Wrote or contributed to the writing of the manuscript: Bäck, Dahlén, Drazen, Evans, Serhan, Shimizu, Yokomizo, and Rovati.

References

Accomazzo MR, Rovati GE, Viganò T, Hernandez A, Bonazzi A, Bolla M, Fumagalli F, Viappiani S, Galbiati E, Ravasi S, et al. (2001) Leukotriene D4-induced activation of smooth-muscle cells from human bronchi is partly Ca^{2+}-independent. *Am J Respir Crit Care Med* **163:**266–272.

Adamek-Guzik T, Guzik TJ, Czerniawska-Mysik G, Korpanty G, Mastalerz L, Radwan J, and Szczeklik A (2002) Urinary leukotriene levels are increased during exacerbation of atopic eczema/dermatitis syndrome. Relation to clinical status. *Allergy* **57:**732–736.

Adams MD, Celniker SE, Holt RA, Evans CA, Gocayne JD, Amanatides PG, Scherer SE, Li PW, Hoskins RA, Galle RF, et al. (2000) The genome sequence of *Drosophila melanogaster*. *Science* **287:**2185–2195.

Adolfsson JL, Ohd JF, and Sjölander A (1996) Leukotriene D4-induced activation and translocation of the G-protein α_{i3}-subunit in human epithelial cells. *Biochem Biophys Res Commun* **226:**413–419.

Ahluwalia N, Lin AY, Tager AM, Pruitt IE, Anderson TJ, Kristo F, Shen D, Cruz AR, Aikawa M, Luster AD, et al. (2007) Inhibited aortic aneurysm formation in BLT1-deficient mice. *J Immunol* **179:**691–697.

Aiello RJ, Bourassa PA, Lindsey S, Weng W, Freeman A, and Showell HJ (2002) Leukotriene B4 receptor antagonism reduces monocytic foam cells in mice. *Arterioscler Thromb Vasc Biol* **22:**443–449.

Al-Shemari H, Bossé Y, Hudson TJ, Cabaluna M, Duval M, Lemire M, Vallee-Smedja S, Frenkiel S, and Desrosiers M (2008) Influence of leukotriene gene polymorphisms on chronic rhinosinusitis. *BMC Med Genet* **9:**21.

Allayee H, Hartiala J, Lee W, Mehrabian M, Irvin CG, Conti DV, and Lima JJ (2007) The effect of montelukast and low-dose theophylline on cardiovascular disease risk factors in asthmatics. *Chest* **132:**868–874.

Allen S, Dashwood M, Morrison K, and Yacoub M (1998) Differential leukotriene constrictor responses in human atherosclerotic coronary arteries. *Circulation* **97:** 2406–2413.

Allen SP, Chester AH, Piper PJ, Sampson AP, Akl ES, and Yacoub MH (1992) Effects of leukotrienes C4 and D4 on human isolated saphenous veins. *Br J Clin Pharmacol* **34:**409–414.

Alten R, Gromnica-Ihle E, Pohl C, Emmerich J, Steffgen J, Roscher R, Sigmund R, Schmolke B, and Steinmann G (2004) Inhibition of leukotriene B4-induced CD11B/CD18 (Mac-1) expression by BIIL 284, a new long acting LTB4 receptor antagonist, in patients with rheumatoid arthritis. *Ann Rheum Dis* **63:**170–176.

Amrani Y, Moore PE, Hoffman R, Shore SA, and Panettieri RA Jr (2001) Interferon-γ modulates cysteinyl leukotriene receptor-1 expression and function in human airway myocytes. *Am J Respir Crit Care Med* **164:**2098–2101.

Antczak A, Montuschi P, Kharitonov S, Gorski P, and Barnes PJ (2002) Increased exhaled cysteinyl-leukotrienes and 8-isoprostane in aspirin-induced asthma. *Am J Respir Crit Care Med* **166:**301–306.

Arango P, Borish L, Frierson HF Jr, and Kountakis SE (2002) Cysteinyl leukotrienes in chronic hyperplastic rhinosinusitis. *Otolaryngol Head Neck Surg* **127:**512–515.

Arita M, Ohira T, Sun YP, Elangovan S, Chiang N, and Serhan CN (2007) Resolvin E1 selectively interacts with leukotriene B4 receptor BLT1 and ChemR23 to regulate inflammation. *J Immunol* **178:**3912–3917.

Arm JP (2004) Leukotriene generation and clinical implications. *Allergy Asthma Proc* **25:**37–42.

Arm JP, O'Hickey SP, Spur BW, and Lee TH (1989) Airway responsiveness to histamine and leukotriene E4 in subjects with aspirin-induced asthma. *Am Rev Respir Dis* **140:**148–153.

Arriba-Mendez S, Sanz C, Isidoro-Garcia M, Davild I, Laffond E, Horeno E, Avila C, and Lorente F (2006) 927T>C polymorphism of the cysteinyl-leukotriene type-1 receptor (CYSLTR1) gene in children with asthma and atopic dermatitis. *Pediatr Allergy Immunol* **17:**323–328.

Asano K, Shiomi T, Hasegawa N, Nakamura H, Kudo H, Matsuzaki T, Hakuno H, Fukunaga K, Suzuki Y, Kanazawa M, et al. (2002) Leukotriene C4 synthase gene A(−444)C polymorphism and clinical response to a CYS-LT(1) antagonist, pranlukast, in Japanese patients with moderate asthma. *Pharmacogenetics* **12:**565–570.

Asero R (2000) Leukotriene receptor antagonists may prevent NSAID-induced exacerbations in patients with chronic urticaria. *Ann Allergy Asthma Immunol* **85:** 156–157.

Ashida Y, Nomura M, Kuriki H, and Maki Y (1987) The effect of inhaled leukotriene D4, histamine, or antigen on central and peripheral airways of guinea pigs: analysis of bronchograms with an interactive image analysis system. *Eur J Pharmacol* **141:**299–304.

Austen KF (2005) The mast cell and the cysteinyl leukotrienes. *Novartis Found Symp* **271:**166–175.

Austen KF (2007) Additional functions for the cysteinyl leukotrienes recognized through studies of inflammatory processes in null strains. *Prostaglandins Other Lipid Mediat* **83:**182–187.

Austen KF, Maekawa A, Kanaoka Y, and Boyce JA (2009) The leukotriene E_4 puzzle: finding the missing pieces and revealing the pathobiologic implications. *J Allergy Clin Immunol* **124:**406–414.

Bäck M (2002) Functional characteristics of cysteinyl-leukotriene receptor subtypes. *Life Sci* **71:**611–622.

Bäck M (2008a) Cysteinyl-leukotrienes in cerebrovascular disease: angels and demons? *Arterioscler Thromb Vasc Biol* **28:**805–806.

Bäck M (2008b) Inflammatory signaling through leukotriene receptors in atherosclerosis. *Curr Atheroscler Rep* **10:**244–251.

Bäck M (2009a) Inhibitors of the 5-lipoxygenase pathway in atherosclerosis. *Curr Pharm Des* **15:**3116–3132.

Bäck M (2009b) Leukotriene signaling in atherosclerosis and ischemia. *Cardiovasc Drugs Ther* **23:**41–48.

Bäck M, Bu DX, Bränström R, Sheikine Y, Yan ZQ, and Hansson GK (2005) Leukotriene B4 signaling through NF-κB-dependent BLT1 receptors on vascular smooth muscle cells in atherosclerosis and intimal hyperplasia. *Proc Natl Acad Sci USA* **102:**17501–17506.

Bäck M, Qiu H, Haeggström JZ, and Sakata K (2004) Leukotriene B4 is an indirectly acting vasoconstrictor in guinea pig aorta via an inducible type of BLT receptor. *Am J Physiol Heart Circ Physiol* **287:**H419–H424.

Bäck M, Sultan A, Ovchinnikova O, and Hansson GK (2007) 5-Lipoxygenase-activating protein: a potential link between innate and adaptive immunity in atherosclerosis and adipose tissue inflammation. *Circ Res* **100:**946–949.

Bafica A, Scanga CA, Serhan C, Machado F, White S, Sher A, and Aliberti J (2005) Host control of *Mycobacterium tuberculosis* is regulated by 5-lipoxygenase-dependent lipoxin production. *J Clin Invest* **115:**1601–1606.

Bagenstose SE, Levin L, and Bernstein JA (2004) The addition of zafirlukast to cetirizine improves the treatment of chronic urticaria in patients with positive autologous serum skin test results. *J Allergy Clin Immunol* **113:**134–140.

Bandeira-Melo C, Hall JC, Penrose JF, and Weller PF (2002a) Cysteinyl leukotrienes induce IL-4 release from cord blood-derived human eosinophils. *J Allergy Clin Immunol* **109:**975–979.

Bandeira-Melo C and Weller PF (2003) Eosinophils and cysteinyl leukotrienes. *Prostaglandins Leukot Essent Fatty Acids* **69:**135–143.

Bandeira-Melo C, Woods LJ, Phoofolo M, and Weller PF (2002b) Intracrine cysteinyl leukotriene receptor-mediated signaling of eosinophil vesicular transport-mediated interleukin-4 secretion. *J Exp Med* **196:**841–850.

Baneres JL, Martin A, Hullot P, Girard JP, Rossi JC, and Parello J (2003) Structure-based analysis of GPCR function: conformational adaptation of both agonist and receptor upon leukotriene B4 binding to recombinant BLT1. *J Mol Biol* **329:**801–814.

Bannenberg G and Serhan CN (2010) Specialized pro-resolving lipid mediators in the inflammatory response: an update. *Biochim Biophys Acta* **1801:**1260–1273.

Barone FC, Schmidt DB, Hillegass LM, Price WJ, White RF, Feuerstein GZ, Clark RK, Lee EV, Griswold DE, and Sarau HM (1992) Reperfusion increases neutrophils and leukotriene B4 receptor binding in rat focal ischemia. *Stroke* **23:**1337–1347; discussion 1347–1348.

Basu S, Jala VR, Mathis S, Rajagopal ST, Del Prete A, Maturu P, Trent JO, and Haribabu B (2007) Critical role for polar residues in coupling leukotriene B4 binding to signal transduction in BLT1. *J Biol Chem* **282:**10005–10017.

Baud L, Goetzl EJ, and Koo CH (1987) Stimulation by leukotriene D_4 of increases in the cytosolic concentration of calcium in dimethylsulfoxide-differentiated HL-60 cells. *J Clin Invest* **80:**983–991.

Bautz F, Denzlinger C, Kanz L, and Möhle R (2001) Chemotaxis and transendothelial migration of $CD34^+$ hematopoietic progenitor cells induced by the inflammatory mediator leukotriene D4 are mediated by the 7-transmembrane receptor CysLT1. *Blood* **97:**3433–3440.

Beller TC, Friend DS, Maekawa A, Lam BK, Austen KF, and Kanaoka Y (2004a) Cysteinyl leukotriene 1 receptor controls the severity of chronic pulmonary inflammation and fibrosis. *Proc Natl Acad Sci USA* **101:**3047–3052.

Beller TC, Maekawa A, Friend DS, Austen KF, and Kanaoka Y (2004b) Targeted gene disruption reveals the role of the cysteinyl leukotriene 2 receptor in increased vascular permeability and in bleomycin-induced pulmonary fibrosis in mice. *J Biol Chem* **279:**46129–46134.

Benned-Jensen T and Rosenkilde MM (2010) Distinct expression and ligand-binding profiles of two constitutively active GPR17 splice variants. *Br J Pharmacol* **159:** 1092–1105.

Bengtsson AM, Massoumi R, and Sjölander A (2008) Leukotriene D_4 induces AP-1 but not NFκB signaling in intestinal epithelial cells. *Prostaglandins Other Lipid Mediat* **85:**100–106.

Bevan S, Dichgans M, Wiechmann HE, Gschwendtner A, Meitinger T, and Markus HS (2008) Genetic variation in members of the leukotriene biosynthesis pathway confer an increased risk of ischemic stroke: a replication study in two independent populations. *Stroke* **39:**1109–1114.

Biber N, Toklu HZ, Solakoglu S, Gultomruk M, Hakan T, Berkman Z, and Dulger FG (2009) Cysteinyl-leukotriene receptor antagonist montelukast decreases blood-brain barrier permeability but does not prevent oedema formation in traumatic brain injury. *Brain Inj* **23:**577–584.

Birke FW, Meade CJ, Anderskewitz R, Speck GA, and Jennewein HM (2001) In vitro and in vivo pharmacological characterization of BIIL 284, a novel and potent leukotriene B_4 receptor antagonist. *J Pharmacol Exp Ther* **297:**458–466.

Bisgaard H, Skoner D, Boza ML, Tozzi CA, Newcomb K, Reiss TF, Knorr B, and Noonan G (2009) Safety and tolerability of montelukast in placebo-controlled pediatric studies and their open-label extensions. *Pediatr Pulmonol* **44:**568–579.

Bizzintino JA, Khoo SK, Zhang G, Martin AC, Rueter K, Geelhoed GC, Goldblatt J, Laing IA, Le Souëf PN, and Hayden CM (2009) Leukotriene pathway polymorphisms are associated with altered cysteinyl leukotriene production in children with acute asthma. *Prostaglandins Leukot Essent Fatty Acids* **81:**9–15.
Blaiss MS (2005) Rhinitis-asthma connection: epidemiologic and pathophysiologic basis. *Allergy Asthma Proc* **26:**35–40.
Bläsius R, Weber RG, Lichter P, and Ogilvie A (1998) A novel orphan G protein-coupled receptor primarily expressed in the brain is localized on human chromosomal band 2q21. *J Neurochem* **70:**1357–1365.
Boehmler AM, Drost A, Jaggy L, Seitz G, Wiesner T, Denzlinger C, Kanz L, and Möhle R (2009) The CysLT1 ligand leukotriene D4 supports $\alpha4\beta1$- and $\alpha5\beta1$-mediated adhesion and proliferation of $CD34^+$ hematopoietic progenitor cells. *J Immunol* **182:**6789–6798.
Boivin B, Vaniotis G, Allen BG, and Hébert TE (2008) G protein-coupled receptors in and on the cell nucleus: a new signaling paradigm? *J Recept Signal Transduct Res* **28:**15–28.
Borderias L, Mincewicz G, Paggiaro PL, Guilera M, Sazonov Kocevar V, Taylor SD, and Badia X (2007) Asthma control in patients with asthma and allergic rhinitis receiving add-on montelukast therapy for 12 months: a retrospective observational study. *Curr Med Res Opin* **23:**721–730.
Bortuzzo C, Hanif R, Kashfi K, Staiano-Coico L, Shiff SJ, and Rigas B (1996) The effect of leukotrienes B and selected HETEs on the proliferation of colon cancer cells. *Biochim Biophys Acta* **1300:**240–246.
Bossé Y, Thompson C, McMahon S, Dubois CM, Stankova J, and Rola-Pleszczynski M (2008) Leukotriene D4-induced, epithelial cell-derived transforming growth factor beta1 in human bronchial smooth muscle cell proliferation. *Clin Exp Allergy* **38:**113–121.
Bouchelouche K, Horn T, Nordling J, Larsen S, and Hald T (2001a) The action of cysteinyl-leukotrienes on intracellular calcium mobilization in human detrusor myocytes. *BJU Int* **87:**690–696.
Bouchelouche K, Kristensen B, Nordling J, Horn T, and Bouchelouche P (2001b) Increased urinary leukotriene E4 and eosinophil protein X excretion in patients with interstitial cystitis. *J Urol* **166:**2121–2125.
Bouchelouche K, Nordling J, Hald T, and Bouchelouche P (2001c) The cysteinyl leukotriene D4 receptor antagonist montelukast for the treatment of interstitial cystitis. *J Urol* **166:**1734–1737.
Boulay ME, Duchesneau E, Jacques E, Chakir J, and Boulet LP (2010) $CysLT_1$-R expression following allergen provocation in asthma and allergic rhinitis. *Prostaglandins Leukot Essent Fatty Acids* **83:**15–22.
Bousquet J, Demoly P, and Humbert M (2009) Montelukast in guidelines and beyond. *Adv Ther* **26:**575–587.
Braccioni F, Dorman SC, O'byrne PM, Inman MD, Denburg JA, Parameswaran K, Baatjes AJ, Foley R, and Gauvreau GM (2002) The effect of cysteinyl leukotrienes on growth of eosinophil progenitors from peripheral blood and bone marrow of atopic subjects. *J Allergy Clin Immunol* **110:**96–101.
Brach MA, de Vos S, Arnold C, Gruss HJ, Mertelsmann R, and Herrmann F (1992) Leukotriene B4 transcriptionally activates interleukin-6 expression involving NK-χB and NF-IL6. *Eur J Immunol* **22:**2705–2711.
Brezinski DA, Nesto RW, and Serhan CN (1992) Angioplasty triggers intracoronary leukotrienes and lipoxin A4. Impact of aspirin therapy. *Circulation* **86:**56–63.
Brink C, Dahlén SE, Drazen J, Evans JF, Hay DW, Nicosia S, Serhan CN, Shimizu T, and Yokomizo T (2003) International Union of Pharmacology. XXXVII: Nomenclature for leukotriene and lipoxin receptors. *Pharmacol Rev* **55:**195–227.
Brochu-Bourque A, Véronneau S, Rola-Pleszczynski M, and Stankova J (2011) Differential signalling defects associated with the M201V polymorphism in the cysteinyl leukotriene type 2 receptor. *J Pharmacol Exp Ther* **336:**431–439.
Broshtilova V and Gantcheva M (2010) Therapeutic Hotline: cysteinyl leukotriene receptor antagonist montelukast in the treatment of atopic dermatitis. *Dermatol Ther* **23:**90–93.
Canetti C, Hu B, Curtis JL, and Peters-Golden M (2003) Syk activation is a leukotriene B4-regulated event involved in macrophage phagocytosis of IgG-coated targets but not apoptotic cells. *Blood* **102:**1877–1883.
Capra V (2004) Molecular and functional aspects of human cysteinyl leukotriene receptors. *Pharmacol Res* **50:**1–11.
Capra V, Accomazzo MR, Gardoni F, Barbieri S, and Rovati GE (2010) A role for inflammatory mediators in heterologous desensitization of CysLT1 receptor in human monocytes. *J Lipid Res* **51:**1075–1084.
Capra V, Accomazzo MR, Ravasi S, Parenti M, Macchia M, Nicosia S, and Rovati GE (2003) Involvement of prenylated proteins in calcium signaling induced by LTD4 in differentiated U937 cells. *Prostaglandins Other Lipid Mediat* **71:**235–251.
Capra V, Ambrosio M, Riccioni G, and Rovati GE (2006) Cysteinyl-leukotriene receptor antagonists: present situation and future opportunities. *Curr Med Chem* **13:**3213–3226.
Capra V, Ravasi S, Accomazzo MR, Citro S, Grimoldi M, Abbracchio MP, and Rovati GE (2005) CysLT1 receptor is a target for extracellular nucleotide-induced heterologous desensitization: a possible feedback mechanism in inflammation. *J Cell Sci* **118:**5625–5636.
Capra V, Ravasi S, Accomazzo MR, Parenti M, and Rovati GE (2004) CysLT1 signal transduction in differentiated U937 cells involves the activation of the small GTP-binding protein Ras. *Biochem Pharmacol* **67:**1569–1577.
Capra V, Thompson MD, Sala A, Cole DE, Folco G, and Rovati GE (2007) Cysteinyl-leukotrienes and their receptors in asthma and other inflammatory diseases: critical update and emerging trends. *Med Res Rev* **27:**469–527.
Carnini C, Accomazzo M, Borroni E, Vitellaro-Zuccarello L, Durand T, Folco G, Rovati G, Capra V, and Sala A (2011) Synthesis of cysteinyl leukotrienes in human endothelial cells: subcellular localization and autocrine signaling through the CysLT2 receptor. *FASEB J*, in press.
Cazzola M, Boveri B, Carlucci P, Santus P, DiMarco F, Centanni S, and Allegra L (2000) Lung function improvement in smokers suffering from COPD with zafirlukast, a $CysLT_1$-receptor antagonist. *Pulm Pharmacol Ther* **13:**301–305.
Celik P, Sakar A, Havlucu Y, Yuksel H, Turkdogan P, and Yorgancioglu A (2005) Short-term effects of montelukast in stable patients with moderate to severe COPD. *Respir Med* **99:**444–450.
Ceruti S, Viganò F, Boda E, Ferrario S, Magni G, Boccazzi M, Rosa P, Buffo A, and Abbracchio MP (2011) Expression of the new P2Y-like receptor GPR17 during oligodendrocyte precursor cell maturation regulates sensitivity to ATP-induced death. *Glia* **59:**363–378.
Ceruti S, Villa G, Genovese T, Mazzon E, Longhi R, Rosa P, Bramanti P, Cuzzocrea S, and Abbracchio MP (2009) The P2Y-like receptor GPR17 as a sensor of damage and a new potential target in spinal cord injury. *Brain* **132:**2206–2218.
Chao SS, Graham SM, Brown CL, Kline JN, and Hussain I (2006) Cysteinyl leukotriene 1 receptor expression in nasal polyps. *Ann Otol Rhinol Laryngol* **115:**394–397.
Chen H, Qin J, Wei P, Zhang J, Li Q, Fu L, Li S, Ma C, and Cong B (2009a) Effects of leukotriene B4 and prostaglandin E_2 on the differentiation of murine Foxp3+ T regulatory cells and Th17 cells. *Prostaglandins Leukot Essent Fatty Acids* **80:**195–200.
Chen Y, Wu H, Wang S, Koito H, Li J, Ye F, Hoang J, Escobar SS, Gow A, Arnett HA, et al. (2009b) The oligodendrocyte-specific G protein-coupled receptor GPR17 is a cell-intrinsic timer of myelination. *Nat Neurosci* **12:**1398–1406.
Chen Z, Gaudreau R, Le Gouill C, Rola-Pleszczynski M, and Stanková J (2004) Agonist-induced internalization of leukotriene B_4 receptor 1 requires G-protein-coupled receptor kinase 2 but not arrestins. *Mol Pharmacol* **66:**377–386.
Chiang N, Gronert K, Clish CB, O'Brien JA, Freeman MW, and Serhan CN (1999) Leukotriene B4 receptor transgenic mice reveal novel protective roles for lipoxins and aspirin-triggered lipoxins in reperfusion. *J Clin Invest* **104:**309–316.
Chibana K, Ishii Y, Asakura T, and Fukuda T (2003) Up-regulation of cysteinyl leukotriene 1 receptor by IL-13 enables human lung fibroblasts to respond to leukotriene C4 and produce eotaxin. *J Immunol* **170:**4290–4295.
Cho KJ, Seo JM, Lee MG, and Kim JH (2010a) BLT2 is upregulated in allergen-stimulated mast cells and mediates the synthesis of Th2 cytokines. *J Immunol* **185:**6329–6337.
Cho KJ, Seo JM, Shin Y, Yoo MH, Park CS, Lee SH, Chang YS, Cho SH, and Kim JH (2010b) Blockade of airway inflammation and hyperresponsiveness by inhibition of BLT2, a low-affinity leukotriene B4 receptor. *Am J Respir Cell Mol Biol* **42:**294–303.
Choi JH, Park HS, Oh HB, Lee JH, Suh YJ, Park CS, and Shin HD (2004) Leukotriene-related gene polymorphisms in ASA-intolerant asthma: an association with a haplotype of 5-lipoxygenase. *Hum Genet* **114:**337–344.
Chou RC, Kim ND, Sadik CD, Seung E, Lan Y, Byrne MH, Haribabu B, Iwakura Y, and Luster AD (2010) Lipid-cytokine-chemokine cascade drives neutrophil recruitment in a murine model of inflammatory arthritis. *Immunity* **33:**266–278.
Christie PE, Schmitz-Schumann M, Spur BW, and Lee TH (1993) Airway responsiveness to leukotriene C4 (LTC4), leukotriene E4 (LTE4) and histamine in aspirin-sensitive asthmatic subjects. *Eur Respir J* **6:**1468–1473.
Christie PE, Tagari P, Ford-Hutchinson AW, Charlesson S, Chee P, Arm JP, and Lee TH (1991) Urinary leukotriene E4 concentrations increase after aspirin challenge in aspirin-sensitive asthmatic subjects. *Am Rev Respir Dis* **143:**1025–1029.
Ciana P, Fumagalli M, Trincavelli ML, Verderio C, Rosa P, Lecca D, Ferrario S, Parravicini C, Capra V, Gelosa P, et al. (2006) The orphan receptor GPR17 identified as a new dual uracil nucleotides/cysteinyl-leukotrienes receptor. *EMBO J* **25:**4615–4627.
Ciccarelli R, D'Alimonte I, Santavenere C, D'Auro M, Ballerini P, Nargi E, Buccella S, Nicosia S, Folco G, Caciagli F, et al. (2004) Cysteinyl-leukotrienes are released from astrocytes and increase astrocyte proliferation and glial fibrillary acidic protein via cys-LT1 receptors and mitogen-activated protein kinase pathway. *Eur J Neurosci* **20:**1514–1524.
Ciebiada M, Górska-Ciebiada M, DuBuske LM, and Górski P (2006) Montelukast with desloratadine or levocetirizine for the treatment of persistent allergic rhinitis. *Ann Allergy Asthma Immunol* **97:**664–671.
Cingi C and Ozlugedik S (2010) Effects of montelukast on quality of life in patients with persistent allergic rhinitis. *Otolaryngol Head Neck Surg* **142:**654–658.
Cipollone F, Mezzetti A, Fazia ML, Cuccurullo C, Iezzi A, Ucchino S, Spigonardo F, Bucci M, Cuccurullo F, Prescott SM, et al. (2005) Association between 5-lipoxygenase expression and plaque instability in humans. *Arterioscler Thromb Vasc Biol* **25:**1665–1670.
Ciprandi G, Tosca MA, Milanese M, Schenone G, and Ricca V (2004) Antihistamines added to an antileukotriene in treating seasonal allergic rhinitis: histamine and leukotriene antagonism. *Eur Ann Allergy Clin Immunol* **36:**67–70, 72.
Cohen P, Noveral JP, Bhala A, Nunn SE, Herrick DJ, and Grunstein MM (1995) Leukotriene D4 facilitates airway smooth muscle cell proliferation via modulation of the IGF axis. *Am J Physiol* **269:**L151–L157.
Conway SP, Etherington C, Peckham DG, and Whitehead A (2003) A pilot study of zafirlukast as an anti-inflammatory agent in the treatment of adults with cystic fibrosis. *J Cyst Fibros* **2:**25–28.
Cookson W (1999) The alliance of genes and environment in asthma and allergy. *Nature* **402:**B5–B11.
Corrigan C, Mallett K, Ying S, Roberts D, Parikh A, Scadding G, and Lee T (2005) Expression of the cysteinyl leukotriene receptors $cysLT_1$ and $cysLT_2$ in aspirin-sensitive and aspirin-tolerant chronic rhinosinusitis. *J Allergy Clin Immunol* **115:**316–322.
Csoma Z, Kharitonov SA, Balint B, Bush A, Wilson NM, and Barnes PJ (2002) Increased leukotrienes in exhaled breath condensate in childhood asthma. *Am J Respir Crit Care Med* **166:**1345–1349.
Currie GP, Srivastava P, Dempsey OJ, and Lee DK (2005) Therapeutic modulation of allergic airways disease with leukotriene receptor antagonists. *QJM* **98:**171–182.
Daglar G, Karaca T, Yuksek YN, Gozalan U, Akbiyik F, Sokmensuer C, Gurel B, and Kama NA (2009) Effect of montelukast and MK-886 on hepatic ischemia-reperfusion injury in rats. *J Surg Res* **153:**31–38.
Dahlén B, Nizankowska E, Szczeklik A, Zetterström O, Bochenek G, Kumlin M, Mastalerz L, Pinis G, Swanson LJ, Boodhoo TI, et al. (1998) Benefits from adding

the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. *Am J Respir Crit Care Med* **157:**1187–1194.
Dahlén SE (2006) Treatment of asthma with antileukotrienes: first line or last resort therapy? *Eur J Pharmacol* **533:**40–56.
Dahlén SE, Hedqvist P, Hammarström S, and Samuelsson B (1980) Leukotrienes are potent constrictors of human bronchi. *Nature* **288:**484–486.
Dahlén SE, Malmström K, Nizankowska E, Dahlén B, Kuna P, Kowalski M, Lumry WR, Picado C, Stevenson DD, Bousquet J, et al. (2002) Improvement of aspirin-intolerant asthma by montelukast, a leukotriene antagonist: a randomized, double-blind, placebo-controlled trial. *Am J Respir Crit Care Med* **165:**9–14.
Dalrymple MB, Pfleger KD, and Eidne KA (2008) G protein-coupled receptor dimers: functional consequences, disease states and drug targets. *Pharmacol Ther* **118:**359–371.
Daniele S, Lecca D, Trincavelli ML, Ciampi O, Abbracchio MP, and Martini C (2010) Regulation of PC12 cell survival and differentiation by the new P2Y-like receptor GPR17. *Cell Signal* **22:**697–706.
Daniels SE, Bhattacharrya S, James A, Leaves NI, Young A, Hill MR, Faux JA, Ryan GF, le Söuef PN, Lathrop GM, et al. (1996) A genome-wide search for quantitative trait loci underlying asthma. *Nature* **383:**247–250.
Datta YH, Romano M, Jacobson BC, Golan DE, Serhan CN, and Ewenstein BM (1995) Peptido-leukotrienes are potent agonists of von Willebrand factor secretion and P-selectin surface expression in human umbilical vein endothelial cells. *Circulation* **92:**3304–3311.
Daub H, Weiss FU, Wallasch C, and Ullrich A (1996) Role of transactivation of the EGF receptor in signalling by G-protein-coupled receptors. *Nature* **379:**557–560.
de Weck AL, Gamboa PM, Esparza R, and Sanz ML (2006) Hypersensitivity to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs). *Curr Pharm Des* **12:**3347–3358.
del Giudice MM, Pezzulo A, Capristo C, Alterio E, Caggiano S, de Benedictis D, and Capristo AF (2009) Leukotriene modifiers in the treatment of asthma in children. *Ther Adv Respir Dis* **3:**245–251.
Del Prete A, Shao WH, Mitola S, Santoro G, Sozzani S, and Haribabu B (2007) Regulation of dendritic cell migration and adaptive immune response by leukotriene B4 receptors: a role for LTB4 in up-regulation of CCR7 expression and function. *Blood* **109:**626–631.
Demitsu T, Katayama H, Saito-Taki T, Yaoita H, and Nakano M (1989) Phagocytosis and bactericidal action of mouse peritoneal macrophages treated with leukotriene B4. *Int J Immunopharmacol* **11:**801–808.
Deshpande DA, Pascual RM, Wang SW, Eckman DM, Riemer EC, Funk CD, and Penn RB (2007) PKC-dependent regulation of the receptor locus dominates functional consequences of cysteinyl leukotriene type 1 receptor activation. *FASEB J* **21:**2335–2342.
Devchand PR, Keller H, Peters JM, Vazquez M, Gonzalez FJ, and Wahli W (1996) The PPARα-leukotriene B4 pathway to inflammation control. *Nature* **384:**39–43.
Deykin A, Wechsler ME, Boushey HA, Chinchilli VM, Kunselman SJ, Craig TJ, DiMango E, Fahy JV, Kraft M, Leone F, et al. (2007) Combination therapy with a long-acting β-agonist and a leukotriene antagonist in moderate asthma. *Am J Respir Crit Care Med* **175:**228–234.
Di Gennaro A, Carnini C, Buccellati C, Ballerio R, Zarini S, Fumagalli F, Viappiani S, Librizzi L, Hernandez A, Murphy RC, et al. (2004) Cysteinyl-leukotrienes receptor activation in brain inflammatory reactions and cerebral edema formation: a role for transcellular biosynthesis of cysteinyl-leukotrienes. *FASEB J* **18:**842–844.
Di Gennaro A, Kenne E, Wan M, Soehnlein O, Lindbom L, and Haeggström JZ (2009) Leukotriene B4-induced changes in vascular permeability are mediated by neutrophil release of heparin-binding protein (HBP/CAP37/azurocidin). *FASEB J* **23:**1750–1757.
Di Lorenzo G, Pacor ML, Mansueto P, Esposito Pellitteri M, Lo Bianco C, Ditta V, Martinelli N, and Rini GB (2004a) Randomized placebo-controlled trial comparing desloratadine and montelukast in monotherapy and desloratadine plus montelukast in combined therapy for chronic idiopathic urticaria. *J Allergy Clin Immunol* **114:**619–625.
Di Lorenzo G, Pacor ML, Pellitteri ME, Morici G, Di Gregoli A, Lo Bianco C, Ditta V, Martinelli N, Candore G, Mansueto P, et al. (2004b) Randomized placebo-controlled trial comparing fluticasone aqueous nasal spray in mono-therapy, fluticasone plus cetirizine, fluticasone plus montelukast and cetirizine plus montelukast for seasonal allergic rhinitis. *Clin Exp Allergy* **34:**259–267.
Diamant Z, Mantzouranis E, and Bjermer L (2009) Montelukast in the treatment of asthma and beyond. *Expert Rev Clin Immunol* **5:**639–658.
Díaz-González F, Alten RH, Bensen WG, Brown JP, Sibley JT, Dougados M, Bombardieri S, Durez P, Ortiz P, de-Miquel G, et al. (2007) Clinical trial of a leucotriene B4 receptor antagonist, BIIL 284, in patients with rheumatoid arthritis. *Ann Rheum Dis* **66:**628–632.
Drazen JM (2003) Leukotrienes in asthma. *Adv Exp Med Biol* **525:**1–5.
Drazen JM, Silverman EK, and Lee TH (2000) Heterogeneity of therapeutic responses in asthma. *Br Med Bull* **56:**1054–1070.
Drazen JM, Yandava CN, Dubé L, Szczerback N, Hippensteel R, Pillari A, Israel E, Schork N, Silverman ES, Katz DA, et al. (1999) Pharmacogenetic association between ALOX5 promoter genotype and the response to anti-asthma treatment. *Nat Genet* **22:**168–170.
Dryden P, Duronio V, Martin L, Hudson AT, and Salari H (1992) Inhibition of human neutrophil responses by α-cyano-3,4-dihydroxythiocinnamamide; a protein-tyrosine kinase inhibitor. *Br J Pharmacol* **106:**656–664.
Ducharme FM, Lasserson TJ, and Cates CJ (2006) Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. *Cochrane Database Syst Rev* **4:**CD003137.
Dugas B, Paul-Eugene N, Cairns J, Gordon J, Calenda A, Mencia-Huerta JM, and Braquet P (1990) Leukotriene B4 potentiates the expression and release of Fc epsilon RII/CD23, and proliferation and differentiation of human B lymphocytes induced by IL-4. *J Immunol* **145:**3406–3411.
Dunn CJ and Goa KL (2001) Zafirlukast: an update of its pharmacology and therapeutic efficacy in asthma. *Drugs* **61:**285–315.
Duroudier NP, Sayers I, Castagna CC, Fenech AG, Halapi E, Swan C, and Hall IP (2007) Functional polymorphism and differential regulation of CYSLTR1 transcription in human airway smooth muscle and monocytes. *Cell Biochem Biophys* **47:**119–130.
Duroudier NP, Strachan DP, Blakey JD, and Hall IP (2009) Association of the cysteinyl leukotriene receptor 1 gene with atopy in the British 1958 birth cohort. *J Allergy Clin Immunol* **124:**566–572, 572.e1–572.e3.
Earashi M, Noguchi M, Kinoshita K, and Tanaka M (1995) Effects of eicosanoid synthesis inhibitors on the in vitro growth and prostaglandin E and leukotriene B secretion of a human breast cancer cell line. *Oncology* **52:**150–155.
Early SB, Barekzi E, Negri J, Hise K, Borish L, and Steinke JW (2007) Concordant modulation of cysteinyl leukotriene receptor expression by IL-4 and IFN-γ on peripheral immune cells. *Am J Respir Cell Mol Biol* **36:**715–720.
el-Hakim IE, Langdon JD, Zakrzewski JT, and Costello JF (1990) Leukotriene B4 and oral cancer. *Br J Oral Maxillofac Surg* **28:**155–159.
El-Swefy S and Hassanen SI (2009) Improvement of hepatic fibrosis by leukotriene inhibition in cholestatic rats. *Ann Hepatol* **8:**41–49.
Emerson MR and LeVine SM (2004) Experimental allergic encephalomyelitis is exacerbated in mice deficient for 12/15-lipoxygenase or 5-lipoxygenase. *Brain Res* **1021:**140–145.
Erbagci Z (2002) The leukotriene receptor antagonist montelukast in the treatment of chronic idiopathic urticaria: a single-blind, placebo-controlled, crossover clinical study. *J Allergy Clin Immunol* **110:**484–488.
Espinosa K, Bossé Y, Stankova J, and Rola-Pleszczynski M (2003) CysLT1 receptor upregulation by TGF-β and IL-13 is associated with bronchial smooth muscle cell proliferation in response to LTD4. *J Allergy Clin Immunol* **111:**1032–1040.
Evans DJ, Barnes PJ, Spaethe SM, van Alstyne EL, Mitchell MI, and O'Connor BJ (1996) Effect of a leukotriene B4 receptor antagonist, LY293111, on allergen induced responses in asthma. *Thorax* **51:**1178–1184.
Evans JF (2003) The cysteinyl leukotriene receptors. *Prostaglandins Leukot Essent Fatty Acids* **69:**117–122.
Evans JF, Ferguson AD, Mosley RT, and Hutchinson JH (2008) What's all the FLAP about?: 5-lipoxygenase-activating protein inhibitors for inflammatory diseases. *Trends Pharmacol Sci* **29:**72–78.
Faccioli LH, Nourshargh S, Moqbel R, Williams FM, Sehmi R, Kay AB, and Williams TJ (1991) The accumulation of ^{111}In-eosinophils induced by inflammatory mediators, in vivo. *Immunology* **73:**222–227.
Faith A, Fernandez MH, Caulfield J, Loke TK, Corrigan C, O'Connor B, Lee TH, and Hawrylowicz CM (2008) Role of cysteinyl leukotrienes in human allergen-specific Th2 responses induced by granulocyte macrophage-colony stimulating factor. *Allergy* **63:**168–175.
Fang SH, Wei EQ, Zhou Y, Wang ML, Zhang WP, Yu GL, Chu LS, and Chen Z (2006) Increased expression of cysteinyl leukotriene receptor-1 in the brain mediates neuronal damage and astrogliosis after focal cerebral ischemia in rats. *Neuroscience* **140:**969–979.
Fang SH, Zhou Y, Chu LS, Zhang WP, Wang ML, Yu GL, Peng F, and Wei EQ (2007) Spatio-temporal expression of cysteinyl leukotriene receptor-2 mRNA in rat brain after focal cerebral ischemia. *Neurosci Lett* **412:**78–83.
Farzaneh-Far R and Moore K (2003) Cysteinyl-leukotrienes and the liver. *Prostaglandins Other Lipid Mediat* **72:**35–50.
Figueroa DJ, Borish L, Baramki D, Philip G, Austin CP, and Evans JF (2003) Expression of cysteinyl leukotriene synthetic and signalling proteins in inflammatory cells in active seasonal allergic rhinitis. *Clin Exp Allergy* **33:**1380–1388.
Figueroa DJ, Breyer RM, Defoe SK, Kargman S, Daugherty BL, Waldburger K, Liu Q, Clements M, Zeng Z, O'Neill GP, et al. (2001) Expression of the cysteinyl leukotriene 1 receptor in normal human lung and peripheral blood leukocytes. *Am J Respir Crit Care Med* **163:**226–233.
Finsnes F, Lyberg T, Christensen G, and Skjønsberg OH (2002) Leukotriene antagonism reduces the generation of endothelin-1 and interferon-gamma and inhibits eosinophilic airway inflammation. *Respir Med* **96:**901–906.
Flamand L, Tremblay MJ, and Borgeat P (2007) Leukotriene B4 triggers the in vitro and in vivo release of potent antimicrobial agents. *J Immunol* **178:**8036–8045.
Ford-Hutchinson AW, Bray MA, Doig MV, Shipley ME, and Smith MJ (1980) Leukotriene B, a potent chemokinetic and aggregating substance released from polymorphonuclear leukocytes. *Nature* **286:**264–265.
Forman BM, Chen J, and Evans RM (1997) Hypolipidemic drugs, polyunsaturated fatty acids, and eicosanoids are ligands for peroxisome proliferator-activated receptors α and δ. *Proc Natl Acad Sci USA* **94:**4312–4317.
Fredman G, Van Dyke TE, and Serhan CN (2010) Resolvin E1 regulates adenosine diphosphate activation of human platelets. *Arterioscler Thromb Vasc Biol* **30:**2005–2013.
Fredriksson R, Lagerström MC, Lundin LG, and Schiöth HB (2003) The G-protein-coupled receptors in the human genome form five main families. Phylogenetic analysis, paralogon groups, and fingerprints. *Mol Pharmacol* **63:**1256–1272.
Fregonese L, Silvestri M, Sabatini F, and Rossi GA (2002) Cysteinyl leukotrienes induce human eosinophil locomotion and adhesion molecule expression via a CysLT1 receptor-mediated mechanism. *Clin Exp Allergy* **32:**745–750.
Fretland DJ, Widomski D, Tsai BS, Zemaitis JM, Levin S, Djuric SW, Shone RL, and Gaginella TS (1990) Effect of the leukotriene B4 receptor antagonist SC-41930 on colonic inflammation in rat, guinea pig and rabbit. *J Pharmacol Exp Ther* **255:**572–576.
Fretland DJ, Widomski DL, Shone RL, Levin S, and Gaginella TS (1991) Effect of the leukotriene B4 receptor antagonist, SC-41930, on experimental allergic encephalomyelitis (EAE) in the guinea pig. *Agents Actions* **34:**172–174.
Friedrich EB, Tager AM, Liu E, Pettersson A, Owman C, Munn L, Luster AD, and Gerszten RE (2003) Mechanisms of leukotriene B4-triggered monocyte adhesion. *Arterioscler Thromb Vasc Biol* **23:**1761–1767.
Frieri M, Therattil J, Wang SF, Huang CY, and Wang YC (2003) Montelukast inhibits interleukin-5 mRNA expression and cysteinyl leukotriene production in

ragweed and mite-stimulated peripheral blood mononuclear cells from patients with asthma. *Allergy Asthma Proc* **24:**359–366.
Fujii M, Tanaka H, and Abe S (2005) Interferon-γ up-regulates expression of cysteinyl leukotriene type 2 receptors on eosinophils in asthmatic patients. *Chest* **128:** 3148–3155.
Fukai H, Ogasawara Y, Migita O, Koga M, Ichikawa K, Shibasaki M, Arinami T, and Noguchi E (2004) Association between a polymorphism in cysteinyl leukotriene receptor 2 on chromosome 13q14 and atopic asthma. *Pharmacogenetics* **14:**683–690.
Fukushima C, Matsuse H, Hishikawa Y, Kondo Y, Machida I, Saeki S, Kawano T, Tomari S, Obase Y, Shimoda T, et al. (2005) Pranlukast, a leukotriene receptor antagonist, inhibits interleukin-5 production via a mechanism distinct from leukotriene receptor antagonism. *Int Arch Allergy Immunol* **136:**165–172.
Fumagalli M, Daniele S, Lecca D, Lee PR, Parravicini C, Fields RD, Rosa P, Antonucci F, Verderio C, Trincavelli ML, et al. (2011) Phenotypic changes, signaling pathway, and functional correlates of GPR17-expressing neural precursor cells during oligodendrocyte differentiation. *J Biol Chem* **286:**10593–10604.
Funk CD (2005) Leukotriene modifiers as potential therapeutics for cardiovascular disease. *Nat Rev Drug Discov* **4:**664–672.
Gaber F, Daham K, Higashi A, Higashi N, Gülich A, Delin I, James A, Skedinger M, Gyllfors P, Nord M, et al. (2008) Increased levels of cysteinyl-leukotrienes in saliva, induced sputum, urine and blood from patients with aspirin-intolerant asthma. *Thorax* **63:**1076–1082.
Gadaleta D, Fantini GA, Silane MF, and Davis JM (1994) Neutrophil leukotriene generation and pulmonary dysfunction after abdominal aortic aneurysm repair. *Surgery* **116:**847–852.
Gagnon L, Filion LG, Dubois C, and Rola-Pleszczynski M (1989) Leukotrienes and macrophage activation: augmented cytotoxic activity and enhanced interleukin 1, tumor necrosis factor and hydrogen peroxide production. *Agents Actions* **26:**141–147.
Gaki E, Papatheodorou G, Ischaki E, Grammenou V, Papa I, and Loukides S (2007) Leukotriene E_4 in urine in patients with asthma and COPD—the effect of smoking habit. *Respir Med* **101:**826–832.
Gan WQ, Man SF, Senthilselvan A, and Sin DD (2004) Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax* **59:**574–580.
Gaudreau R, Beaulieu ME, Chen Z, Le Gouill C, Lavigne P, Stanková J, and Rola-Pleszczynski M (2004) Structural determinants regulating expression of the high affinity leukotriene B4 receptor: involvement of dileucine motifs and α-helix VIII. *J Biol Chem* **279:**10338–10345.
Gaudreau R, Le Gouill C, Venne MH, Stankova J, and Rola-Pleszczynski M (2002) Threonine 308 within a putative casein kinase 2 site of the cytoplasmic tail of leukotriene B_4 receptor (BLT1) is crucial for ligand-induced, G-protein-coupled receptor-specific kinase 6-mediated desensitization. *J Biol Chem* **277:**31567–31576.
Gaudreault E and Gosselin J (2009) Leukotriene B4 potentiates CpG signaling for enhanced cytokine secretion by human leukocytes. *J Immunol* **183:**2650–2658.
Gauvreau GM, Parameswaran KN, Watson RM, and O'Byrne PM (2001) Inhaled leukotriene E_4, but not leukotriene D_4, increased airway inflammatory cells in subjects with atopic asthma. *Am J Respir Crit Care Med* **164:**1495–1500.
Gauvreau GM, Plitt JR, Baatjes A, and MacGlashan DW (2005) Expression of functional cysteinyl leukotriene receptors by human basophils. *J Allergy Clin Immunol* **116:**80–87.
Ge S, Zhou G, Cheng S, Liu D, Xu J, Xu G, and Liu X (2009) Anti-atherogenic effects of montelukast associated with reduced MCP-1 expression in a rabbit carotid balloon injury model. *Atherosclerosis* **205:**74–79.
Gimbrone MA Jr, Brock AF, and Schafer AI (1984) Leukotriene B4 stimulates polymorphonuclear leukocyte adhesion to cultured vascular endothelial cells. *J Clin Invest* **74:**1552–1555.
Gladue RP, Carroll LA, Milici AJ, Scampoli DN, Stukenbrok HA, Pettipher ER, Salter ED, Contillo L, and Showell HJ (1996) Inhibition of leukotriene B4-receptor interaction suppresses eosinophil infiltration and disease pathology in a murine model of experimental allergic encephalomyelitis. *J Exp Med* **183:**1893–1898.
Goldman DW, Enkel H, Gifford LA, Chenoweth DE, and Rosenbaum JT (1986) Lipopolysaccharide modulates receptors for leukotriene B4, C5a, and formyl-methionyl-leucyl-phenylalanine on rabbit polymorphonuclear leukocytes. *J Immunol* **137:**1971–1976.
Goldman DW, Gifford LA, Olson DM, and Goetzl EJ (1985) Transduction by leukotriene B4 receptors of increases in cytosolic calcium in human polymorphonuclear leukocytes. *J Immunol* **135:**525–530.
Goldman DW and Goetzl EJ (1984) Heterogeneity of human polymorphonuclear leukocyte receptors for leukotriene B4. Identification of a subset of high affinity receptors that transduce the chemotactic response. *J Exp Med* **159:**1027–1041.
Goodarzi K, Goodarzi M, Tager AM, Luster AD, and von Andrian UH (2003) Leukotriene B4 and BLT1 control cytotoxic effector T cell recruitment to inflamed tissues. *Nat Immunol* **4:**965–973.
Grainger J and Drake-Lee A (2006) Montelukast in allergic rhinitis: a systematic review and meta-analysis. *Clin Otolaryngol* **31:**360–367.
Grattan CE (2003) Aspirin sensitivity and urticaria. *Clin Exp Dermatol* **28:**123–127.
Grayson MH and Korenblat PE (2007) The role of antileukotriene drugs in management of rhinitis and rhinosinusitis. *Curr Allergy Asthma Rep* **7:**209–215.
Greenberger PA (2003) Therapy in the management of the rhinitis/asthma complex. *Allergy Asthma Proc* **24:**403–407.
Griffiths RJ, Pettipher ER, Koch K, Farrell CA, Breslow R, Conklyn MJ, Smith MA, Hackman BC, Wimberly DJ, and Milici AJ (1995) Leukotriene B4 plays a critical role in the progression of collagen-induced arthritis. *Proc Natl Acad Sci USA* **92:**517–521.
Gronert K, Maheshwari N, Khan N, Hassan IR, Dunn M, and Laniado Schwartzman M (2005) A role for the mouse 12/15-lipoxygenase pathway in promoting epithelial wound healing and host defense. *J Biol Chem* **280:**15267–15278.
Gronert K, Martinsson-Niskanen T, Ravasi S, Chiang N, and Serhan CN (2001) Selectivity of recombinant human leukotriene D_4, leukotriene B_4, and lipoxin A_4 receptors with aspirin-triggered 15-epi-LXA_4 and regulation of vascular and inflammatory responses. *Am J Pathol* **158:**3–9.
Grönroos E, Andersson T, Schippert A, Zheng L, and Sjölander A (1996) Leukotriene D_4-induced mobilization of intracellular Ca^{2+} in epithelial cells is critically dependent on activation of the small GTP-binding protein Rho. *Biochem J* **316:**239–245.
Grönroos E, Schippert A, Engström M, and Sjölander A (1995) The regulation of leukotriene D4-induced calcium influx in human epithelial cells involves protein tyrosine phosphorylation. *Cell Calcium* **17:**177–186.
Grönroos E, Thodeti CK, and Sjölander A (1998) Leukotriene D4 induces a rapid increase in cAMP in the human epithelial cell line, Int 407: a potential role for this signal in the regulation of calcium influx through the plasma membrane. *Cell Calcium* **24:**9–16.
Guo Y, Zhang W, Giroux C, Cai Y, Ekambaram P, Dilly AK, Hsu A, Zhou S, Maddipati KR, Liu J, et al. (2011) Identification of the orphan G protein coupled receptor GPR31 as a receptor for 12(*S*)hydroxyeicosatetraenoic acid. *J Biol Chem* doi:10.1074/jbc.M110.216564.
Gurevich VV and Gurevich EV (2008) How and why do GPCRs dimerize? *Trends Pharmacol Sci* **29:**234–240.
Gyllfors P, Bochenek G, Overholt J, Drupka D, Kumlin M, Sheller J, Nizankowska E, Isakson PC, Mejza F, Lefkowith JB, et al. (2003) Biochemical and clinical evidence that aspirin-intolerant asthmatic subjects tolerate the cyclooxygenase 2-selective analgetic drug celecoxib. *J Allergy Clin Immunol* **111:**1116–1121.
Haeggström JZ (2004) Leukotriene A4 hydrolase/aminopeptidase, the gatekeeper of chemotactic leukotriene B4 biosynthesis. *J Biol Chem* **279:**50639–50642.
Hafstrom I, Palmblad J, Malmsten CL, Rådmark O, and Samuelsson B (1981) Leukotriene B4—a stereospecific stimulator for release of lysosomal enzymes from neutrophils. *FEBS Lett* **130:**146–148.
Hahn RA, MacDonald BR, Morgan E, Potts BD, Parli CJ, Rinkema LE, Whitesitt CA, and Marshall WS (1992) Evaluation of LY203647 on cardiovascular leukotriene D4 receptors and myocardial reperfusion injury. *J Pharmacol Exp Ther* **260:**979–989.
Hallstrand TS and Henderson WR Jr (2010) An update on the role of leukotrienes in asthma. *Curr Opin Allergy Clin Immunol* **10:**60–66.
Hanaka H, Shimizu T, and Izumi T (2002) Nuclear-localization-signal-dependent and nuclear-export-signal-dependent mechanisms determine the localization of 5-lipoxygenase. *Biochem J* **361:**505–514.
Hao L, Sayers I, Cakebread JA, Barton SJ, Beghé B, Holgate ST, Sampson AP, and Holloway JW (2006) The cysteinyl-leukotriene type 1 receptor polymorphism 927T/C is associated with atopy severity but not with asthma. *Clin Exp Allergy* **36:**735–741.
Haribabu B, Verghese MW, Steeber DA, Sellars DD, Bock CB, and Snyderman R (2000) Targeted disruption of the leukotriene B_4 receptor in mice reveals its role in inflammation and platelet-activating factor-induced anaphylaxis. *J Exp Med* **192:** 433–438.
Haribabu B, Zhelev DV, Pridgen BC, Richardson RM, Ali H, and Snyderman R (1999) Chemoattractant receptors activate distinct pathways for chemotaxis and secretion. Role of G-protein usage. *J Biol Chem* **274:**37087–37092.
Hartiala KT, Langlois L, Goldstein IM, and Rosenbaum JT (1985) Endotoxin-induced selective dysfunction of rabbit polymorphonuclear leukocytes in response to endogenous chemotactic factors. *Infect Immun* **50:**527–533.
Hasegawa S, Ichiyama T, Hashimoto K, Suzuki Y, Hirano R, Fukano R, and Furukawa S (2010) Functional expression of cysteinyl leukotriene receptors on human platelets. *Platelets* **21:**253–259.
Hashidate T, Murakami N, Nakagawa M, Ichikawa M, Kurokawa M, Shimizu T, and Nakamura M (2010) AML1 enhances the expression of leukotriene B4 type-1 receptor in leukocytes. *FASEB J* **24:**3500–3510.
Hashimoto A, Endo H, Hayashi I, Murakami Y, Kitasato H, Kono S, Matsui T, Tanaka S, Nishimura A, Urabe K, et al. (2003) Differential expression of leukotriene B4 receptor subtypes (BLT1 and BLT2) in human synovial tissues and synovial fluid leukocytes of patients with rheumatoid arthritis. *J Rheumatol* **30:**1712–1718.
Hashimoto K, Ichiyama T, Hasegawa M, Hasegawa S, Matsubara T, and Furukawa S (2009) Cysteinyl leukotrienes induce monocyte chemoattractant protein-1 in human monocyte/macrophages via mitogen-activated protein kinase and nuclear factor-κB pathways. *Int Arch Allergy Immunol* **149:**275–282.
Hébert MJ, Takano T, Holthöfer H, and Brady HR (1996) Sequential morphologic events during apoptosis of human neutrophils. Modulation by lipoxygenase-derived eicosanoids. *J Immunol* **157:**3105–3115.
Heimbürger M and Palmblad JE (1996) Effects of leukotriene C4 and D4, histamine and bradykinin on cytosolic calcium concentrations and adhesiveness of endothelial cells and neutrophils. *Clin Exp Immunol* **103:**454–460.
Heise CE, O'Dowd BF, Figueroa DJ, Sawyer N, Nguyen T, Im DS, Stocco R, Bellefeuille JN, Abramovitz M, Cheng R, et al. (2000) Characterization of the human cysteinyl leukotriene 2 receptor. *J Biol Chem* **275:**30531–30536.
Heller EA, Liu E, Tager AM, Sinha S, Roberts JD, Koehn SL, Libby P, Aikawa ER, Chen JQ, Huang P, et al. (2005) Inhibition of atherogenesis in BLT1-deficient mice reveals a role for LTB4 and BLT1 in smooth muscle cell recruitment. *Circulation* **112:**578–586.
Henderson WR Jr, Tang LO, Chu SJ, Tsao SM, Chiang GK, Jones F, Jonas M, Pae C, Wang H, and Chi EY (2002) A role for cysteinyl leukotrienes in airway remodeling in a mouse asthma model. *Am J Respir Crit Care Med* **165:**108–116.
Hennig R, Ding XZ, Tong WG, Schneider MB, Standop J, Friess H, Büchler MW, Pour PM, and Adrian TE (2002) 5-Lipoxygenase and leukotriene B_4 receptor are expressed in human pancreatic cancers but not in pancreatic ducts in normal tissue. *Am J Pathol* **161:**421–428.
Hennig R, Ding XZ, Tong WG, Witt RC, Jovanovic BD, and Adrian TE (2004) Effect of LY293111 in combination with gemcitabine in colonic cancer. *Cancer Lett* **210:**41–46.
Hennig R, Ventura J, Segersvard R, Ward E, Ding XZ, Rao SM, Jovanovic BD, Iwamura T, Talamonti MS, Bell RH Jr, et al. (2005) LY293111 improves efficacy

of gemcitabine therapy on pancreatic cancer in a fluorescent orthotopic model in athymic mice. *Neoplasia* **7:**417–425.
Higashi N, Taniguchi M, Mita H, Kawagishi Y, Ishii T, Higashi A, Osame M, and Akiyama K (2004) Clinical features of asthmatic patients with increased urinary leukotriene E4 excretion (hyperleukotrienuria): involvement of chronic hyperplastic rhinosinusitis with nasal polyposis. *J Allergy Clin Immunol* **113:**277–283.
Hikiji H, Ishii S, Yokomizo T, Takato T, and Shimizu T (2009) A distinctive role of the leukotriene B4 receptor BLT1 in osteoclastic activity during bone loss. *Proc Natl Acad Sci USA* **106:**21294–21299.
Hlawaty H, Jacob MP, Louedec L, Letourneur D, Brink C, Michel JB, Feldman L, and Bäck M (2009) Leukotriene receptor antagonism and the prevention of extracellular matrix degradation during atherosclerosis and in-stent stenosis. *Arterioscler Thromb Vasc Biol* **29:**518–524.
Ho CY and Tan CT (2007) Comparison of antileukotrienes and antihistamines in the treatment of allergic rhinitis. *Am J Rhinol* **21:**439–443.
Hock CE, Beck LD, and Papa LA (1992) Peptide leukotriene receptor antagonism in myocardial ischaemia and reperfusion. *Cardiovasc Res* **26:**1206–1211.
Holgate ST, Peters-Golden M, Panettieri RA, and Henderson WR Jr (2003) Roles of cysteinyl leukotrienes in airway inflammation, smooth muscle function, and remodeling. *J Allergy Clin Immunol* **111:**S18–S36.
Hong X, Zhou H, Tsai HJ, Wang X, Liu X, Wang B, Xu X, and Xu X (2009) Cysteinyl leukotriene receptor 1 gene variation and risk of asthma. *Eur Respir J* **33:**42–48.
Hoover RL, Karnovsky MJ, Austen KF, Corey EJ, and Lewis RA (1984) Leukotriene B4 action on endothelium mediates augmented neutrophil/endothelial adhesion. *Proc Natl Acad Sci USA* **81:**2191–2193.
Horrillo R, Planagumà A, González-Périz A, Ferré N, Titos E, Miquel R, López-Parra M, Masferrer JL, Arroyo V, and Clària J (2007) Comparative protection against liver inflammation and fibrosis by a selective cyclooxygenase-2 inhibitor and a nonredox-type 5-lipoxygenase inhibitor. *J Pharmacol Exp Ther* **323:**778–786.
Hoshino M, Izumi T, and Shimizu T (1998) Leukotriene D4 activates mitogen-activated protein kinase through a protein kinase Cα-Raf-1-dependent pathway in human monocytic leukemia THP-1 cells. *J Biol Chem* **273:**4878–4882.
Houard X, Ollivier V, Louedec L, Michel JB, and Bäck M (2009) Differential inflammatory activity across human abdominal aortic aneurysms reveals neutrophil-derived leukotriene B4 as a major chemotactic factor released from the intraluminal thrombus. *FASEB J* **23:**1376–1383.
Huang L, Zhao A, Wong F, Ayala JM, Struthers M, Ujjainwalla F, Wright SD, Springer MS, Evans J, and Cui J (2004) Leukotriene B4 strongly increases monocyte chemoattractant protein-1 in human monocytes. *Arterioscler Thromb Vasc Biol* **24:**1783–1788.
Huang WW, Garcia-Zepeda EA, Sauty A, Oettgen HC, Rothenberg ME, and Luster AD (1998) Molecular and biological characterization of the murine leukotriene B4 receptor expressed on eosinophils. *J Exp Med* **188:**1063–1074.
Huang XJ, Zhang WP, Li CT, Shi WZ, Fang SH, Lu YB, Chen Z, and Wei EQ (2008) Activation of CysLT receptors induces astrocyte proliferation and death after oxygen-glucose deprivation. *Glia* **56:**27–37.
Huber M, Kästner S, Schölmerich J, Gerok W, and Keppler D (1989) Analysis of cysteinyl leukotrienes in human urine: enhanced excretion in patients with liver cirrhosis and hepatorenal syndrome. *Eur J Clin Invest* **19:**53–60.
Hui Y, Cheng Y, Smalera I, Jian W, Goldhahn L, Fitzgerald GA, and Funk CD (2004) Directed vascular expression of human cysteinyl leukotriene 2 receptor modulates endothelial permeability and systemic blood pressure. *Circulation* **110:**3360–3366.
Hui Y, Yang G, Galczenski H, Figueroa DJ, Austin CP, Copeland NG, Gilbert DJ, Jenkins NA, and Funk CD (2001) The murine cysteinyl leukotriene 2 (CysLT2) receptor. cDNA and genomic cloning, alternative splicing, and in vitro characterization. *J Biol Chem* **276:**47489–47495.
Hung CH, Li CY, Hua YM, Chen CJ, Yang KD, and Jong YJ (2006) Effects of leukotriene receptor antagonists on monocyte chemotaxis, p38 and cytoplasmic calcium. *Pediatr Allergy Immunol* **17:**250–258.
Hwang SW, Cho H, Kwak J, Lee SY, Kang CJ, Jung J, Cho S, Min KH, Suh YG, Kim D, et al. (2000) Direct activation of capsaicin receptors by products of lipoxygenases: endogenous capsaicin-like substances. *Proc Natl Acad Sci USA* **97:**6155–6160.
Ichiyama T, Hasegawa M, Hashimoto K, Matsushige T, Hirano R, and Furukawa S (2009) Cysteinyl leukotrienes induce macrophage inflammatory protein-1 in human monocytes/macrophages. *Int Arch Allergy Immunol* **148:**147–153.
Ichiyama T, Hasegawa M, Ueno Y, Makata H, Matsubara T, and Furukawa S (2005) Cysteinyl leukotrienes induce monocyte chemoattractant protein 1 in human monocytes/macrophages. *Clin Exp Allergy* **35:**1214–1219.
Ichiyama T, Hasegawa S, Umeda M, Terai K, Matsubara T, and Furukawa S (2003) Pranlukast inhibits NF-κB activation in human monocytes/macrophages and T cells. *Clin Exp Allergy* **33:**802–807.
Ichiyama T, Kajimoto M, Hasegawa M, Hashimoto K, Matsubara T, and Furukawa S (2007) Cysteinyl leukotrienes enhance tumour necrosis factor-α-induced matrix metalloproteinase-9 in human monocytes/macrophages. *Clin Exp Allergy* **37:**608–614.
Ihaku D, Cameron L, Suzuki M, Molet S, Martin J, and Hamid Q (1999) Montelukast, a leukotriene receptor antagonist, inhibits the late airway response to antigen, airway eosinophilia, and IL-5-expressing cells in Brown Norway rats. *J Allergy Clin Immunol* **104:**1147–1154.
Ihara A, Wada K, Yoneda M, Fujisawa N, Takahashi H, and Nakajima A (2007) Blockade of leukotriene B4 signaling pathway induces apoptosis and suppresses cell proliferation in colon cancer. *J Pharmacol Sci* **103:**24–32.
Iizuka Y, Okuno T, Saeki K, Uozaki H, Okada S, Misaka T, Sato T, Toh H, Fukayama M, Takeda N, et al. (2010) Protective role of the leukotriene B4 receptor BLT2 in murine inflammatory colitis. *FASEB J* **24:**4678–4690.
Iizuka Y, Yokomizo T, Terawaki K, Komine M, Tamaki K, and Shimizu T (2005) Characterization of a mouse second leukotriene B4 receptor, mBLT2: BLT2-dependent ERK activation and cell migration of primary mouse keratinocytes. *J Biol Chem* **280:**24816–24823.
Ishinaga H, Takeuchi K, Kishioka C, Suzuki S, Basbaum C, and Majima Y (2005) Pranlukast inhibits NF-κB activation and MUC2 gene expression in cultured human epithelial cells. *Pharmacology* **73:**89–96.
Islam SA, Thomas SY, Hess C, Medoff BD, Means TK, Brander C, Lilly CM, Tager AM, and Luster AD (2006) The leukotriene B4 lipid chemoattractant receptor BLT1 defines antigen-primed T cells in humans. *Blood* **107:**444–453.
Israel E (2000) The protective effects of leukotriene modifiers in aspirin-induced asthma. *Postgrad Med* **108:**40–44.
Israel E (2005) Genetics and the variability of treatment response in asthma. *J Allergy Clin Immunol* **115:**S532–S538.
Ito S, Ito Y, Katagiri H, Suzuki T, Hoka S, Yokomizo T, Shimizu T, and Majima M (2008) Leukotriene B4/leukotriene B4 receptor pathway is involved in hepatic microcirculatory dysfunction elicited by endotoxin. *Shock* **30:**87–91.
Ito T, Toki Y, Hieda N, Okumura K, Hashimoto H, Ogawa K, and Satake T (1989) Protective effects of a thromboxane synthetase inhibitor, a thromboxane antagonist, a lipoxygenase inhibitor and a leukotriene C4, D4 antagonist on myocardial injury caused by acute myocardial infarction in the canine heart. *Jpn Circ J* **53:**1115–1121.
Jala VR, Shao WH, and Haribabu B (2005) Phosphorylation-independent β-arrestin translocation and internalization of leukotriene B4 receptors. *J Biol Chem* **280:**4880–4887.
James AJ, Penrose JF, Cazaly AM, Holgate ST, and Sampson AP (2006) Human bronchial fibroblasts express the 5-lipoxygenase pathway. *Respir Res* **7:**102.
Jarvis B and Markham A (2000) Montelukast: a review of its therapeutic potential in persistent asthma. *Drugs* **59:**891–928.
Jawien J (2002) A new insight into aspirin-induced asthma. *Eur J Clin Invest* **32:**134–138.
Jawien J, Gajda M, Wołkow P, Zurańska J, Olszanecki R, and Korbut R (2008) The effect of montelukast on atherogenesis in apoE/LDLR-double knockout mice. *J Physiol Pharmacol* **59:**633–639.
Jiang W, Hall SR, Moos MP, Cao RY, Ishii S, Ogunyankin KO, Melo LG, and Funk CD (2008) Endothelial cysteinyl leukotriene 2 receptor expression mediates myocardial ischemia-reperfusion injury. *Am J Pathol* **172:**592–602.
Jiang Y, Borrelli L, Bacskai BJ, Kanaoka Y, and Boyce JA (2009) P2Y6 receptors require an intact cysteinyl leukotriene synthetic and signaling system to induce survival and activation of mast cells. *J Immunol* **182:**1129–1137.
Jiang Y, Borrelli LA, Kanaoka Y, Bacskai BJ, and Boyce JA (2007) CysLT2 receptors interact with CysLT1 receptors and down-modulate cysteinyl leukotriene dependent mitogenic responses of mast cells. *Blood* **110:**3263–3270.
Jiang Y, Kanaoka Y, Feng C, Nocka K, Rao S, and Boyce JA (2006) Cutting edge: Interleukin 4-dependent mast cell proliferation requires autocrine/intracrine cysteinyl leukotriene-induced signaling. *J Immunol* **177:**2755–2759.
Joost P and Methner A (2002) Phylogenetic analysis of 277 human G-protein-coupled receptors as a tool for the prediction of orphan receptor ligands. *Genome Biol* **3:**RESEARCH0063.
Jupp J, Hillier K, Elliott DH, Fine DR, Bateman AC, Johnson PA, Cazaly AM, Penrose JF, and Sampson AP (2007) Colonic expression of leukotriene-pathway enzymes in inflammatory bowel diseases. *Inflamm Bowel Dis* **13:**537–546.
Kaetsu Y, Yamamoto Y, Sugihara S, Matsuura T, Igawa G, Matsubara K, Igawa O, Shigemasa C, and Hisatome I (2007) Role of cysteinyl leukotrienes in the proliferation and the migration of murine vascular smooth muscle cells in vivo and in vitro. *Cardiovasc Res* **76:**160–166.
Kamohara M, Takasaki J, Matsumoto M, Matsumoto Si, Saito T, Soga T, Matsushime H, and Furuichi K (2001) Functional characterization of cysteinyl leukotriene $CysLT_2$ receptor on human coronary artery smooth muscle cells. *Biochem Biophys Res Commun* **287:**1088–1092.
Kamohara M, Takasaki J, Matsumoto M, Saito T, Ohishi T, Ishii H, and Furuichi K (2000) Molecular cloning and characterization of another leukotriene B4 receptor. *J Biol Chem* **275:**27000–27004.
Kaneko I, Suzuki K, Matsuo K, Kumagai H, Owada Y, Noguchi N, Hishinuma T, and Ono M (2009) Cysteinyl leukotrienes enhance the degranulation of bone marrow-derived mast cells through the autocrine mechanism. *Tohoku J Exp Med* **217:**185–191.
Kato K, Yokomizo T, Izumi T, and Shimizu T (2000) Cell-specific transcriptional regulation of human leukotriene B_4 receptor gene. *J Exp Med* **192:**413–420.
Kato Y, Fujisawa T, Nishimori H, Katsumata H, Atsuta J, Iguchi K, and Kamiya H (2005) Leukotriene D4 induces production of transforming growth factor-beta1 by eosinophils. *Int Arch Allergy Immunol* **137 (Suppl 1):**17–20.
Kawano T, Matsuse H, Kondo Y, Machida I, Saeki S, Tomari S, Mitsuta K, Obase Y, Fukushima C, Shimoda T, et al. (2003) Cysteinyl leukotrienes induce nuclear factor κB activation and RANTES production in a murine model of asthma. *J Allergy Clin Immunol* **112:**369–374.
Keam SJ, Lyseng-Williamson KA, and Goa KL (2003) Pranlukast: a review of its use in the management of asthma. *Drugs* **63:**991–1019.
Kelefiotis D, Bresnahan BA, Stratidakis I, and Lianos EA (1995) Eicosanoid-induced growth and signaling events in rat glomerular mesangial cells. *Prostaglandins* **49:**269–283.
Kemp JP (2003) Recent advances in the management of asthma using leukotriene modifiers. *Am J Respir Med* **2:**139–156.
Kenakin T (1997) Differences between natural and recombinant G protein-coupled receptor systems with varying receptor/G protein stoichiometry. *Trends Pharmacol Sci* **18:**456–464.
Kenakin T (2002) Drug efficacy at G protein-coupled receptors. *Annu Rev Pharmacol Toxicol* **42:**349–379.
Keppler D, Huber M, and Baumert T (1988) Leukotrienes as mediators in diseases of the liver. *Semin Liver Dis* **8:**357–366.
Kihara Y, Yokomizo T, Kunita A, Morishita Y, Fukayama M, Ishii S, and Shimizu T (2010) The leukotriene B4 receptor, BLT1, is required for the induction of experimental autoimmune encephalomyelitis. *Biochem Biophys Res Commun* **394:**673–678.
Kim GY, Lee JW, Cho SH, Seo JM, and Kim JH (2009) Role of the low-affinity

leukotriene B4 receptor BLT2 in VEGF-induced angiogenesis. *Arterioscler Thromb Vasc Biol* **29:**915–920.
Kim HJ, Kim DK, Kim H, Koh JY, Kim KM, Noh MS, Lee S, Kim S, Park SH, Kim JJ, et al. (2008) Involvement of the BLT2 receptor in the itch-associated scratching induced by 12-(*S*)-lipoxygenase products in ICR mice. *Br J Pharmacol* **154:**1073–1078.
Kim MH, Lee YJ, Kim MO, Kim JS, and Han HJ (2010) Effect of leukotriene D4 on mouse embryonic stem cell migration and proliferation: Involvement of PI3K/Akt as well as GSK-3β/β-catenin signaling pathways. *J Cell Biochem* **111:**686–698.
Kim N and Luster AD (2007) Regulation of immune cells by eicosanoid receptors. *ScientificWorldJournal* **7:**1307–1328.
Kim ND, Chou RC, Seung E, Tager AM, and Luster AD (2006a) A unique requirement for the leukotriene B4 receptor BLT1 for neutrophil recruitment in inflammatory arthritis. *J Exp Med* **203:**829–835.
Kim SH, Oh JM, Kim YS, Palmer LJ, Suh CH, Nahm DH, and Park HS (2006b) Cysteinyl leukotriene receptor 1 promoter polymorphism is associated with aspirin-intolerant asthma in males. *Clin Exp Allergy* **36:**433–439.
Kim SH, Yang EM, Park HJ, Ye YM, Lee HY, and Park HS (2007a) Differential contribution of the CysLTR1 gene in patients with aspirin hypersensitivity. *J Clin Immunol* **27:**613–619.
Kim SH, Ye YM, Hur GY, Lee SK, Sampson AP, Lee HY, and Park HS (2007b) CysLTR1 promoter polymorphism and requirement for leukotriene receptor antagonist in aspirin-intolerant asthma patients. *Pharmacogenomics* **8:**1143–1150.
Kimura K, Noguchi E, Shibasaki M, Arinami T, Yokouchi Y, Takeda K, Yamakawa-Kobayashi K, Matsui A, and Hamaguchi H (1999) Linkage and association of atopic asthma to markers on chromosome 13 in the Japanese population. *Hum Mol Genet* **8:**1487–1490.
Kitaura J, Kinoshita T, Matsumoto M, Chung S, Kawakami Y, Leitges M, Wu D, Lowell CA, and Kawakami T (2005) IgE− and IgE+Ag-mediated mast cell migration in an autocrine/paracrine fashion. *Blood* **105:**3222–3229.
Kiwamoto T, Ishii Y, Morishima Y, Yoh K, Kikuchi N, Haraguchi N, Masuko H, Kawaguchi M, Nomura A, Sakamoto T, et al. (2011) Blockade of cysteinyl leukotriene-1 receptors suppresses airway remodelling in mice overexpressing GATA-3. *Clin Exp Allergy* **41:**116–128.
Kjeldsen L, Bjerrum OW, Askaa J, and Borregaard N (1992) Subcellular localization and release of human neutrophil gelatinase, confirming the existence of separate gelatinase-containing granules. *Biochem J* **287:**603–610.
Klotsman M, York TP, Pillai SG, Vargas-Irwin C, Sharma SS, van den Oord EJ, and Anderson WH (2007) Pharmacogenetics of the 5-lipoxygenase biosynthetic pathway and variable clinical response to montelukast. *Pharmacogenet Genomics* **17:**189–196.
Kondo K, Umemura K, Ohmura T, Hashimoto H, and Nakashima M (1998) Suppression of intimal hyperplasia by a 5-lipoxygenase inhibitor, MK-886: studies with a photochemical model of endothelial injury. *Thromb Haemost* **79:**635–639.
Kopriva F, Janostáková A, Jarmila S, Zápalka M, and Hajduch M (2006) Montelukast decreases plasma endothelin-1 and serum eosinophil cationic protein levels in paediatric atopic asthma. *Clin Drug Investig* **26:**351–356.
Krey G, Braissant O, L'Horset F, Kalkhoven E, Perroud M, Parker MG, and Wahli W (1997) Fatty acids, eicosanoids, and hypolipidemic agents identified as ligands of peroxisome proliferator-activated receptors by coactivator-dependent receptor ligand assay. *Mol Endocrinol* **11:**779–791.
Kristo F, Hardy GJ, Anderson TJ, Sinha S, Ahluwalia N, Lin AY, Passeri J, Scherrer-Crosbie M, and Gerszten RE (2010) Pharmacological inhibition of BLT1 diminishes early abdominal aneurysm formation. *Atherosclerosis* **210:**107–113.
Kroeze WK, Sheffler DJ, and Roth BL (2003) G-protein-coupled receptors at a glance. *J Cell Sci* **116:**4867–4869.
Kumasawa F, Hashimoto S, Onose A, Jibiki I, Mizumura K, Matsumoto K, Maruoka S, Gon Y, Kobayashi T, Takahashi N, et al. (2005) Apoptosis signal-regulating kinase 1 in leukotriene D_4-induced activator protein-1 activation in airway smooth muscle cells. *Eur J Pharmacol* **517:**11–16.
Kuniyeda K, Okuno T, Terawaki K, Miyano M, Yokomizo T, and Shimizu T (2007) Identification of the intracellular region of the leukotriene B_4 receptor type 1 that is specifically involved in G_i activation. *J Biol Chem* **282:**3998–4006.
Kurowski M, Kuna P, and Górski P (2004) Montelukast plus cetirizine in the prophylactic treatment of seasonal allergic rhinitis: influence on clinical symptoms and nasal allergic inflammation. *Allergy* **59:**280–288.
Kushiya M, Saito K, Kikuchi I, Kobayashi T, Hagiwara K, Kanazawa M, and Nagata M (2006) Differential effects of salbutamol and montelukast on eosinophil adhesion and superoxide anion generation. *Int Arch Allergy Immunol* **140 (Suppl 1):**17–22.
Labat C, Ortiz JL, Norel X, Gorenne I, Verley J, Abram TS, Cuthbert NJ, Tudhope SR, Norman P, and Gardiner P (1992) A second cysteinyl leukotriene receptor in human lung. *J Pharmacol Exp Ther* **263:**800–805.
Lagos JA and Marshall GD (2007) Montelukast in the management of allergic rhinitis. *Ther Clin Risk Manag* **3:**327–332.
Laitinen A, Lindqvist A, Halme M, Altraja A, and Laitinen LA (2005) Leukotriene E_4-induced persistent eosinophilia and airway obstruction are reversed by zafirlukast in patients with asthma. *J Allergy Clin Immunol* **115:**259–265.
Lamoureux J, Stankova J, and Rola-Pleszczynski M (2006) Leukotriene D_4 enhances immunoglobulin production in CD40-activated human B lymphocytes. *J Allergy Clin Immunol* **117:**924–930.
Langlois A, Ferland C, Tremblay GM, and Laviolette M (2006) Montelukast regulates eosinophil protease activity through a leukotriene-independent mechanism. *J Allergy Clin Immunol* **118:**113–119.
Langmack EL and Martin RJ (2010) Heterogeneity of response to asthma controller therapy: clinical implications. *Curr Opin Pulm Med* **16:**13–18.
Larré S, Tran N, Fan C, Hamadeh H, Champigneulles J, Azzouzi R, Cussenot O, Mangin P, and Olivier JL (2008) PGE2 and LTB4 tissue levels in benign and cancerous prostates. *Prostaglandins Other Lipid Mediat* **87:**14–19.
Lecca D, Trincavelli ML, Gelosa P, Sironi L, Ciana P, Fumagalli M, Villa G, Verderio C, Grumelli C, Guerrini U, et al. (2008) The recently identified P2Y-like receptor GPR17 is a sensor of brain damage and a new target for brain repair. *PLoS One* **3:**e3579.
Lee DK, Haggart K, Robb FM, and Lipworth BJ (2004a) Montelukast protects against nasal lysine-aspirin challenge in patients with aspirin-induced asthma. *Eur Respir J* **24:**226–230.
Lee DK, Jackson CM, Soutar PC, Fardon TC, and Lipworth BJ (2004b) Effects of single or combined histamine H1-receptor and leukotriene CysLT1-receptor antagonism on nasal adenosine monophosphate challenge in persistent allergic rhinitis. *Br J Clin Pharmacol* **57:**714–719.
Lee KS, Kim SR, Park HS, Park SJ, Min KH, Lee KY, Jin SM, and Lee YC (2007a) Cysteinyl leukotriene upregulates IL-11 expression in allergic airway disease of mice. *J Allergy Clin Immunol* **119:**141–149.
Lee SY, Kim HB, Kim JH, Kim BS, Kang MJ, Jang SO, Seo HJ, and Hong SJ (2007b) Responsiveness to montelukast is associated with bronchial hyperresponsiveness and total immunoglobulin E but not polymorphisms in the leukotriene C4 synthase and cysteinyl leukotriene receptor 1 genes in Korean children with exercise-induced asthma (EIA). *Clin Exp Allergy* **37:**1487–1493.
Lee TH, Austen KF, Corey EJ, and Drazen JM (1984) Leukotriene E_4-induced airway hyperresponsiveness of guinea pig tracheal smooth muscle to histamine and evidence for three separate sulfidopeptide leukotriene receptors. *Proc Natl Acad Sci USA* **81:**4922–4925.
Leikauf GD, Claesson HE, Doupnik CA, Hybbinette S, and Grafström RC (1990) Cysteinyl leukotrienes enhance growth of human airway epithelial cells. *Am J Physiol* **259:**L255–L261.
Leonardi S, Marchese G, Marseglia GL, and La Rosa M (2007) Montelukast in allergic diseases beyond asthma. *Allergy Asthma Proc* **28:**287–291.
Leppert D, Hauser SL, Kishiyama JL, An S, Zeng L, and Goetzl EJ (1995) Stimulation of matrix metalloproteinase-dependent migration of T cells by eicosanoids. *FASEB J* **9:**1473–1481.
Lewis RA, Drazen JM, Austen KF, Clark DA, and Corey EJ (1980) Identification of the C_6-S-conjugate of leukotriene A with cysteine as a naturally occurring slow reacting substance of anaphylaxis (SRS-A). Importance of the 11-cis-geometry for biological activity. *Biochem Biophys Res Commun* **96:**271–277.
Li AM, Abdullah VJ, Tsen CS, Au CT, Lam HS, So HK, Chan MH, Leung AW, Chan IH, Lam CW, et al. (2009) Leukotriene receptor antagonist in the treatment of childhood allergic rhinitis—a randomized placebo-controlled study. *Pediatr Pulmonol* **44:**1085–1092.
Liao T, Ke Y, Shao WH, Haribabu B, Kaplan HJ, Sun D, and Shao H (2006) Blockade of the interaction of leukotriene b4 with its receptor prevents development of autoimmune uveitis. *Invest Ophthalmol Vis Sci* **47:**1543–1549.
Lima JJ, Zhang S, Grant A, Shao L, Tantisira KG, Allayee H, Wang J, Sylvester J, Holbrook J, Wise R, et al. (2006) Influence of leukotriene pathway polymorphisms on response to montelukast in asthma. *Am J Respir Crit Care Med* **173:**379–385.
Lin Q, Ruuska SE, Shaw NS, Dong D, and Noy N (1999) Ligand selectivity of the peroxisome proliferator-activated receptor α. *Biochemistry* **38:**185–190.
Lindström P, Lerner R, Palmblad J, and Patarroyo M (1990) Rapid adhesive responses of endothelial cells and of neutrophils induced by leukotriene B4 are mediated by leucocytic adhesion protein CD18. *Scand J Immunol* **31:**737–744.
Lipworth BJ, Dempsey OJ, Aziz I, and Wilson AM (2000) Effects of adding a leukotriene antagonist or a long-acting β_2-agonist in asthmatic patients with the glycine-16β_2-adrenoceptor genotype. *Am J Med* **109:**114–121.
Liu A, Claesson HE, Mahshid Y, Klein G, and Klein E (2008) Leukotriene B_4 activates T cells that inhibit B-cell proliferation in EBV-infected cord blood-derived mononuclear cell cultures. *Blood* **111:**2693–2703.
Liu AH (2000) Allergy and asthma: classic TH2 diseases (?). *Allergy Asthma Proc* **21:**227–230.
Lötzer K, Funk CD, and Habenicht AJ (2005) The 5-lipoxygenase pathway in arterial wall biology and atherosclerosis. *Biochim Biophys Acta* **1736:**30–37.
Lötzer K, Spanbroek R, Hildner M, Urbach A, Heller R, Bretschneider E, Galczenski H, Evans JF, and Habenicht AJ (2003) Differential leukotriene receptor expression and calcium responses in endothelial cells and macrophages indicate 5-lipoxygenase-dependent circuits of inflammation and atherogenesis. *Arterioscler Thromb Vasc Biol* **23:**e32–e36.
Lundeen KA, Sun B, Karlsson L, and Fourie AM (2006) Leukotriene B_4 receptors BLT1 and BLT2: expression and function in human and murine mast cells. *J Immunol* **177:**3439–3447.
Lynch KR, O'Neill GP, Liu Q, Im DS, Sawyer N, Metters KM, Coulombe N, Abramovitz M, Figueroa DJ, Zeng Z, et al. (1999) Characterization of the human cysteinyl leukotriene $CysLT_1$ receptor. *Nature* **399:**789–793.
Maeba S, Ichiyama T, Ueno Y, Makata H, Matsubara T, and Furukawa S (2005) Effect of montelukast on nuclear factor κB activation and proinflammatory molecules. *Ann Allergy Asthma Immunol* **94:**670–674.
Maekawa A, Austen KF, and Kanaoka Y (2002) Targeted gene disruption reveals the role of cysteinyl leukotriene 1 receptor in the enhanced vascular permeability of mice undergoing acute inflammatory responses. *J Biol Chem* **277:**20820–20824.
Maekawa A, Balestrieri B, Austen KF, and Kanaoka Y (2009) GPR17 is a negative regulator of the cysteinyl leukotriene 1 receptor response to leukotriene D4. *Proc Natl Acad Sci USA* **106:**11685–11690.
Maekawa A, Kanaoka Y, Lam BK, and Austen KF (2001) Identification in mice of two isoforms of the cysteinyl leukotriene 1 receptor that result from alternative splicing. *Proc Natl Acad Sci USA* **98:**2256–2261.
Maekawa A, Kanaoka Y, Xing W, and Austen KF (2008) Functional recognition of a distinct receptor preferential for leukotriene E_4 in mice lacking the cysteinyl leukotriene 1 and 2 receptors. *Proc Natl Acad Sci USA* **105:**16695–16700.
Maekawa A, Xing W, Austen KF, and Kanaoka Y (2010) GPR17 regulates immune pulmonary inflammation induced by house dust mites. *J Immunol* **185:**1846–1854.
Magnusson C, Ehrnström R, Olsen J, and Sjölander A (2007) An increased expression of cysteinyl leukotriene 2 receptor in colorectal adenocarcinomas correlates with high differentiation. *Cancer Res* **67:**9190–9198.
Magnusson C, Liu J, Ehrnström R, Manjer J, Jirström K, Andersson T, and Sjö-

lander A (2011) Cysteinyl leukotriene receptor expression pattern affects migration of breast cancer cells and survival of breast cancer patients. *Int J Cancer* **129:**9–22.
Magnusson C, Mezhybovska M, Lörinc E, Fernebro E, Nilbert M, and Sjölander A (2010) Low expression of CysLT1R and high expression of CysLT2R mediate good prognosis in colorectal cancer. *Eur J Cancer* **46:**826–835.
Malmsten CL, Palmblad J, Udén AM, Rådmark O, Engstedt L, and Samuelsson B (1980) Leukotriene B4: a highly potent and stereospecific factor stimulating migration of polymorphonuclear leukocytes. *Acta Physiol Scand* **110:**449–451.
Mamedova L, Capra V, Accomazzo MR, Gao ZG, Ferrario S, Fumagalli M, Abbracchio MP, Rovati GE, and Jacobson KA (2005) $CysLT_1$ leukotriene receptor antagonists inhibit the effects of nucleotides acting at P2Y receptors. *Biochem Pharmacol* **71:**115–125.
Mancuso P and Peters-Golden M (2000) Modulation of alveolar macrophage phagocytosis by leukotrienes is Fc receptor-mediated and protein kinase C-dependent. *Am J Respir Cell Mol Biol* **23:**727–733.
Marinissen MJ and Gutkind JS (2001) G-protein-coupled receptors and signaling networks: emerging paradigms. *Trends Pharmacol Sci* **22:**368–376.
Marrache AM, Gobeil F, Zhu T, and Chemtob S (2005) Intracellular signaling of lipid mediators via cognate nuclear G protein-coupled receptors. *Endothelium* **12:**63–72.
Martin TR, Gerard NP, Galli SJ, and Drazen JM (1988) Pulmonary responses to bronchoconstrictor agonists in the mouse. *J Appl Physiol* **64:**2318–2323.
Martin V, Sawyer N, Stocco R, Unett D, Lerner MR, Abramovitz M, and Funk CD (2001) Molecular cloning and functional characterization of murine cysteinyl-leukotriene 1 ($CysLT_1$) receptors. *Biochem Pharmacol* **62:**1193–1200.
Massoumi R, Larsson C, and Sjölander A (2002) Leukotriene D_4 induces stress-fibre formation in intestinal epithelial cells via activation of RhoA and PKCdelta. *J Cell Sci* **115:**3509–3515.
Massoumi R, Nielsen CK, Azemovic D, and Sjölander A (2003) Leukotriene D_4-induced adhesion of Caco-2 cells is mediated by prostaglandin E_2 and upregulation of $\alpha 2\beta 1$-integrin. *Exp Cell Res* **289:**342–351.
Massoumi R and Sjölander A (1998) The inflammatory mediator leukotriene D4 triggers a rapid reorganisation of the actin cytoskeleton in human intestinal epithelial cells. *Eur J Cell Biol* **76:**185–191.
Massoumi R and Sjölander A (2001) Leukotriene D_4 affects localisation of vinculin in intestinal epithelial cells via distinct tyrosine kinase and protein kinase C controlled events. *J Cell Sci* **114:**1925–1934.
Mastalerz L, Gawlewicz-Mroczka A, Nizankowska E, Cmiel A, and Szczeklik A (2002a) Protection against exercise-induced bronchoconstriction by montelukast in aspirin-sensitive and aspirin-tolerant patients with asthma. *Clin Exp Allergy* **32:**1360–1365.
Mastalerz L, Nizankowska E, Sanak M, Mejza F, Pierzchalska M, Bazan-Socha S, Bestynska-Krypel A, Cmiel A, and Szczeklik A (2002b) Clinical and genetic features underlying the response of patients with bronchial asthma to treatment with a leukotriene receptor antagonist. *Eur J Clin Invest* **32:**949–955.
Masuda K, Yokomizo T, Izumi T, and Shimizu T (1999) cDNA cloning and characterization of guinea-pig leukotriene B4 receptor. *Biochem J* **342:**79–85.
Mathis SP, Jala VR, Lee DM, and Haribabu B (2010) Nonredundant roles for leukotriene B_4 receptors BLT1 and BLT2 in inflammatory arthritis. *J Immunol* **185:**3049–3056.
Matsuyama M, Hayama T, Funao K, Kawahito Y, Sano H, Takemoto Y, Nakatani T, and Yoshimura R (2007) Overexpression of cysteinyl LT1 receptor in prostate cancer and CysLT1R antagonist inhibits prostate cancer cell growth through apoptosis. *Oncol Rep* **18:**99–104.
Mattern MR, Mong S, Mong SM, Bartus JO, Sarau HM, Clark MA, Foley JJ, and Crooke ST (1990) Transient activation of topoisomerase I in leukotriene D4 signal transduction in human cells. *Biochem J* **265:**101–107.
McHugh D, McMaster RS, Pertwee RG, Roy S, Mahadevan A, Razdan RK, and Ross RA (2006) Novel compounds that interact with both leukotriene B_4 receptors and vanilloid TRPV1 receptors. *J Pharmacol Exp Ther* **316:**955–965.
McIntyre TM, Zimmerman GA, and Prescott SM (1986) Leukotrienes C_4 and D_4 stimulate human endothelial cells to synthesize platelet-activating factor and bind neutrophils. *Proc Natl Acad Sci USA* **83:**2204–2208.
McMahon B, Mitchell D, Shattock R, Martin F, Brady HR, and Godson C (2002) Lipoxin, leukotriene, and PDGF receptors cross-talk to regulate mesangial cell proliferation. *FASEB J* **16:**1817–1819.
McMahon B, Stenson C, McPhillips F, Fanning A, Brady HR, and Godson C (2000) Lipoxin A_4 antagonizes the mitogenic effects of leukotriene D_4 in human renal mesangial cells. Differential activation of MAP kinases through distinct receptors. *J Biol Chem* **275:**27566–27575.
Mechiche H, Candenas L, Pinto FM, Nazeyrollas P, Clément C, and Devillier P (2004) Characterization of cysteinyl leukotriene receptors on human saphenous veins: antagonist activity of montelukast and its metabolites. *J Cardiovasc Pharmacol* **43:**113–120.
Medoff BD, Seung E, Wain JC, Means TK, Campanella GS, Islam SA, Thomas SY, Ginns LC, Grabie N, Lichtman AH, et al. (2005) BLT1-mediated T cell trafficking is critical for rejection and obliterative bronchiolitis after lung transplantation. *J Exp Med* **202:**97–110.
Meliton AY, Munoz NM, and Leff AR (2007) Blockade of avidity and focal clustering of β_2-integrin by cysteinyl leukotriene antagonism attenuates eosinophil adhesion. *J Allergy Clin Immunol* **120:**1316–1323.
Mellor EA, Austen KF, and Boyce JA (2002) Cysteinyl leukotrienes and uridine diphosphate induce cytokine generation by human mast cells through an interleukin 4-regulated pathway that is inhibited by leukotriene receptor antagonists. *J Exp Med* **195:**583–592.
Mellor EA, Frank N, Soler D, Hodge MR, Lora JM, Austen KF, and Boyce JA (2003) Expression of the type 2 receptor for cysteinyl leukotrienes (CysLT2R) by human mast cells: functional distinction from CysLT1R. *Proc Natl Acad Sci USA* **100:**11589–11593.
Mellor EA, Maekawa A, Austen KF, and Boyce JA (2001) Cysteinyl leukotriene receptor 1 is also a pyrimidinergic receptor and is expressed by human mast cells. *Proc Natl Acad Sci USA* **98:**7964–7969.
Meltzer EO, Malmstrom K, Lu S, Prenner BM, Wei LX, Weinstein SF, Wolfe JD, and Reiss TF (2000) Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo-controlled clinical trial. *J Allergy Clin Immunol* **105:**917–922.
Mesnier D and Banères JL (2004) Cooperative conformational changes in a G-protein-coupled receptor dimer, the leukotriene B_4 receptor BLT1. *J Biol Chem* **279:**49664–49670.
Mezhybovska M, Wikström K, Ohd JF, and Sjölander A (2006) The inflammatory mediator leukotriene D_4 induces β-catenin signaling and its association with antiapoptotic Bcl-2 in intestinal epithelial cells. *J Biol Chem* **281:**6776–6784.
Michalik L, Auwerx J, Berger JP, Chatterjee VK, Glass CK, Gonzalez FJ, Grimaldi PA, Kadowaki T, Lazar MA, O'Rahilly S, et al. (2006) International Union of Pharmacology. LXI. Peroxisome proliferator-activated receptors. *Pharmacol Rev* **58:**726–741.
Micheletto C, Tognella S, Visconti M, Pomari C, Trevisan F, and Dal Negro RW (2004) Montelukast 10 mg improves nasal function and nasal response to aspirin in ASA-sensitive asthmatics: a controlled study vs placebo. *Allergy* **59:**289–294.
Micheletto C, Visconti M, Tognella S, Facchini FM, and Dal Negro RW (2006) Aspirin induced asthma (AIA) with nasal polyps has the highest basal LTE4 excretion: a study vs AIA without polyps, mild topic asthma, and normal controls. *Eur Ann Allergy Clin Immunol* **38:**20–23.
Milanese M, Riccio AM, Gamalero C, De Giovanni B, Brichetto L, Baroffio M, Crimi E, Brusasco V, and Canonica GW (2005) A model of allergen-driven human airway contraction: β_2 pathway dysfunction without cytokine involvement. *Ann Allergy Asthma Immunol* **94:**273–278.
Milligan G (2009) G protein-coupled receptor hetero-dimerization: contribution to pharmacology and function. *Br J Pharmacol* **158:**5–14.
Minciullo PL, Saija A, Bonanno D, Ferlazzo E, and Gangemi S (2004) Montelukast-induced generalized urticaria. *Ann Pharmacother* **38:**999–1001.
Mirshafiey A and Jadidi-Niaragh F (2010) Immunopharmacological role of the leukotriene receptor antagonists and inhibitors of leukotrienes generating enzymes in multiple sclerosis. *Immunopharmacol Immunotoxicol* **32:**219–227.
Mita H, Endoh S, Kudoh M, Kawagishi Y, Kobayashi M, Taniguchi M, and Akiyama K (2001a) Possible involvement of mast-cell activation in aspirin provocation of aspirin-induced asthma. *Allergy* **56:**1061–1067.
Mita H, Hasegawa M, Saito H, and Akiyama K (2001b) Levels of cysteinyl leukotriene receptor mRNA in human peripheral leucocytes: significantly higher expression of cysteinyl leukotriene receptor 2 mRNA in eosinophils. *Clin Exp Allergy* **31:**1714–1723.
Miyahara N, Ohnishi H, Matsuda H, Miyahara S, Takeda K, Koya T, Matsubara S, Okamoto M, Dakhama A, Haribabu B, et al. (2008) Leukotriene B_4 receptor 1 expression on dendritic cells is required for the development of Th2 responses and allergen-induced airway hyperresponsiveness. *J Immunol* **181:**1170–1178.
Miyahara N, Takeda K, Miyahara S, Matsubara S, Koya T, Joetham A, Krishnan E, Dakhama A, Haribabu B, and Gelfand EW (2005a) Requirement for leukotriene B_4 receptor 1 in allergen-induced airway hyperresponsiveness. *Am J Respir Crit Care Med* **172:**161–167.
Miyahara N, Takeda K, Miyahara S, Taube C, Joetham A, Koya T, Matsubara S, Dakhama A, Tager AM, Luster AD, et al. (2005b) Leukotriene B_4 receptor-1 is essential for allergen-mediated recruitment of $CD8^+$ T cells and airway hyperresponsiveness. *J Immunol* **174:**4979–4984.
Mohle R, Boehmler AM, Denzlinger C, and Kanz L (2003) Nonpeptide mediators in the hematopoietic microenvironment. *Ann NY Acad Sci* **996:**61–66.
Mollerup J, Eriksen HN, Albertsen J, Wulff T, Lambert IH, and Hoffmann EK (2007) Homologous desensitisation of the mouse leukotriene B_4 receptor involves protein kinase C-mediated phosphorylation of serine 127. *Cell Physiol Biochem* **20:**143–156.
Montuschi P, Kharitonov SA, Ciabattoni G, and Barnes PJ (2003) Exhaled leukotrienes and prostaglandins in COPD. *Thorax* **58:**585–588.
Montuschi P, Sala A, Dahlén SE, and Folco G (2007) Pharmacological modulation of the leukotriene pathway in allergic airway disease. *Drug Discov Today* **12:**404–412.
Moos MP and Funk CD (2008) Endothelial cysteinyl leukotriene 2 receptor expression and myocardial ischemia/reperfusion injury. *Trends Cardiovasc Med* **18:**268–273.
Moos MP, Mewburn JD, Kan FW, Ishii S, Abe M, Sakimura K, Noguchi K, Shimizu T, and Funk CD (2008) Cysteinyl leukotriene 2 receptor-mediated vascular permeability via transendothelial vesicle transport. *FASEB J* **22:**4352–4362.
Moraes J, Assreuy J, Canetti C, and Barja-Fidalgo C (2010) Leukotriene B_4 mediates vascular smooth muscle cell migration through $\alpha v\beta 3$ integrin transactivation. *Atherosclerosis* **212:**406–413.
Mueller CF, Wassmann K, Widder JD, Wassmann S, Chen CH, Keuler B, Kudin A, Kunz WS, and Nickenig G (2008) Multidrug resistance protein-1 affects oxidative stress, endothelial dysfunction, and atherogenesis via leukotriene C_4 export. *Circulation* **117:**2912–2918.
Murray J, Ward C, O'Flaherty JT, Dransfield I, Haslett C, Chilvers ER, and Rossi AG (2003) Role of leukotrienes in the regulation of human granulocyte behaviour: dissociation between agonist-induced activation and retardation of apoptosis. *Br J Pharmacol* **139:**388–398.
Nabe T, Yamashita K, Miura M, Kawai T, and Kohno S (2002) Cysteinyl leukotriene-dependent interleukin-5 production leading to eosinophilia during late asthmatic response in guinea-pigs. *Clin Exp Allergy* **32:**633–640.
Nag S, Lamkhioued B, and Renzi PM (2002) Interleukin-2-induced increased airway responsiveness and lung Th2 cytokine expression occur after antigen challenge through the leukotriene pathway. *Am J Respir Crit Care Med* **165:**1540–1545.
Nagata M and Saito K (2003) The roles of cysteinyl leukotrienes in eosinophilic inflammation of asthmatic airways. *Int Arch Allergy Immunol* **131 (Suppl 1):**7–10.
Nagata M, Saito K, Kikuchi I, Hagiwara K, and Kanazawa M (2005) Effect of the

cysteinyl leukotriene antagonist pranlukast on transendothelial migration of eosinophils. *Int Arch Allergy Immunol* **137 (Suppl 1):**2–6.
Nagata M, Saito K, Tsuchiya K, and Sakamoto Y (2002) Leukotriene D_4 upregulates eosinophil adhesion via the cysteinyl leukotriene 1 receptor. *J Allergy Clin Immunol* **109:**676–680.
Nagy E, Andersson DC, Caidahl K, Eriksson MJ, Eriksson P, Franco-Cereceda A, Hansson GK, and Bäck M (2011) Upregulation of the 5-lipoxygenase pathway in human aortic valves correlates with severity of stenosis and leads to leukotriene-induced effects on valvular myofibroblasts. *Circulation* **123:**1316–1325.
Naik S, Billington CK, Pascual RM, Deshpande DA, Stefano FP, Kohout TA, Eckman DM, Benovic JL, and Penn RB (2005) Regulation of cysteinyl leukotriene type 1 receptor internalization and signaling. *J Biol Chem* **280:**8722–8732.
Nannini LJ Jr and Flores DM (2003) Bronchodilator effect of zafirlukast in subjects with chronic obstructive pulmonary disease. *Pulm Pharmacol Ther* **16:**307–311.
Narala VR, Adapala RK, Suresh MV, Brock TG, Peters-Golden M, and Reddy RC (2010) Leukotriene B_4 is a physiologically relevant endogenous peroxisome proliferator-activated receptor-α agonist. *J Biol Chem* **285:**22067–22074.
Nathan RA, Bernstein JA, Bielory L, Bonuccelli CM, Calhoun WJ, Galant SP, Hanby LA, Kemp JP, Kylstra JW, Nayak AS, et al. (1998) Zafirlukast improves asthma symptoms and quality of life in patients with moderate reversible airflow obstruction. *J Allergy Clin Immunol* **102:**935–942.
Nayak A (2004) A review of montelukast in the treatment of asthma and allergic rhinitis. *Expert Opin Pharmacother* **5:**679–686.
Nayak A and Langdon RB (2007) Montelukast in the treatment of allergic rhinitis: an evidence-based review. *Drugs* **67:**887–901.
Nayak AS, Philip G, Lu S, Malice MP, Reiss TF, and Montelukast Fall Rhinitis Investigator Group (2002) Efficacy and tolerability of montelukast alone or in combination with loratadine in seasonal allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial performed in the fall. *Ann Allergy Asthma Immunol* **88:**592–600.
Neu I, Mallinger J, Wildfeuer A, and Mehlber L (1992) Leukotrienes in the cerebrospinal fluid of multiple sclerosis patients. *Acta Neurol Scand* **86:**586–587.
Neu IS, Metzger G, Zschocke J, Zelezny R, and Mayatepek E (2002) Leukotrienes in patients with clinically active multiple sclerosis. *Acta Neurol Scand* **105:**63–66.
Neves JS, Radke AL, and Weller PF (2010) Cysteinyl leukotrienes acting via granule membrane-expressed receptors elicit secretion from within cell-free human eosinophil granules. *J Allergy Clin Immunol* **125:**477–482.
Ng CF, Sun FF, Taylor BM, Wolin MS, and Wong PY (1991) Functional properties of guinea pig eosinophil leukotriene B_4 receptor. *J Immunol* **147:**3096–3103.
Nielsen CK, Campbell JI, Ohd JF, Mörgelin M, Riesbeck K, Landberg G, and Sjölander A (2005a) A novel localization of the G-protein-coupled CysLT1 receptor in the nucleus of colorectal adenocarcinoma cells. *Cancer Res* **65:**732–742.
Nielsen CK, Massoumi R, Sonnerlind M, and Sjölander A (2005b) Leukotriene D_4 activates distinct G-proteins in intestinal epithelial cells to regulate stress fibre formation and to generate intracellular Ca^{2+} mobilisation and ERK1/2 activation. *Exp Cell Res* **302:**31–39.
Nieves D and Moreno JJ (2006) Role of 5-lipoxygenase pathway in the regulation of RAW 264.7 macrophage proliferation. *Biochem Pharmacol* **72:**1022–1030.
Nonaka Y, Hiramoto T, and Fujita N (2005) Identification of endogenous surrogate ligands for human P2Y12 receptors by in silico and in vitro methods. *Biochem Biophys Res Commun* **337:**281–288.
Noonan MJ, Chervinsky P, Brandon M, Zhang J, Kundu S, McBurney J, and Reiss TF (1998) Montelukast, a potent leukotriene receptor antagonist, causes dose-related improvements in chronic asthma. Montelukast Asthma Study Group. *Eur Respir J* **11:**1232–1239.
Norel X and Brink C (2004) The quest for new cysteinyl-leukotriene and lipoxin receptors: recent clues. *Pharmacol Ther* **103:**81–94.
Nothacker HP, Wang Z, Zhu Y, Reinscheid RK, Lin SH, and Civelli O (2000) Molecular cloning and characterization of a second human cysteinyl leukotriene receptor: discovery of a subtype selective agonist. *Mol Pharmacol* **58:**1601–1608.
O'Flaherty JT, Rossi AG, Redman JF, and Jacobson DP (1991) Tumor necrosis factor-α regulates expression of receptors for formyl-methionyl-leucyl-phenylalanine, leukotriene B4, and platelet-activating factor. Dissociation from priming in human polymorphonuclear neutrophils. *J Immunol* **147:**3842–3847.
O'Sullivan S, Dahlén B, Dahlén SE, and Kumlin M (1996) Increased urinary excretion of the prostaglandin D_2 metabolite 9α,11β-prostaglandin F_2 after aspirin challenge supports mast cell activation in aspirin-induced airway obstruction. *J Allergy Clin Immunol* **98:**421–432.
Obase Y, Matsuse H, Shimoda T, Haahtela T, and Kohno S (2005) Pathogenesis and management of aspirin-intolerant asthma. *Treat Respir Med* **4:**325–336.
Obase Y, Shimoda T, Tomari SY, Mitsuta K, Kawano T, Matsuse H, and Kohno S (2002) Effects of pranlukast on chemical mediators in induced sputum on provocation tests in atopic and aspirin-intolerant asthmatic patients. *Chest* **121:**143–150.
Ogasawara H, Ishii S, Yokomizo T, Kakinuma T, Komine M, Tamaki K, Shimizu T, and Izumi T (2002) Characterization of mouse cysteinyl leukotriene receptors mCysLT1 and mCysLT2: differential pharmacological properties and tissue distribution. *J Biol Chem* **277:**18763–18768.
Ohd JF, Nielsen CK, Campbell J, Landberg G, Löfberg H, and Sjölander A (2003) Expression of the leukotriene D_4 receptor CysLT1, COX-2, and other cell survival factors in colorectal adenocarcinomas. *Gastroenterology* **124:**57–70.
Ohd JF, Wikström K, and Sjölander A (2000) Leukotrienes induce cell-survival signaling in intestinal epithelial cells. *Gastroenterology* **119:**1007–1018.
Ohshima N, Nagase H, Koshino T, Miyamasu M, Yamaguchi M, Hirai K, Yamamoto K, Fujisawa T, Nakagawa N, Kishikawa K, et al. (2002) A functional study on $CysLT_1$ receptors in human eosinophils. *Int Arch Allergy Immunol* **129:**67–75.
Okubo K and Baba K (2008) A double-blind non-inferiority clinical study of montelukast, a cysteinyl leukotriene receptor 1 antagonist, compared with pranlukast in patients with seasonal allergic rhinitis. *Allergol Int* **57:**383–390.
Okuno T, Ago H, Terawaki K, Miyano M, Shimizu T, and Yokomizo T (2003) Helix 8 of the leukotriene B_4 receptor is required for the conformational change to the low affinity state after G-protein activation. *J Biol Chem* **278:**41500–41509.
Okuno T, Iizuka Y, Okazaki H, Yokomizo T, Taguchi R, and Shimizu T (2008) 12(*S*)-Hydroxyheptadeca-5*Z*,8*E*,10*E*-trienoic acid is a natural ligand for leukotriene B_4 receptor 2. *J Exp Med* **205:**759–766.
Ortiz JL, Gorenne I, Cortijo J, Seller A, Labat C, Sarria B, Abram TS, Gardiner PJ, Morcillo E, and Brink C (1995) Leukotriene receptors on human pulmonary vascular endothelium. *Br J Pharmacol* **115:**1382–1386.
Ortolani C, Mirone C, Fontana A, Folco GC, Miadonna A, Montalbetti N, Rinaldi M, Sala A, Tedeschi A, and Valente D (1987) Study of mediators of anaphylaxis in nasal wash fluids after aspirin and sodium metabisulfite nasal provocation in intolerant rhinitic patients. *Ann Allergy* **59:**106–112.
Ott VL, Cambier JC, Kappler J, Marrack P, and Swanson BJ (2003) Mast cell-dependent migration of effector $CD8^+$ T cells through production of leukotriene B_4. *Nat Immunol* **4:**974–981.
Øymar K and Aksnes L (2005) Increased levels of urinary leukotriene E_4 in children with severe atopic eczema/dermatitis syndrome. *Allergy* **60:**86–89.
Ozen Z, Mumbuc S, Sari I, Baglam T, Karatas E, and Kanlikama M (2007) Cysteinyl leukotriene receptor expression in aspirin-sensitive nasal polyposis patients. *ORL J Otorhinolaryngol Relat Spec* **69:**176–180.
Pacor ML, Di Lorenzo G, and Corrocher R (2001) Efficacy of leukotriene receptor antagonist in chronic urticaria. A double-blind, placebo-controlled comparison of treatment with montelukast and cetirizine in patients with chronic urticaria with intolerance to food additive and/or acetylsalicylic acid. *Clin Exp Allergy* **31:**1607–1614.
Palmblad J, Lerner R, and Larsson SH (1994) Signal transduction mechanisms for leukotriene B_4 induced hyperadhesiveness of endothelial cells for neutrophils. *J Immunol* **152:**262–269.
Palmblad J, Malmsten CL, Udén AM, Rådmark O, Engstedt L, and Samuelsson B (1981) Leukotriene B_4 is a potent and stereospecific stimulator of neutrophil chemotaxis and adherence. *Blood* **58:**658–661.
Palmer LJ, Silverman ES, Weiss ST, and Drazen JM (2002) Pharmacogenetics of asthma. *Am J Respir Crit Care Med* **165:**861–866.
Panettieri RA, Tan EM, Ciocca V, Luttmann MA, Leonard TB, and Hay DW (1998) Effects of LTD_4 on human airway smooth muscle cell proliferation, matrix expression, and contraction in vitro: differential sensitivity to cysteinyl leukotriene receptor antagonists. *Am J Respir Cell Mol Biol* **19:**453–461.
Papayianni A, Serhan CN, and Brady HR (1996) Lipoxin A_4 and B_4 inhibit leukotriene-stimulated interactions of human neutrophils and endothelial cells. *J Immunol* **156:**2264–2272.
Parameswaran K, Watson R, Gauvreau GM, Sehmi R, and O'Byrne PM (2004) The effect of pranlukast on allergen-induced bone marrow eosinophilopoiesis in subjects with asthma. *Am J Respir Crit Care Med* **169:**915–920.
Parhamifar L, Jeppsson B, and Sjölander A (2005) Activation of cPLA2 is required for leukotriene D_4-induced proliferation in colon cancer cells. *Carcinogenesis* **26:**1988–1998.
Parhamifar L, Sime W, Yudina Y, Vilhardt F, Mörgelin M, and Sjölander A (2010) A ligand-induced tyrosine phosphorylation of cysteinyl leukotriene receptor 1 triggers internalization and signaling in intestinal epithelial cells. *PLoS One* **5:**e14439.
Park JS, Chang HS, Park CS, Lee JH, Lee YM, Choi JH, Park HS, Kim LH, Park BL, Choi YH, et al. (2005) Association analysis of cysteinyl-leukotriene receptor 2 (CYSLTR2) polymorphisms with aspirin intolerance in asthmatics. *Pharmacogenet Genomics* **15:**483–492.
Park JS, Jang AS, Park SW, Lee YM, Uh ST, Kim YH, Cha JY, Park SM, and Park CS (2010) Protection of leukotriene receptor antagonist against aspirin-induced bronchospasm in asthmatics. *Allergy Asthma Immunol Res* **2:**48–54.
Paruchuri S, Broom O, Dib K, and Sjölander A (2005) The pro-inflammatory mediator leukotriene D_4 induces phosphatidylinositol 3-kinase and Rac-dependent migration of intestinal epithelial cells. *J Biol Chem* **280:**13538–13544.
Paruchuri S, Hallberg B, Juhas M, Larsson C, and Sjölander A (2002) Leukotriene D_4 activates MAPK through a Ras-independent but PKCε-dependent pathway in intestinal epithelial cells. *J Cell Sci* **115:**1883–1893.
Paruchuri S, Jiang Y, Feng C, Francis SA, Plutzky J, and Boyce JA (2008) Leukotriene E_4 activates peroxisome proliferator-activated receptor γ and induces prostaglandin D_2 generation by human mast cells. *J Biol Chem* **283:**16477–16487.
Paruchuri S, Mezhybovska M, Juhas M, and Sjölander A (2006) Endogenous production of leukotriene D_4 mediates autocrine survival and proliferation via $CysLT_1$ receptor signalling in intestinal epithelial cells. *Oncogene* **25:**6660–6665.
Paruchuri S and Sjölander A (2003) Leukotriene D_4 mediates survival and proliferation via separate but parallel pathways in the human intestinal epithelial cell line Int 407. *J Biol Chem* **278:**45577–45585.
Paruchuri S, Tashimo H, Feng C, Maekawa A, Xing W, Jiang Y, Kanaoka Y, Conley P, and Boyce JA (2009) Leukotriene E_4-induced pulmonary inflammation is mediated by the P2Y12 receptor. *J Exp Med* **206:**2543–2555.
Patry C, Müller E, Laporte J, Rola-Pleszczynski M, Sirois P, and de Brum-Fernandes AJ (1996) Leukotriene receptors in HL-60 cells differentiated into eosinophils, monocytes and neutrophils. *Prostaglandins Leukot Essent Fatty Acids* **54:**361–370.
Payan DG, Missirian-Bastian A, and Goetzl EJ (1984) Human T-lymphocyte subset specificity of the regulatory effects of leukotriene B4. *Proc Natl Acad Sci USA* **81:**3501–3505.
Pedersen KE, Bochner BS, and Undem BJ (1997) Cysteinyl leukotrienes induce P-selectin expression in human endothelial cells via a non-CysLT1 receptor-mediated mechanism. *J Pharmacol Exp Ther* **281:**655–662.
Peres CM, Aronoff DM, Serezani CH, Flamand N, Faccioli LH, and Peters-Golden M (2007) Specific leukotriene receptors couple to distinct G proteins to effect stimulation of alveolar macrophage host defense functions. *J Immunol* **179:**5454–5461.
Pérez-Novo CA, Claeys C, Van Cauwenberge P, and Bachert C (2006) Expression of eicosanoid receptors subtypes and eosinophilic inflammation: implication on chronic rhinosinusitis. *Respir Res* **7:**75.
Perng DW, Wu YC, Chang KT, Wu MT, Chiou YC, Su KC, Perng RP, and Lee YC

(2006) Leukotriene C4 induces TGF-β1 production in airway epithelium via p38 kinase pathway. *Am J Respir Cell Mol Biol* **34:**101–107.
Peters-Golden M, Gleason MM, and Togias A (2006) Cysteinyl leukotrienes: multi-functional mediators in allergic rhinitis. *Clin Exp Allergy* **36:**689–703.
Peters-Golden M and Henderson WR Jr (2005) The role of leukotrienes in allergic rhinitis. *Ann Allergy Asthma Immunol* **94:**609–618; quiz 618–620, 669.
Peters-Golden M and Henderson WR Jr (2007) Leukotrienes. *N Engl J Med* **357:** 1841–1854.
Pétrin D, Turcotte S, Gilbert AK, Rola-Pleszczynski M, and Stankova J (2006) The anti-apoptotic effect of leukotriene B4 in neutrophils: a role for phosphatidylinositol 3-kinase, extracellular signal-regulated kinase and Mcl-1. *Cell Signal* **18:** 479–487.
Pettersson A, Richter J, and Owman C (2003) Flow cytometric mapping of the leukotriene B4 receptor, BLT1, in human bone marrow and peripheral blood using specific monoclonal antibodies. *Int Immunopharmacol* **3:**1467–1475.
Pettersson A, Sabirsh A, Bristulf J, Kidd-Ljunggren K, Ljungberg B, Owman C, and Karlsson U (2005) Pro- and anti-inflammatory substances modulate expression of the leukotriene B4 receptor, BLT1, in human monocytes. *J Leukoc Biol* **77:**1018–1025.
Phan H, Moeller ML, and Nahata MC (2009) Treatment of allergic rhinitis in infants and children: efficacy and safety of second-generation antihistamines and the leukotriene receptor antagonist montelukast. *Drugs* **69:**2541–2576.
Philip G, Nayak AS, Berger WE, Leynadier F, Vrijens F, Dass SB, and Reiss TF (2004) The effect of montelukast on rhinitis symptoms in patients with asthma and seasonal allergic rhinitis. *Curr Med Res Opin* **20:**1549–1558.
Piatti G, Ceriotti L, Cavallaro G, Ambrosetti U, Mantovani M, Pistone A, and Centanni S (2003) Effects of zafirlukast on bronchial asthma and allergic rhinitis. *Pharmacol Res* **47:**541–547.
Picado C, Ramis I, Rosellò J, Prat J, Bulbena O, Plaza V, Montserrat JM, and Gelpí E (1992) Release of peptide leukotriene into nasal secretions after local instillation of aspirin in aspirin-sensitive asthmatic patients. *Am Rev Respir Dis* **145:**65–69.
Pillai SG, Cousens DJ, Barnes AA, Buckley PT, Chiano MN, Hosking LK, Cameron LA, Fling ME, Foley JJ, Green A, et al. (2004) A coding polymorphism in the CYSLT2 receptor with reduced affinity to LTD4 is associated with asthma. *Pharmacogenetics* **14:**627–633.
Pizzichini E, Leff JA, Reiss TF, Hendeles L, Boulet LP, Wei LX, Efthimiadis AE, Zhang J, and Hargreave FE (1999) Montelukast reduces airway eosinophilic inflammation in asthma: a randomized, controlled trial. *Eur Respir J* **14:**12–18.
Pollock K and Creba J (1990) Leukotriene D_4 induced calcium changes in U937 cells may utilize mechanisms additional to inositol phosphate production that are pertussis toxin insensitive but are blocked by phorbol myristate acetate. *Cell Signal* **2:**563–568.
Porreca E, Di Febbo C, Di Sciullo A, Angelucci D, Nasuti M, Vitullo P, Reale M, Conti P, Cuccurullo F, and Poggi A (1996) Cysteinyl leukotriene D4 induced vascular smooth muscle cell proliferation: a possible role in myointimal hyperplasia. *Thromb Haemost* **76:**99–104.
Porreca E, Di Febbo C, Reale M, Barbacane R, Mezzetti A, Cuccurullo F, and Conti P (1995) Modulation of rat vascular smooth muscle cell (VSMC) proliferation by cysteinyl leukotriene D4: a role for mediation of interleukin 1. *Atherosclerosis* **113:**11–18.
Poulin S, Thompson C, Thivierge M, Véronneau S, McMahon S, Dubois CM, Stankova J, and Rola-Pleszczynski M (2011) Cysteinyl-leukotrienes induce vascular endothelial growth factor production in human monocytes and bronchial smooth muscle cells. *Clin Exp Allergy* **41:**204–217.
Price DB, Swern A, Tozzi CA, Philip G, and Polos P (2006) Effect of montelukast on lung function in asthma patients with allergic rhinitis: analysis from the COMPACT trial. *Allergy* **61:**737–742.
Prinster SC, Hague C, and Hall RA (2005) Heterodimerization of G protein-coupled receptors: specificity and functional significance. *Pharmacol Rev* **57:**289–298.
Profita M, Sala A, Bonanno A, Siena L, Ferraro M, Di Giorgi R, Montalbano AM, Albano GD, Gagliardo R, and Gjomarkaj M (2008) Cysteinyl leukotriene-1 receptor activation in a human bronchial epithelial cell line leads to signal transducer and activator of transcription 1-mediated eosinophil adhesion. *J Pharmacol Exp Ther* **325:**1024–1030.
Przylipiak A, Hafner J, Przylipiak J, Runnebaum B, Rabe T, and Köhn FM (1998) Influence of leukotrienes on in vitro growth of human mammary carcinoma cell line MCF-7. *Eur J Obstet Gynecol Reprod Biol* **77:**61–65.
Pullerits T, Praks L, Ristioja V, and Lötvall J (2002) Comparison of a nasal glucocorticoid, antileukotriene, and a combination of antileukotriene and antihistamine in the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol* **109:**949–955.
Qian XD, Wei EQ, Zhang L, Sheng WW, Wang ML, Zhang WP, and Chen Z (2006) Pranlukast, a cysteinyl leukotriene receptor 1 antagonist, protects mice against brain cold injury. *Eur J Pharmacol* **549:**35–40.
Qiu H, Johansson AS, Sjöström M, Wan M, Schröder O, Palmblad J, and Haeggström JZ (2006) Differential induction of BLT receptor expression on human endothelial cells by lipopolysaccharide, cytokines, and leukotriene B4. *Proc Natl Acad Sci USA* **103:**6913–6918.
Queto T, Gaspar-Elsas MI, Masid-de-Brito D, Vasconcelos ZF, Ferraris FK, Penido C, Cunha FQ, Kanaoka Y, Lam BK, and Xavier-Elsas P (2010) Cysteinyl-leukotriene type 1 receptors transduce a critical signal for the up-regulation of eosinophilopoiesis by interleukin-13 and eotaxin in murine bone marrow. *J Leukoc Biol* **87:**885–893.
Rådmark O and Samuelsson B (2009) 5-Lipoxygenase: mechanisms of regulation. *J Lipid Res* **50 (Suppl):**S40–S45.
Rajah R, Nunn SE, Herrick DJ, Grunstein MM, and Cohen P (1996) Leukotriene D4 induces MMP-1, which functions as an IGFBP protease in human airway smooth muscle cells. *Am J Physiol* **271:**L1014–L1022.
Ravasi S, Citro S, Viviani B, Capra V, and Rovati GE (2006) CysLT1 receptor-induced human airway smooth muscle cells proliferation requires ROS generation, EGF receptor transactivation and ERK1/2 phosphorylation. *Respir Res* **7:**42.
Rediske J, Morrissey MM, and Jarvis M (1993) Human monocytes respond to leukotriene B4 with a transient increase in cytosolic calcium. *Cell Immunol* **147:** 438–445.
Reid DW, Misso N, Aggarwal S, Thompson PJ, and Walters EH (2007) Oxidative stress and lipid-derived inflammatory mediators during acute exacerbations of cystic fibrosis. *Respirology* **12:**63–69.
Reimers A, Pichler C, Helbling A, Pichler WJ, and Yawalkar N (2002) Zafirlukast has no beneficial effects in the treatment of chronic urticaria. *Clin Exp Allergy* **32:**1763–1768.
Riccioni G, Capra V, D'Orazio N, Bucciarelli T, and Bazzano LA (2008) Leukotriene modifiers in the treatment of cardiovascular diseases. *J Leukoc Biol* **84:**1374–1378.
Riccioni G, Di Ilio C, and D'Orazio N (2004) An update of the leukotriene modulators for the treatment of asthma. *Expert Opin Investig Drugs* **13:**763–776.
Richards IM, Griffin RL, Oostveen JA, Morris J, Wishka DG, and Dunn CJ (1989) Effect of the selective leukotriene B4 antagonist U-75302 on antigen-induced bronchopulmonary eosinophilia in sensitized guinea pigs. *Am Rev Respir Dis* **140:**1712–1716.
Rioux N and Castonguay A (1998) Inhibitors of lipoxygenase: a new class of cancer chemopreventive agents. *Carcinogenesis* **19:**1393–1400.
Rodrigo GJ and Yañez A (2006) The role of antileukotriene therapy in seasonal allergic rhinitis: a systematic review of randomized trials. *Ann Allergy Asthma Immunol* **96:**779–786.
Rola-Pleszczynski M, Chavaillaz PA, and Lemaire I (1986) Stimulation of interleukin 2 and interferon γ production by leukotriene B4 in human lymphocyte cultures. *Prostaglandins Leukot Med* **23:**207–210.
Rola-Pleszczynski M and Lemaire I (1985) Leukotrienes augment interleukin 1 production by human monocytes. *J Immunol* **135:**3958–3961.
Rola-Pleszczynski M and Stanková J (1992) Leukotriene B4 enhances interleukin-6 (IL-6) production and IL-6 messenger RNA accumulation in human monocytes in vitro: transcriptional and posttranscriptional mechanisms. *Blood* **80:**1004–1011.
Rovati GE, Baroffio M, Citro S, Brichetto L, Ravasi S, Milanese M, Crimi E, and Brusasco V (2006) Cysteinyl-leukotrienes in the regulation of β_2-adrenoceptor function: an in vitro model of asthma. *Respir Res* **7:**103.
Rovati GE and Capra V (2007) Cysteinyl-leukotriene receptors and cellular signals. *ScientificWorldJournal* **7:**1375–1392.
Rovati GE, Capra V, and Nicosia S (1997) More on the classification of cysteinyl leukotriene receptors. *Trends Pharmacol Sci* **18:**148–149.
Rubinstein I, Kumar B, and Schriever C (2004) Long-term montelukast therapy in moderate to severe COPD—a preliminary observation. *Respir Med* **98:**134–138.
Runarsson G, Liu A, Mahshid Y, Feltenmark S, Pettersson A, Klein E, Björkholm M, and Claesson HE (2005) Leukotriene B4 plays a pivotal role in CD40-dependent activation of chronic B lymphocytic leukemia cells. *Blood* **105:**1274–1279.
Sabirsh A, Bristulf J, and Owman C (2004) Exploring the pharmacology of the leukotriene B4 receptor BLT1, without the confounding effects of BLT2. *Eur J Pharmacol* **499:**53–65.
Sabirsh A, Bywater RP, Bristulf J, Owman C, and Haeggström JZ (2006) Residues from transmembrane helices 3 and 5 participate in leukotriene B4 binding to BLT1. *Biochemistry* **45:**5733–5744.
Saegusa S, Tsubone H, and Kuwahara M (2001) Leukotriene D_4-induced Rho-mediated actin reorganization in human bronchial smooth muscle cells. *Eur J Pharmacol* **413:**163–171.
Saengpanich S, deTineo M, Naclerio RM, and Baroody FM (2003) Fluticasone nasal spray and the combination of loratadine and montelukast in seasonal allergic rhinitis. *Arch Otolaryngol Head Neck Surg* **129:**557–562.
Saito K, Nagata M, Kikuchi I, and Sakamoto Y (2004) Leukotriene D_4 and eosinophil transendothelial migration, superoxide generation, and degranulation via β_2 integrin. *Ann Allergy Asthma Immunol* **93:**594–600.
Sakata K, Dahlén SE, and Bäck M (2004) The contractile action of leukotriene B_4 in the guinea-pig lung involves a vascular component. *Br J Pharmacol* **141:**449–456.
Sampson AP, Pizzichini E, and Bisgaard H (2003) Effects of cysteinyl leukotrienes and leukotriene receptor antagonists on markers of inflammation. *J Allergy Clin Immunol* **111:**S49–S59; discussion S59–S61.
Sampson AP, Spencer DA, Green CP, Piper PJ, and Price JF (1990) Leukotrienes in the sputum and urine of cystic fibrosis children. *Br J Clin Pharmacol* **30:**861–869.
Samuelsson B (1983) From studies of biochemical mechanism to novel biological mediators: prostaglandin endoperoxides, thromboxanes, and leukotrienes. Nobel Lecture, 8 December 1982. *Biosci Rep* **3:**791–813.
Sanada S, Tanaka T, Kameyoshi Y, and Hide M (2005) The effectiveness of montelukast for the treatment of anti-histamine-resistant chronic urticaria. *Arch Dermatol Res* **297:**134–138.
Sánchez-Borges M, Acevedo N, Vergara C, Jiménez S, Zabner-Oziel P, Monzón A, and Caraballo L (2009) The A-444C polymorphism in the leukotriene C4 synthase gene is associated with aspirin-induced urticaria. *J Investig Allergol Clin Immunol* **19:**375–382.
Sanz C, Isidro-García M, Dávila I, Moreno E, Laffond E, and Lorente F (2006) Analysis of 927T>C CYSLTRI and −444A>C LTC4S polymorphisms in patients with asthma. *J Investig Allergol Clin Immunol* **16:**331–337.
Sarau HM, Ames RS, Chambers J, Ellis C, Elshourbagy N, Foley JJ, Schmidt DB, Muccitelli RM, Jenkins O, Murdock PR, et al. (1999) Identification, molecular cloning, expression, and characterization of a cysteinyl leukotriene receptor. *Mol Pharmacol* **56:**657–663.
Sardana N, Santos C, Lehman E, and Craig T (2010) A comparison of intranasal corticosteroid, leukotriene receptor antagonist, and topical antihistamine in reducing symptoms of perennial allergic rhinitis as assessed through the Rhinitis Severity Score. *Allergy Asthma Proc* **31:**5–9.
Saussy DL Jr, Sarau HM, Foley JJ, Mong S, and Crooke ST (1989) Mechanisms of leukotriene E_4 partial agonist activity at leukotriene D_4 receptors in differentiated U-937 cells. *J Biol Chem* **264:**19845–19855.
Scadding GK, Durham SR, Mirakian R, Jones NS, Drake-Lee AB, Ryan D, Dixon TA, Huber PA, Nasser SM, and British Society for Allergy and Clinical Immunology

(2008) BSACI guidelines for the management of rhinosinusitis and nasal polyposis. *Clin Exp Allergy* **38:**260–275.
Schmitt-Grohé S, Eickmeier O, Naujoks C, Schubert R, Lentze MJ, Zielen S, and Rietschel E (2007) Effects of long-term treatment with montelukast in mild cystic fibrosis (long term treatment with montelukast in cystic fibrosis). *Respir Med* **101:**684.
Schmitt-Grohé S, Eickmeier O, Schubert R, Bez C, and Zielen S (2002) Anti-inflammatory effects of montelukast in mild cystic fibrosis. *Ann Allergy Asthma Immunol* **89:**599–605.
Sehmi R, Wardlaw AJ, Cromwell O, Kurihara K, Waltmann P, and Kay AB (1992) Interleukin-5 selectively enhances the chemotactic response of eosinophils obtained from normal but not eosinophilic subjects. *Blood* **79:**2952–2959.
Seo KW, Lee SJ, Kim CE, Yun MR, Park HM, Yun JW, Bae SS, and Kim CD (2010) Participation of 5-lipoxygenase-derived LTB_4 in 4-hydroxynonenal-enhanced MMP-2 production in vascular smooth muscle cells. *Atherosclerosis* **208:**56–61.
Serezani CH, Aronoff DM, Sitrin RG, and Peters-Golden M (2009) FcγRI ligation leads to a complex with BLT1 in lipid rafts that enhances rat lung macrophage antimicrobial functions. *Blood* **114:**3316–3324.
Serhan CN, Chiang N, and Van Dyke TE (2008) Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. *Nat Rev Immunol* **8:**349–361.
Serhan CN, Radin A, Smolen JE, Korchak H, Samuelsson B, and Weissmann G (1982) Leukotriene B_4 is a complete secretagogue in human neutrophils: a kinetic analysis. *Biochem Biophys Res Commun* **107:**1006–1012.
Shao WH, Del Prete A, Bock CB, and Haribabu B (2006) Targeted disruption of leukotriene B4 receptors BLT1 and BLT2: a critical role for BLT1 in collagen-induced arthritis in mice. *J Immunol* **176:**6254–6261.
Sharon P and Stenson WF (1984) Enhanced synthesis of leukotriene B4 by colonic mucosa in inflammatory bowel disease. *Gastroenterology* **86:**453–460.
Sheng WW, Li CT, Zhang WP, Yuan YM, Hu H, Fang SH, Zhang L, and Wei EQ (2006) Distinct roles of CysLT1 and CysLT2 receptors in oxygen glucose deprivation-induced PC12 cell death. *Biochem Biophys Res Commun* **346:**19–25.
Shimizu T (2009) Lipid mediators in health and disease: enzymes and receptors as therapeutic targets for the regulation of immunity and inflammation. *Annu Rev Pharmacol Toxicol* **49:**123–150.
Shimizu T, Rådmark O, and Samuelsson B (1984) Enzyme with dual lipoxygenase activities catalyzes leukotriene A_4 synthesis from arachidonic acid. *Proc Natl Acad Sci USA* **81:**689–693.
Shin EH, Lee HY, and Bae YS (2006) Leukotriene B4 stimulates human monocyte-derived dendritic cell chemotaxis. *Biochem Biophys Res Commun* **348:**606–611.
Shin JA, Chang HS, Park SM, Jang AS, Park SW, Park JS, Uh ST, Il Lim G, Rhim T, Kim MK, et al. (2009) Genetic effect of CysLTR2 polymorphisms on its mRNA synthesis and stabilization. *BMC Med Genet* **10:**106.
Shiota N, Shimoura K, and Okunishi H (2006) Pathophysiological role of mast cells in collagen-induced arthritis: study with a cysteinyl leukotriene receptor antagonist, montelukast. *Eur J Pharmacol* **548:**158–166.
Shirasaki H, Kanaizumi E, Seki N, Kikuchi M, Watanabe K, Konno N, and Himi T (2006) Distribution of specific binding sites for cysteinyl leukotriene 1 receptor antagonist in human nasal mucosa. *Acta Otolaryngol* **126:**948–951.
Shirasaki H, Kanaizumi E, Watanabe K, Matsui T, Sato J, Narita S, Rautiainen M, and Himi T (2002) Expression and localization of the cysteinyl leukotriene 1 receptor in human nasal mucosa. *Clin Exp Allergy* **32:**1007–1012.
Shirasaki H, Seki N, Fujita M, Kikuchi M, Kanaizumi E, Watanabe K, and Himi T (2007) Agonist- and T_H2 cytokine-induced up-regulation of cysteinyl leukotriene receptor messenger RNA in human monocytes. *Ann Allergy Asthma Immunol* **99:**340–347.
Showell HJ, Conklyn MJ, Alpert R, Hingorani GP, Wright KF, Smith MA, Stam E, Salter ED, Scampoli DN, Meltzer S, et al. (1998) The preclinical pharmacological profile of the potent and selective leukotriene B4 antagonist CP-195543. *J Pharmacol Exp Ther* **285:**946–954.
Silverman ES, Liggett SB, Gelfand EW, Rosenwasser LJ, Baron RM, Bolk S, Weiss ST, and Drazen JM (2001) The pharmacogenetics of asthma: a candidate gene approach. *Pharmacogenomics J* **1:**27–37.
Sjölander A, Grönroos E, Hammarström S, and Andersson T (1990) Leukotriene D_4 and E_4 induce transmembrane signaling in human epithelial cells. Single cell analysis reveals diverse pathways at the G-protein level for the influx and the intracellular mobilization of Ca^{2+}. *J Biol Chem* **265:**20976–20981.
Sjöström M, Jakobsson PJ, Heimburger M, Palmblad J, and Haeggström JZ (2001) Human umbilical vein endothelial cells generate leukotriene C4 via microsomal glutathione S-transferase type 2 and express the $CysLT_1$ receptor. *Eur J Biochem* **268:**2578–2586.
Sjöström M, Jakobsson PJ, Juremalm M, Ahmed A, Nilsson G, Macchia L, and Haeggström JZ (2002) Human mast cells express two leukotriene C_4 synthase isoenzymes and the $CysLT_1$ receptor. *Biochim Biophys Acta* **1583:**53–62.
Sjöström M, Johansson AS, Schröder O, Qiu H, Palmblad J, and Haeggström JZ (2003) Dominant expression of the CysLT2 receptor accounts for calcium signaling by cysteinyl leukotrienes in human umbilical vein endothelial cells. *Arterioscler Thromb Vasc Biol* **23:**E37–E41.
Skoglund G and Claesson HE (1991) Intracellular mechanisms involved in leukotriene C4-stimulated adhesion of U-937 cells. *Cell Signal* **3:**399–404.
Sladek K and Szczeklik A (1993) Cysteinyl leukotrienes overproduction and mast cell activation in aspirin-provoked bronchospasm in asthma. *Eur Respir J* **6:**391–399.
Sloniewsky DE, Ridge KM, Adir Y, Fries FP, Briva A, Sznajder JI, and Sporn PH (2004) Leukotriene D4 activates alveolar epithelial Na,K-ATPase and increases alveolar fluid clearance. *Am J Respir Crit Care Med* **169:**407–412.
Smith JR, Subbarao K, Franc DT, Haribabu B, and Rosenbaum JT (2004) Susceptibility to endotoxin induced uveitis is not reduced in mice deficient in BLT1, the high affinity leukotriene B_4 receptor. *Br J Ophthalmol* **88:**273–275.
Snyder DS, Castro R, and Desforges JF (1989) Antiproliferative effects of lipoxygenase inhibitors on malignant human hematopoietic cell lines. *Exp Hematol* **17:**6–9.
Song P, Crimi E, Milanese M, Duan J, Rehder K, and Brusasco V (1998) Anti-inflammatory agents and allergen-induced β_2-receptor dysfunction in isolated human bronchi. *Am J Respir Crit Care Med* **158:**1809–1814.
Soter NA, Lewis RA, Corey EJ, and Austen KF (1983) Local effects of synthetic leukotrienes (LTC4, LTD4, LTE4, and LTB4) in human skin. *J Invest Dermatol* **80:**115–119.
Sousa AR, Parikh A, Scadding G, Corrigan CJ, and Lee TH (2002) Leukotriene-receptor expression on nasal mucosal inflammatory cells in aspirin-sensitive rhinosinusitis. *N Engl J Med* **347:**1493–1499.
Spanbroek R, Grabner R, Lotzer K, Hildner M, Urbach A, Ruhling K, Moos MP, Kaiser B, Cohnert TU, Wahlers T, et al. (2003) Expanding expression of the 5-lipoxygenase pathway within the arterial wall during human atherogenesis. *Proc Natl Acad Sci USA* **100:**1238–1243.
Spencer DA, Sampson AP, Green CP, Costello JF, Piper PJ, and Price JF (1992) Sputum cysteinyl-leukotriene levels correlate with the severity of pulmonary disease in children with cystic fibrosis. *Pediatr Pulmonol* **12:**90–94.
Stankova J, Turcotte S, Harris J, and Rola-Pleszczynski M (2002) Modulation of leukotriene B4 receptor-1 expression by dexamethasone: potential mechanism for enhanced neutrophil survival. *J Immunol* **168:**3570–3576.
Steele VE, Holmes CA, Hawk ET, Kopelovich L, Lubet RA, Crowell JA, Sigman CC, and Kelloff GJ (1999) Lipoxygenase inhibitors as potential cancer chemopreventives. *Cancer Epidemiol Biomarkers Prev* **8:**467–483.
Steinke JW, Bradley D, Arango P, Crouse CD, Frierson H, Kountakis SE, Kraft M, and Borish L (2003) Cysteinyl leukotriene expression in chronic hyperplastic sinusitis-nasal polyposis: importance to eosinophilia and asthma. *J Allergy Clin Immunol* **111:**342–349.
Steinke JW, Crouse CD, Bradley D, Hise K, Lynch K, Kountakis SE, and Borish L (2004) Characterization of interleukin-4-stimulated nasal polyp fibroblasts. *Am J Respir Cell Mol Biol* **30:**212–219.
Stelmach I, Korzeniewska A, Stelmach W, Majak P, Grzelewski T, and Jerzynska J (2005) Effects of montelukast treatment on clinical and inflammatory variables in patients with cystic fibrosis. *Ann Allergy Asthma Immunol* **95:**372–380.
Stelmach R and Cukier A (2006) Treating allergic rhinitis and asthma: different sides of the same fence. *Expert Opin Pharmacother* **7:**1245–1249.
Sterrett S, Morton J, Perry D, and Donovan J (2006) Eosinophilic cystitis: successful long-term treatment with montelukast sodium. *Urology* **67:**423.e19–423.e21.
Stevenson DD and Simon RA (2001) Lack of cross-reactivity between rofecoxib and aspirin in aspirin-sensitive patients with asthma. *J Allergy Clin Immunol* **108:**47–51.
Stevenson DD and Szczeklik A (2006) Clinical and pathologic perspectives on aspirin sensitivity and asthma. *J Allergy Clin Immunol* **118:**773–786; quiz 787–788.
Stokes J and Casale TB (2004) Rationale for new treatments aimed at IgE immunomodulation. *Ann Allergy Asthma Immunol* **93:**212–217; quiz 217–219, 271.
Storms W (2007) Update on montelukast and its role in the treatment of asthma, allergic rhinitis and exercise-induced bronchoconstriction. *Expert Opin Pharmacother* **8:**2173–2187.
Strauch E, Moske O, Thoma S, Storm Van's Gravesande K, Ihorst G, Brandis M, and Kuehr J (2003) A randomized controlled trial on the effect of montelukast on sputum eosinophil cationic protein in children with corticosteroid-dependent asthma. *Pediatr Res* **54:**198–203.
Subbarao K, Jala VR, Mathis S, Suttles J, Zacharias W, Ahamed J, Ali H, Tseng MT, and Haribabu B (2004) Role of leukotriene B4 receptors in the development of atherosclerosis: potential mechanisms. *Arterioscler Thromb Vasc Biol* **24:**369–375.
Sun FF, Crittenden NJ, Czuk CI, Taylor BM, Stout BK, and Johnson HG (1991) Biochemical and functional differences between eosinophils from animal species and man. *J Leukoc Biol* **50:**140–150.
Sun R, Ba X, Cui L, Xue Y, and Zeng X (2009) Leukotriene B4 regulates proliferation and differentiation of cultured rat myoblasts via the BLT1 pathway. *Mol Cells* **27:**403–408.
Suzuki M, Kato M, Kimura H, Fujiu T, and Morikawa A (2003) Inhibition of human eosinophil activation by a cysteinyl leukotriene receptor antagonist (pranlukast; ONO-1078). *J Asthma* **40:**395–404.
Suzuki S, Takeuchi K, Ishinaga H, Basbaum C, and Majima Y (2008) Leukotriene D4 upregulates MUC2 gene transcription in human epithelial cells. *Pharmacology* **81:**221–228.
Szczeklik A, Sladek K, Dworski R, Nizankowska E, Soja J, Sheller J, and Oates J (1996) Bronchial aspirin challenge causes specific eicosanoid response in aspirin-sensitive asthmatics. *Am J Respir Crit Care Med* **154:**1608–1614.
Szczeklik A and Stevenson DD (2003) Aspirin-induced asthma: advances in pathogenesis, diagnosis, and management. *J Allergy Clin Immunol* **111:**913–921; quiz 922.
Tager AM, Bromley SK, Medoff BD, Islam SA, Bercury SD, Friedrich EB, Carafone AD, Gerszten RE, and Luster AD (2003) Leukotriene B_4 receptor BLT1 mediates early effector T cell recruitment. *Nat Immunol* **4:**982–990.
Tager AM, Dufour JH, Goodarzi K, Bercury SD, von Andrian UH, and Luster AD (2000) BLTR mediates leukotriene B_4-induced chemotaxis and adhesion and plays a dominant role in eosinophil accumulation in a murine model of peritonitis. *J Exp Med* **192:**439–446.
Tahan F, Jazrawi E, Moodley T, Rovati GE, and Adcock IM (2008) Montelukast inhibits tumour necrosis factor-α-mediated interleukin-8 expression through inhibition of nuclear factor-κB p65-associated histone acetyltransferase activity. *Clin Exp Allergy* **38:**805–811.
Takamatsu Y, Shimada K, Chijiiwa K, Kuroki S, Yamaguchi K, and Tanaka M (2004) Role of leukotrienes on hepatic ischemia/reperfusion injury in rats. *J Surg Res* **119:**14–20.
Takasaki J, Kamohara M, Matsumoto M, Saito T, Sugimoto T, Ohishi T, Ishii H, Ota T, Nishikawa T, Kawai Y, et al. (2000) The molecular characterization and tissue distribution of the human cysteinyl leukotriene $CysLT_2$ receptor. *Biochem Biophys Res Commun* **274:**316–322.
Tanimoto Y, Takahashi K, and Kimura I (1992) Effects of cytokines on human basophil chemotaxis. *Clin Exp Allergy* **22:**1020–1025.
Tantisira KG, Lima J, Sylvia J, Klanderman B, and Weiss ST (2009) 5-lipoxygenase

pharmacogenetics in asthma: overlap with Cys-leukotriene receptor antagonist loci. *Pharmacogenet Genomics* **19:**244–247.
Taylor-Clark TE, Nassenstein C, and Undem BJ (2008) Leukotriene D_4 increases the excitability of capsaicin-sensitive nasal sensory nerves to electrical and chemical stimuli. *Br J Pharmacol* **154:**1359–1368.
Tedeschi A (2009) Paradoxical exacerbation of chronic urticaria by H1-antihistamines and montelukast. *Eur Ann Allergy Clin Immunol* **41:**187–189.
Telleria JJ, Blanco-Quiros A, Varillas D, Armentia A, Fernandez-Carvajal I, Jesus Alonso M, and Diez I (2008) ALOX5 promoter genotype and response to montelukast in moderate persistent asthma. *Respir Med* **102:**857–861.
Terawaki K, Yokomizo T, Nagase T, Toda A, Taniguchi M, Hashizume K, Yagi T, and Shimizu T (2005) Absence of leukotriene B_4 receptor 1 confers resistance to airway hyperresponsiveness and Th2-type immune responses. *J Immunol* **175:**4217–4225.
Thivierge M, Doty M, Johnson J, Stanková J, and Rola-Pleszczynski M (2000) IL-5 up-regulates cysteinyl leukotriene 1 receptor expression in HL-60 cells differentiated into eosinophils. *J Immunol* **165:**5221–5226.
Thivierge M, Stanková J, and Rola-Pleszczynski M (2001) IL-13 and IL-4 up-regulate cysteinyl leukotriene 1 receptor expression in human monocytes and macrophages. *J Immunol* **167:**2855–2860.
Thivierge M, Stankova J, and Rola-Pleszczynski M (2006) Toll-like receptor agonists differentially regulate cysteinyl-leukotriene receptor 1 expression and function in human dendritic cells. *J Allergy Clin Immunol* **117:**1155–1162.
Thivierge M, Stankova J, and Rola-Pleszczynski M (2009) Cysteinyl-leukotriene receptor type 1 expression and function is down-regulated during monocyte-derived dendritic cell maturation with zymosan: involvement of IL-10 and prostaglandins. *J Immunol* **183:**6778–6787.
Thodeti CK, Adolfsson J, Juhas M, and Sjölander A (2000) Leukotriene D_4 triggers an association between $G\beta\gamma$ subunits and phospholipase C-γ1 in intestinal epithelial cells. *J Biol Chem* **275:**9849–9853.
Thodeti CK, Nielsen CK, Paruchuri S, Larsson C, and Sjölander A (2001) The ε isoform of protein kinase C is involved in regulation of the LTD_4-induced calcium signal in human intestinal epithelial cells. *Exp Cell Res* **262:**95–103.
Thomas M (2006) Allergic rhinitis: evidence for impact on asthma. *BMC Pulm Med* **6 (Suppl 1):**S4.
Thompson C, Cloutier A, Bossé Y, Poisson C, Larivée P, McDonald PP, Stankova J, and Rola-Pleszczynski M (2008a) Signaling by the cysteinyl-leukotriene receptor 2. Involvement in chemokine gene transcription. *J Biol Chem* **283:**1974–1984.
Thompson C, Cloutier A, Bossé Y, Thivierge M, Gouill CL, Larivée P, McDonald PP, Stankova J, and Rola-Pleszczynski M (2006) CysLT1 receptor engagement induces activator protein-1- and NF-κB-dependent IL-8 expression. *Am J Respir Cell Mol Biol* **35:**697–704.
Thompson C, McMahon S, Bossé Y, Dubois CM, Stankova J, and Rola-Pleszczynski M (2008b) Leukotriene D_4 upregulates furin expression through CysLT1 receptor signaling. *Am J Respir Cell Mol Biol* **39:**227–234.
Thompson MD, Burnham WM, and Cole DE (2005) The G protein-coupled receptors: pharmacogenetics and disease. *Crit Rev Clin Lab Sci* **42:**311–392.
Thompson MD, Capra V, Takasaki J, Maresca G, Rovati GE, Slutsky AS, Lilly C, Zamel N, McIntyre Burnham W, Cole DE, et al. (2007) A functional G300S variant of the cysteinyl leukotriene 1 receptor is associated with atopy in a Tristan da Cunha isolate. *Pharmacogenet Genomics* **17:**539–549.
Thompson MD, Storm van's Gravesande K, Galczenski H, Burnham WM, Siminovitch KA, Zamel N, Slutsky A, Drazen JM, George SR, Evans JF, et al. (2003) A cysteinyl leukotriene 2 receptor variant is associated with atopy in the population of Tristan da Cunha. *Pharmacogenetics* **13:**641–649.
Titos E, Clària J, Planagumà A, López-Parra M, González-Périz A, Gaya J, Miquel R, Arroyo V, and Rodés J (2005) Inhibition of 5-lipoxygenase-activating protein abrogates experimental liver injury: role of Kupffer cells. *J Leukoc Biol* **78:**871–878.
Toda A, Terawaki K, Yamazaki S, Saeki K, Shimizu T, and Yokomizo T (2010) Attenuated Th1 induction by dendritic cells from mice deficient in the leukotriene B4 receptor 1. *Biochimie* **92:**682–691.
Toda A, Yokomizo T, Masuda K, Nakao A, Izumi T, and Shimizu T (1999) Cloning and characterization of rat leukotriene B_4 receptor. *Biochem Biophys Res Commun* **262:**806–812.
Toki Y, Hieda N, Torii T, Hashimoto H, Ito T, Ogawa K, and Satake T (1988) The effects of lipoxygenase inhibitor and peptidoleukotriene antagonist on myocardial injury in a canine coronary occlusion-reperfusion model. *Prostaglandins* **35:**555–571.
Tomari S, Matsuse H, Machida I, Kondo Y, Kawano T, Obase Y, Fukushima C, Shimoda T, and Kohno S (2003) Pranlukast, a cysteinyl leukotriene receptor 1 antagonist, attenuates allergen-specific tumour necrosis factor α production and nuclear factor κB nuclear translocation in peripheral blood monocytes from atopic asthmatics. *Clin Exp Allergy* **33:**795–801.
Tong WG, Ding XZ, Talamonti MS, Bell RH, and Adrian TE (2005) LTB4 stimulates growth of human pancreatic cancer cells via MAPK and PI-3 kinase pathways. *Biochem Biophys Res Commun* **335:**949–956.
Tornhamre S, Stenke L, Granzelius A, Sjölinder M, Näsman-Glaser B, Roos C, Widell S, and Lindgren JA (2003) Inverse relationship between myeloid maturation and leukotriene C_4 synthase expression in normal and leukemic myelopoiesis-consistent overexpression of the enzyme in myeloid cells from patients with chronic myeloid leukemia. *Exp Hematol* **31:**122–130.
Trandafir CC, Nishihashi T, Ji X, Wang A, and Kurahashi K (2005) Cysteinyl leukotrienes and leukotriene B mediate vasoconstriction to arginine vasopressin in rat basilar artery. *Clin Exp Pharmacol Physiol* **32:**1027–1033.
Tryselius Y, Nilsson NE, Kotarsky K, Olde B, and Owman C (2000) Cloning and characterization of cDNA encoding a novel human leukotriene B_4 receptor. *Biochem Biophys Res Commun* **274:**377–382.
Turner CR, Breslow R, Conklyn MJ, Andresen CJ, Patterson DK, Lopez-Anaya A, Owens B, Lee P, Watson JW, and Showell HJ (1996) In vitro and in vivo effects of leukotriene B_4 antagonism in a primate model of asthma. *J Clin Invest* **97:**381–387.
Ueda T, Takeno S, Furukido K, Hirakawa K, and Yajin K (2003) Leukotriene receptor antagonist pranlukast suppresses eosinophil infiltration and cytokine production in human nasal mucosa of perennial allergic rhinitis. *Ann Otol Rhinol Laryngol* **112:**955–961.
Underwood DC, Osborn RR, Newsholme SJ, Torphy TJ, and Hay DW (1996) Persistent airway eosinophilia after leukotriene (LT) D4 administration in the guinea pig: modulation by the LTD4 receptor antagonist, pranlukast, or an interleukin-5 monoclonal antibody. *Am J Respir Crit Care Med* **154:**850–857.
Usery JB, Self TH, Muthiah MP, and Finch CK (2008) Potential role of leukotriene modifiers in the treatment of chronic obstructive pulmonary disease. *Pharmacotherapy* **28:**1183–1187.
Uzonyi B, Lötzer K, Jahn S, Kramer C, Hildner M, Bretschneider E, Radke D, Beer M, Vollandt R, Evans JF, et al. (2006) Cysteinyl leukotriene 2 receptor and protease-activated receptor 1 activate strongly correlated early genes in human endothelial cells. *Proc Natl Acad Sci USA* **103:**6326–6331.
Vaddi K and Newton RC (1994) Regulation of monocyte integrin expression by β-family chemokines. *J Immunol* **153:**4721–4732.
van Adelsberg J, Philip G, Pedinoff AJ, Meltzer EO, Ratner PH, Menten J, Reiss TF, and Montelukast Fall Rhinitis Study Group (2003) Montelukast improves symptoms of seasonal allergic rhinitis over a 4-week treatment period. *Allergy* **58:**1268–1276.
Van Hoecke H, Vandenbulcke L, and Van Cauwenberge P (2007) Histamine and leukotriene receptor antagonism in the treatment of allergic rhinitis: an update. *Drugs* **67:**2717–2726.
Vannella KM, McMillan TR, Charbeneau RP, Wilke CA, Thomas PE, Toews GB, Peters-Golden M, and Moore BB (2007) Cysteinyl leukotrienes are autocrine and paracrine regulators of fibrocyte function. *J Immunol* **179:**7883–7890.
Vaquerizo MJ, Casan P, Castillo J, Perpiña M, Sanchis J, Sobradillo V, Valencia A, Verea H, Viejo JL, Villasante C, et al. (2003) Effect of montelukast added to inhaled budesonide on control of mild to moderate asthma. *Thorax* **58:**204–210.
Vegesna RV, Wu HL, Mong S, and Crooke ST (1988) Staurosporine inhibits protein kinase C and prevents phorbol ester-mediated leukotriene D_4 receptor desensitization in RBL-1 cells. *Mol Pharmacol* **33:**537–542.
Veien NK, Busch-Sørensen M, and Stausbøl-Grøn B (2005) Montelukast treatment of moderate to severe atopic dermatitis in adults: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* **53:**147–149.
Virchow JC Jr, Prasse A, Naya I, Summerton L, and Harris A (2000) Zafirlukast improves asthma control in patients receiving high-dose inhaled corticosteroids. *Am J Respir Crit Care Med* **162:**578–585.
Virchow JC and Bachert C (2006) Efficacy and safety of montelukast in adults with asthma and allergic rhinitis. *Respir Med* **100:**1952–1959.
Virchow JC Jr, Faehndrich S, Nassenstein C, Bock S, Matthys H, and Luttmann W (2001) Effect of a specific cysteinyl leukotriene-receptor 1-antagonist (montelukast) on the transmigration of eosinophils across human umbilical vein endothelial cells. *Clin Exp Allergy* **31:**836–844.
Wada K, Arita M, Nakajima A, Katayama K, Kudo C, Kamisaki Y, and Serhan CN (2006) Leukotriene B_4 and lipoxin A_4 are regulatory signals for neural stem cell proliferation and differentiation. *FASEB J* **20:**1785–1792.
Wahn U and Dass SB (2008) Review of recent results of montelukast use as a monotherapy in children with mild asthma. *Clin Ther* **30 (Spec No):**1026–1035.
Walch L, Norel X, Bäck M, Gascard JP, Dahlén SE, and Brink C (2002) Pharmacological evidence for a novel cysteinyl-leukotriene receptor subtype in human pulmonary artery smooth muscle. *Br J Pharmacol* **137:**1339–1345.
Walch L, Norel X, Gascard JP, and Brink C (2000) Functional studies of leukotriene receptors in vascular tissues. *Am J Respir Crit Care Med* **161:**S107–S111.
Wan KS (2009) Efficacy of leukotriene receptor antagonist with an anti-H1 receptor antagonist for treatment of chronic idiopathic urticaria. *J Dermatolog Treat* **20:**194–197.
Wan M, Sabirsh A, Wetterholm A, Agerberth B, and Haeggström JZ (2007) Leukotriene B_4 triggers release of the cathelicidin LL-37 from human neutrophils: novel lipid-peptide interactions in innate immune responses. *FASEB J* **21:**2897–2905.
Wang D and Dubois RN (2010a) Eicosanoids and cancer. *Nat Rev Cancer* **10:**181–193.
Wang D and Dubois RN (2010b) Eicosanoids and cancer. *Nat Rev Cancer* **10:**181–193.
Wang ML, Huang XJ, Fang SH, Yuan YM, Zhang WP, Lu YB, Ding Q, and Wei EQ (2006) Leukotriene D_4 induces brain edema and enhances $CysLT_2$ receptor-mediated aquaporin 4 expression. *Biochem Biophys Res Commun* **350:**399–404.
Watanabe S, Yamasaki A, Hashimoto K, Shigeoka Y, Chikumi H, Hasegawa Y, Sumikawa T, Takata M, Okazaki R, Watanabe M, et al. (2009) Expression of functional leukotriene B_4 receptors on human airway smooth muscle cells. *J Allergy Clin Immunol* **124:**59–65.e1–3.
Weller CL, Collington SJ, Brown JK, Miller HR, Al-Kashi A, Clark P, Jose PJ, Hartnell A, and Williams TJ (2005) Leukotriene B_4, an activation product of mast cells, is a chemoattractant for their progenitors. *J Exp Med* **201:**1961–1971.
Wenzel SE, Trudeau JB, Kaminsky DA, Cohn J, Martin RJ, and Westcott JY (1995) Effect of 5-lipoxygenase inhibition on bronchoconstriction and airway inflammation in nocturnal asthma. *Am J Respir Crit Care Med* **152:**897–905.
Whitney LW, Ludwin SK, McFarland HF, and Biddison WE (2001) Microarray analysis of gene expression in multiple sclerosis and EAE identifies 5-lipoxygenase as a component of inflammatory lesions. *J Neuroimmunol* **121:**40–48.
Wikström K, Juhas M, and Sjölander A (2003a) The anti-apoptotic effect of leukotriene D_4 involves the prevention of caspase 8 activation and Bid cleavage. *Biochem J* **371:**115–124.
Wikström K, Ohd JF, and Sjölander A (2003b) Regulation of leukotriene-dependent induction of cyclooxygenase-2 and Bcl-2. *Biochem Biophys Res Commun* **302:**330–335.
Wilson AM, O'Byrne PM, and Parameswaran K (2004) Leukotriene receptor antag-

onists for allergic rhinitis: a systematic review and meta-analysis. *Am J Med* **116:**338–344.
Winkler JD, Sarau HM, Foley JJ, and Crooke ST (1988) Phorbol 12-myristate 13-acetate inhibition of leukotriene D4-induced signal transduction was rapidly reversed by staurosporine. *Biochem Biophys Res Commun* **157:**521–529.
Winkler JD, Sarau HM, Foley JJ, and Crooke ST (1990) Inhibitors of protein kinase C selectively enhanced leukotriene D4-induced calcium mobilization in differentiated U-937 cells. *Cell Signal* **2:**427–437.
Woolhouse IS, Bayley DL, and Stockley RA (2002) Sputum chemotactic activity in chronic obstructive pulmonary disease: effect of α_1-antitrypsin deficiency and the role of leukotriene B_4 and interleukin 8. *Thorax* **57:**709–714.
Woszczek G, Chen LY, Alsaaty S, Nagineni S, and Shelhamer JH (2010) Concentration-dependent noncysteinyl leukotriene type 1 receptor-mediated inhibitory activity of leukotriene receptor antagonists. *J Immunol* **184:**2219–2225.
Woszczek G, Chen LY, Nagineni S, Alsaaty S, Harry A, Logun C, Pawliczak R, and Shelhamer JH (2007) IFN-γ induces cysteinyl leukotriene receptor 2 expression and enhances the responsiveness of human endothelial cells to cysteinyl leukotrienes. *J Immunol* **178:**5262–5270.
Woszczek G, Chen LY, Nagineni S, Kern S, Barb J, Munson PJ, Logun C, Danner RL, and Shelhamer JH (2008a) Leukotriene D_4 induces gene expression in human monocytes through cysteinyl leukotriene type I receptor. *J Allergy Clin Immunol* **121:**215–221.e1.
Woszczek G, Chen LY, Nagineni S, and Shelhamer JH (2008b) IL-10 inhibits cysteinyl leukotriene-induced activation of human monocytes and monocyte-derived dendritic cells. *J Immunol* **180:**7597–7603.
Woszczek G, Pawliczak R, Qi HY, Nagineni S, Alsaaty S, Logun C, and Shelhamer JH (2005) Functional characterization of human cysteinyl leukotriene 1 receptor gene structure. *J Immunol* **175:**5152–5159.
Wu Y, Zhou C, Tao J, and Li S (2006) Montelukast prevents the decrease of interleukin-10 and inhibits NF-κB activation in inflammatory airway of asthmatic guinea pigs. *Can J Physiol Pharmacol* **84:**531–537.
Wunder F, Tinel H, Kast R, Geerts A, Becker EM, Kolkhof P, Hütter J, Ergüden J, and Härter M (2010) Pharmacological characterization of the first potent and selective antagonist at the cysteinyl leukotriene 2 ($CysLT_2$) receptor. *Br J Pharmacol* **160:**399–409.
Xu ZZ, Zhang L, Liu T, Park JY, Berta T, Yang R, Serhan CN, and Ji RR (2010) Resolvins RvE1 and RvD1 attenuate inflammatory pain via central and peripheral actions. *Nat Med* **16:**592–597.
Yamaoka KA, Claésson HE, and Rosén A (1989) Leukotriene B4 enhances activation, proliferation, and differentiation of human B lymphocytes. *J Immunol* **143:**1996–2000.
Yamaoka KA, Dugas B, Paul-Eugene N, Mencia-Huerta JM, Braquet P, and Kolb JP (1994) Leukotriene B_4 enhances IL-4-induced IgE production from normal human lymphocytes. *Cell Immunol* **156:**124–134.
Yamaoka KA and Kolb JP (1993) Leukotriene B_4 induces interleukin 5 generation from human T lymphocytes. *Eur J Immunol* **23:**2392–2398.
Yang G, Haczku A, Chen H, Martin V, Galczenski H, Tomer Y, Van Besien CR, Evans JF, Panettieri RA, Funk CD, et al. (2004) Transgenic smooth muscle expression of the human CysLT1 receptor induces enhanced responsiveness of murine airways to leukotriene D4. *Am J Physiol Lung Cell Mol Physiol* **286:**L992–L1001.
Yasuda D, Okuno T, Yokomizo T, Hori T, Hirota N, Hashidate T, Miyano M, Shimizu T, and Nakamura M (2009) Helix 8 of leukotriene B4 type-2 receptor is required for the folding to pass the quality control in the endoplasmic reticulum. *FASEB J* **23:**1470–1481.
Yokomizo T, Izumi T, Chang K, Takuwa Y, and Shimizu T (1997) A G-protein-coupled receptor for leukotriene B_4 that mediates chemotaxis. *Nature* **387:**620–624.
Yokomizo T, Izumi T, and Shimizu T (2001a) Co-expression of two LTB4 receptors in human mononuclear cells. *Life Sci* **68:**2207–2212.
Yokomizo T, Izumi T, and Shimizu T (2001b) Leukotriene B4: metabolism and signal transduction. *Arch Biochem Biophys* **385:**231–241.
Yokomizo T, Kato K, Hagiya H, Izumi T, and Shimizu T (2001c) Hydroxyeicosanoids bind to and activate the low affinity leukotriene B_4 receptor, BLT2. *J Biol Chem* **276:**12454–12459.
Yokomizo T, Kato K, Terawaki K, Izumi T, and Shimizu T (2000) A second leukotriene B_4 receptor, BLT2. A new therapeutic target in inflammation and immunological disorders. *J Exp Med* **192:**421–432.
Yoshisue H, Kirkham-Brown J, Healy E, Holgate ST, Sampson AP, and Davies DE (2007) Cysteinyl leukotrienes synergize with growth factors to induce proliferation of human bronchial fibroblasts. *J Allergy Clin Immunol* **119:**132–140.
Yu GL, Wei EQ, Wang ML, Zhang WP, Zhang SH, Weng JQ, Chu LS, Fang SH, Zhou Y, Chen Z, et al. (2005a) Pranlukast, a cysteinyl leukotriene receptor-1 antagonist, protects against chronic ischemic brain injury and inhibits the glial scar formation in mice. *Brain Res* **1053:**116–125.
Yu GL, Wei EQ, Zhang SH, Xu HM, Chu LS, Zhang WP, Zhang Q, Chen Z, Mei RH, and Zhao MH (2005b) Montelukast, a cysteinyl leukotriene receptor-1 antagonist, dose- and time-dependently protects against focal cerebral ischemia in mice. *Pharmacology* **73:**31–40.
Yuan YM, Fang SH, Qian XD, Liu LY, Xu LH, Shi WZ, Zhang LH, Lu YB, Zhang WP, and Wei EQ (2009) Leukotriene D_4 stimulates the migration but not proliferation of endothelial cells mediated by the cysteinyl leukotriene $CysLT_1$ receptor via the extracellular signal-regulated kinase pathway. *J Pharmacol Sci* **109:**285–292.
Zembowicz A, Mastalerz L, Setkowicz M, Radziszewski W, and Szczeklik A (2003) Safety of cyclooxygenase 2 inhibitors and increased leukotriene synthesis in chronic idiopathic urticaria with sensitivity to nonsteroidal anti-inflammatory drugs. *Arch Dermatol* **139:**1577–1582.
Zhang J, Migita O, Koga M, Shibasaki M, Arinami T, and Noguchi E (2006) Determination of structure and transcriptional regulation of CYSLTR1 and an association study with asthma and rhinitis. *Pediatr Allergy Immunol* **17:**242–249.
Zhang WP, Hu H, Zhang L, Ding W, Yao HT, Chen KD, Sheng WW, Chen Z, and Wei EQ (2004) Expression of cysteinyl leukotriene receptor 1 in human traumatic brain injury and brain tumors. *Neurosci Lett* **363:**247–251.
Zhao L, Moos MP, Gräbner R, Pédrono F, Fan J, Kaiser B, John N, Schmidt S, Spanbroek R, Lötzer K, et al. (2004) The 5-lipoxygenase pathway promotes pathogenesis of hyperlipidemia-dependent aortic aneurysm. *Nat Med* **10:**966–973.
Zhou G, Zhou Z, Ge S, Liu D, Zhang R, Xu G, Zhu W, Yin Q, Chen AF, and Liu X (2009) IL-18 accelerates the cell apoptosis by up-regulating cysteinyl leukotriene 2 receptor expression in human umbilical vein endothelial cells at the early stage of administration. *Vascul Pharmacol* **50:**171–177.
Zhu J, Qiu YS, Figueroa DJ, Bandi V, Galczenski H, Hamada K, Guntupalli KK, Evans JF, and Jeffery PK (2005) Localization and upregulation of cysteinyl leukotriene-1 receptor in asthmatic bronchial mucosa. *Am J Respir Cell Mol Biol* **33:**531–540.
Zijlstra FJ, van Dijk AP, Garrelds IM, Ouwendijk RJ, and Wilson JH (1992) Species differences in the pattern of eicosanoids produced by inflamed and non-inflamed tissue. *Agents Actions* **Spec No:**C73–C75.
Zijlstra FJ, van Dijk AP, Ouwendijk RJ, van Riemsdijk-Overbeeke IC, and Wilson JH (1993) Eicosanoid production by the mucosa in inflammatory bowel disease after 5-ASA treatment. *Agents Actions* **38 (Spec No):**C122–C124.