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INTERNATIONAL UNION OF BASIC AND CLINICAL PHARMACOLOGY REVIEW

Update on leukotriene, lipoxin and oxoeicosanoid receptors: IUPHAR Review 7

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This article, written by members of the International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR) subcommittee for the leukotriene receptors, confirms the existing nomenclature for these receptors and reviews our current understanding of their structure, pharmacology and functions and their likely physiological roles in health and disease. More information on this receptor family can be found in the Concise Guide to PHARMACOLOGY (http://onlinelibrary.wiley.com/doi/10.1111/bph.12445/abstract) and for each member of the family in the corresponding database. http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=35&familyType=GPCR

The endogenous ligands for the LT, lipoxin (LX) and oxoeicosanoid receptors are bioactive products produced by the action of the lipoxygenase family of enzymes. The LT receptors BLT_1 and BLT_2, are activated by LTB_4 and the $CysLT_1$ and $CysLT_2$ receptors are activated by the cysteinyl-LTs, whereas oxoeicosanoids exert their action through the OXE receptor. In contrast to these pro-inflammatory mediators, LXA_4 transduces responses associated with the resolution of inflammation through the receptor FPR2/ALX (ALX/FPR2). The aim of the present review is to give a state of the field on these receptors, with focus on recent important findings. For example, BLT_1 receptor signalling in cancer and the dual role of the BLT_2 receptor in pro- and anti-inflammatory actions have added more complexity to lipid mediator signalling. Furthermore, a cross-talk between the CysLT and P2Y receptor systems has been described, and also the presence of novel receptors for cysteinyl-LTs, such as GPR17 and GPR99. Finally, lipoxygenase metabolites derived from ω-3 essential polyunsaturated acids, the resolvins, activate the receptors GPR32 and ChemR23. In conclusion, the receptors for the lipoxygenase products make up a sophisticated and tightly controlled system of endogenous pro- and anti-inflammatory signalling in physiology and pathology.

Abbreviations

AQP4, aquaporin 4; ATRA, all-*trans* retinoic acid; AT-RvD3, aspirin-triggered resolvin; BMDM, bone marrow-derived macrophages; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DC, dendritic cell; EAE, experimental autoimmune encephalitis; GRK, GPCR kinase; OGD, oxygen-glucose deprivation; LX, lipoxin; OIR, oxygen-induced retinopathy; RSV, respiratory syncytial virus; Rv, resolvin

Links to online information in the IUPHAR/BPS Guide to PHARMACOLOGY and the BJP's 'Concise Guide to Pharmacology 2013/14

Targets	Ligands	
5-lipoxygenase (5-LOX)	5-(6-chloro-2-hexyl-1H-indol-1-yl)-5-oxo-valeric acid	IL-1β
12-lipoxygenase (12-LOX)	5-Oxo-ETE	IL-2
15-lipoxygenase (15-LOX)	5S-HETE	IL-4
adenylyl cyclase (AC)	12-epi LTB	IL-5
Akt	12-hydroxyheptadecatrienoic acid (12-HHT)	IL-6
Aquaporin 4 (AQP4)	12S-HETE	IL-8 (CXCL8)
BLT_1 receptor	15S-HETE	leukotriene A (LTA)
BLT_2 receptor	acetylsalicylic acid (aspirin)	leukotriene B (LTB)
C5a receptors	ADP	leukotriene C (LTC)
CB receptor	all-trans-retinoic acid (ATRA)	leukotriene D (LTD)
Chemerin receptor (ChemR23)	anandamide	leukotriene E (LTE)
cyclooxygenase-2 (COX-2)	annexin I-(2-26) (Ac2-26)	lipoxin A (LXA)
$CysLT_1$ receptor	arachidonic acid	LL-37
$CysLT_2$ receptor	aspirin-triggered lipoxin A (15-epi-LXA, ATL)	LY255283
ERK	aspirin-triggered RvD1	montelukast
FPR2/ALX (ALX/FPR2)	BAY u9773	N-methyl LTC
GPR17	BayCysLT2	PACAP
GPR32	cAMP	PDGF
c-Jun N-terminal kinase (JNK)	carbachol	pobilukast
Leukotriene A (LTA) hydrolase	CCL26 (eotaxin-3)	pranlukast
MMP-9	CGEN-855A	resolvin D1 (RvD1)
OXE receptor	chemerin	resolvin E1 (RvE1)
Oxoglutarate receptor (GPR99)	docosahexaenoic acid (DHA)	resolvins
P2Y receptors	eicosapentaenoic acid (EPA)	rosuvastatin
P2Y12 receptor	fluticasone	serum amyloid A (SAA)
p38 MAP kinase	forskolin	SHAAG
phospholipase A (PLA)	G-CSF	TGF-β
phospholipase C (PLC)	glutathione	thromboxane A
PI3K	GM-CSF	U75302
PPARγ	Gue1654	UDP
TNFα	HAMI3379	UDP-galactose
	hydroxyproline	UDP-glucose
	IFN-γ	WKYMVM
	IL-10	WRW4
	IL-13	zafirlukast

This table lists protein targets and ligands that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and the Concise Guide to PHARMACOLOGY 2013/14 (Alexander *et al.*, 2013a,b).

Introduction

The endogenous ligands for the LT, lipoxin (LX) and oxoeicosanoid receptors are bioactive products produced by the action of the lipoxygenase family of enzymes shown in Figure 1 (Brink *et al.*, 2003; Brink *et al.*, 2004; Chiang *et al.*, 2006; Bäck *et al.*, 2011). The metabolism of arachidonic acid by 5-lipoxygenase yields the epoxide intermediate LTA_4, which serves as precursor for the LT receptor agonists (Figure 1). Subsequent metabolism through the enzyme LTA_4 hydrolase leads to formation of the dihydroxy-LT LTB_4, which is the ligand for the BLT receptors (Figure 1). Alternatively, conjugation of LTA_4 with glutathione yields the cysteinyl-LTs acting on the two CysLT receptor (CysLTR) subtypes, $CysLT_1$ and $CysLT_2$ (Figure 1). There is also evidence in the literature for additional CysLT receptor subtypes, derived from functional *in vitro* studies (Lee *et al.*, 1984; Snyder and Krell, 1984; Bäck *et al.*, 2000; Sakata and Bäck, 2002; Walch *et al.*, 2002), radioligand binding (Capra *et al.*, 1998; Ravasi *et al.*, 2000; 2002) and mice lacking both $CysLT_1$ and $CysLT_2$ receptors (Maekawa *et al.*, 2008). LTE_4 has, for example, been suggested to signal through $P2Y_{12}$ receptors in some studies (Nonaka *et al.*, 2005; Paruchuri *et al.*, 2009; Fredman *et al.*, 2010), although not replicated in all settings (Foster *et al.*, 2013). In support of common receptors mediating purinergic and LT signalling, the orphan GPR17 (Figure 1) has been postulated to be activated by both cysteinyl-LTs and nucleotides (Ciana *et al.*, 2006); this will be further discussed below. In addition, recent evidence point to yet another receptor for cysteinyl-LTs, namely, GPR99 (Kanaoka *et al.*, 2013) as indicated in Figure 1.

Oxoeicosanoids are another family of biologically active arachidonic acid derivatives that have been intimately associated with cellular migration (Powell *et al.*, 1995). 5-Oxo-ETE, formed by the oxidation of 5S-HETE by 5-hydroxyeicosanoid dehydrogenase (Figure 1) is a potent chemoattractant for human granulocytes and monocytes by means of the OXE receptor (Brink *et al.*, 2004).

The dual lipoxygenation of arachidonic acid by either the 15- and 5-lipoxygenase or the 5- and 12-lipoxygenase produces eicosanoids known as lipoxins (LXs), as indicated in Figure 1 (Chiang *et al.*, 2006). These eicosanoids are inhibitory or anti-inflammatory mediators, which act as a 'stop signal' during inflammatory reactions (Serhan, 2007; Capra *et al.*, 2013) through a receptor with high sequence homology (70%) to the formyl peptide receptors (FPR). However, although a number of peptides activate this receptor, LXA_4 is the most potent native endogenous ligand, and the nomenclature recommended for this receptor is FPR2/ALX. The term ALX/FPR2 for the same receptor is suggested when the lipoxin-binding property is of primary concern (Ye *et al.*, 2009).

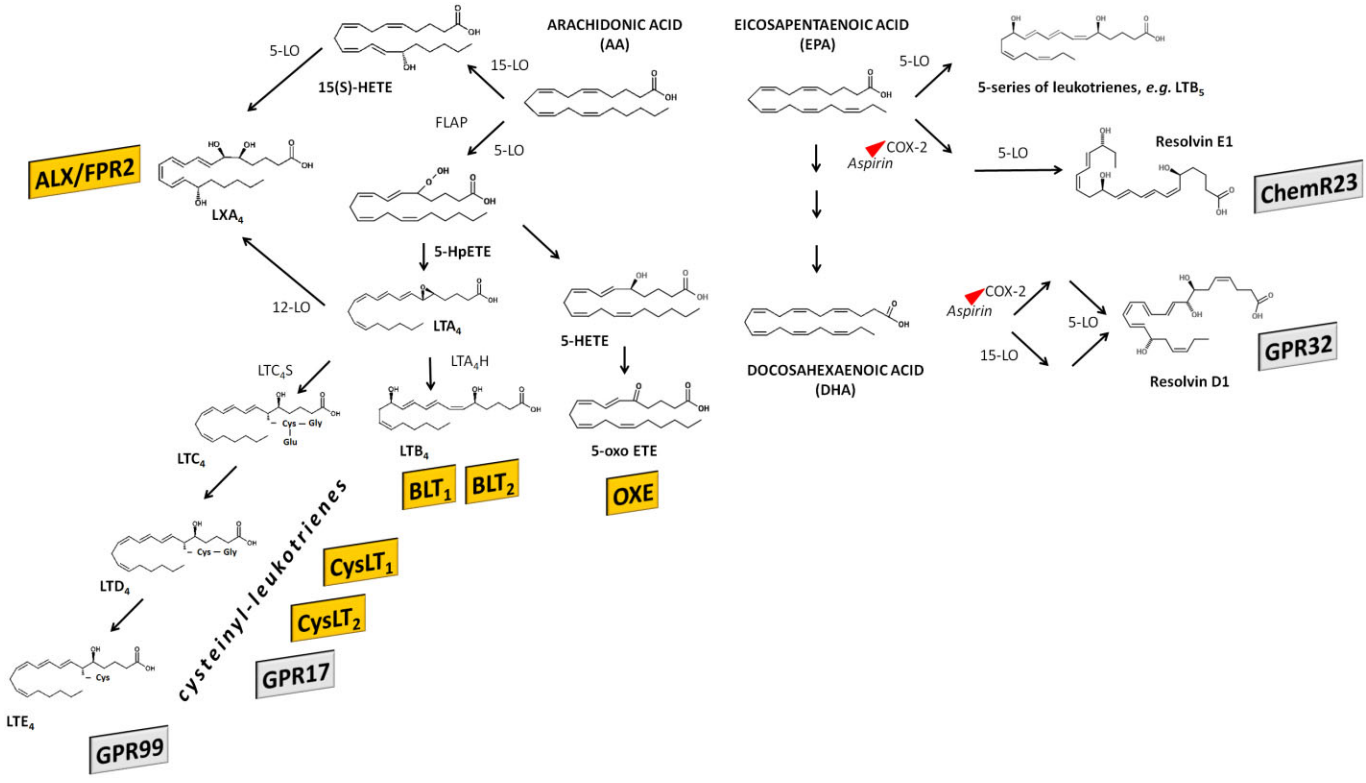

Figure 1

Members of the LT receptor family are depicted in yellow, whereas shaded rectangles indicate related receptors, for which formal ligand pairing is yet to be agreed. ETE, eicosatetraenoic acid; FLAP, 5-lipoxygenase activating protein; GPR, G protein-coupled receptor; HETE, hydroxyeicosatetraenoic acid; HpETE, hydroperoxyeicosatetraenoic acid; LO, lipoxygenase; LTC_4S, LT C_4 synthase; LTA_4H, LTA_4 hydrolase; LX, lipoxin.

Besides the 20:4, n-6 fatty acid arachidonic acid, also ω-3 essential polyunsaturated fatty acids, such as eicosapentaenoic acid (EPA; 20:5, n-3) and docosahexaenoic acid (DHA; 22:6, n-3), are metabolized by lipoxygenases in human cells (Figure 1). For example, when metabolized by 5-lipoxygenase, EPA generates LTs of the 5-series (e.g. LTB_5, see Figure 1), which are less biologically active and compete with LT binding to the LT receptors, suggesting that lipoxygenase metabolites of ω-3 fatty acids may act as inhibitors of inflammation (Stanke-Labesque *et al.*, 2008). Furthermore, EPA and DHA can enter into the lipoxygenase metabolism and lead to the biosynthesis of either E-series (for EPA-derived), or D-series (for DHA-derived) of resolvins (Rv). These ω-3-derived mediators have been characterized as mediators of inflammation resolution by means of signalling through two GPCRs, GPR32 and ChemR23, as will be further discussed below.

The LT, LX and oxoeicosanoid receptor cloning, ligand affinity, expression and functional significance have been reviewed in previous IUPHAR reports (Brink *et al.*, 2003; Brink *et al.*, 2004; Chiang *et al.*, 2006; Bäck *et al.*, 2011) and are summarized in Tables 1–6. The aim of the present review is to give a state of the field on these receptors, with focus on recent important findings.

BLT receptors

The dihydroxy-LT, LTB_4 stimulates neutrophil chemotaxis and secretion but may also affect immunomodulation through the activation of several leukocyte populations (Bäck *et al.*, 2011; Nakamura and Shimizu, 2011). In addition, receptors for LTB_4 are expressed on non-myeloid cells, such as vascular smooth muscle and endothelial cells (Bäck *et al.*, 2005). Chemotaxis, one of the principal effects of LTB_4, occurs via activation of the BLT_1 receptor subtype (Yokomizo *et al.*, 1997), which is the high-affinity LTB_4 receptor. The open reading frame of the gene encoding a second subtype of BLT receptor was identified during the analysis of the BLT_1 promoter (Yokomizo *et al.*, 2000). This receptor was named BLT_2 and either HEK or CHO cells transfected with BLT_2 cDNA exhibited low affinity to LTB_4 and in addition responded to various other hydroxy fatty acids including 12-epi LTB_4, 12S-HETE and 15S-HETE (Yokomizo *et al.*, 2000). Search for endogenous high-affinity ligands for BLT_2 receptors resulted in the identification of 12-HHT (12(S)-hydroxyheptadeca-5Z, 8E, 10E-trienoic acid), previously known as a by-product of TxA_2 biosynthesis, as a high-affinity BLT_2 receptor ligand (Okuno *et al.*, 2008). Pro-inflammatory LTB_4 signalling through the BLT_1 and BLT_2 receptors has been implicated in several diseases (Bäck *et al.*, 2011; Nakamura and Shimizu, 2011), such as bronchial asthma (Miyahara *et al.*, 2005; Terawaki *et al.*, 2005), rheumatoid arthritis (Kim *et al.*, 2006; Chou *et al.*, 2010), atherosclerosis (Bäck and Hansson, 2006), abdominal aortic aneurysms (Houard *et al.*, 2009), bone metabolism (Hikiji *et al.*, 2009), multiple sclerosis (Kihara *et al.*, 2010) and cancer (Yokota *et al.*, 2012).

BLT_1 receptor

Structure–function relationships. Of the receptors addressed in the present review, the human BLT_1 receptor is the best characterized in terms of structure–function relationships. Like several rhodopsin family GPCRs, the BLT_1 receptor bears an 8th helix (H8) domain consisting of Val^{298}-Gly-Phe-Val-Ala-Lys-Leu-Leu-Glu-Gly^{307} (Okuno *et al.*, 2003). Two aromatic residues, Tyr^{285} and Phe^{300}, may stabilize the inactive form of the BLT_1 receptor by holding H8 at an almost right angle from the C-terminus of the seventh transmembrane region (Okuno *et al.*, 2003). Thus, H8-deficient BLT_1 receptor mutants exhibit a prolonged intracellular signalling after LTB_4 stimulation (Okuno *et al.*, 2003). Hydrophobic amino acid residues in the H8, Val^{301}, Leu^{304} and Leu^{305}, may act as anchors to the plasma membrane, whereas Thr^{308} located after the H8 is one of the ligand-induced phosphorylation sites mediated by the GPCR kinase GRK6, and involved in BLT_1 receptor inactivation (Gaudreau *et al.*, 2002). Recently, Aratake *et al.* reported an inhibitory role of the H8 on the LTB_4-elicited internalization of the BLT_1 receptor (Aratake *et al.*, 2012). The human BLT_1 receptor with the mutations of Leu^{304} and Leu^{305} in the H8 exhibited an augmentation of LTB_4-induced internalization, whereas the wild-type (WT) receptor exhibited minimal internalization. Furthermore, phosphorylations of 5 Ser and Thr residues between 308 and 319 were important for this enhanced internalization of the mutant BLT_1 receptor. Therefore, the H8 of BLT_1 may repress LTB_4-induced internalization by suppressing excessive phosphorylations.

BLT_1 receptors in inflammation. The generation of BLT_1 receptor-deficient mice confirmed the loss of responsiveness to LTB_4 in BLT_1 receptor null leukocytes (Haribabu *et al.*, 2000; Tager *et al.*, 2000) and the suppression of several inflammation disease models (Bäck *et al.*, 2011). In contrast, transgenic mice overexpressing the human BLT_1 receptor exhibited enhanced responsiveness of leukocytes in acute dermal inflammation (Chiang *et al.*, 1999). Recently, Monterio *et al.* reported that macrophages, but not mast cells, are involved in the migration of neutrophils, by generating LTB_4 in haem-induced neutrophilic inflammation, for example, malaria and sickle cell disease (Monteiro *et al.*, 2011). BLT_1 receptor antagonists, CP-105696 and LY-292476, significantly impaired the haem-induced peritoneal neutrophilia, demonstrating further involvement of the BLT_1 receptor in this inflammatory response (Monteiro *et al.*, 2011).

BLT_1 receptors in cardiovascular disease (CVD). Recurring nocturnal episodes of airway obstruction, known as obstructive sleep apnea syndrome, causes intermittent hypoxia, which is a detrimental stimuli for the cardiovascular system associated with, for example, early atherosclerosis and an increased cardiovascular risk (Stanke-Labesque *et al.*, 2014). Neutrophil granulocytes derived from patients with obstructive sleep apnea exhibit increased LTB_4 production in response to calcium ionophore stimulation, compared with cells derived from healthy subjects (Stanke-Labesque *et al.*, 2012). In addition, expression of LT-synthesizing enzymes in neutrophils correlates with measures of subclinical atherosclerosis and vascular remodelling in these patients (Stanke-Labesque *et al.*, 2012). In support of a role for the LTB_4-BLT_1 pathway in sleep apnea-associated atherosclerosis, mice deficient in both apolipoprotein E and the BLT_1 receptor are protected from the accelerated atherosclerosis observed after subjecting

Table 1

The BLT_1 receptor

Agonists	LTB_4 (full agonist)	Affinity	9.2–9.8 (pKd); 9.4 (pKi)
	20-OH-LTB_4 (full agonist)		8.1 (pKi)
	12(R)-HETE (full agonist)		7.5 (pKi)
Antagonists	BIIL-260	Affinity	8.5 (pIC_{50}), 8.8 (pKi)
	LY-293111		6.6 (pKi)
	CP-195543		8.6 (pIC_{50}), 8.2 (pKi)
	ONO-4057		8.4 (pKi)
	LY-255283		6.6 (pKi)
Transduction mechanisms			
	Transducer	$G_{i/0}$ family; $G_{q/G11}$; $G\alpha_{16}$	
	Effector/response	Adenylate cyclase inhibition; PLC stimulation, MAKP activation	
Receptor distribution			
Human granulocytes, monocytes, dendritic cells, T-lymphocytes, B-lymphocytes			
Human coronary artery smooth muscle cells and bronchial smooth muscle cells			
Human umbilical cord endothelial cells			
Human atherosclerotic lesions, human abdominal aortic aneurysms			
Synovial tissues derived from patients with rheumatoid arthritis			
Pancreatic and colon cancers			
Examples of functional assays			
CHO cells transfected with human BLT_1: chemotaxis, increase in intracellular calcium			
Retinoic acid-differentiated HL-60 cells: increase in intracellular calcium			
Human coronary artery smooth muscle cells: increase in whole cell currents			
Murine RAW264.7 cells and bronchial smooth muscle cells: MAPK activation			
Rodent RBL-2H3 cells: PI3K activation			
Example of physiological functions			
Human granulocytes: chemotaxis and release of lysosomal enzymes			
Murine macrophages: phagocytosis			
Murine T-lymphocytes: Il-2 production			
Guinea pig pulmonary artery: vasoconstriction			
Examples of pathophysiological functions (confirmed in BLT_1-deficient mice)			
Bronchial asthma/airway hyperresponsiveness			
Rheumatoid arthritis (confirmed in both BLT_1-null and BLT_1/BLT_2-null mice)			
Atherosclerosis			
Osteoporosis (regulation of osteoclast function)			
Multiple sclerosis			
Atopic dermatitis			
Tumour			

Full information and references available in the IUPHAR/BPS Guide to PHARMACOLOGY, http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=267&familyId=35&familyType=GPCR.

apolipoprotein E-deficient mice to intermittent hypoxia *in vivo* (Li *et al.*, 2011).

Hypertension is associated with increased levels of LTB_4 measured in the saliva (Labat *et al.*, 2013). In addition, cerebral LTB_4 levels are increased in spontaneously hypertensive rats compared with Wistar-Kyoto rats (Waki *et al.*, 2013). In the latter study, microinjection of the BLT_1 receptor antagonist U75302 into the solitary nucleus of spontaneously hypertensive rats lowered arterial pressure, suggesting that LTB_4-BLT_1 receptor inflammatory circuits in the brain stem may be associated with neurogenic hypertension (Waki *et al.*, 2013).

BLT_1 receptors in rheumatoid arthritis. Several studies have revealed that BLT_1 receptor-deficient mice are protected from the development of arthritis using different models,

Table 2

The BLT_2 receptor

Agonists	12-HHT	Affinity	7.72 (pEC_{50})
	CAY10583		7.7 (pEC_{50})
	LTB4		7.64 (pKd)
	LTB4		7.6 (pIC_{50})
	12-epi LTB4		7.52 (pEC_{50})
	12(S)-HETE		7.52 (pEC_{50})
	15(S)-HETE		7.52 (pEC_{50})
Antagonists	ZK158252	Affinity	6.0–7.1 (pIC_{50})
	CP195543		6.0 (pIC_{50})
	LY255283		6.0 (pIC_{50})
Transduction mechanisms			
Transducer		$G_{i/0}$ family; $G_{q/11}$ family	
Effector/response		Adenylate cyclase inhibition; PLC stimulation	
Examples of receptor distribution			
Human spleen, liver, ovary and leukocytes			
Human atherosclerotic lesions, human abdominal aortic aneurysms			
Synovial tissues derived from patients with rheumatoid arthritis			
Murine small intestine and skin			
Examples of functional assays			
CHO cells transfected with the human BLT_2: chemotaxis, increase in intracellular calcium			
MDCK cells trasnfected with human BLT_2: increase in transendothelial resistance.			
Guinea pig lung parenchyma: contraction			
Examples of physiological functions			
Chemotaxis			
Angiogenesis			
Examples of pathophysiological functions (confirmed in BLT_2-deficient mice)			
Rheumatoid arthritis (in BLT_1/BLT_2-null mice)			
Endothelial function			
Protection against colitis			
Attenuated allergic airway eosinophilia			
Tumour			

Full information and references available in the IUPHAR/BPS Guide to PHARMACOLOGY, http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=268&familyId=35&familyType=GPCR. Currently, LY255283 is used as a BLT_2 receptor-specific antagonist, but this compound also inhibits BLT_1 in a non-competitive manner. 12-HHT, 12-hydroxyheptadecatrienoic acid.

associated with decreased articular neutrophil recruitment (Kim *et al.*, 2006) resulting in reduced production of IL-1 and chemokines in the joint (Chou *et al.*, 2010). In this disease, the recruitment of neutrophils is orchestrated via two pathways, C5a receptor signalling-induced LTB_4 release followed by BLT_1 receptor activation, and Fcγ receptor signalling-elicited IL-1β release (Sadik *et al.*, 2012).

BLT_1 receptors in other diseases. Atopic dermatitis is an inflammatory skin disease. Although LTB_4 concentration is elevated in skin lesions of patients with atopic dermatitis, little is known about the role of LTB_4 in this disease. Recently, Oyoshi *et al*. reported an essential role of the LTB_4-BLT_1 receptor pathway in neutrophils for allergic skin inflammation (Oyoshi *et al.*, 2012b). In the latter study, allergic skin inflammation was significantly decreased in BLT_1-deficient mice, and it was demonstrated that both LTB_4 production and BLT_1 receptor expression in neutrophils were important for the development of this disease (Oyoshi *et al.*, 2012b).

Recently, the role of the BLT_1 receptor signalling in tumour immunology has been investigated. Yokota *et al*. examined the effect of the BLT_1-deficiency on the anti-tumour memory responses elicited by s.c. administration of GM-CSF gene-transduced WEHI3B (WGM) leukaemia cells using BLT_1 receptor-deficient mice (Yokota *et al.*, 2012). They found that the BLT_1 receptor deficiency resulted in reduced tumour-infiltrating myeloid-derived suppressor cells, increase in matured dendritic cells (DCs) in tumour tissues and

Table 3

The $CysLT_1$ receptor

Agonists	LTD_4 (full agonist)	Affinity	7.3–9.4 (pEC_{50}); 8.1 (pIC50); 8.6–10.6 (pKd)
	LTC_4 (full agonist)		7.4–7.7 (pEC_{50}); 6.4–6.5 (pIC_{50}); 7.0–8.1 (pKi)
	LTE_4 (partial agonist)		6.4–7.2 (pEC_{50}); 6.6–6.97 (pIC_{50})
	N-methyl-LTC_4 (partial agonist)		5.7 (pEC_{50})
Antagonists	Montelukast	Affinity	8.6 (pKi); 8.3–8.6 (pIC_{50})
	Zafirlukast		8.9 (pKi); 7.7–9.6 (pIC_{50})
	Pranlukast		7.1–8.8 (pKi); 8.1–10.0 (pIC_{50})
	Pobilukast		7.1 (pKi); 7.5–8.2 (pIC_{50})
	Iralukast		7.8 (pKi)
	Verlukast		8.0 (pIC_{50})
	BAYu9773		5.3–6.4 (pIC_{50})
Transduction mechanisms			
Transducer		Gq/11 family; Gi/0 family	
Effector/response		PI turnover and Ca^{2+} mobilization; PLC stimulation	
Examples of receptor distribution			
Lung, bronchus, bronchiole smooth muscle, airway mucosa			
Nasal polyps			
Peripheral blood leukocytes, macrophages			
Human saphenous vein, human coronary artery smooth muscle cells			
Aortic valves			
Spleen, small intestine and placenta			
Colorectal carcinoma cells			
Examples of functional assays			
Several cell types: activation of MAPK			
X. laevis melanophores transfected with human $CysLT_1$: pigment dispersion			
X. laevis oocyte infected with human $CysLT_1$: Cl current			
HEK293 or COS-7 cells transfected with human $CysLT_1$: $[Ca^{2+}]i$ increase			
Examples of physiological functions			
Bronchoconstriction			
Cell proliferation			
Chemotactic activity and migration			
Actin reorganization			
Release of inflammatory mediators and cytokines			
Cell adhesion			
Activation of transcription factors			
Examples of pathophysiological functions (confirmed in $CysLT_1$-deficient mice)			
Bleomycin-induced pulmonary inflammation			
Zymosan-induced peritonitis			
Cutaneous anaphylaxis			

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augmentation of $CD4^+$ T-lymphocyte stimulation capacity during GM-CSF-triggered tumour regression, demonstrating that the lack of the LTB_4-BLT_1 receptor pathway induced long-term anti-tumour memory responses after immunization with WGM leukaemia cells. In another study however, BLT_1 receptor-deficient mice exhibited accelerated tumour growth and reduced survival compared with WT mice in a cervical cancer model (Sharma *et al.*, 2013). These findings were associated with a decreased number of $CD8^+$ T-lymphocytes and NK cells in tumours derived from BLT_1 receptor-deficient mice, and decreased IFN-γ and IL-2 expression (Sharma *et al.*, 2013). Taken together, those studies

Table 4

The $CysLT_2$ receptor

Agonists	LTC_4 (full agonist)	Affinity	7.0–8.6 (pEC_{50}); 8.4–8.5 (pIC_{50}); 7.0–10.8 (pKd)
	LTD_4 (full agonist)		6.8-8.6 (pEC_{50}); 7.2–8.2 (pIC_{50}); 7.3–9.4 (pKd)
	LTE_4 (partial agonist)		5.6–7.1 (pEC_{50}); 5.7-6.2 (pIC_{50}); 6.5 (pKi)
	N-methyl-LTC_4 (full agonist)		6.9–8.1 (pEC_{50})
	BAYu9773 (partial agonist)		7.0–7.2 (pEC_{50}); 6.2–6.4 (pIC_{50})
Antagonists	BAYu9773	Affinity	6.8-7.7 (pA_2); 6.5–6.7 (pK_B); 5.3–7.7 (pIC_{50})
	BayCysLT2		8.3–8.4 (pA_2); 6.6–7.3 (pIC_{50})
	HAMI3379		7.4–8.4 (pIC_{50})
Transduction mechanisms			
	Transducer		Gq/11 family; Gi/0 family
	Effector/response		PLC stimulation; p38 activation
Examples of receptor distribution			
Human saphenous vein, human coronary artery smooth muscle cells			
Human umbilical vein endothelial cells			
Heart (atria, left ventricle, pericardium)			
Peripheral blood leukocytes, human platelets			
Brain and spinal cord			
Nasal polyps, nasal mucosa			
Colorectal cancer tissue			
Spleen, adrenals and placenta			
Colorectal carcinoma cells			
Examples of functional assays			
HEK293 or COS-7 cells transfected with human CysLT2: $[Ca^{2+}]i$ increase			
Vascular smooth muscle and endothelial cells: $[Ca^{2+}]i$ increase			
Mast cells and umbilical vein endothelial cells: Increased IL-8 secretion, P38 activation			
C2C12 myofibroblasts transfected with the human $CysLT_2$ receptor: β-arrestin binding			
Examples of physiological functions			
Secretion of von Willebrand factor and P-selectin expression in endothelial cells			
Vasoconstriction and endothelium-dependent relaxation			
Up-regulation of early response genes			
Examples of pathophysiological functions (confirmed in $CysLT_2$-deficient mice)			
Skin fibrosis			
Pulmonary inflammation and fibrosis			
Increased vascular permeability			
Colitis			
Retinal oedema			

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suggest that BLT_1 receptor signalling on both suppressor and effector cells of the adaptive immune system may be involved in tumour progression and regression.

BLT_2 receptors

Whereas BLT_2 receptor-deficient mice exhibit reduced severity in arthritis models (Mathis *et al.*, 2010), this deletion induces more severe colitis induced by dextran sulfate, possibly due to the loss of intestinal barrier function maintained by BLT_2 receptors (Iizuka *et al.*, 2010). In line with the latter findings, BLT_2 receptor-deficient mice also exhibit more severe eosinophilic inflammation induced by sensitization and elicitation by ovalbumin accompanied by the reduced accumulation of IL-13 in the allergic airway (Matsunaga *et al.*, 2013). Taken together, these findings indicate a protective role of the BLT_2 receptor in intestinal and airway inflammation.

Table 5

The OXE receptor

Agonists	5-oxo-ETE (full agonist)	Affinity	8.3–8.5 (pEC_{50}); 8.4 (pKd)
	5-oxo-C20:3		8.0 (pEC_{50})
	5-oxo-ODE		8.0 (pEC_{50})
	5-oxo-15-HETE		7.7 (pEC_{50})
	5S-HpETE		6.2–7.5 (pEC_{50})
Antagonists	5-(6-chloro-2-hexyl-1H-indol-1-yl)-5-oxo-valeric acid		6.4 (pIC_{50})
	5-oxo-12-HETE		6.3 (pIC_{50})
Transduction mechanisms			
Transducer		$G_{i/0}$ family	
Effector/response		PLA_2 and PLC stimulation, adenylate cyclase inhibition, stimulation of PI3K, ERK and p38 MAPK.	
Examples of receptor distribution			
Peripheral blood leukocytes, macrophages			
Prostate tumour tissue			
Liver, kidney, lung, spleen, placenta, small intestine, colon, skeletal muscle, heart			
H295R adrenocortical cells			
Cancer cell lines			
Examples of functional assays			
Human granulocytes: increased cytosolic calcium levels, formation of F-actin, shape change, surface expression of CD11b			
Human eosinophil granulocytes: increased surface expression of CD69 and loss of L-selectin from the cell surface			
Human eosinophil granulocytes: release of eosinophil peroxidase and arylsulfatase human neutrophil granulocytes: release of β-glucuronidase and lysozyme			
Examples of physiological function			
Stimulation of the respiratory burst (superoxide production)			
Chemotaxis			
Transendothelial migration			
GM-CSF release			
Cancer cell proliferation			
Steroidogenesis in adrenocortical cells			

Full information and references available in the IUPHAR/BPS Guide to PHARMACOLOGY, http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=271&familyId=35&familyType=GPCR. As there is no orthologue of OXER1 in mice, gene knockout studies cannot be done in this species.

Pharmacological treatment of apolipoprotein E-deficient mice fed a high-fat diet using the BLT_2 receptor antagonist LY255283 did not alter atherosclerotic lesion size (Hoyer *et al.*, 2012). However, aortic segments derived from LY255283-treated mice exhibited lower levels of reactive oxygen species (ROS), and increased carbachol-induced endothelium-dependent relaxations compared with untreated mice (Hoyer *et al.*, 2012), suggesting that BLT_2 receptor signalling may be involved in endothelial dysfunction. However, it should be taken into consideration that although LY255283 has been used as a BLT_2 receptor-specific antagonist, this compound was recently shown to inhibit also the BLT_1 receptor in a non-competitive manner (Matsunaga *et al.*, 2013).

Screening a human thymus cDNA to identify BLT_2 receptor-interacting proteins recently identified that RanBPM, a member of the Ran-GTPase-binding protein family, which can bind at the C-terminal of the BLT_2 receptor in the absence of LTB_4, whereas the co-localization of these proteins was abolished in the presence of LTB_4 (Wei *et al.*, 2013). RanBPM overexpression attenuated, whereas knockdown promoted, BLT_2 receptor-mediated motility and generation of ROS in response to either LTB_4 or 12HHT (Wei *et al.*, 2013), suggesting that RanBPM may act as a negative regulator of BLT_2 receptor signalling in cell motility. Finally, the BLT_2 receptor dissociation from RanBPM was dependent on phosphorylation of BLT_2 receptors at Thr^{355}, a site previously identified by the same investigators as critical for LTB_4-induced BLT_2 receptor-mediated chemotaxis through PI3K-Akt signalling (Wei *et al.*, 2011).

Several recent *in vitro* studies on BLT_2 receptor signalling have focused on different cancer cells. For example, human ovarian and prostate cancer cells express BLT_2 receptors coupled to activation of NAD(P)H oxidase-4 (NOX4) and

Table 6

The ALX/FPR2 receptor

Agonists	Lipid mediators:	Affinity
	LXA_4 and ATL (full agonist)	12 (pEC_{50}); 8.3–9.3 (pKd)
	RvD1 and AT-RvD1 (full agonist)	11.9 (pEC_{50})
	Formyl peptides	
	PSMα3 (full agonist)	8.7 (pEC_{50})
	Host-derived non-amyloidogenic peptides	
	Annexin A1 (full agonist)	5.8–6.1 (pEC_{50}); 6.5 (pKd)
	SHAAGtide (full agonist)	7.7 (pEC_{50})
	LL-37 (full agonist)	6.0 (pEC_{50})
	Host-derived amyloidogenic peptides	
	SAA (full agonist)	6.6 (pEC_{50})
	Peptides identified from library screen	
	WKYMVm (full agonist)	9.0–10.1 (pEC_{50})
Antagonists	compound 1754-31	7.1 (pIC_{50})
	WRWWWW	6.6 (pIC_{50})
	t-Boc-FLFLF	4.3–6.0 (pIC_{50})
Transduction mechanisms		
Transducer		$G_{i/0}$ family
Effector/response		PLC, PLA_2 and PLD stimulation
Examples of receptor distribution		
Peripheral blood leukocytes		
Synovial fibroblasts		
Intestinal epithelial cells		
Lung, kidney, spleen and placenta		
Examples of functional assays		
PMN, HL-60 cells or CHO cells overexpressing human ALX/FPR2: PLD activation, arachidonic acid release, PSDP increase		
Human macrophages: phagocytosis		
THP-1 cells: calcium mobilization, adherence, chemotaxis		
Human T-cells. ERK activation		
Examples of physiological functions		
LXA_4 and ATL induce anti-inflammatory signals such as reducing CD11b/CD18, expression, blocking ROS production, NF-κB activation, pro-inflammatory cytokines/chemokines.		
LXA_4 and ATL give pro-resolving signals, stimulating non-phlogistic monocyte activation (calcium mobilization, adherence and chemotaxis), and macrophage phagocytosis of apoptotic PMN		
Examples of pathophysiological functions (confirmed in either Fpr2 or Fpr2/3-deficient mice)		
Mesenteric ischaemia reperfusion		
Carrageenan-induced paw oedema		
K/BxN serum-induced arthritis		
Allergic airway inflammation		

Full information and references available in the IUPHAR/BPS Guide to PHARMACOLOGY, http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=223&familyId=35&familyType=GPCR.
ATL, aspirin-triggered lipoxin (15-epi-LXA_4); SAA, serum amyloid A; SHAAGtide, 18 amino acids from the N-terminal of human CCL23.

subsequent generation of ROS and MMP expression (Lee *et al.*, 2012; Seo *et al.*, 2012), suggesting a BLT_2 receptor-dependent pathway in cancer growth, invasiveness and metastasis. In support of the latter, LY255283 inhibits peritoneal metastasis formation 35 days after injection of ovarian cancer cells into athymic mice (Seo *et al.*, 2012).

CysLT receptors

Ever since the identification of cysteinyl-LTs chemical structure and their association with inflammation (Samuelsson, 1983), the pathophysiological role of cysteinyl-LTs has been mainly focused on their potent bronchoconstrictive effects

and asthma (Drazen, 2003; Capra *et al.*, 2007; Hallstrand and Henderson, 2010; Laidlaw and Boyce, 2012). However, the cloning of the second CysLT receptor, expressed by cardiovascular and cerebral tissues (Brink *et al.*, 2003; Bäck *et al.*, 2011; see also Table 3) has fostered the research for new functions of these lipid mediators in other physiological and pathological conditions, particularly in CVDs. Indeed, CysLT receptor signalling is emerging as a crucial component in vascular inflammation (Bäck, 2007) and an increasing number of data suggest a major role for cysteinyl-LTs in the pathogenesis and progression of several CVDs (Capra *et al.*, 2013), such as atherosclerosis (Bäck and Hansson, 2006), myocardial infarction, stroke (Ingelsson *et al.*, 2012), aortic stenosis (Nagy *et al.*, 2011) and intimal hyperplasia.

CysLT$_1$ receptor

CysLT$_1$ receptors in respiratory diseases. The role of CysLT$_1$ receptor signalling in bronchial asthma depends both on the bronchoconstrictive and pro-inflammatory effects of the cysteinyl-LTs (Bäck *et al.*, 2011). Furthermore, bronchial fibroblasts derived from asthmatic subjects express more CysLT$_1$ receptor mRNA compared with bronchial fibroblasts derived from non-asthmatic subjects (Eap *et al.*, 2012). These authors also showed that activation of the asthmatic bronchial fibroblast CysLT$_1$ receptor by cysteinyl-LTs resulted in increased TGF-β1 which in turn increased pro-collagen (Eap *et al.*, 2012). In airway epithelial cells, IL-13 up-regulates the expression of the CysLT$_1$ receptor, which is associated with an increased release of CCL26 (eotaxin-3), a potent eosinophil chemoattractant (Provost *et al.*, 2012). Taken together, those studies suggest that CysLT$_1$ receptor activation on bronchial fibroblasts and epithelial cells further contribute to the cysteinyl-LTs-induced bronchial narrowing and eosinophil recruitment in asthma. Indeed, cells proliferation and bronchial narrowing are hallmarks of chronic asthma. In this regard, an intriguing study (Capra and Rovati, 2014) has recently demonstrated that rosuvastatin, the latest agent of this lipid-lowering class to be introduced on the market, dose-dependently inhibited LTD$_4$-induced human airway smooth muscle cells growth. The letter effect was exerted by means of inhibited prenylation of signalling proteins, most likely small G proteins such as Ras that are activated in a CysLT$_1$ receptor-dependent manner (McMahon *et al.*, 2002; Capra *et al.*, 2003; 2004; Ravasi *et al.*, 2006; Poulin *et al.*, 2011).

Cysteinyl-LTs are increased in children following infection with respiratory syncytial virus (RSV), associated with a potential subsequent development of asthma-like symptoms. In a mouse model of primary and secondary RSV-infection of newborn mice, pretreatment with montelukast, a selective CysLT$_1$ receptor antagonist, decreased RSV-induced airway hyperresponsiveness, airway inflammation and increased IFN-γ production in primary, but not secondary, infected neonate mice (Han *et al.*, 2010).

In addition to asthma, CysLT$_1$ receptor signalling has also been implicated in chronic obstructive pulmonary disease (COPD). Bronchial mucosa samples from patients with COPD exacerbations of increased CysLT$_1$ receptor protein and mRNA expression was demonstrated on inflammatory cells, particularly mast cells and monocytes/macrophages (Zhu *et al.*, 2012).

In line with an activation of the 5-lipoxygenase pathway, urinary LTE$_4$ has been associated with the degree of obstructive sleep apnea in adults (Stanke-Labesque *et al.*, 2009) and children (Shen *et al.*, 2011). In addition, increased cysteinyl-LTs and CysLT$_1$ receptor expression have been shown in tonsillar tissues derived from children with sleep apnea in China (Shen *et al.*, 2012) and in Greece (Tsaoussoglou *et al.*, 2012), suggesting that CysLT$_1$ receptor signalling may contribute to local proliferative and inflammatory pathways within tonsils in paediatric sleep-disordered breathing (Stanke-Labesque *et al.*, 2014). In support of the latter notion, a recent randomized double-blind study of 46 children showed that a 12 week treatment with daily, oral montelukast reduced the severity of obstructive sleep apnea and the underlying adenoidal hypertrophy (Goldbart *et al.*, 2012).

A role for activation of CysLT$_1$ receptors by cysteinyl-LTs in experimental pulmonary fibrosis has been supported by montelukast treatment in several mouse models. In a bleomycin-induced pulmonary fibrosis model in mice, montelukast decreased expression of IL-6, IL-13, IL-10 and TGF-β and attenuated lung fibrosis and hydroxyproline content (Shimbori *et al.*, 2011). In a GATA-3 transcription factor overexpression model, montelukast-treated mice exhibited less airway inflammation in response to ovalbumin challenge, as demonstrated by decreased levels of T$_H$2 cytokines and TGF-β and decreased smooth muscle cell hyperplasia (Kiwamoto *et al.*, 2011).

CysLT$_1$ receptor expression increases during T$_H$2 cell differentiation (Parmentier *et al.*, 2012). Human T$_H$2 cells selectively express the CysLT$_1$ receptor, whereas CysLT$_2$ receptor, GPR17 and P2Y$_{12}$ (other receptors that can respond to cysteinyl-LT; see below) are undetectable. The T$_H$2 cell CysLT$_1$ receptor couples through both Gα$_q$ and Gα$_i$ to transduce a chemotactic response. In addition, the dectin-2-cysteinyl-LT pathway is essential for T$_H$2 predominant immunity in mice in response to house dust mite, in part through the CysLT$_1$ receptor (Barrett *et al.*, 2011).

CysLT$_1$ receptors in CVDs. Cysteinyl-LTs are locally produced in coronary atherosclerotic plaques and contribute to vascular inflammation. Although previous studies have shown a dominant CysLT$_2$ receptor expression in vascular smooth muscle cells, lipopolysaccharide stimulation induces CysLT$_1$ receptor expression in human coronary artery vascular smooth muscle cells (Eaton *et al.*, 2012). Interestingly, the CysLT$_1$ receptor exhibited a perinuclear expression in those cells, and its activation was coupled to a predominant nuclear calcium signalling and up-regulation of pro-atherosclerotic genes such as PAI-2 (Eaton *et al.*, 2012). A nuclear membrane localization of the CysLT$_1$ receptor expression was initially reported in intestinal epithelial cells (Nielsen *et al.*, 2005), and perinuclear expression of the CysLT$_1$ receptor has subsequently been demonstrated in human aortic valve myofibroblasts (Nagy *et al.*, 2011). In the latter cells, the LTC$_4$-induced rise in intracellular calcium was most pronounced in the nuclear and perinuclear region of the cell, associated with mitochondrial permeability transition, changes in cell morphology, increased ROS production and an up-regulation of mRNA encoding bone morphogenic proteins (Nagy *et al.*, 2011), all important pathophysiological processes in the calcification of

the aortic valve observed in patients with calcific aortic stenosis.

The clinical use of the $CysLT_1$ receptor antagonists has allowed testing the hypothesis of their beneficial role in CVD in observational studies. In a pharmacoepidemiological cohort of approximately 7 million subjects, montelukast exposure was associated with a lower risk for recurrent stroke and with a lower risk for recurrent myocardial infarction in male subjects (Ingelsson *et al.*, 2012).

$CysLT_1$ receptors in other diseases. In a mouse model of experimental autoimmune encephalitis (EAE) expression of the $CysLT_1$ receptor mRNA was up-regulated in spleen and lymph node tissue and in the spinal cord, and cysteinyl-LT concentrations in the blood and CSF were higher than in normal mice (Wang *et al.*, 2011). In this EAE mouse model, treatment with $CysLT_1$ receptor-selective antagonists, either montelukast or zafirlukast, reduced CNS $CD4^+$ T-lymphocyte influx and demyelination, associated with decreased EAE disease scores.

A role for $CysLT_1$ receptor signalling in various cancers has also been demonstrated. LTD_4-induced $CysLT_1$ receptor activation on chronic lymphocytic leukaemia cells and normal B-lymphocytes increases calcium and promote chemotaxis. $CysLT_1$ receptor antagonists induced apoptosis and reduced viability suggesting a potential therapeutic treatment (Drost *et al.*, 2012). In line with the latter suggestion, high $CysLT_1$ and low $CysLT_2$ receptor protein expression in breast cancer tissue is associated with increased cancer-related mortality (Magnusson *et al.*, 2011).

Clinical use of $CysLT_1$ receptor antagonists. It is worth noting here that LT modifiers (including LT receptor antagonists and 5-lipoxygenase inhibitors) are a class of drugs that may be used as an add-on treatment for adult patient with mild persistent asthma not satisfactorily controlled with inhaled glucocorticosteroids, or as alternative treatment particularly in patients suffering from aspirin-sensitive asthma or concomitant allergic rhinitis (Scott and Peters-Golden, 2013). They are generally well tolerated and present few, if any, class-related side effects. LT modifiers can also be safely used in children at all level of asthma severity, particularly against exercise-induced bronchoconstriction, considering virtually the absence of safety concerns (from the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2012. Available from http://www.ginasthma.org/). However, LT modifiers are generally less effective than inhaled glucocorticosteroids when used alone as controller (Chauhan and Ducharme, 2012), while long-acting β_2-adrenoceptor agonists are modestly superior to LT receptor antagonists in reducing oral corticosteroid-treated exacerbations (Chauhan and Ducharme, 2014).

A number of clinical studies have been published from 2011 to 2013 using the selective $CysLT_1$ receptor antagonists montelukast or pranlukast in asthmatics. For example, montelukast pretreatment decreased hypertonic saline induced bronchoconstriction in asthmatics (Kazani *et al.*, 2011), and provided disease control, similar to that of fluticasone. in actively smoking asthmatics (Price *et al.*, 2013). Furthermore, in an allergen challenge model, pranlukast pretreatment inhibited nasal obstruction and nasal eosinophil cationic protein in allergic Japanese children (Gotoh *et al.*, 2012). Finally, a pilot study indicated that montelukast prevented inflammatory cell responses in patients with persistent rhinitis, with particular emphasis on macrophages and neutrophils (Braido *et al.*, 2012).

LT receptor antagonists have also been studied outside their respiratory indications. A prospective study with zafirlukast in female patients with long-standing mild/severe capsular contracture after surgical procedure for breast prosthesis. The results show a significant decrease in breast compliance values after 6 months of treatment, followed by a substantial increase 1 year after the end of drug intake, suggesting that the control of inflammation is crucial to prevent this multifactorial process (Mazzocchi *et al.*, 2012). Finally, a retrospective study in children with food allergies suggested that montelukast can prevent food-induced adverse allergic reactions such as abdominal pain, which occur during oral immunotherapy (Takahashi *et al.*, 2014).

$CysLT_2$ receptor

$CysLT_2$ receptors in CVDs. A number of studies have reported the involvement of the $CysLT_2$ receptor in the inflammatory process subsequent to brain vascular insults, such as vascular ischaemia or oxygen-glucose deprivation (OGD; Bäck *et al.*, 2011). In a model of focal cerebral ischaemia in the rat, a spatiotemporal up-regulation of the $CysLT_2$ receptor was associated with neuronal and glial cell activation (Zhao *et al.*, 2011). The same authors also demonstrated that the mechanism underlying $CysLT_2$-mediated ischaemic astrocyte injury induced by OGD involves increased expression of the $CysLT_2$ receptor and of the water channel aquaporin 4 (AQP4). The latter was supported by reduced cell injury and AQP4 up-regulation by the $CysLT_2$ receptor antagonist Bay-CysLT2, (also known as CysLT2cpd; Carnini *et al.*, 2011), but not by the highly selective $CysLT_1$ receptor antagonist montelukast (Qi *et al.*, 2011). Furthermore, intracerebroventricular injection of HAMI3379, another even more selective $CysLT_2$ receptor antagonist (Wunder *et al.*, 2010), before focal cerebral ischaemia in rats protects against acute brain injury attenuating the neurological deficits and reducing infarct volume, brain oedema, IgG exudation, neuronal degeneration and neuronal loss (Shi *et al.*, 2012). Of note, the protective effect induced by $CysLT_2$ receptor antagonism was similar to that of pranlukast. In the latter context, it should be considered that pranlukast, zafirlukast and pobilukast have been found to be partially active also at the $CysLT_2$ receptor (Heise *et al.*, 2000; Wunder *et al.*, 2010; Capra *et al.*, 2014).

In further support of neuronal effects of cysteinyl-LTs mainly being $CysLT_2$ receptor-dependent, HAMI3379 inhibited OGD/recovery, as well as LTD_4 and N-methyl-LTC_4-induced cell injury and neuronal loss in mixed cultures of cortical cells (Zhang *et al.*, 2013). Although no effect of HAMI3379 was observed on OGD/recovery-induced neuronal injury in primary neurons, this antagonist inhibited neuronal loss and necrosis in neuron-microglial co-cultures, indicating that microglial activation may be crucial in this signalling. Similar effects were obtained by $CysLT_2$ receptor knock-down by shRNA, further supporting that these neuronal effects might indeed be $CysLT_2$ receptor-dependent (Zhang *et al.*, 2013)

As mentioned above, the $CysLT_2$ receptor is highly expressed in endothelial cells of some vascular beds, and has been implicated in a variety of cardiovascular functions. BayCysLT2 administered either before or after ischaemia/reperfusion in transgenic mice overexpressing endothelium specific human $CysLT_2$ receptors attenuated the increased myocardial infarction damage, while this $CysLT_2$ receptor antagonist decreased neutrophil infiltration and leukocyte adhesion molecule (L-selectin) expression (Ni *et al.*, 2011).

$CysLT_2$ receptors in other diseases. Using a loss-of-function murine model ($CysLT_2$R-LacZ), $CysLT_2$ receptor expression has been identified in neurons of the myenteric and submucosal plexus in the small intestine, colonic myenteric plexus, dorsal root ganglia and inferior ganglion of the vagal nerve (Barajas-Espinosa *et al.*, 2011). In this model, LTC_4/D_4 stimulation of colonic submucosal venules elicited a reduced permeability response in $CysLT_2$ receptor knockout ($CysLT_2^{-/-}$) mice compared with WT mice, while basal neuronal activity of colonic-projecting nociceptive neurons from dorsal root ganglia showed significantly higher excitability. These data suggest that $CysLT_2$ receptor signalling in the murine colonic myenteric plexus may be involved in colitis disease progression, controlling inflammation-associated tissue oedema, and in the increased neuronal sensitivity to nociceptive stimuli (Barajas-Espinosa *et al.*, 2011).

Sensitization and challenge using the dust mite *Dermatophagoides farinae* induces a marked augmentation of eosinophilic pulmonary inflammation, serum IgE, and T_H2 cytokines in $CysLT_2$ receptor-deficient compared with WT mice (Barrett *et al.*, 2012). These observations could be replicated in WT mice sensitized by adoptive transfer of *D. farina*-pulsed $CysLT_2$ receptor-deficient bone marrow-derived DCs. Those results, taken together with a previous observation of a counter-regulatory role of $CysLT_2$ with respect to $CysLT_1$ receptor activity by dimerization (Jiang *et al.*, 2007), suggest that the $CysLT_2$ receptor negatively regulates the development of cysteinyl-LT–dependent T_H2 pulmonary inflammation by inhibiting both $CysLT_1$ receptor signalling and *D. farinae*-induced LTC_4 synthase-dependent cell surface expression of $CysLT_1$ receptors on DCs (Barrett *et al.*, 2012).

Proliferative diabetic retinopathy is associated with an increased synthesis of LTs (Talahalli *et al.*, 2010) and oxygen-induced retinopathy (OIR) in mice induces $CysLT_2$ receptor up-regulation. $CysLT_2$ receptor knockout mice exhibit decreased vascular leakage and retinal oedema, but, surprisingly, increased tissue damage (vaso-obliteration/vasoproliferation) compared with WT mice. In addition, only PGs and hydroxyeicosatetraenoic acids, but not LTs, were detected in A23187-treated retina preparations (Barajas-Espinosa *et al.*, 2012). Taken together, these data point to a confusing role of $CysLT_2$ receptor signalling in OIR progression that could be interpreted as either beneficial or detrimental to retinal health.

As mentioned above, atopic dermatitis is a chronic, relapsing, inflammatory skin disease characterized by dermal thickening, eosinophil infiltration and increased levels of LTE_4 in the urine. Although the role of cysteinyl-LTs in the inflammation associated with atopic dermatitis is unclear, there are reports suggesting improvements in atopic dermatitis with the use of LT receptor antagonists at the doses generally recommended for asthma treatment (see Capra *et al.*, 2006 and Bäck *et al.*, 2011 for more details). Recently, it has been reported that skin thickening and collagen deposition were significantly reduced in ovalbumin-sensitized skin of $CysLT_2$ receptor knockout mice. In addition, LTC_4 stimulation caused increased collagen synthesis by human skin fibroblasts, which, in turn, secreted factors that elicited keratinocyte proliferation. These effects were blocked by the dual $CysLT_1/CysLT_2$ receptor antagonist BAY u9773 (Oyoshi *et al.*, 2012a).

Since the discovery that activation of $CysLT_1$ receptors could induce MAPK phosphorylation and thus, proliferation, survival and migration in a variety of cells, a number of papers have reported $CysLT_1$ receptor expression in brain tumours, as well as in prostate and breast cancer cells (Bäck *et al.*, 2011). Interestingly, while low expression of $CysLT_1$ and high expression of $CysLT_2$ receptors correlated with high differentiation in epithelial colon cancer cells (Magnusson *et al.*, 2007) and mediate good prognosis in colon (Magnusson *et al.*, 2010) and breast cancer patients (Magnusson *et al.*, 2011), very recently, the same group also demonstrated that all-*trans* retinoic acid (ATRA) induced $CysLT_2$ receptor and LTC_4 synthase mRNA expression (without affecting $CysLT_1$ receptor expression) and differentiation of colorectal cancer cells. This latter effect was inhibited by the $CysLT_2$ receptor-specific antagonist BayCysLT2, suggesting that ATRA can have anti-tumorigenic effects through the cysteinyl-LT pathway (Bengtsson *et al.*, 2013).

OXE receptor

5-Oxo-ETE is formed by the oxidation of 5S-HETE by 5-hydroxyeicosanoid dehydrogenase, a highly selective $NADP^+$-dependent enzyme (Powell *et al.*, 1992) found in most inflammatory cells as well as a variety of structural cells (Grant *et al.*, 2009). Soon after the discovery of this pathway, 5-oxo-ETE was found to be a potent chemoattractant for human neutrophils (Powell *et al.*, 1993) and subsequently also for eosinophils (Powell *et al.*, 1995; Schwenk and Schroder, 1995), monocytes (Sozzani *et al.*, 1996) and basophils (Iikura *et al.*, 2005; Sturm *et al.*, 2005). Consistent with this, it promotes migration of eosinophils through basement membrane and endothelial cells (Dallaire *et al.*, 2003), probably mediated by both its chemoattractant effects as well as by stimulation of MMP-9 secretion (Langlois *et al.*, 2006). 5-Oxo-ETE also induces a variety of other responses in eosinophils and neutrophils, including calcium mobilization, actin polymerization, CD11b expression and shedding of L-selectin (Grant *et al.*, 2009). Although it is less effective in eliciting degranulation and the respiratory burst in resting granulocytes, once these cells have been primed with cytokines, including TNFα, G-CSF or GM-CSF, their responsiveness to 5-oxo-ETE is dramatically increased (O'Flaherty *et al.*, 1996a,b; Czech *et al.*, 1997). Interestingly, 5-oxo-ETE induces the release of GM-CSF from monocytes, which has been shown to prolong eosinophil survival (Stamatiou *et al.*, 2004) and could also potentially enhance the responsiveness of leukocytes to this substance.

Biological responses to 5-oxo-ETE are mediated by the OXE receptor, which is encoded by the OXER1 gene (Brink

et al., 2004). This receptor was identified independently by three groups and was previously known as TG1019 (Hosoi *et al.*, 2002), R527 (Jones *et al.*, 2003) and GPCR48 (Takeda *et al.*, 2002). Consistent with the biological activities of 5-oxo-ETE, OXE receptors are highly expressed in human eosinophils ≈ basophils > neutrophils > macrophages (Hosoi *et al.*, 2002; Iikura *et al.*, 2005) and is also expressed in a variety of cancer cell lines (O'Flaherty *et al.*, 2005; Sundaram and Ghosh, 2006) as well as an adrenocortical cell line (Cooke *et al.*, 2013). Although OXE receptor orthologues exist in a variety of species, including non-human primates, cows, dogs, cats, ferrets and elephants, as well as various fish species, including zebrafish, neither mice nor rats possess an OXE orthologue. The lack of OXER1 in mice has been a significant impediment to progress in our understanding of the pathophysiological role of 5-oxo-ETE and the OXE receptor. In contrast to rodents, zebrafish possess an OXER1 orthologue that plays an important role in leukocyte infiltration (Enyedi *et al.*, 2013). Down-regulation of the zebrafish OXE receptor blocks infiltration of leukocytes in response to both 5-oxo-ETE and injury, suggesting that 5-oxo-ETE is a key regulator of this process.

The OXE receptor is coupled to $G_{i/o}$, as responses to 5-oxo-ETE can be blocked by *Pertussis* toxin (Powell *et al.*, 1996; Czech *et al.*, 1997; O'Flaherty *et al.*, 2000; Hosoi *et al.*, 2002). Activation of this receptor results in stimulation of a number of second messenger pathways, including PLC, PI3K and ERK and p38 MAPK, as well as inhibition of AC (Norgauer *et al.*, 1996; O'Flaherty *et al.*, 1996b; Hosoi *et al.*, 2005; Langlois *et al.*, 2009). MAPK-mediated activation of $cPLA_2$ has also been observed (O'Flaherty *et al.*, 1996b). With the exception of inhibition of AC, which is mediated by α_i, OXE receptor signalling is mediated by release of the βγ subunits from $G\alpha_i\beta\gamma$ (Blattermann *et al.*, 2012). The benzobisthiazole derivative Gue1654 has been reported to selectively block βγ-mediated OXE receptor signalling without affecting α_i-mediated inhibition of AC (Blattermann *et al.*, 2012).

As a major target of 5-oxo-ETE is the eosinophil, the OXE receptor could play an important role in eosinophilic disorders such as asthma and allergic rhinitis. Consistent with this, intradermal injection of 5-oxo-ETE results in accumulation of eosinophils in human skin, which is more pronounced in asthmatic subjects compared with controls (Muro *et al.*, 2003). The availability of OXE receptor antagonists such as the recently reported indole derivative 5-(6-chloro-2-hexyl-1H-indol-1-yl)-5-oxo-valeric acid (Gore *et al.*, 2013) should make it possible to investigate this in animal models that possess OXER1 orthologues. OXE receptor antagonists could be an important future addition to asthma therapy, administered either alone or along with $CysLT_1$ receptor antagonists or corticosteroids. The OXE receptor could also be an important drug target in cancer, as it appears to play a role in cancer cell proliferation and its down-regulation with siRNA has an antiproliferative effect (Sundaram and Ghosh, 2006).

ALX/FPR2 receptor

Lipoxin A_4 (LXA_4) is generated from arachidonic acid through either human 15- and 5-lipoxygenase or the 5- and 12-lipoxygenase (Figure 1). In addition, acetylation of the PG-synthesizing enzyme COX-2 by acetylsalicylic acid (aspirin) induces the biosynthesis of carbon-15 epimers of lipoxins (15-epi-lipoxins), also referred to as aspirin-triggered lipoxins. LXA_4 and 15-epi-LXA_4, as well as the DHA-derived resolvin RvD1 and aspirin-triggered RvD1 signal through the FPR2/ALX receptor (Table 6), referred to as ALX/FPR2 when the lipoxin-binding property is of primary concern (Ye *et al.*, 2009). This receptor has the property of responding both to these lipid mediators and to a number of peptide/protein agonists, as indicated in Table 6. These peptide ligands are associated with both pro-inflammatory signalling (e.g. SAA) and pro-resolution (e.g. annexin A1) signalling pathways (Ye *et al.*, 2009; Brancaleone *et al.*, 2013).

Several lines of evidence have convincingly demonstrated LXA_4 and 15-epi-LXA_4 as mediators of the resolution of inflammation by means of limiting neutrophil infiltration/activation and promoting non-phlogistic activation of monocytes (Chiang *et al.*, 2006) as well as stimulating a pro-solving phenotype NK cells with potential relevance for asthma pathobiology (Barnig *et al.*, 2013; Peebles, 2013). More recently, RvD1 was identified as another lipid mediator of resolution (Serhan *et al.*, 2002), which could activate human ALX/FPR2 (Krishnamoorthy *et al.*, 2010) recently confirmed *in vivo* in ALX/FPR2 deficient mice (Norling *et al.*, 2012).

LXA_4 and ALX/FPR2 receptors in vitro

Functional *in vitro* studies of cells with endogenous and recombinant ALX/FPR2 expression have generated contradictory results in terms of lipoxin signalling. For example, HEK cells tagged with an ALX/FPR2-β-arrestin-coupled system have revealed dose-dependent interactions of β-arrestin and the ALX/FPR2 receptor for both LXA_4 (Krishnamoorthy *et al.*, 2010) and 15-epi-LXA_4 (Dalli *et al.*, 2013a). In contrast, other investigators reported no β-arrestin translocation induced by LXA_4 in cells expressing the recombinant human ALX/FPR2 receptors (Forsman *et al.*, 2011), while another study using a fusion protein consisting of β-arrestin-2 and EGFP did not observe any apparent translocation of cytosolic β-arrestin in the presence of LXA_4 (Hanson *et al.*, 2013). Furthermore, whereas the ALX/FPR2 receptor agonist WKYMVM inhibited forskolin-induced cAMP levels in either CHO or HEK293 cells transfected with ALX/FPR2 cDNA, LXA_4 and 15-epi-LXA_4 were inactive (Hanson *et al.*, 2013; Planaguma *et al.*, 2013). Likewise, WKYMVM, but not LXA_4, increased ERK phosphorylation in human neutrophils (Bae *et al.*, 2003) and in HEK293 cells transfected with ALX/FPR2 cDNA (Hanson *et al.*, 2013). However, it is difficult to assess these negative findings with LXA_4, whose potent bioactions are now documented by many laboratories, and interpretation with caution may be recommended. First, the use of commercial LXA_4 in studies reporting lack of actions for LXA_4, without validation of the physical integrity of this molecule just prior to testing in these systems, may be delicate. Second, several of the above studies lacked a positive control for LXA_4-induced responses (Hanson *et al.*, 2013) hence making negative observations in ALX/FPR2 receptor expressing cells somewhat difficult to interpret.

There are, in addition, studies supporting differential signalling pathways for different ALX/FPR2 receptor agonists. In ALX/FPR2-transfected CHO cells, WKYMVM, but not LXA_4, increased intracellular calcium concentrations. Interestingly,

also peptide ALX/FPR2 receptor agonists exhibited a differential response in the latter cells, which responded to SHAAG and PACAP, but were unresponsive to the glucocorticoid-derived annexin A1 peptide, Ac2–26 (Hanson *et al.*, 2013). In contrast, both LXA_4 and Ac2–26 stimulated receptor internalization in HeLa cells transiently expressing HA-tagged FPR2/ALX receptors (Maderna *et al.*, 2010), suggesting similar signalling pathways for these ligands. Furthermore, a previous study has demonstrated that LXA_4 mediates the Ca^{2+} release-activated Ca^{2+} current I_{CRAC} in K562 erythroleukaemia cells (Li *et al.*, 2008). Interestingly, the latter response was mimicked by annexin and the ALX/FPR2 receptor agonist BML-111, and inhibited by interference RNA against ALX/FPR receptors (Li *et al.*, 2008), further supporting specific signalling pathways through ALX/FPR2 receptors for pro-resolution mediators of both protein and lipid structure.

Taken together, the divergent results obtained for different ligands in cells expressing recombinant human ALX/FPR2 receptors may hence be an indication of biased agonism at this receptor. Interestingly, a recent study revealed constitutive dimerization of ALX/FPR2 receptors in transfected HEK293 cells, either as homodimers or heterodimers with FPR1 receptors (Cooray *et al.*, 2013). The homodimer was activated by LXA_4 and Annexin A1 (but not by either SAA or LL-37) and associated with p38/MAPK and heat shock protein 27 signalling leading to IL-10 release. On the other hand, the ALX/FPR2 and FPR1 receptor heterodimers elicited JNK responses. Although different agonists were not tested against the heterodimer, those results provide an initial suggestion that agonist-biased ALX/FPR2 receptor dimerization can distinguish between agonists with distinct downstream signalling (Cooray *et al.*, 2013).

In human airway epithelial cells, LXA_4 induces an increase in intracellular calcium, which is inhibited by the ALX/FPR2 receptor antagonist BOC-2 (Verriere *et al.*, 2012). Furthermore, human lung type II alveolar A549 epithelial cells, which do not express ALX/FPR2 receptors, are unresponsive to LXA_4 (Bonnans *et al.*, 2003). When the latter cells are transfected to constitutively express full-length recombinant human ALX/FPR2 receptors, LXA_4 and 15-epi-LXA_4 suppress IL-6 release induced by acid injury, and IL-8 release induced by either TNF or SAA, whereas the cytokine release induced by those stimuli are unaltered by lipoxin stimulation in untransfected A549 cells (Bonnans *et al.*, 2006; Bozinovski *et al.*, 2012). Although both SAA and lipoxins may signal through ALX/FPR2 receptors, lipoxins induced not only a rightward shift but also a depressed E_{max} of the SAA-induced IL-8 release, arguing against simple competitive antagonism at a single binding site as a mechanism of inhibition. Applying a Schild analysis to the interaction of lipoxin and SAA yielded a regression slope less than unity and those authors concluded that LXA_4 and 15-epi-LXA_4 may suppress the response to SAA by means of an allosteric type of non-competitive interaction at ALX/FPR2 receptors (Bozinovski *et al.*, 2012). The notion of LXA_4 as an allosteric modulator may however not be selective for only the ALX/FPR2 receptor interactions with LXA_4, since LXA_4 also has recently been reported to allosterically enhance anandamide-induced activation of CB_1 receptors within the brain in an FPR2/ALX receptor-independent manner to mediate protective effect against β-amyloid-induced spatial memory impairment in mice (Pamplona *et al.*, 2012).

The uptake of apoptotic neutrophils by macrophages, known as efferocytosis is one of the cardinal signs of resolution of inflammation (Serhan, 2011). Efferocytosis is stimulated by either LXA_4 or Ac2–26 in bone marrow-derived macrophages (BMDM), whereas BMDMs derived from Fpr2/Fpr3 knockout mice (cf. below) did not increase efferocytosis in response to these agonists (Maderna *et al.*, 2010). Furthermore, NK cells were recently shown to express the ALX/FPR receptor, and LXA_4 significantly increased NK cell-mediated apoptosis of granulocytes, an effect that was inhibited by the ALX/FPR2 receptor antagonist WRW4 (Barnig *et al.*, 2013). Taken together, these results support a role of LXA_4 signalling through ALX/FPR receptors in granulocyte turnover during the resolution of inflammation.

LXA_4 and ALX/FPR2 receptors in vivo

The generation of mice with a genetically targeted ALX/FPR2 receptor orthologue has allowed the exploration of ALX/FPR2 signalling in different disease models. The murine FPR gene family consists of at least eight members as opposed to only three in humans, and both the proteins encoded by the mFpr2 and mFpr3 (mFpr-rs1) genes share the lipoxin binding capacity of the human ALX/FPR2 receptor (Ye *et al.*, 2009; He *et al.*, 2013). There is however also evidence of LXA_4-induced responses in mFpr-rs4-expressing HEK293 cells (Riviere *et al.*, 2009).

In the first report of Fpr2 knockout, the gene cassette and a GFP reporter was inserted in reverse orientation into intron 1 of Fpr2, which prevented transcriptional read-through of the Fpr2 as well as Fpr3 genes (Dufton *et al.*, 2010). These mice (which were later termed Fpr2/Fpr3 knockout mice) exhibit an increased number of adherent and emigrated leukocytes after mesentery ischaemia-reperfusion, an increased carrageenan-induced paw oedema and also an exacerbation and prolongation of K/BxN serum-induced arthritis (Dufton *et al.*, 2010; Brancaleone *et al.*, 2013), consistent with the pro-resolution signalling through these murine receptors. Importantly, LXA_4 inhibited cell recruitment into dorsal air pouches inflamed with IL-1β selectively in WT mice but not in Fpr2/Fpr3 receptor knockouts, supporting that LXA_4 exerts its action through the murine Fpr2 and/or Fpr3 receptors *in vivo* (Dufton *et al.*, 2010).

In the second report, selective Fpr2 receptor deletion was obtained through a recombinase approach (Chen *et al.*, 2010). Those Fpr2 knockout mice exhibit reduced ovalbumin/alum-induced allergic airway inflammation, associated with lower levels of IL-4, IL-5 and IL-13 in BAL and a reduced recruitment of DCs to draining lymph nodes (Chen *et al.*, 2010). Studies of dextran sulphate-induced colitis in this strain revealed that, whereas Fpr2 receptor knockout conferred protection in terms of body weight loss and disease scores in the acute phase, these mice exhibited a delayed healing and increased mortality compared with WT mice after dextran sulphate withdrawal (Chen *et al.*, 2013). In addition, Fpr2 receptor knockout mice display increased susceptibility to chronic inflammation-associated colon tumours (Chen *et al.*, 2013) and exacerbated infection and mortality in response to *Listeria monocytogenesis* infection. Whether the

opposing and time-dependent phenotypes in terms of exacerbated inflammation and protection in those studies are related to the different disease models or the different Fpr gene targeting remains to be established.

Further *in vivo* evidence for lipoxin signalling through ALX/FPR2 receptors has been provided using the ALX/FPR2 receptor antagonist BOC-2. In a murine model of pneumosepsis, LXA_4 treatment 24 h after *Klebsiella pneumoniae* inoculation improved the survival rate of septic mice, an effect that was abolished by the ALX/FPR2 antagonist BOC-2 (Sordi *et al.*, 2013). In addition, LXA_4 induces a significant reduction of cerebral infarct size and neurological score when administered before 2 h middle cerebral artery occlusion followed by 24 h reperfusion in rats, an effect that is only partially blocked by the ALX/FPR2 receptor antagonist BOC-2 (Wu *et al.*, 2013), while another study suggested PPARγ may also be involved in the neuroprotective effects of LXA_4 in experimental stroke (Sobrado *et al.*, 2009). Finally, using the peptide ALX/FPR2 receptor agonist CGEN-855A, Hecht and co-workers demonstrated inhibition of neutrophil recruitment to inflamed air pouch and protection against myocardial ischaemia-reperfusion injury (Hecht *et al.*, 2009)

Other related receptors

GPR17

The orphan GPR17 (Figure 1), phylogenetically located at an intermediate position between P2Y and CysLT receptors, has been originally postulated to be activated by cysteinyl-LTs, nucleotides and sugar-nucleotides (UDP, UDP-glucose, UDP-galactose), leading to both AC inhibition and intracellular calcium increases (Ciana *et al.*, 2006). Subsequently, a different group confirmed the activation of GPR17 by uracil nucleotides, but was unable to demonstrate activation or binding by cysteinyl-LTs, while demonstrating that both short and long isoforms were constitutively active through $G\alpha_i$ (Benned-Jensen and Rosenkilde, 2010). A very recent paper, however, examining the activation of GPR17 for four independent downstream signalling responses in a broad range of cell types, indicated that GPR17 was not activated or internalized by either uracil nucleotides, or cysteinyl-LTs (Qi *et al.*, 2013). Moreover, data from the same report are consistent with GPR17 acting as a negative regulator for $CysLT_1$ receptor-mediated responses, as previously hypothesized by Maekawa and collaborators both *in vitro* and *in vivo* (Maekawa *et al.*, 2009; 2010). Thus, the formal pairing of GPR17 as a dual receptor for cysteinyl-LTs and nucleotides is yet to be agreed (Davenport *et al.*, 2013).

Oxoglutarate receptor (formally GPR99)

GPR99, a close relative of GPR91, originally described as an orphan GPCR with homology to the P2Y nucleotide receptor subfamily (Wittenberger *et al.*, 2002), was initially recognized as an oxoglutarate receptor based on its binding of and activation by 2-oxoglutarate (α-ketoglutarate) with potency in the high micromolar range via a G_q-mediated pathway (He *et al.*, 2004). This pairing has been replicated in a β-arrestin assay (Southern *et al.*, 2013), again with high potency values and eventually named the oxoglutarate receptor in a Receptor Nomenclature and Drug Classification (NC-IUPHAR) committee pairing paper (Davenport *et al.*, 2013). However, recent evidence points to GPR99 as an additional receptor for LTE_4. Cells transfected with the human GPR99 exhibit both functional and binding responses to LTE_4 with an affinity in the low nanomolar range, while confirming an apparent affinity for oxoglutarate in the high micromolar range. In addition, GPR99 deletion in mice prevents LTE_4-induced vascular leakage, but not that induced by LTC_4 or LTD_4 (Kanaoka *et al.*, 2013). These results, particularly the potencies and affinities values, suggest that GPR99 might have a preference for LTE_4 and qualify it as a candidate for the elusive LTE_4 receptor, although further investigations on binding and signalling mechanisms and independent confirmations by a different group are necessary to distinguish the preferred endogenous ligands for GPR99.

Chemerin receptor (ChemR23)

ChemR23, an orphan GPCR related to chemokine receptors, was initially described as one of three GPCRs activated by the chemotactic protein chemerin (Wittamer *et al.*, 2003; 2004) and therefore, classified as a pro-inflammatory receptor. However, several subsequent studies using ChemR23 knockout mice in different disease models, such as zymosan-induced peritonitis (Cash *et al.*, 2008), LPS-induced lung injury (Luangsay *et al.*, 2009), viral pneumonia (Bondue *et al.*, 2011b) and cigarette smoke exposure (Demoor *et al.*, 2011) have pointed to an anti-inflammatory role.

Indeed, ChemR23 was in addition identified as a high-affinity RvE1 receptor through screening of the ability of RvE1 to inhibit TNFα-induced NF-κB activation in HEK293 cells after transfection with candidate GPCRs (Arita *et al.*, 2005). Later, RvE1 was also shown to bind to the human BLT_1 receptor, albeit with lower affinity (Arita *et al.*, 2007). Radioligand studies demonstrated concentration-dependent RvE1 binding to CHO cells expressing ChemR23, but not to mock-transfected CHO cells, associated with Akt phosphorylation also demonstrable in human macrophages during phagocytosis (Ohira *et al.*, 2010). In addition, RvE1 displayed nanomolar potency using a β-arrestin assay in ChemR23-overexpressing cells (Krishnamoorthy *et al.*, 2010) Further studies supported RvE1 signalling also through endogenously expressed ChemR23. For example, RvE1 enhanced phagocytosis in human monocyte-derived macrophages, which was inhibited by a ChemR23 antibody (Ohira *et al.*, 2010). ChemR23 is also expressed on human platelets and RvE1 inhibited ADP-induced platelet activation (Dona *et al.*, 2008). In addition, RvE1 inhibited ADP-induced activation in $P2Y_{12}$ receptor expressing CHO cells transfected with ChemR23, but not in mock transfected cells, supporting a ChemR23-dependent effect of RvE1 (Fredman *et al.*, 2010). Finally, RvE1 inhibits PDGF-BB-induced proliferation in primary mouse fibroblasts, an effect that is abolished after siRNA-based knock-down of ChemR23 (Qu *et al.*, 2012). RvE1 signalling through ChemR23 has also received support from *in vivo* studies. Transgenic mice overexpressing ChemR23 under the CD11b promoter exhibit decreased number of leukocytes in peritoneal exudate after zymosan-induced peritonitis, and decreased alveolar bone loss after molar ligation (Gao *et al.*, 2013). In addition, the RvE1-induced leukocyte clearance was

enhanced in ChemR23 transgenic mice in the peritonitis model (Gao *et al.*, 2013), supporting the notion of ChemR23 as a pro-resolution receptor.

Although some authors have questioned the evidence of RvE1 signalling through ChemR23 (Bondue *et al.*, 2011a; Davenport *et al.*, 2013), only unpublished data were cited in those reviews. These discrepancies, might, at least in part, be explained In light of the recent identified possibility for ChemR23 to form heterodimers with other chemokine receptors (de Poorter *et al.*, 2013).

GPR32

Screening systems to identify receptors for RvD1 revealed two candidates for this lipid mediator, namely ALX/FPR2 and the orphan receptor GPR32 (Krishnamoorthy *et al.*, 2010). This RvD1–GPR32 interaction in human macrophages stimulated miRNA involved in resolution of inflammatory signals (Recchiuti *et al.*, 2011; Recchiuti and Serhan, 2012). Two subsequent studies confirmed this ligand receptor interaction, and extended the observation to show that two other resolvins, RvD5 and RvD3, also activated GPR32 with a similar concentration-response relation (Chiang *et al.*, 2012; Dalli *et al.*, 2013b). Given the relationship between the structures of RvD1, RvD3 and RvD5 and the fact that they are biosynthetically related, this functional mimicry is understandable. However, in an evaluation of 10 500 candidate ligands screened using a β-arrestin assay for 82 GPCRs, RvD1 was not listed to pick out activation of GPR32-expressing cells. Importantly, is should be noted that neither the ligand concentration(s) nor conditions tested were specified in that report and the commercial RvD1 was not validated for structural integrity (Southern *et al.*, 2013) as may be required to fairly assess the potential of these ligand receptor interactions. In further support of biological function associated with the activation of GPR32 by the D-series resolvins, macrophages transfected to express the human GPR32 exhibit an increased phagocytosis of fluorescent *Escherichia coli* in response to either RvD1 or RvD5 (Chiang *et al.*, 2012). Recently, these observations were extended to show that impedance changes in GPR32-expressing CHO cells were increased upon binding RvD3 and the aspirin-triggered resolvin (AT-RvD3).

Summary and conclusions

Lipid mediators, in particular metabolites of the arachidonic acid cascade, are important signalling molecules for maintenance of homeostasis and development of disease processes. In particular, LTs have proved to be powerful inflammatory and immune regulating mediators in many inflammatory processes, whereas mediators of the lipoxin and resolvin pro-resolution families, activated during host defence, counter-regulate inflammation and promote its resolution. However, as we tried to highlight in this updated report, and despite the many progress in this field of research due to the efforts of a large number of scientists and to the tumultuous progress in technology, there are many issues that still need to be clarified. For example, BLT_1 receptor signalling in cancer and the dual role of the BLT_2 receptor in pro- and anti-inflammation. Furthermore, the role of cysteinyl-LTs in physiological and pathological conditions other than asthma, particularly in CVDs (Bäck and Hansson, 2006; Bäck, 2007; Nagy *et al.*, 2011; Ingelsson *et al.*, 2012; Capra *et al.*, 2013), or the very interesting issue of the cross-talk between the CysLT and P2Y receptor systems at different levels, agonists/antagonists (Mamedova *et al.*, 2005; Nonaka *et al.*, 2005; Paruchuri *et al.*, 2009; Fredman *et al.*, 2010; Woszczek *et al.*, 2010; Foster *et al.*, 2013) or function/regulation (Capra *et al.*, 2005; Jiang *et al.*, 2009). Likewise, the subcellular localization of functional $CysLT_1$ receptors in the perinuclear region (Nielsen *et al.*, 2005; Nagy *et al.*, 2011; Eaton *et al.*, 2012) opens up for novel signalling pathways for cysteinyl-LTs. Another fascinating notion is the presence of novel receptors for cysteinyl-LTs, such as GPR17 (Ciana *et al.*, 2006; Maekawa *et al.*, 2009; 2010; Benned-Jensen and Rosenkilde, 2010; Qi *et al.*, 2013) or GPR99 (Kanaoka *et al.*, 2013) and resolvin, such as GPR32 (Krishnamoorthy *et al.*, 2010; 2012; Chiang *et al.*, 2012; Southern *et al.*, 2013) and Chem23 (Arita *et al.*, 2005; 2007; Fredman *et al.*, 2010; Bondue *et al.*, 2011a). In conclusion, more comprehensive investigations with *in vitro* and *in vivo* models are certainly needed to shed new light on the ever growing roles of this sophisticated and tightly controlled system of endogenous mediators in physiology and pathology.

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Conflicts of interest

None.

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