0031-6997/03/5501-133–166$7.00
PHARMACOLOGICAL REVIEWS
Vol. 55, No. 1
30105/1044813
Pharmacol Rev 55:133–166, 2003
Printed in U.S.A

Interleukins in Atherosclerosis: Molecular Pathways and Therapeutic Potential

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***Abstract*——Interleukins are considered to be key players in the chronic vascular inflammatory response that is typical of atherosclerosis. Thus, the expression of proinflammatory interleukins and their receptors has been demonstrated in atheromatous tissue, and the serum levels of several of these cytokines have been found to be positively correlated with (coronary) arterial disease and its sequelae. In vitro studies have confirmed the involvement of various interleukins in pro-atherogenic processes, such as the up-regulation of adhesion molecules on endothelial cells, the activation of macrophages, and smooth muscle cell proliferation. Furthermore, studies in mice deficient or transgenic for specific interleukins have demonstrated that, whereas some interleukins are indeed intrinsically pro-atherogenic, others may have anti-atherogenic qualities. As the roles of individual interleukins in atherosclerosis are being uncovered, novel anti-atherogenic therapies, aimed at the modulation of interleukin function, are being explored. Several approaches have produced promising results in this respect, including the transfer of anti-inflammatory interleukins and the administration of decoys and antibodies directed against proinflammatory interleukins. The chronic nature of the disease and the generally pleiotropic effects of interleukins, however, will demand high specificity of action and/or effective targeting to prevent the emergence of adverse side effects with such treatments. This may prove to be the real challenge for the development of interleukin-based anti-atherosclerotic therapies, once the mediators and their targets have been delineated.**

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Article, publication date, and citation information can be found at http://pharmrev.aspetjournals.org.
DOI: 10.1124/pr.55.1.5.

I. Introduction

Atherosclerosis remains, despite a recent decline, the most common cause of death in the Western world. The disease course of atherosclerosis is characterized by its chronicity, and progression in its initial stages is particularly insidious. Chronic inflammation is the pathological hallmark of atherosclerosis (Ross, 1986, 1993a, 1999), and inflammatory processes are instrumental in all stages of this disease. Even prior to the development of detectable intimal lesions, the expression pattern of the endothelium has been shown to be inflammatory in nature, conforming to the response-to-injury hypothesis as first postulated by the late Russell Ross (Ross and Glomset, 1973). Thus, in lesion-prone sites of the arterial tree, the endothelial expression of adhesion molecules is up-regulated, reflecting endothelial dysfunction secondary to unfavorable hemorheology (Nakashima et al., 1998) and/or hypercholesterolemia (Rosenfeld, 1991; Li et al., 1993; Sakai et al., 1997; Nakashima et al., 1998). In turn, this leads to the adhesion, extravasation, and intimal accumulation of circulating leukocytes (Nageh et al., 1997; Gerszten et al., 1998; Nakashima et al., 1998; Ramos et al., 1999; Dong et al., 2000), and thus to the development of the earliest detectable lesion—the fatty streak—which consists solely of lipid-laden macrophages and T lymphocytes (Stary et al., 1994). These cell types are also present in more advanced plaques, in addition to smooth muscle cells and extracellular lipid and matrix deposits (Stary et al., 1994, 1995). The cellular constituents of the atherosclerotic lesion are thought to participate actively in the propagation of inflammation and, eventually, plaque destabilization (Ross, 1999; Sukhova et al., 1999). As well as contributing to the bulk of the lesion, plaque cells are involved in the production and degradation of extracellular matrix and contribute toward the formation of a necrotic lesion core by the elaboration of toxic mediators. These cellular functions are partly autonomous but to a large extent subject to autocrine and paracrine control mechanisms. A plethora of mediators has been shown to be involved in intercellular signaling in atheromatous tissue, including small molecules such as nitric oxide (Ignarro et al., 1999; Li and Forstermann, 2000), lipid mediators such as eicosanoids and sterols (Hajjar and Pomerantz, 1992; Edwards and Ericsson, 1999; Schnaper et al., 2000), and polypeptides such as cytokines (Frostegard et al., 1999; Meager, 1999).

Whereas fatty streaks are now known to develop even in utero under the influence of maternal hypercholesterolemia (Napoli et al., 1997), plaques rarely give rise to symptoms before the sixth or seventh decade of life. If primary prevention is to be the cardinal aim, the protracted nature of lesion development will necessitate a therapeutic strategy with a comparably prolonged duration of effectivity. In conjunction with the as yet perfunctory levels of prognostic accuracy for the identification of patients at risk of symptomatic atherosclerosis, this poses stringent demands with respect to the tolerability of any preventive intervention, including the use of immunomodulatory therapies.

The rate of atherogenesis largely depends on the level of exposure to major risk factors, including a positive family history, hypercholesterolemia, smoking, diabetes mellitus, and hypertension. Although the avoidance of risk factors undoubtedly constitutes the most rewarding approach to the prevention of atherosclerosis, it has thus far been frustrated by inadequate patient compliance and the influence of genetic factors in determining an individual's predisposition to atherosclerosis. This has led to the introduction of a variety of pharmacological interventions, including the widespread use of an extremely effective class of lipid-lowering drugs: the HMG-CoA reductase inhibitors, or so-called *statins* (Braunstein et al., 2001). Despite recent concerns regarding the induction of rhabdomyolysis, a rare and potentially lethal side effect of statin usage, these drugs continue to be the mainstay of most cholesterol-lowering regimens. In several clinical prevention trials (e.g., CARE; Ridker et al., 1998), statins have also been found to exert additional, lipid-independent, anti-inflammatory effects. These may contribute significantly to their anti-atherogenic properties, and this has indeed been corroborated in recent animal studies (Williams et al., 1998). Indeed, immunomodulation could be an attractive paradigm for the development of therapeutic alternatives to statins in atherosclerosis prevention. This may be of particular benefit to those whose lipid levels are (partially) unresponsive to statin therapy; as in a substantial number of patients in the U.S. National Cholesterol Education Program, LDL[1] cholesterol levels cannot be attained by statin monotherapy alone (Brown et al., 1998).

To enable rational drug design aimed at immunomodulation in atherosclerosis, the pivotal inflammatory processes involved in this disease need to be delineated. In this regard, extensive efforts have been devoted to outlining the involvement of cytokines, because these

[1] Abbreviations: LDL, low density lipoprotein; TNF, tumor necrosis factor; TNFR, TNF receptor; IL, interleukin; IFNγ, interferon γ; Th, T helper cell; MCP-1, monocyte chemoattractant protein-1; RANTES, regulated on activation normal T cell expressed and secreted; MIP-1, macrophage inflammatory protein-1; ICE, IL-1β-converting enzyme; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; AP-1, activating protein-1; ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular cell adhesion molecule-1; SMC, smooth muscle cell; MMP, matrix metalloproteinase; SOCS, suppressor of cytokine signaling; LPS, lipopolysaccharide; GM-CSF, granulocyte-macrophage colony-stimulating factor; G-CSF, granulocyte-colony-stimulating factor; Jak, Janus kinase; STAT, signal transducer and activator of transcription; ODN, oligodeoxynucleotide; PKC, protein kinase C; PDGF, platelet-derived growth factor; TGFβ, transforming growth factor β; AAV, adeno-associated virus; IKK, IκB kinase; iNOS, inducible nitric-oxide synthase; WIN 67694, Z-Val-Ala-Asp-CH_2O(CO)[2,6-CI2)]Ph; SB 203580, 4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-1*H*-imidazole; VE 13,045, carbobenzyloxy-Val-Ala-Asp(O-et)-CH_2O-dichlorobenzoate.

cell-regulatory proteins are known to be key players in the initiation and control of inflammation in general. The term "cytokine" was first coined in the 1970s and encompasses a large number of (glyco)proteins involved in cell-to-cell signaling. Cytokines are conventionally classified by assignment to one of six families: interleukins, the tumor necrosis factor family, interferons, colony-stimulating factors, growth factors, and chemokines (Henderson and Higgs, 2000). Considerable overlap between these families exists, however, and alternative methods of subdivision have been suggested. Depending on the aim of classification it may be preferable to distinguish cytokines with an essentially proinflammatory mode of action [including tumor necrosis factor (TNF), interleukin-12 (IL-12), IL-18, and interferon γ (IFNγ)] from those with largely anti-inflammatory properties (including IL-4, IL-10, IL-13, and the endogenous IL-1 receptor antagonist, IL-1ra) or T helper cell type I (Th1; including IL-2, IFNγ, and TNF) from T helper cell type II (Th2; including IL-3, IL-4, IL-5, IL-6, IL-10, and IL-13) cytokines. Alternatively, it may be desirable to identify cytokines according to their major function, such as those effecting chemoattraction [chemokines, including monocyte chemoattractant protein-1 (MCP-1), RANTES, macrophage inflammatory protein-1 (MIP-1), IL-8, and IL-16] or on the basis of receptor sequence homology (e.g., those employing the gp130 signal transduction protein, such as IL-6, IL-11, IL-12, oncostatin M, and cardiotrophin-1). Nonetheless, a substantial degree of pleiotropism in cytokine effector functions makes most of these subdivisions somewhat arbitrary.

Members of each conventional cytokine family have been found to be involved in atherogenesis, and all cell types present in the atherosclerotic plaque are capable of producing and responding to cytokine mediators. It is conceivable, therefore, that intervention in cytokine signaling could provide effective prevention and/or treatment of atherosclerosis, and proof-of-principle data to this effect have been obtained in a variety of in vitro and in vivo studies, although this has not yet yielded clinically applicable protocols. In this review, we shall focus mainly on interleukins in our aim to outline the results that have been achieved to date in delineating the pathophysiological role and the therapeutic potential of cytokines in atherosclerosis. In addition, we shall discuss the potential of the modulation of cytokine activity as a therapeutic approach to the primary and secondary prevention of atherosclerosis. Following an overview of the roles ascribed to a variety of interleukins in the pathogenesis of atherosclerosis, we shall describe recent progress in this field and perceived future opportunities.

II. Interleukin Families in Atherosclerosis

By definition, interleukins are produced mainly *by* leukocytes and exert their effects mainly *on* leukocytes. Endothelial cells and smooth muscle cells, however, also express a variety of interleukins and/or their respective receptors, and their effects in atherogenesis are therefore by no means restricted to macrophages and T cells. Thus far, more than 30 major members of the interleukin family have been identified, and the majority of these have been shown to play a role in atherogenesis. As applies to cytokines in general, it is possible to subdivide the interleukins into families according to the homology of their amino acid sequences or the homology of the receptor complexes to which they bind (Fig. 1). Of these subgroups, the gp130 receptor family comprises principally pro-atherogenic interleukins, but most other families have both anti- and pro-atherogenic members (e.g., IL-1 family, IL-2 family, and γc receptor family). It has not proved feasible to pinpoint an interleukin that acts as the cardinal culprit in the atherosclerotic process. On the contrary, it seems rather more likely that the delicate balance between pro- and anti-inflammatory signals that generally serves to keep inflammation in check, goes awry in atherosclerosis, leading to a self-perpetuating mechanism of lesion formation (Ross, 1993b; Tedgui and Mallat, 2001). Considering the extensive interplay of soluble mediators in the atherosclerotic plaque, however, it may prove possible to devise an anti-atherosclerotic therapy aimed at modifying the effect of a single interleukin, provided that due attention is paid to the mechanisms of redundancy, which have been shown to exist in cytokine signaling. In doing so, candidate interleukins cannot be identified solely by virtue of a demonstrated systemic or local modulation of their expression in the course of atherogenesis. On the contrary, it is of paramount importance to determine whether cytokine responses that have been observed in relation to the development of atherosclerosis are *compensatory* to, *contributory* to, or merely *associated* with this disease. Making this distinction will require well designed intervention studies in animal models, in which the effect of attenuation or administration of a particular interleukin can be evaluated. The currently favored approach entails the up- or down-regulation of interleukin expression in atherosclerosis-prone mouse strains by means of gene insertion ("transgenics") or gene deletion ("knockouts"), respectively. Administration of an interleukin or its ablation by specific antibodies/antagonists, however, can also provide valuable data regarding its role in atherogenesis. When pertinent, the results of such studies will be discussed in the next section.

Since the effects exerted by cytokines may differ significantly depending on their local environment, it will also be necessary to distinguish between the role of systemic and local variations in cytokine levels. This type of information could in the future be derived from cell- or organ-specific gene overexpression through the use of specific promoters and gene deletion by means of the cre-lox system (Perkins, 2002) or by comparison of

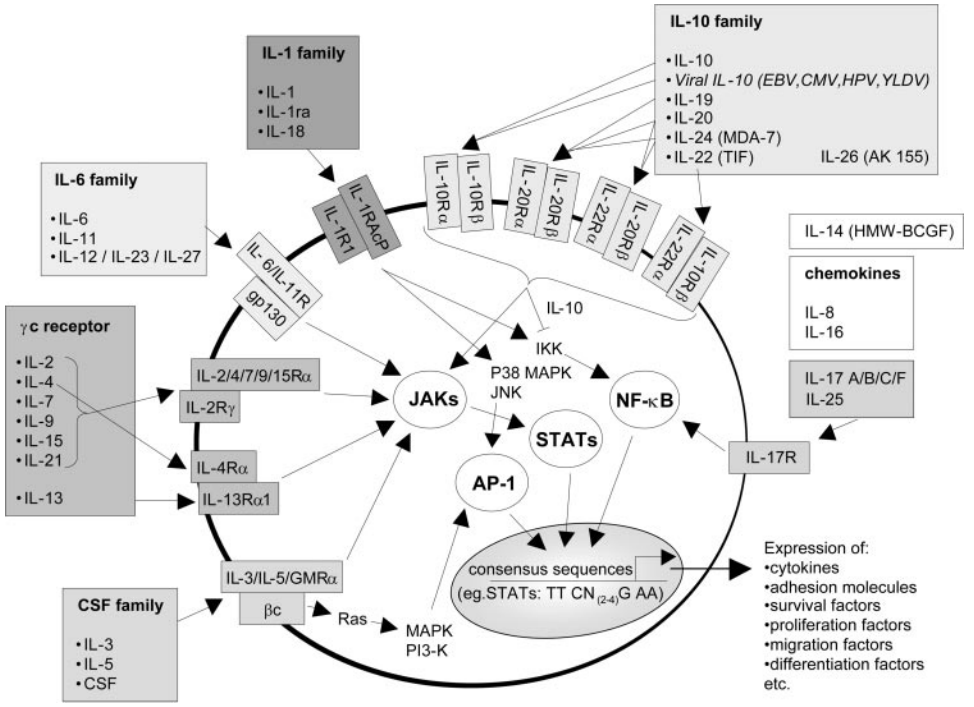

FIG 1. Schematic representation of the receptor specificity and mechanism of action of interleukin families thought to be involved in atherogenesis. Most receptors have been found to consist of heterodimeric complexes, frequently incorporating an interleukin-specific chain in addition to a common chain that is shared by the interleukin family members (including IL-2Rγ, βc, and gp130). Receptor activation initiates intracellular phosphorylation cascades that are mediated by kinases (including p38 MAPK, c-Jun N-terminal kinase, and JAKs), resulting in the activation and/or nuclear translocation of transcription factors (including AP-1, STATs, NF-κB). Binding of these factors to DNA consensus sequences, in conjunction with the required cofactors, effects the expression of specific patterns of pro- and/or anti-inflammatory mediators.

the effects of local and systemic administration of cytokines.

A. Interleukin-1

The IL-1 family comprises four proteins that share considerable sequence homology and contain a β-pleated sheet structure (Dinarello, 1997): IL-1α, IL-1β, IL-1 receptor antagonist (IL-1Ra), and IL-18 (also known as IFNγ-inducing factor). Release of mature IL-1α requires extracellular calpain-mediated cleavage of a pro-IL-1α, whereas mature IL-1β is derived proteolytically from pro-IL-1β by intracellular IL-1β-converting enzyme (ICE or caspase-1) activity. Upon binding of IL-1α or IL-1β to the IL-1 receptor type I (IL-1RI), IL-1R accessory protein (IL-1RIAcP) is recruited by the receptor complex, and intracellular signal transduction is triggered through a p38 mitogen-activated protein kinase (MAPK)-activated phosphorylation cascade. Due to extensive signal amplification, minute amounts of IL-1 can have considerable biological activity, and as little as 1 ng/kg intravenous IL-1β causes symptoms in humans. The signaling cascade culminates in the nuclear translocation of the transcription factors nuclear factor kappa B (NF-κB) and activating protein-1 (AP-1) and the ensuing transcription of a variety of proinflammatory genes, including autocrine amplification of IL-1 production (Suzuki et al., 1989). In addition to the IL-1RI, IL-1 may also bind to the so-called type II interleukin-1 receptor, the expression of which appears to be regulated by IL-4 (Colotta et al., 1993b). Binding of IL-1 to this receptor does not result in cellular activation, and IL-1RII is therefore presumed to act as a decoy that negatively regulates IL-1 activity.

A further member of the IL-1 cytokine family, IFNγ-inducing factor, has been termed IL-18, on the basis of its pleiotropic Th1-inducing effects (Ushio et al., 1996). It has been assigned to the IL-1 family on the grounds of sequence homology (26% with IL-1β) and similarity of the IL-18 receptor to IL-1R (Torigoe et al., 1997; Dinarello, 1999). Like IL-1β, IL-18 is dependent on ICE for proteolytic processing, and on nuclear translocation of NF-κB for transcriptional activation.

Owing to its proinflammatory effects on endothelial cells (Jirik et al., 1989; Loppnow and Libby, 1989a,b; Sironi et al., 1989; Suzuki et al., 1989; Sica et al., 1990b; Bochner et al., 1991; Clinton et al., 1992; Collins et al., 1995; Garcia et al., 2000), smooth muscle cells (Loppnow and Libby, 1989a, 1990; Wang et al., 1991; Clinton et al., 1992; Braun et al., 1995; Stanford et al., 2000), and macrophages (Sica et al., 1990b), and due to its production by all of these cell types in atherosclerotic lesions (Moyer et al., 1991; Tipping and Hancock, 1993; Galea et al., 1996), IL-1 was one of the first cytokines to be considered instrumental in the propagation of vessel wall inflammation in atherosclerosis. It is thought to facilitate early lesion formation by increasing leukocyte adhesion to endothelial cells (Bevilacqua et al., 1985; Wang et al., 1995) and mediating leukocyte transmigra-

tion (Moser et al., 1989; Furie anf McHugh, 1989). Subsequently, locally produced IL-1 may serve to maintain an inflammatory milieu by autocrine and paracrine stimulation of cytokine (Jirik et al., 1989; Loppnow and Libby, 1989a,b, 1990, 1992; Sironi et al., 1989; Sica et al., 1990a,b; Wang et al., 1991; Clinton et al., 1992; Li et al., 1995; Taki et al., 1999; Garcia et al., 2000; Stanford et al., 2000) and adhesion molecule expression (Osborn et al., 1989; Bochner et al., 1991; Braun et al., 1995; Collins et al., 1995). In the advanced plaque, IL-1-induced up-regulation of matrix metalloproteinases may destabilize the proteinaceous scaffold of the cap and thereby have a hand in plaque rupture (Galis et al., 1995; Libby et al., 1995); this hypothesis is corroborated clinically by the fact that a particular IL-1β gene polymorphism has been found to be associated with myocardial infarction in chlamydia pneumoniae seropositive patients (Momiyama et al., 2001), and that pericardial fluid levels of IL-1β are raised in patients with unstable angina pectoris (Oyama et al., 2001).

Because the IL-18 signal transduction cascade is similar to that activated by IL-1, it is perhaps unsurprising that IL-18 has also been found to up-regulate the expression of intercellular adhesion molecule 1 (ICAM-1) and cytokines by monocytes, including IL-1β, IL-6, and IL-8 (Dinarello, 1999), and the production of vascular cell adhesion molecule-1 (VCAM-1) by endothelial cells (Vidal-Vanaclocha et al., 2000). It is, therefore, entirely conceivable that IL-18 may have pro-atherogenic properties, and Mallat et al. (2001a) have indeed demonstrated IL-18 in atherosclerotic plaques in human carotids, which is primarily localized to macrophages. They found the corresponding receptor, IL-18R, to be expressed on endothelial cells and macrophages and barely present on SMCs. These findings have subsequently been confirmed histologically and in vitro by Gerdes et al. (2002), who also demonstrated the functionality of the IL-18 receptor on these cells through IL-18-mediated induction of pro-atherogenic factors, including IL-6, IL-8, ICAM-1, and matrix metalloproteinases. In addition, the serum level of IL-18 has recently been identified as a strong predictor of cardiovascular death in stable and unstable angina (Blankenberg et al., 2002). The pro-atherogenic effects of IL-18 are thought to be mediated by IFNγ, since the induction of atherosclerosis by exogenous IL-18 is abrogated by IFNγ deficiency in apolipoprotein E knockout (apoE$-/-$) mice (Whitman et al., 2002). A role for IL-18 in plaque destabilization was suggested by the up-regulation of IL-18 mRNA levels in symptomatic and ulcerative atherosclerotic plaques (Mallat et al., 2001a).

In comparison with the proinflammatory reprobates of the IL-1 family, IL-1ra appears positively angelic. IL-1ra displays affinity for the IL-1R, but it does not induce a cellular response; it is therefore believed to be an endogenous inhibitor of IL-1 signaling (Dinarello, 1997). IL-1ra is produced by monocytes (Arend et al., 1990), macrophages (Janson et al., 1991), and smooth muscle cells (Beasley et al., 1995). Recombinant intracellular IL-1ra has been shown to counteract the IL-1-induced production of IL-6, IL-8, and monocyte chemotactic protein by human endothelial cells (Bertini et al., 1992), and to inhibit smooth muscle cell proliferation (Porreca et al., 1993). Moreover, vascular inflammation is the major phenotypic characteristic of IL-1ra-deficient mice (Nicklin et al., 2000), whereas atherogenesis is reduced in IL-1ra transgenic mice on a high fat diet (Devlin et al., 2002), and fatty streak formation is reduced in apoE$-/-$ mice by IL-1ra administration (Elhage et al., 1998). Il-1ra has been found to be present in carotid atherosclerotic plaques (Gottsater et al., 2002), and the relevance of IL-1ra to human atherosclerosis is underscored by the fact that certain IL-1ra alleles are associated with coronary artery disease (Francis et al., 1999) and restenosis (Kastrati et al., 2000; Francis et al., 2001).

B. Interleukin-2

This family of cytokines encompasses a group of interleukins which share a common receptor subunit, the "common γ chain" (γc chain), which acts in unison with a subtype specific α chain to initiate the signaling cascade. As the common receptor subunit was initially discovered in relation to IL-2, it has also been termed the "IL-2 receptor γ chain" (Takeshita et al., 1990), and the group of cytokines that interact with this receptor has consequently been termed the "IL-2 family" (Leonard and Lin, 2000). The members of this interleukin family are primarily involved in T cell development and activation, and mutations of the γc chain cause X-linked severe combined immunodeficiency in humans (Noguchi et al., 1993b) and lead to thymic hypoplasia in mice (Cao et al., 1995).

In addition to IL-2, the family includes IL-4 (Russell et al., 1993), IL-7 (Noguchi et al., 1993a), IL-9 (Russell et al., 1994), IL-15 (Giri et al., 1994a), and IL-21 (Vosshenrich and Di Santo, 2001). All members interact with receptor complexes consisting of an interleukin-specific α chain and the common γc chain (Fig. 1). Moreover, the IL-4 α chain is also a component of the IL-13 receptor complex (Zurawski et al., 1993), and for purposes of classification, we shall include IL-13 in this interleukin family. A substantial degree of functional redundancy is extolled by the IL-2 family members, which is comprehensible in view of considerable overlap in their signaling pathways. Thus, Janus kinase 1 (Jak1) and Jak3 have been found to be activated by the subtype-specific chains and the constant γc chain, respectively (Miyazaki et al., 1994; Russell et al., 1994; Leonard and Lin, 2000), which ultimately cascades into the activation of transcription by the common downstream effector molecules "signal transducer and activator of transcription" 5a (Stat5a), Stat5b, and Stat3 (Lin et al., 1995; Lin and Leonard, 2000). IL-4 and IL-13 are somewhat distinct in

activating Jak2 and Stat-6 via a γc chain-independent pathway (Palmer Crocker et al., 1996).

IL-2 (Arbustini et al., 1991; Frostegard et al., 1999) and the IL-2R receptor (Kishikawa et al., 1993) are expressed in atheromatous tissue, but a direct causal role for IL-2 in atherogenesis remains to be proven. Nonetheless, serum IL-2 levels have been found to be elevated in ischemic heart disease (Mazzone et al., 1999) and especially unstable angina pectoris (Mizia-Stec et al., 2002), and the risk of acute myocardial infarction is increased following IL-2 treatment for cancer (Kragel et al., 1990). A possible explanation for the presumed pro-atherogenic effect of IL-2 may lie in its ability to induce a T helper cell shift toward a Th1 phenotype. T cells have been shown to be present in atherosclerotic lesions (Hansson et al., 1988), and Th1 cells, in particular, are believed to actively promote atherogenesis (de Boer et al., 1999; Frostegard et al., 1999; Huber et al., 2001; Laurat et al., 2001; Song et al., 2001). In its capacity as an autocrine stimulator of Th1 cell differentiation and proliferation (Kurt-Jones et al., 1987; Harel-Bellan et al., 1988), IL-2 may promote the expansion and activation of this T cell subset, and, consequently, plaque development.

Conversely, IL-4 is known to promote Th2-type responses (partly by autocrine activation) and to exert immunosuppressive effects on macrophages, including the suppression of proinflammatory cytokine production and the stimulation of IL-1ra elaboration (Paul, 1991). This cytokine is therefore considered to be potentially anti-atherogenic. The highly pleiotropic effects of IL-4, however, reserve a rather more complicated role for IL-4 in atherosclerosis. Thus, whereas mice deficient in Stat6, which is one of the mediators activated by IL-4, develop larger atherosclerotic lesions than their wild-type counterparts (Huber et al., 2001), IL-4 deficient mice do not display increased susceptibility to diet-induced atherosclerosis (George et al., 2000a). They have even been found to be relatively resistant to the acceleration of fatty streak formation by heat shock protein 65 or mycobacterium tuberculosis (George et al., 2000b). Similarly, reconstitution with IL-4-deficient bone marrow in LDLr−/− mice reduces atherosclerotic lesion formation in the aortic arch and the thoracic aorta compared with reconstitution with wild-type bone marrow (King et al., 2002). Although IL-4 expression in atherosclerotic plaques appears to be limited (Uyemura et al., 1996), among the pro-atherogenic effects of IL-4 we may count the up-regulation of P-selectin (Khew-Goodall et al., 1999) and 15-lipoxygenase (Lee et al., 2001b) expression by endothelial cells, VCAM-1 (Barks et al., 1997) and matrix metalloproteinase 1 (MMP-1) (Sasaguri et al., 1998) expression by vascular smooth muscle cells, and the augmentation of CD36 receptor expression (Feng et al., 2000) and cholesterol esterification (Cornicelli et al., 2000) in macrophages. On the other hand, IL-4 has also been shown to inhibit smooth muscle cell proliferation (Vadiveloo et al., 1994; Sasaguri et al., 1998) and macrophage adhesiveness (Elliott et al., 1991). The net effect of IL-4 in atherosclerosis thus still hangs in the balance, and it may vary with the stage of the disease.

IL-9 was initially identified as a mast cell and T cell growth factor (Renauld et al., 1990) and has subsequently been shown to lead to exaggerated Th2-type inflammatory responses (Godfraind et al., 1998; McLane et al., 1998) and thymic lymphomas (Renauld et al., 1994) in IL-9 transgenic mice. IL-9 is not entirely independent in its actions, however, since IL-9 production by T lymphocytes requires IL-2-mediated stimulation (Houssiau et al., 1992), and the mitogenic effect of IL-9 on T lymphocytes requires their preactivation (Uyttenhove et al., 1988). In a murine model of Gram-negative bacterial shock, IL-9 led to suppression of TNFα, IL-12, and IFNγ, possibly mediated by an induction of IL-10 expression (Grohmann et al., 2000). In agreement with this study, IL-9 has been found to induce the expression of the intracellular cytokine signal inhibitors cytokine-inducible SH2-containing protein, suppressor of cytokine signaling (SOCS)-2 and SOCS-3 (Lejeune et al., 2001). SOCS-3, in particular, may impair signaling by pro-atherogenic cytokines that act through the gp130 receptor, including IL-6 and IL-12. Some of the activities of IL-9 may also be mediated by its induction of IL-22 (IL-TIF), which shares 22% sequence homology with IL-10 (Dumoutier et al., 2000). Although its role in atherosclerosis has thus far not been elucidated, it appears that IL-9 may be potentially anti-atherogenic through a deflection of the immune response from a Th1 to a Th2 type. Albeit that a caveat needs to be added, as overzealous stimulation of Th2 responses may well prove to be detrimental in the later stages of atherosclerosis. Thus, mast cells have been identified in advanced plaques (Kaartinen et al., 1994a; Jeziorska et al., 1997) and are presumed to promote plaque instability by the secretion of chymase (Kaartinen et al., 1994b; Kovanen, 1997) and the stimulation of calcification (Jeziorska et al., 1998). Their stimulation may promote, rather than impede, the development of atherosclerotic complications.

IL-15 is produced by a variety of cells, including monocytes (Musso et al., 1999) and endothelial cells (Oppenheimer-Marks et al., 1998; Krishnaswamy et al., 1999), and has an activity profile similar to IL-2, without sharing sequence homology (Waldmann and Tagaya, 1999). IL-15 mediates extravasation of lymphocytes through its stimulatory and chemotactic effects on natural killer cells (Carson et al., 1994; Allavena et al., 1997) and T lymphocytes (Giri et al., 1995; Sancho et al., 1999) and by the up-regulation of hyaluronan on the endothelium (Estess et al., 1999). Recently, atherosclerotic lesions in humans and apoE−/− mice were found to contain IL-15-responsive T cells as well as IL-15 itself, which colocalizes with oxidized LDL-positive macrophages (Houtkamp et al., 2001, Wuttge et al., 2001). IL-15 may

therefore accelerate atherogenesis by promoting the recruitment and antigen-independent induction of T lymphocytes.

Despite sharing only 20 to 25% sequence homology and differing from IL-4 in lacking an effect on T cell function (Zurawski and de Vries, 1994), IL-13 is highly akin to IL-4 with respect to its immunomodulatory properties (Opal and DePalo, 2000), which is likely to be attributable to IL-4R-mediated Stat6 activation by both cytokines (Hart et al., 1999). In monocytes, IL-13 attenuates the expression of a wide range of inflammatory cytokines, including IL-1, IL-6, IL-8, IL-10, IL-12, MIP-1α, granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), IFNα, and TNFα, while up-regulating the expression of IL-1ra (de Waal Malefyt et al., 1993; Mijatovic et al., 1997). Nitric oxide production is inhibited by IL-13 in macrophages (Doherty et al., 1993; Bogdan et al., 1997) and smooth muscle cells (Ruetten and Thiemermann, 1997). The properties of IL-13 are not exclusively anti-inflammatory, however, as exemplified by the IL-13-mediated potentiation of IL-8 receptor expression, 15-lipoxygenase expression, and LDL oxidation by monocytes (Nassar et al., 1994; Folcik et al., 1997; Bonecchi et al., 2000), and of IL-8 and MCP-1 release in response to IL-1α or TNFα in SMCs (Jordan et al., 1997). Moreover, IL-13 is known to enhance the transmigration of leukocytes by stimulating the endothelial expression of adhesion molecules (Bochner et al., 1995; Ying et al., 1997) and chemotactic factors (Goebeler et al., 1997). In analogy with IL-4, the overall effect of IL-13 in atherosclerosis is still controvertible.

The complex actions of IL-2 family members in the vascular wall are depicted in Fig. 2.

C. The gp130 Family

The common receptor subunit shared by the members of this family of cytokines, gp130, was first discovered as a signal transducer for IL-6 (Hibi et al., 1990). The other factors to employ this receptor subunit in combination with their own specific subunit, are IL-11 (Yin et al., 1993), IL-12 (Chua et al., 1994), leukemia inhibitory factor (Gearing et al., 1991), oncostatin M (Gearing et al., 1992), cardiotrophin-1 (Ip et al., 1992), ciliary neurotrophic factor (Pennica et al., 1995), and neurotrophin-1/B cell-stimulating factor-3 (Senaldi et al., 1999) (Fig. 1). Following gp130 binding, the Janus kinases Jak1, Jak3, and Tyk2 and the transcription factors Stat1 and Stat3 are phosphorylated (Heinrich et al., 1998). In this review, we shall restrict the discussion to the interleukin members of the gp130 family.

In addition, two novel heterodimeric interleukins with an activity profile similar to IL-12 have recently been identified. IL-23 is composed of a p19 subunit and the p40 subunit of IL-12 (Oppmann et al., 2000), and this cytokine acts through a receptor composed of IL-12Rβ1 and a novel cytokine receptor subunit, IL-23R (Parham et al., 2002). IL-27 is made up of an IL-12 p40-related and an IL-12 p35-related protein and binds to the gp130-related receptor WSX-1/TCCR (Pflanz et al., 2002).

Endothelial cells, smooth muscle cells, and macrophages are capable of elaborating IL-6, and its expression has been observed in atherosclerotic lesions in humans, hypercholesterolemic rabbits, and apoE-deficient mice (Ikeda et al., 1992; Kishikawa et al., 1993; Seino et al., 1994; Rus et al., 1996; Sukovich et al., 1998; Schieffer et al., 2000). Although the endothelium is largely unresponsive to IL-6 (Podor et al., 1989), addition of the soluble IL-6Rα subunit (sIL-6R) enables endothelial cells to mount an inflammatory response to IL-6, by interacting with membrane-bound gp130 (Jones et al., 2001). This process has been termed "*trans*-signaling", and it may lead to increased endothelial cell adhesiveness by the up-regulation of E-selectin, ICAM-1, and VCAM-1, and the release of inflammatory mediators, including MCP-1, IL-8, and IL-6 itself (Modur et al., 1997; Romano et al., 1997). Thus, sIL-6R present in serum and/or elaborated locally by cells in the intima may serve to augment endothelial adhesion and extravasation of leukocytes into the atherosclerotic plaque. Monocytes and macrophages, on the other hand, produce IL-6R autonomously and therefore do not depend on ambient sIL-6R levels for IL-6-mediated modulation of gene expression (Akira and Kishimoto, 1996). The effector functions of IL-6 in cells of the monocyte/macrophage lineage include the differentiation of monocytes to macrophages (Chomarat et al., 2000), the up-regulation of acute phase response gene expression in hepatocytes and macrophages (Perlmutter, 1989), and the priming of macrophages for enhanced TNFα production in response to lipopolysaccharide (LPS) administration (Cochran and Finch-Arietta, 1992). In smooth muscle cells, IL-6 induces proliferation directly (Nabata et al., 1990; Ikeda et al., 1991) and indirectly through the initiation of an autocrine loop mediated by the up-regulation of gp130 (Klouche et al., 1999). In addition, smooth muscle cells are stimulated by IL-6 to express ICAM-1 (Ikeda et al., 1993) and to evolve into foam cells (Klouche et al., 2000).

Whereas homozygous deletion of gp130 in mice leads to intrauterine death due to myocardial hypoplasia (Yoshida et al., 1996), IL-6-deficient mice develop normally despite an attenuated acute phase response and impaired cellular immunity to virus infection (Kopf et al., 1994). This is a reflection of the functional redundancy in gp130-mediated signaling and thus of the extent to which the other members of the gp130 family can take over IL-6-mediated functions. IL-6 was initially described as a lymphocyte stimulatory factor but has since been found to exert a plethora of inflammatory effects (Hirano et al., 1990). With the possible exception of IL-1, IL-6 is the cytokine with the most extensively studied pro-atherogenic profile. Causality has been established through the exacerbation of early atherosclerosis by recombinant IL-6 in various atherosclerosis-prone murine

models (Huber et al., 1999). Interestingly, the progression of atherosclerotic lesions to an advanced phenotype appears to be inhibited by IL-6 in apoE-deficient mice, uncovering a potentially biphasic mode of action in atherogenesis (Elhage et al., 2001), which is perhaps partly explained by its observed anti-inflammatory properties (Barton et al., 1996; Xing et al., 1998) and its inhibition of macrophage class A scavenger receptor expression (Liao et al., 1999). Nonetheless, inhibition of IL-6 signaling may be considered to constitute an attractive therapeutic strategy for the prevention of coronary heart disease (Stein and Kung Sutherland, 1998; Yudkin et al., 2000).

Clinically, elevated levels of IL-6 and its hepatic byproduct C-reactive protein (Verma et al., 2002) are associated with increased risks of coronary and peripheral atherosclerosis (Erren et al., 1999; Mazzone et al., 1999; Flex et al., 2002; Bermudez et al., 2002; Kato et al., 2002; Stenvinkel et al., 2002; van der Meer et al., 2002), myocardial infarction (Ridker et al., 2000b; Ikeda et al., 2001), and the risk of death of patients with cardiovascular disease (Volpato et al., 2001), and IL-6 has been suggested to mediate the pro-atherogenic properties of cytomegalovirus (Blankenberg et al., 2001). In a large multicenter study, IL-6 gene polymorphisms were found to correlate with the severity of coronary artery disease and the risk of myocardial infarction (Georges et al., 2001), and carotid atherosclerosis has been shown to be independently linked with an IL-6 promoter polymorphism (Rauramaa et al., 2000; Rundek et al., 2002), as has the risk of coronary artery disease (Humphries et al., 2001). In addition, lower levels of soluble IL-6 receptor, a naturally occurring IL-6 antagonist, are linked with the risk of myocardial infarction (Ueda et al., 1999). Although these clinical findings do not establish causality, they have identified a strong association between IL-6 levels and atherosclerosis.

Despite sharing considerable redundancy with IL-6 with respect to its signaling and effector functions, IL-11 has been judged to be a more anti-inflammatory member of the gp130 family of cytokines based on the net effect of its pleiotropic actions (Schwertschlag et al., 1999; Taki et al., 1999). In macrophages, recombinant IL-11 has been found to attenuate macrophage expression of TNFα, IL-1β, IL-12, and nitric oxide following an LPS challenge (Trepicchio et al., 1996; Leng and Elias et al., 1997). These effects are direct and mediated by NF-κB down-regulation (Trepicchio et al., 1997), as is IL-11-mediated attenuation of smooth muscle cell proliferation and cytokine production (Zimmerman et al., 2002). In endothelial cells, IL-11 provides protection against immune-mediated injury (Mahboubi et al., 2000), and inhibits apoptosis through up-regulation of survivin (Mahboubi et al., 2001). In CD4+ lymphocytes, IL-11 has been found to induce a shift from a Th1 to a Th2 phenotype (Bozza et al., 2001). This effect has been put to use in immunomodulatory treatment employing IL-11 in psoriasis (Trepicchio et al., 1999) and Crohn's disease (Sands et al., 1999), and it may also offer therapeutic possibilities in the setting of atherosclerosis.

Activated monocytes are the primary source of IL-12 (D'Andrea et al., 1992), a cytokine that induces proliferation (Gately et al., 1991) and a shift toward a Th1 expression pattern in lymphocytes (Hsieh et al., 1993). IL-12 was originally implicated in atherosclerosis by Uyemura et al. (1996), who observed an abundance of p40 mRNA and IL-12 p70 protein in atherosclerotic lesions, and up-regulation of IL-12 production by monocytes following the addition of highly oxidized LDL. Subsequently, atherosclerotic lesions in apoE-deficient mice were found to contain IL-12, and their progression to be accelerated by daily injections of recombinant IL-12 (Lee et al., 1999). Conversely, a selective defect of macrophage IL-12 synthesis due to 12/15-lipoxygenase deficiency reduces lesion formation in atherosclerosis-prone Apobec-1−/−/ApoE−/− mice (Zhao et al., 2002). In clinical practice, raised serum levels of IL-12 have been found to be associated with acute myocardial infarction (Zhou et al., 2001a).

D. Granulocyte-Macrophage Colony-Stimulating Factor

The genes encoding the members of this family—IL-3, IL-5, and GM-CSF—are clustered on the human chromosome 5 (van Leeuwen et al., 1989) (Fig. 1). Their products bind to receptor complexes consisting of a common β chain (βc) and a cytokine-specific α chain (Hayashida et al., 1990; Kitamura et al., 1991), resulting in the activation of JAK/STAT, the ras/MAPK, and the phosphatidylinositol-3 kinase pathway (Guthridge et al., 1998). The primary effector functions to be identified for this family are the promotion of hematopoietic proliferation, survival, and differentiation, which is confirmed by the invariable occurrence of a myeloproliferative disorder in human common β chain transgenic mice (Nishinakamura et al., 1995). Since mice deficient for IL-3, IL-5, or GM-CSF suffer from pulmonary alveolar proteinosis, signaling via receptors involving the common β chain is thought to exert additional pleiotropic actions on mature cells of the monocyte/macrophage lineage (D'Andrea et al., 1998).

Indeed, IL-3 has been found to stimulate adhesion (Elliott et al., 1990) and c-jun expression in monocytes (Mufson et al., 1992). It is elaborated by activated T lymphocytes in atheromatous tissue and acts on smooth muscle cells to increase migration and proliferation (Brizzi et al., 2001). Moreover, receptors for IL-3 are also present on endothelial cells (Colotta et al., 1993a), which respond to the binding of IL-3 by increased proliferation, by augmented adhesion molecule, major histocompatibility complex II, and cytokine production, and by participating in angiogenesis in vivo (Brizzi et al., 1993; Korpelainen et al., 1995; Dentelli et al., 1999). IL-3 is thus believed to play a role in the early stages of atherogenesis by facilitating leukocyte extravasation and in

advanced lesions by augmenting macrophage activation, smooth muscle cell accumulation, and neovascularization of the plaque.

The involvement of IL-5 in the stimulation of B cell and eosinophil responses has been meticulously documented, with the aid of, *inter aliter*, IL-5 transgenic (Tominaga et al., 1991), and IL-5-deficient mouse models (Kopf et al., 1996). Its role in atherosclerosis remains uncharted territory, however. IL-5 is produced by endothelial cells (Krishnaswamy et al., 1999), but their expression of the IL-5α receptor subunit is limited (Colotta et al., 1993a). IL-5 expression appears to be scanty in advanced human atherosclerotic plaques, and is associated with the presence of eosinophils (Frostegard et al., 1999). Because IL-5 is an archetypal Th2 lymphokine, it may activate mast cells in the atherosclerotic plaque, which have been associated with the development of unstable lesions and plaque rupture (Kaartinen, 1994a,b, 1996a,b, 1998; Kovanen et al., 1995). Notwithstanding its low prevalence, the significance of locally produced IL-5 may thus increase in importance with the age of the lesion, and this could lead to destabilization of the atheroma.

E. Interleukin-10

This family comprises a sizeable array of mammalian and viral molecules that possess a considerable degree of sequence similarity with its founder member, IL-10 (Rich and Kupper, 2001; Volk et al., 2001). These include IL-19, IL-20, IL-22, IL-24/MDA-7, IL-26/AK155, and the IL-10 homologs encoded by Epstein-Barr virus, cytomegalovirus, herpesvirus papio, and Yaba-like disease virus (Fickenscher et al., 2002; Wolk et al., 2002; Fig. 1).

IL-10 was initially identified as a cytokine synthesis inhibitory factor (CSIF) (Fiorentino et al., 1989), but has subsequently been found to be a pleiotropic immunoregulatory cytokine that is secreted by a wide variety of cells, including lymphocytes and monocytes/macrophages (Lalani et al., 1997b; Moore et al., 2001). IL-10 signaling is mediated by Jak1 and Stat3 and entails the down-regulation of NF-κB activity (Schottelius et al., 1999). Its effector functions include induction of a shift of T cell cytokine expression from a Th1 to a Th2 profile (Fiorentino et al., 1989), and attenuation of the production of proinflammatory cytokines by macrophages (Bogdan et al., 1991; de Waal Malefyt et al., 1991a; Lang et al., 2002) and polymorphonuclear neutrophils (Cassatella et al., 1993). In addition, IL-10 effects differentiation of monocytes to macrophages (Allavena et al., 1998), suppression of antigen-presenting activity (de Waal Malefyt et al., 1991b), a decline in the release of reactive nitrogen and oxygen intermediates (Gazzinelli et al., 1992; Mallat et al., 1999a; Haddad and Fahlman, 2002), and inhibition of ICAM-1 expression (Song et al., 1997). Monocyte adhesion to endothelial cells is attenuated by IL-10 through modulation of monocyte CD18 and CD62-L expression (Mtairag et al., 2001) and attenuation of ICAM-1 and VCAM-1 expression on endothelial cells (Krakauer, 1995; Lindner et al., 1997). IL-10 has been found to be present in mature plaques (Uyemura et al., 1996; Mallat et al., 1999a) and is thought to play an active role in curbing the inflammatory milieu of the vessel wall (Tedgui and Mallat, 2001). This is supported by the observation that IL-10 knockout (IL-10$-/-$) mice suffer from accelerated atherosclerosis, whereas IL-10 transgenic mice are relatively protected (Pinderski-Oslund et al., 1999). Clinical poignancy is added by the fact that a hypoactive allele of the IL-10 promoter sequence increases the risk of cardiovascular events in hemodialysis patients (Girndt et al., 2002), whereas serum levels of IL-10 have been found to be decreased in patients with unstable angina compared with patients with chronic stable angina (Smith et al., 2001). Indeed, as IL-10 is known to down-regulate MMP-9 production and up-regulate tissue inhibitor of metalloproteinase-1 (TIMP-1) expression in macrophages (Lacraz et al., 1995), IL-10 may have a direct stabilizing influence on advanced plaques. Moreover, the combined weight of these data has led to extensive speculation about the therapeutic applicability of IL-10 in atherosclerosis (Terkeltaub, 1999).

F. Chemokines

On the basis of their chemoattractant activity for leukocytes, the interleukins IL-8 and IL-16 have been classified as chemokines (Center and Cruikshank, 1982; Mukaida et al., 1989). IL-16 has not been scrutinized in an atherosclerotic context, and any potential influence is likely to be mediated mainly by its effects on lymphocyte function, which include stimulation of migration, proliferation, and cytokine production (Cruikshank et al., 2000). IL-8, on the other hand, is well established as a pro-atherogenic factor (Reape and Groot, 1999). Its expression is induced in monocytes and macrophages following the addition of oxidized LDL and cholesterol, respectively (Terkeltaub et al., 1994; Wang et al., 1996). Atheromatous tissue has been found to contain IL-8, most of which is thought to be derived from intimal macrophages (Apostolopoulos et al., 1996; Wang et al., 1996). In addition, cytokine-stimulated vascular smooth muscle cells elaborate IL-8 (Wang et al., 1991), and endothelial cells respond to cyclic stretch by up-regulation of IL-8 production (Okada et al., 1998). Boisvert et al. (1998) have discovered an important role for macrophage-derived IL-8 in atherosclerotic lesion development, as transplantation of IL-8$-/-$ bone marrow to irradiated and atherogenic diet-fed LDLr$-/-$ mice resulted in less extensive intimal macrophage accumulation than transplantation using IL-8+/+ donors. IL-8 is presumed to accelerate atherogenesis by increasing the endothelial adhesiveness for monocytes (Gerszten et al., 1999), by its mitogenic and chemoattractant actions on smooth muscle cells (Yue et al., 1994), and by mediating angiogenesis in the atherosclerotic plaque (Simonini et

al., 2000). Furthermore, IL-8 may cause destabilization of advanced plaques through its inhibitory effect on TIMP-1 expression in macrophages and an ensuing increase in metalloproteinase activity (Moreau et al., 1999). Interestingly, IL-8 levels have been found to be elevated in peripheral blood monocytes from hypercholesterolemic patients (Porreca et al., 1999), and serum IL-8 levels to be associated with unstable angina pectoris and acute myocardial infarction (Zhou et al., 2001a), reflecting the potential clinical relevance of IL-8-mediated functions in atherosclerosis.

G. Interleukin-17

The term IL-17 harbors a family of proinflammatory cytokines, of which the founder member was found to be an ortholog of murine CTLA-8 (Rouvier et al., 1993) and its gene to have been captured by the T lymphotropic herpesvirus saimiri (Rouvier et al., 1993, Yao et al., 1995a,b; Fossiez et al., 1998). It is primarily produced by activated memory T cells and Th1/Th0 cells (Aarvak et al., 1999) and binds to a ubiquitously expressed receptor (Yao et al., 1995a). More recently, the variants IL-17B, IL-17C, IL-17E, IL-17F, and IL-25 have been cloned, which are considered to signal through subtype-specific receptors (Li et al., 2000b; Hymowitz et al., 2001; Lee et al., 2001a; Hurst et al., 2002). IL-17 induces the expression of proinflammatory mediators by a variety of cells, including the production of IL-6 and IL-8 by stromal cells (Yao et al., 1995a,b), ICAM-1 by fibroblasts and keratinocytes (Yao et al., 1995b; Albanesi et al., 1999), as well as IL-1β, IL-1ra, IL-6, IL-10, TNFα, prostaglandin E_2, MMP-3, and MMP-9 by macrophages (Jovanovic et al., 1998, 2001). Binding of IL-17 to its receptor results in an increase in Ca^{2+} influx, a decrease of intracellular cAMP levels, activation of mitogen-activated protein kinases, and stimulation of NF-κB activity (Jovanovic et al., 1998; Awane et al., 1999). The activity profiles of IL-17B and IL-17C differ from that of IL-17 in that they fail to induce IL-6 in fibroblasts but are capable of stimulating the release of TNFα and IL-1β from the monocytic cell line THP-1 (Li et al., 2000b). IL-17E has been shown to stimulate NF-κB activity and the production of IL-8 in TK-10 cells (Lee et al., 2001a). The IL-17 family has not yet been implicated in atherogenesis, but its proinflammatory effects on macrophages, the stimulation of endothelial IL-2 and MCP-1 elaboration by IL-17F (Starnes et al., 2001), the production of IL-17 by activated T cells, and the widespread expression of the IL-17 receptor make this interleukin family a potential pro-atherogenic candidate.

III. Modulation of Cytokine Function As a Therapeutic Strategy for Atherosclerosis

From the preceding discussion it will have become evident that, despite having been thoroughly researched with respect to their basic immunological functions, many of the interleukins identified to date have yet to be typecast on the atherosclerotic stage (Table 1). When classified according to their perceived role in atherogenesis, a large number thus remain in the "unknown" category. A similarly sizable group has been found to be pro-atherogenic, and only a small subset has been adjudicated to possess an equivocal (IL-4, IL-13) or anti-atherogenic (IL-1ra, IL-9, IL-10, IL-11) propensity. It therefore appears that the most rewarding strategies of interleukin modulation for the prevention of atherosclerosis are likely to involve the down-regulation of signaling mediated by proinflammatory cytokines. Nonetheless, due attention also needs to be paid to the intriguing therapeutic possibility of harnessing the anti-atherogenic potential of anti-inflammatory interleukins. The modulation of (patho)physiological effects exerted by cytokines that have thus far been adjudicated to have either an overtly pro- or an anti-atherogenic role on the evidence of animal intervention studies are, in the short term, the most likely candidates for the development of such strategies (Table 2; Fig. 3).

The function of interleukins is tightly regulated at a number of levels in their production, processing, and signaling cascades. Interleukins being proteins, the first step in their production necessitates the binding of nuclear transcription factors to enable gene transcription. Following mRNA translation, the production of mature molecules requires additional proteolytic processing for a number of interleukins and interleukin receptors. The ambient concentration of some interleukins is known to be negatively regulated following exposure on the cell surface or release into the surrounding extracellular

TABLE 1
The (causative, associative, or presumed) role of interleukin family members in atherosclerosis

	Pro-Atherogenic	Equivocal	Anti-Atherogenic	Unknown
IL-1 family	**IL-1α/β**			
	IL-18			
			IL-1ra	
IL-2 family	IL-2			
		IL-4		
				IL-7
			IL-9	
	IL-15			IL-21
		IL-13		
CSF family	*IL-3*			
				IL-5
gp130 family	**IL-6**			
			IL-11	
	IL-12			
				IL-23
				IL-27
Chemokines	**IL-8**			
				IL-16
IL-10 family			**IL-10**	
				IL-19
				IL-20
				IL-22
				IL-24
				IL-26
IL-17 family	*IL-17A/B/C/E/F*			IL-25
Unclassified				IL-14

Bold type represents causative role; italic type represents presumed role; lightface roman type represents associative role.

TABLE 2

Primary vascular sources, targets, and selected effects of interleukins for which a pro- or anti-atherogenic role has been established in murine intervention studies.

	Primary Sources	Primary Vascular Effector Cells and Direct Effects						Murine Intervention Studies
		Endothelial Cells		Monocytes/Macrophages		Smooth Muscle Cells		
		⇑	⇓	⇑	⇓	⇑	⇓	
IL-1	EC, T cell, MΦ, SMC (IL-1ra: EC, MΦ, SMC)	IL-1, IL-6, IL-8, MCP-1, M-CSF, fractalkine, IL-1R1, ICAM-1, VCAM-1, E-selectin, tissue factor, heme oxygenase, apoptosis	proliferation	IL-6 PDGF-AA, superoxide	apolipoprotein E	IL-6, IL-8, IL-11, MCP-1, M-CSF, GM-CSF,ICAM-1, VCAM-1, iNOS, COX-2, Mn-SOD, stromelysin, interstitial collagenase, proliferation	proliferation	⇑ vascular inflammation in IL-1ra-deficient mice ⇓ atherogenesis in IL-1ra-transgenic mice
IL-6	EC, MΦ, SMC	IL-6, migration	HGF proliferation	MCP-1	SR-A	Proliferation		rIL-6 ⇓ fatty streak formation rIL-6 ⇑ atherogenesis rIL-6 ⇓ plaque progression
IL-8	EC, MΦ, SMC	Monocyte adhesion			TIMP-1	Chemotaxis, proliferation		⇑ atherogenesis following transfer of IL-8-transgenic bone marrow
IL-12	EC, MΦ	VCAM-1						rIL-12 ⇑ plaque progression
IL-9	T cell				TNFα oxidative burst			IL-9 ⇓ atherogenesis IL-9 immunization ⇑ atherogenesis
IL-10	T cell, MΦ		IL-6, IL-8	TIMP-1, differentiation, phagocytosis	Cytokine production, TNFα		PLA_2, proliferation	⇑ atherogenesis in IL-10-deficient mice
			VCAM-1, ICAM-1, P-selectin, E-selectin, angiogenesis		ICAM-1, CD18, CD62-L, tissue factor			⇓ atherogenesis in IL-10-transgenic mice
					iNOS			⇓ atherogenesis following transfer of IL-10-transgenic bone marrow
					MMP-9			plasmid-mediated/ adenoviral IL-10 gene transfer ⇓ atherogenesis
					MHC II, B7, NF-κB activation, activation, proliferation			

Cox-2, cyclooxygenase-2; EC, endothelial cell; HGF, hepatic growth factor; M-CSF, monocyte colony-stimulating factor; PLA_2, phospholipase A_2; SR-A, scavenger receptor-A; TIMP-1, tissue inhibitor of metalloproteinase-1.

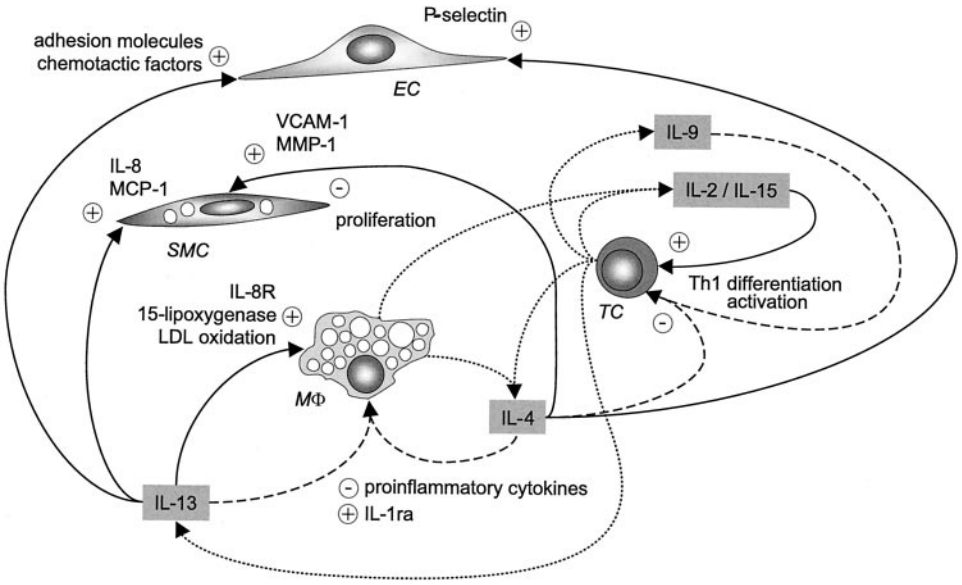

FIG 2. Overview of the complex actions of IL-2 family members in the vascular wall. All members are produced by cellular constituents of the atherosclerotic plaque (dotted line: EC, endothelial cell; SMC, smooth muscle cell; MΦ, macrophage; TC, T cell) and exert effects that are considered to be either pro-atherogenic (continuous line) or anti-atherogenic (dashed line).

space. This may involve neutralization of interleukins by binding to a specific antibody or to a soluble form of its corresponding receptor.

Interleukin molecules that escape endogenous regulation mechanisms can bind to their target receptor and thus initiate a signaling sequence. The abundance of the membrane-bound form of interleukin receptors may be controlled by endocytosis and degradation via the ubiquitin-proteasome system. The signaling cascade is frequently rather complex and often shares redundancy with those activated by other members of a particular interleukin family. A varied array of pathways has been found to convey interleukin signaling to the nucleus, frequently involving receptor-mediated activation of kinases (including Jaks, Tyks, and MAPKs) and subsequent activation of nuclear transcription factors (including STATs, NF-κB, and AP-1) (Fig. 1). Intracellular signal transduction is negatively controlled by specific inhibitors of the Jak-STAT pathway that regulate its components by dephosphorylation, degradation by the ubiquitin-proteasome pathway, and binding of dominant-negative STATs. Signaling eventually culminates in the transcriptional activation of a cytokine-specific set of genes, the products of which mediate the biological functions of the cytokine in question by intracellular, autocrine, paracrine and endocrine mechanisms.

In theory, any step in the production and effector pathways of a particular interleukin may be considered to represent a potential target for therapies aimed at modulating its biological activity (Fig. 4). In practice, various approaches are not yet feasible due to a lack of detailed understanding of the mechanisms involved.

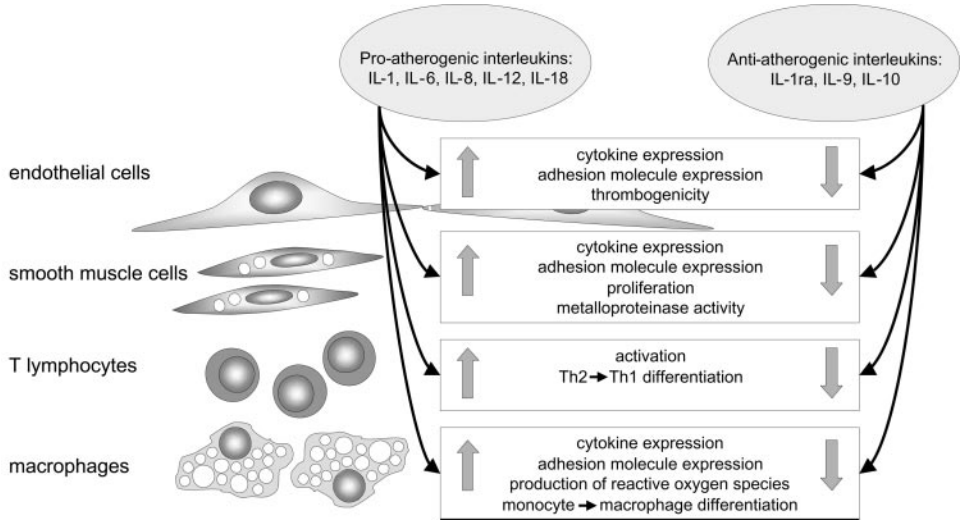

FIG 3. Primary vascular target cells and summarized actions of proven pro- and anti-atherogenic interleukins.

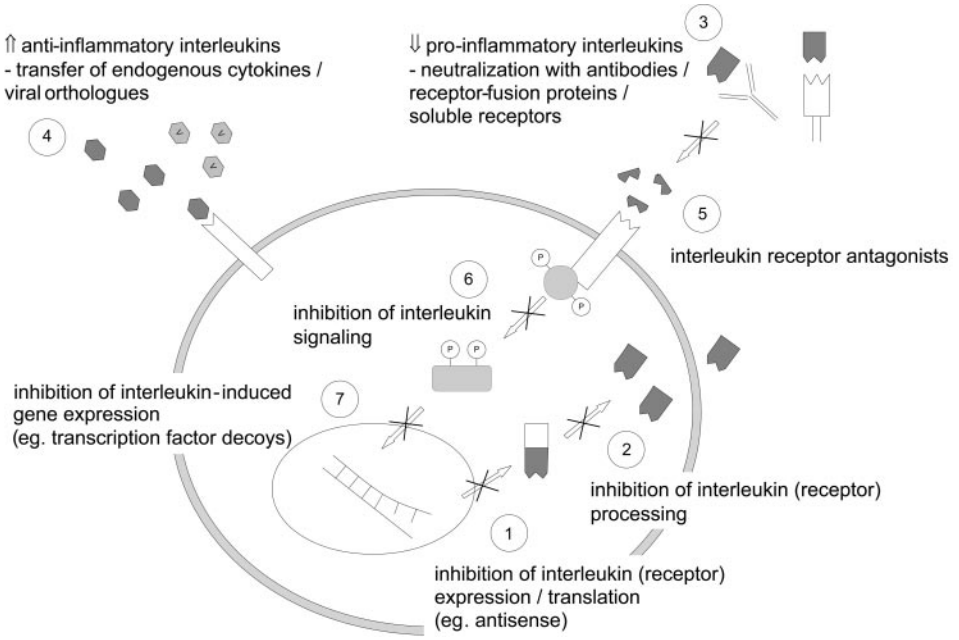

FIG 4. Depiction of potential strategies for the modification of interleukin activity as a therapy for atherosclerosis.

Moreover, the specificity of such interventions is frequently limited by considerable redundancy in interleukin processing and signaling pathways. Although this may be desirable if the goal of the intervention is a general reduction of proinflammatory signaling, a more subtle change of cellular functions may require direct alteration of extracellular interleukin levels or interleukin-receptor interaction. In the specific case of atherosclerosis, the more difficult hurdles on the course to the clinical use of cytokine modulation therapy are hidden in the insidious and chronic nature of the atherosclerotic process (Ross 1986, 1993a, 1999). Inherent in this observation is the need for any strategy aimed at *primary* prevention to be comparably chronic in its duration of action. In view of the high prevalence of the disease and its still poorly predictable course, such a strategy would also need to be safe, effective, and affordable. Most of the interleukin-based treatments that have been conceived thus far do not answer these demands. In the meantime, it may be more realistic to focus on a remedy that is capable of effecting *secondary* or *tertiary* prevention. An example of the latter is the phenotypic stabilization of unstable atherosclerotic atheromata to avert the risk of plaque rupture and fatal thrombosis. This may be achievable by the use of a short, and possibly localized, course of anti-interleukin therapy.

In this review, we discuss examples of techniques directed at modulating each of the steps described above. We shall pay particular attention to methods that have been shown to hold promise for the prevention of atherosclerosis or those that interfere with the function of interleukins thought to be involved in atherogenesis.

A. Inhibition of Expression/Translation of Interleukins and Their Receptors

The foremost approach to the specific inhibition of interleukin (receptor) expression and translation has been the use of short strands of (modified) nucleotides that are complimentary to stretches of mRNA encoding the target protein. This is thought to lead to formation of DNA:RNA duplexes and subsequent degradation of the mRNA sequence by RNaseH. The advent of this oligonucleotide-based "antisense" therapy was hailed as the dawn of a new era of highly specific and effective treatments for a variety of diseases, ranging from cancer to hypertension (Raizada et al., 2000; Lebedeva and Stein, 2001). This unbridled optimism has been somewhat deflated in recent years, however, as it has transpired that the mechanism of action of antisense molecules is frequently less specific and far more complex than originally conceived (Lebedeva and Stein, 2001). Moreover, unmodified oligonucleotides are rapidly degraded in vivo, and efficient transfection of target cells with antisense constructs has proved difficult. Nonetheless, several studies describing the antisense-mediated down-regulation of interleukin production have been reported (Crooke, 2000).

IL-1α is known to inhibit endothelial cell proliferation, and thereby to promote the type of endothelial injury that is thought to precipitate atherogenesis (Ross, 1986). Furthermore, IL-1α is an autocrine stimulator of adhesion molecule expression, including ICAM-1 and E-selectin, and the up-regulation of these molecules by hypoxic endothelial cells has been found to be mediated by IL-1α (Shreeniwas et al., 1992). Antisense oligodeoxynucleotides (ODNs) directed against IL-1α have been

found to prevent endothelial cell senescence, to prolong their life span, and to hinder adhesion molecule production in vitro (Maier et al., 1990; Maier and Ragnotti, 1993). Moreover, the IL-1α -mediated up-regulation of cyclooxygenase expression in endothelial cells has been shown to be limited by the addition of ODNs directed against protein kinase C (PKC), which is a mediator in the signal transduction pathway that leads to IL-1α induction (Hsu et al., 1999). Because interleukin-1 also affects smooth muscle cell function, Hsu et al. (1999) transfected vascular smooth muscle cells in vitro with an Epstein-Barr virus-derived vector expressing IL-1 antisense transcripts, which repressed the expression of matrix genes such as type I collagen and fibronectin by smooth muscle cells and prolonged their life span. In macrophages, more specifically the macrophage-like cell line U937, the expression of IL-1β can also be down-regulated by means of antisense techniques employing phosphorothioate oligonucleotides (Yahata et al., 1996).

The platelet-derived growth factor (PDGF)-mediated up-regulation of IL-6 in smooth muscle cells can be attenuated by antisense ODNs directed against this pro-atherogenic interleukin (Roth et al., 1995). This has been shown to inhibit cell division, and has thus established IL-6 as a mediator of PDGF-induced smooth muscle cell proliferation. The feasibility of antisense-mediated inhibition of IL-6 expression in the vessel wall has been demonstrated by ex vivo pressure-mediated transfection of naked oligonucleotides into human saphenous vein explants, which resulted in 70 to 75% inhibition of IL-6 expression, as measured 2 h after the transfection procedure (Mann et al., 1999).

Chemokine function has also been successfully repressed by antisense techniques. Thus, the role of IL-8 as a monocyte-derived angiogenic factor was revealed in vitro by the inhibition of monocyte-induced angiogenic activity following the administration of an IL-8 antisense oligonucleotide (Koch et al., 1992), and pretreatment of human pulmonary artery endothelial cells with antisense against MCP-1 has been shown to reduce TNFα-induced *trans*-endothelial monocyte migration (Maus et al., 2000).

Rather than inhibiting the production of interleukins themselves, antisense strategies could also be deployed against interleukin signaling by altering the expression of the relevant receptor. Indeed, ODNs directed against the IL-1 receptor have been shown to diminish IL-1-stimulated prostaglandin E_2 synthesis in murine and human fibroblasts (Burch and Mahan, 1991), and in vivo applicability was confirmed by the finding that subcutaneous injection of IL-1 receptor antisense in mice decreased neutrophil accumulation at sites of IL-1 injection.

Intriguingly, ODNs containing cytidine phosphate guanosine motifs have been identified as potent stimulators of Th1 type responses, and this type of aspecific effect needs to be taken into account during the design of anti-inflammatory antisense sequences (Chu et al., 1997). In a drive to enhance the specificity as well as the efficacy, tolerability, and duration of action of antisense-mediated mRNA cleavage, the attention has turned to the use of ribozymes. These are RNA molecules with intrinsic endonuclease activity, which bind to target RNA in a base pair-specific fashion, and subsequently catalyze the cleavage of this RNA strand by facilitating the hydrolysis of phosphodiester bonds (Zaug et al., 1986; James and Gibson, 1998). Indeed, stable expression of ribozymes aimed at IL-1β and ICE can effect a dramatic decrease in the steady-state levels of their target mRNAs in the monocytic cell line THP-1 (Leavitt et al., 2000) and minimized hammerhead ribozymes have been shown to be active against IL-2 (Sioud et al., 1997). In vivo efficacy and in vitro reduction of TNF-induced IL-6 production has been demonstrated for IL-6 ribozymes (Mahieu et al., 1994). The first cardiovascular target to have been successfully inhibited by ribozyme therapy directed against cytokine expression is transforming growth factor β (TGFβ) production in smooth muscle cells (Su et al., 2000). In vivo, TGFβ ribozymes have been shown to reduce neointima formation in a rat model of vascular injury (Yamamoto et al., 2000).

Although ribozymes may prove to be more effective and specific than antisense oligonucleotides due to their enzymatic mode of action, they share similar limitations to their biological activity. Thus, efficient cellular transfection is difficult to achieve, and once it has occurred, the duration of action is curtailed by a short intracellular half-life. Both problems have been extensively addressed, to varying degrees of success. Cellular uptake has been increased by the use of lipid, peptide, and polymer delivery systems, and nuclease-mediated degradation has been inhibited by chemical modifications of the oligonucleotide backbone (Morishita et al., 1994; Hughes et al., 2001; Lebedeva and Stein, 2001). Circumventing both disadvantages in a single approach may be possible by cloning ribozymes into an expression vector that affords avid transfection of target cells in addition to an extended duration of expression. These are characteristics of viral vectors—retroviruses, adenoviruses, and adeno-associated viruses (AAVs) being the main protagonists. These viral vectors have all been used as a carrier for ribozymes, but AAVs are particularly promising as they combine the main advantage of adenoviruses, i.e., high efficiency of transduction, with the prolonged expression due to integration of transgenes in the genome that is typical of retroviruses (Monahan and Samulski, 2000). AAVs have been shown to be capable of transducing endothelial and vascular smooth muscle cells in vitro, but expression in vivo is confined to the adventitia (Lynch et al., 1997). Therefore, to constitute a useful gene transfer vehicle in the prevention of atherosclerosis, the issue of targeting accuracy needs to be addressed, for instance by selecting the most suitable virus serotype, or by using an adenovirus/AAV hybrid

system (Recchia et al., 1999; Monahan and Samulski, 2000).

B. Inhibition of Interleukin Processing

As mentioned, the production of mature forms of various cytokines requires proteolytic processing of inactive precursors. This is exemplified by the conversion of pro-IL-1β and pro-IL-18 by ICE/caspase-1 (Wilson et al., 1994; Tone et al., 1997), and the cleavage of membrane-bound TNFα by TNFα-converting enzyme (Black et al., 1997). Interestingly, the shedding of the soluble form of several interleukin receptors has also been found to require metalloproteinase activity, including IL-1R, IL-2R, and IL-6R (Mullberg et al., 1995, 1997). With respect to atherosclerosis, interference with proteinase-dependent processing may constitute an attractive strategy to attenuate the release of active IL-1β or to inhibit sIL-6R-mediated transfer of IL-6 sensitivity to cells that do not themselves express IL-6R (Jones et al., 2001).

Several naturally occurring ICE inhibitors have been described (Croucher et al., 2000). Thus, cowpox virus protein A (CrmA) protects cells infected by cowpox from immunological clearance by preventing the release of IL-1β (Ray et al., 1992), whereas the baculovirus protein p35 performs a similar function in baculovirus-infected cells (Bump et al., 1995). Smooth muscle cells produce an endogenous ICE inhibitor, which has been identified as serpin proteinase inhibitor 9 (PI-9) (Schonbeck et al., 1997; Young et al., 2000). Interestingly, protein levels of this enzyme have been found to be decreased in unstable plaques in conjunction with a reciprocal up-regulation of IL-1β, suggesting an endogenous anti-inflammatory role for constitutive PI-9 expression. Consequently, inhibition of caspase-1 activity might be an effective strategy in the prevention of lesion destabilization. In considering the feasibility of therapeutic ICE inhibition, one might either opt to capitalize on the potency of naturally occurring antagonists, or one could interpret their action as a paradigm for the development of synthetic ICE inhibitors (Livingston, 1997). Several such compounds have been developed that display activity in vitro. This includes the down-regulation by WIN 67694 of the LPS-induced release of IL-1β by murine macrophages (Miller et al., 1995), and the reduction of human myocardial ischemic dysfunction in an ex vivo organ culture model by YVAD (Pomerantz et al., 2001). In vivo, a single intraperitoneal dose of VE-13,045 administered after an LPS challenge reduced murine IL-1β serum levels by 50 to 70% (Ku et al., 1996). Prior to clinical use, however, the specificity for caspase-1 of the compound in question needs to be warranted, in view of the degree of conservation that has been found to exist between the active sites of the caspase family members. Moreover, due heed should be paid to the potentially detrimental inhibition of caspase-1-mediated apoptosis, which could contribute toward tissue hyperplasia or even neoplasia.

C. Neutralization of Proinflammatory Interleukins

The biological activity of interleukins is partially regulated by anti-cytokine antibodies, soluble cytokine receptors, and cytokine-binding proteins, the elaboration of which is frequently controlled by the interleukin concerned (Heaney and Golde, 1998; Slifka and Whitton, 2000). Soluble interleukin receptors are produced by alternative splicing of mRNA or by proteolytic cleavage of full-length receptors. For instance, IL-1 activity is inhibited by the soluble type II IL-1 receptor (Giri et al., 1990), which is shed from neutrophils in response to proinflammatory stimuli, including TNF, IL-13, and endotoxin (Colotta et al., 1994; Giri et al., 1994b). Its pathophysiological roles are thought to include the limitation of IL-1 activity in sepsis (Giri et al., 1994b). Whereas the plasma level of soluble IL-2R has been deemed to be a marker for T cell activation in ischemic heart disease (Simon et al., 2001), high levels of sIL-2R paradoxically reduce the relative risk of lesion instability, which is known to be associated with increased inflammatory activity in the plaque (Blum et al., 1995; Takeshita et al., 1997; Simon et al., 2001). Moreover, in vitro studies have evidenced the inhibition of IL-2-induced activation of peripheral mononuclear cells by sIL-2R (Zorn et al., 1994). Soluble IL-4-binding proteins are known to occur in mice (Fernandez-Botran and Vitetta, 1990) and humans (Fanslow et al., 1993). The benefit of sIL-4R in preventing IL-4-mediated inflammatory responses has been demonstrated in a murine model of asthma (Henderson et al., 2000), and its administration has been found to be safe and to stabilize lung functions in patients with moderate asthma (Renz, 1999).

For some soluble interleukin receptors, however, the effects are rather less clear-cut (Heaney and Golde, 1998). The *trans*-signaling activity conferred by sIL-6R has already been discussed (Jones et al., 2001), as well as its role in endothelial cell activation (Modur et al., 1997; Romano et al., 1997). By contrast, the soluble receptor subunit for another member of the IL-6 family, IL-11, has been found to antagonize IL-11 activity (Curtis et al., 1997). Likewise, the soluble form of the gp130 subunit shared by the IL-6 family of receptors is thought to inhibit IL-6 mediated signaling by binding the IL-6/sIL-6R complex (Narazaki et al., 1993; Muller-Newen et al., 1998; Jostock et al., 2001).

Antagonistic binding proteins have recently also been found for IL-13, IL-18, and IL-22 (Zhang et al., 1997; Xu et al., 1998b; Novick et al., 1999). IL-18-binding protein (IL-18bp) has been characterized as a modulator of the Th1 response on the basis of its ability to inhibit IL-18-mediated up-regulation of IFNγ, IL-8, NF-κB, and VCAM-1 (Reznikov et al., 2000; Vidal-Vanaclocha et al., 2000). The human IL-18bp gene encodes at least four isoforms (Kim et al., 2000b), and its expression is increased by IFNγ in a range of human cell lines (Muhl et

al., 2000). Serum levels of IL-18bp are raised in septic patients, with a concomitant decrease in free IL-18, and its roles are therefore presumed to include the provision of negative feedback in states of high inflammatory activity (Novick et al., 2001). Recently, Mallat et al. (2001b) have demonstrated the anti-atherogenic potential of IL-18bp. They have found electrotransfer of an expression plasmid encoding murine IL-18bp to attenuate atherosclerotic lesion development in the aorta of apoE−/− mice. This treatment also resulted in changes in plaque composition, comprising a decrease in inflammatory cell content and an increase of smooth muscle cell and collagen content of the lesion. IL-18bp therefore appears to have a beneficial effect on plaque stability as well as plaque progression. Moreover, IL-18bp may promote ischemia-induced neovascularization by inhibiting the anti-angiogenic role of IL-18, and its administration could therefore also aid postinfarction myocardial recovery (Mallat et al., 2002). Interestingly, poxvirus proteins have been identified that share considerable sequence homology with human IL-18bp. These inhibit virus elimination by the host's immune system by binding IL-18, attenuating IL-18-induced IFNγ production, and impairing natural killer cell cytotoxicity (Born et al., 2000; Calderara et al., 2001) and may be promising anti-atherogenic agents in their own right. Similar protective functions appear to be served by the viral capture and modification of other cytokine receptor genes (Spriggs, 1996; McFadden et al., 1998), including the IL-1R (Spriggs et al., 1992) and IL-8R (Rosenkilde et al., 1999), and the chemokine binding proteins M-T1 and M-T7 (Upton et al., 1992; Graham et al., 1997; Lalani et al., 1997a). The latter is an IFNγR homolog and has been used successfully in the attenuation of angioplasty-induced neointima formation in rat carotid arteries (Liu et al., 2000). A 38-kDa glycopeptide encoded by the tanapox virus binds IL-2, IL-5, and IFNγ, and inhibits the TNFα-induced expression of E-selectin, VCAM-1, and ICAM-1 by tanapox virus-infected primary endothelial cells (Paulose et al., 1998).

Other cytokines have also been targeted by soluble receptor therapy, the foremost example being the antagonism of TNFα. TNFα has been suggested to be pro-atherogenic by virtue of its presence in atherosclerotic lesions and its proinflammatory effects on all cell types involved in atherogenesis, including the up-regulation of adhesion molecules, chemoattractants, cytokines, and growth factors (LeBoeuf and Schreyer, 1998). Although systemic TNFα levels are not correlated with an increased propensity to atherosclerosis, the level of TNFα is an independent risk factor for the occurrence of acute coronary events in patients with coronary artery disease (Ridker et al., 2000a; Sack, 2002). Most importantly, however, TNFα levels are known to be raised in congestive heart failure and to exacerbate heart failure in murine models, probably due to excessive myocardial remodeling (Bradham et al., 2002).

TNFR-IgG fusion proteins have proven their worth in reducing the TNFα -mediated induction of proinflammatory interleukins, including IL-1β and IL-6 (Abraham et al., 1994; Kubota et al., 2000; Kadokami et al., 2001). Two TNFα blockers have recently been evaluated in clinical trials: etanercept (Enbrel), a fusion protein of the soluble form of the TNFR and the Fc portion of human immunoglobulin IgG1 and infliximab (Remicade), a chimeric IgG1 monoclonal antibody that contains a murine binding site for TNFα. Despite encouraging results in early clinical studies, in which subcutaneous etanercept administration appeared to be safe and to result in improvement of cardiac function in patients with advanced heart failure (Bozkurt et al., 2001), a large-scale phase II/III trial (RENEWAL) has recently been prematurely discontinued due to a lack of benefit (Louis et al., 2001). The introduction of infliximab as a therapy for rheumatoid arthritis, on the other hand, has been marred by the recent report of a case of sudden death in a patient without heart failure following a single 200 mg infusion (de' Clari et al., 2002). Moreover, a phase II clinical trial investigating the use of infliximab in advanced congestive heart failure has been placed on hold after the death of seven patients in the treatment group.

The experience with infliximab, in particular, may point to a potentially protective effect of TNFα in heart failure. Thus, TNFα has been found to induce protein synthesis in cardiac myocytes (Hiraoka et al., 2001) and to lead to inflammatory autoregulation by means of the translocation of functionally inactive NF-κB p50 homodimers (Haudek et al., 2001).

In an atherosclerotic context, blockade of TNFα by administration of soluble TNFR has been found to accelerate endothelial recovery after balloon angioplasty of rat carotid arteries (Krasinski et al., 2001). Because endothelial damage is thought to be an important process in atherogenesis and atherosclerotic plaque erosion, the inhibition of TNFα-mediated impairment of endothelial function could yield considerable merit. In an analogous approach, adenovirus-mediated transfer of a secreted TGFβ type II receptor has been demonstrated to inhibit luminal loss after percutaneous transluminal coronary angioplasty of porcine coronary arteries (Kingston et al., 2001). Specific targeting to inflammatory tissues may refine such gene transfer approaches, as demonstrated by gene vectors in which the TNFR-IgG fusion protein sequence has been placed under the control of a serum amyloid A promoter. Serum amyloid A levels increase dramatically in inflammatory conditions, and the plasmid-mediated expression of such a construct has been shown to be activated in vitro by IL-1β and TNFα (Rygg et al., 2001). Nonetheless, TNFα also exerts potentially anti-atherogenic functions, including the inhibition of lipoprotein lipase (Tengku-Muhammad et al., 1996) and the attenuation of macrophage scavenger receptor activity (van Lenten and Fogelman, 1992; Hsu et

al., 1996; Schreyer et al., 1996). In addition, TNFα deficiency has no effect on atherogenesis in apoE−/− mice (Schreyer et al., 2002), whereas TNFR1 deficiency even predisposes to atherosclerosis (Schreyer et al., 1996). As is the case with respect to heart failure, controversy thus still shrouds antagonism of TNFα activity as a treatment for atherosclerosis, which is also borne out by the fact that administration of TNF-binding protein in apoE−/− mice attenuates fatty streak formation in females, whereas it has no effect in male mice (Elhage et al., 1998).

Virus-encoded interleukin and interleukin receptor homologs are also thought to function as antigens and haptens, respectively, in the generation of autoantibodies against a series of interleukins that have been found to occur naturally in healthy humans and certain disease states (Bendtzen et al., 1998), including antibodies against IL-1α (Bendtzen et al., 1989, 1994), IL-6 (Hansen et al., 1991; Bendtzen et al., 1994), and IL-10 (Bendtzen et al., 1994). The (patho)physiological role of these antibodies remains somewhat unclear, although most neutralize their target interleukins in vitro (Svenson et al., 1992; Hansen et al., 1993, 1995). Several have also been found to attenuate interleukin activity in vivo, and anti-cytokine therapy by means of monoclonal antibodies has also been investigated in the context of atherosclerosis. An important role has been assigned to CD40L-CD40 interactions in the pathogenesis of atherosclerosis (Mach et al., 1997). Accordingly, treatment with anti-CD40L antibody reduces de novo atherogenesis in atherosclerosis-prone mice (Mach et al., 1998) and cardiac allograft arteriopathy in a murine heterotopic cardiac transplant model (Wang et al., 2002) and has also been found to alter the histological appearance of pre-existing atherosclerotic lesions toward a more stabilized phenotype (Lutgens et al., 2000; Schonbeck et al., 2000). By contrast, antibody-mediated neutralization of TGFβ signaling accelerates atherogenesis in apoE−/− mice, and leads to the development of a more inflammatory plaque phenotype (Mallat et al., 2001c). Despite being a CD40-inducible protein (Zan et al., 1998), TGFβ thus appears to have anti-atherogenic properties, and its inhibition would therefore be undesirable in the prevention of atherogenesis.

The chronic nature of atherosclerosis and the generally rapid clearance of administered antibodies, however, would necessitate repeated parenteral administration to ensure prolonged efficacy. Eliciting an endogenous antibody response by immunization with the cytokine in question may circumvent this problem. A humoral immune response has previously been shown to be mounted against most therapeutically administered recombinant interleukin preparations (Revoltella, 1998), and this observation has paved the way for the introduction of intentional interleukin immunization. Svenson et al. (2000) have immunized mice with recombinant murine IL-1α in conjunction with purified protein derivative of tuberculin, which resulted in the development of IL-1α neutralizing autoantibodies that attenuate the expression of IL-6 in vivo. Alternatively, a synthetic interleukin receptor antagonist may be used as an antigen for the induction of autoimmunity against interleukins, as has been demonstrated for IL-6 (Ciapponi et al., 1997), or vaccination may be conducted with a DNA vaccine encoding antigenic epitopes of the cytokine concerned (Youssef et al., 1998). Thus, rats have been found to mount a protracted immune response to Fas ligand after a course of vaccinations with FasL cDNA (Wildbaum et al., 2000). The resulting autoantibodies inhibited the production of TNFα by cultured T lymphocytes in vitro and provided protection against experimental autoimmune encephalomyelitis in vivo.

In considering the therapeutic scope of humoral anti-interleukin immune response induction, however, one needs to take into account that some anti-cytokine antibodies have been found to stabilize cytokine functions rather than solely neutralizing their activity (Bendtzen et al., 1990; Wendling et al., 1993). Antibodies to IL-3, IL-4, and IL-7 have thus been demonstrated to form complexes with their target interleukins, which prolongs their in vivo half-life (Finkelman et al., 1993). This has led to the realization that the efficacy of monoclonal anti-interleukin therapy constitutes a balance between the neutralization avidity and the rate of clearance of the formed complex. These characteristics may partly depend on the specific epitope recognized by the antibody, and meticulous preclinical assessment of complex clearance is therefore indicated prior to clinical evaluation.

D. Interleukin Receptor Antagonists

Endogenous regulation of interleukin activity also occurs at the level of ligand-receptor interaction. A major exponent of this type of modulation is the control of IL-1 signaling by the endogenous IL-1 receptor antagonist, IL-1ra (Arend et al., 1998; Smith, 2000). First discovered in the 1980s (Arend et al., 1985), this factor has been extensively studied as a potential anti-inflammatory compound. Systemic treatment with IL-1ra has been proven to be beneficial in the treatment of rheumatoid arthritis in animal models and in humans, as judged by histological and clinical improvement (Bresnihan et al., 1998; Cunnane et al., 2001). As discussed above, IL-1ra has also been suggested as an important protective factor in atherogenesis (Francis et al., 1999) and restenosis (Kastrati et al., 2000), and its administration is currently under scrutiny as a potential anti-atherogenic therapy. Elhage et al. (1998) have demonstrated that subcutaneous injection of IL-1ra by means of an osmotic pump (25 mg/kg/day for 1 month) leads to a significant reduction in fatty streak formation in the aortic sinus of apoE−/− mice on an atherogenic diet (Elhage et al., 1998). Short-term treatment with IL-1ra has been found to be well tolerated. Due to the central role of IL-1 in the

immune response, however, long-term systemic treatment with an inhibitor of this factor may not be desirable. It is encouraging, therefore, that local gene therapeutic approaches involving IL-1ra have provided promising results in the attenuation of cerebral, pancreatic, and articular inflammation in animal models (Yang et al., 1997; Fernandes et al., 1999; Giannoukakis et al., 1999) and are currently awaiting evaluation in clinical trials (Del Vecchio et al., 2001).

In lieu of naturally occurring antagonists, inhibitors of interleukin receptors have also been developed by synthetic means. Phage display techniques have led to the development of AF12198, a 15-mer peptide with nanomolar affinity for the human type I IL-1 receptor, which does not bind to the human type II receptor (Akeson et al., 1996), and inhibits IL-1-induced ICAM-1 expression by endothelial cells in vitro. Moreover, it downregulates IL-6 induction in cynomolgus monkeys and is thus considered to be the first small molecule to show IL-1 receptor antagonist activity in vivo.

In general, the development of small interleukin receptor antagonists has proved difficult, however, due to the complex and multipoint high-affinity interactions between interleukin receptors and their ligands. A more rewarding strategy has been the mutation of existing ligands. IL-6 ligand-receptor interaction can be blocked by IL-6 variants that have been mutated to display increased affinity for IL-6R and decreased binding to gp130 (Sun et al., 1997; Devlin et al., 1998; Honemann et al., 2001). Due to their interference with gp130 interaction, these IL-6 receptor antagonists may also function as IL-11 antagonists (Sun et al., 1997). IL-12, in its active form, consists of two disulfide-bonded subunits, p40 and p35, and synthetic antagonists have been devised for human (Ling et al., 1995) and murine IL-12 (Gillessen et al., 1995) by homodimerization of the IL-12 p40 subunit. The p40 homodimer acts as a potent IL-12 antagonist in vitro, reduces the murine Th1 type response to endotoxin in vitro (Gately et al., 1996), and protects mice from septic shock following LPS injection (Mattner et al., 1997). Considering the importance that has been assigned to Th1-mediated processes in atherosclerosis, this approach may also hold promise in the prevention of atherogenesis.

The possibility of attenuating interleukin binding by introducing a blocking antibody response to its receptor has also been explored. In vitro, binding of IL-2 to IL-2R can be inhibited by the addition of humanized antibodies that are bispecific for anti-IL-2 receptor α and β (Pilson et al., 1997). In addition to its inhibitory activity on IL-2 signaling, this antibody displays activity against IL-15, possibly by virtue of competing for the shared IL-2β receptor subunit. In a monkey model of autoimmune uveitis, this antibody has been demonstrated to markedly reduce inflammation after twice-weekly intravenous injections for 4 weeks (Guex-Crosier et al., 1997). Furthermore, antagonism of IL-2 by means of anti-IL-2R antibodies, including the commercial preparations basiliximab and dacluzimab, has proven an effective addition to the immunosuppressive regimen following renal allograft transplantation (Vincenti et al., 1998; Onrust and Wiseman, 1999). This therapeutic efficacy is believed to also be partly due to inhibition of IL-15-mediated responses (Boelaars-van Haperen et al., 2001). With respect to other interleukins, antibody blockade of IL-4R and IL-6R has been found to alleviate antigen-induced airway hyperresponsiveness and collagen-induced arthritis, respectively (Gavett et al., 1997; Takagi et al., 1998; Mihara et al., 2001), and antibody directed at IL-18R reduces LPS-induced inflammation and mortality in mice (Xu et al., 1998a).

Opsonization and complement activation are believed to contribute to the mechanism of action of interleukin-receptor antibodies, and the ensuing elimination of cells expressing the relevant receptor may attenuate inflammatory pathways elicited by interleukin binding. In analogy, the specificity of interleukin binding has been employed in devising a "Trojan horse" strategy for the targeting of cytotoxic compounds. This entails the administration of fusion proteins consisting of an interleukin and a toxic polypeptide domain, as used in the transfer of pseudomonas exotoxin to IL-4R-expressing breast carcinoma cells (LeMaistre et al., 1998) and of diphtheria toxin to IL-2R-expressing lymphomas (Leland et al., 2000). Significant toxic side effects may limit this type of therapy to acutely life-threatening and incurable diseases (Bagel et al., 1998). This would almost certainly exclude atherosclerosis as a candidate ailment, although it could be applicable in a short-term strategy for the prevention of restenosis following angioplasty of atherosclerotic lesions. Thus, it is interesting to note that Miller et al. (1996) have found atherosclerotic vascular thickening in rabbits following aortic balloon angioplasty to be reduced by an interleukin-2 receptor-specific fusion protein, termed DAB_{486}-IL-2, in which the receptor binding domain of diphtheria toxin had been replaced by a human IL-2 sequence. DAB_{486}-IL-2 was administered for 10 days following angioplasty (0.1 mg/kg/day i.v.), found to be well tolerated for the duration of the experiment, and to result in complete inhibition of lesion formation compared with controls.

E. Up-Regulation of Anti-Inflammatory Interleukins

As has been discussed in a previous section, several interleukins have been ascribed a putative anti-atherogenic role, including IL-9, IL-10, IL-11, and potentially IL-4 and IL-13 (Table 1). All of these cytokines are known to induce a Th2 type cytokine response, and have been implicated in the pathogenesis of Th2-mediated diseases (Barnes, 2001a). Consistently, their inhibition has been suggested as a potential treatment for these conditions, including asthma (Henderson et al., 2000; Barnes 2001b; Zhou et al., 2001b). Overexpression of these interleukins, on the other hand, has been specu-

lated to ameliorate a variety of Th1-mediated inflammatory conditions, such as rheumatoid arthritis, septic shock, and atherosclerosis. Their up-regulation may therefore hold promise as a therapeutic modality in these diseases, and several studies to this effect have been reported.

Endotoxin-elicited shock has been used as a model for the evaluation of the role and the therapeutic potential of all of these interleukins in Th1-mediated inflammation. The protective effect of IL-4 has been studied in a murine model of Gram-negative septic shock following *Pseudomonas aeruginosa* infection (Giampietri et al., 2000). Mortality was found to be reduced by IL-4 treatment, correlating with a decrease in TNFα elaboration. Similarly beneficial effects have been found after prophylactic injections of recombinant IL-9 in this model (Grohmann et al., 2000). This effect is accompanied by a reduction in TNFα, IL-12 p40, and IFNγ levels, and appears to be IL-9-specific, as heat-inactivated IL-9 did not improve survival rates. Circulating IL-10 levels were found to be markedly augmented by IL-9 injection, and this may be partly responsible for an indirect suppression of proinflammatory cytokine expression, as IL-10 itself also reduces TNFα production and lethality in murine endotoxemia (Gerard et al., 1993). Conversely, IL-9 production in mast cells is greatly stimulated by IL-10, closing a potent positive feedback loop (Stassen et al., 2000). IL-11, on the other hand, inhibits LPS-induced up-regulation of TNFα, IL-1β, and IFNγ by an IL-10-independent mechanism in vivo, and has been found to result in a 60% inhibition of LPS-induced elaboration of TNFα, IL-1β, IL-12 p40, and nitric oxide by murine peritoneal macrophages in vitro (Trepicchio et al., 1997). Moreover, IL-11 reduces lung TNFα levels and neutrophil sequestration, and improves pulmonary vasomotor function in a model of LPS-induced lung injury (Sheridan et al., 1999). IL-13 even leads to a paradoxical decrease in IL-10 levels following intraperitoneal LPS injection, despite TNFα, IFNγ, and IL-12 attenuation, and is therefore also presumed to exert its protective effect in endotoxemic shock through an IL-10-independent pathway (Muchamuel et al., 1997).

The chondroprotective and anti-colitic properties of anti-inflammatory interleukins have also been evaluated. Locally applied recombinant human IL-4 and IL-10 attenuated cartilage degradation and mononuclear cell activity in human rheumatoid synovium that had been engrafted subcutaneously to SCID CB17 mice. Moreover, IL-10, but not IL-4, decreased the expression of ICAM-1 by synovial cells in this model (Jorgensen et al., 1998). IL-11 also significantly reduced the severity of collagen-induced arthritis in mice (Walmsley et al., 1998), and possibly of rheumatoid arthritis in humans (Moreland et al., 2001). In a rat model of inflammatory bowel disease, intraperitoneal adenoviral transfer of IL-4 has been found to significantly inhibit tissue damage, serum and colon IFNγ levels, and myeloperoxidase activity in the distal colon (Hogaboam et al., 1997).

Surprisingly little is known about the atheroprotective role of these interleukins, and IL-10 is undoubtedly the most extensively studied candidate in this respect. A relative deficiency of IL-10 signaling has been implicated in the pathogenesis of a variety of chronic autoimmune conditions, including rheumatoid arthritis, Crohn's disease, multiple sclerosis, and psoriasis. Promising results have been obtained in studies addressing the therapeutic potential of IL-10 administration in animal models of these diseases (Croxford et al., 1998; Kim et al., 2000a; Lubberts et al., 2000), and the outcomes of early clinical trials have been encouraging with respect to safety and efficacy, but these require confirmation on a larger scale (van Deventer et al., 1997; Asadullah et al., 1999; Colombel et al., 2001). The advantageous potential of IL-10 in dampening the inflammatory background of atherosclerosis is strongly suggested by several in vitro and animal studies (Terkeltaub, 1999). Thus, atherogenesis is decreased in IL-10 transgenic mice on a high-fat diet, whereas IL-10 knockout (IL-10−/−) mice display an increased atherogenic tendency (Pinderski-Oslund et al., 1999), which is ameliorated by plasmid-mediated transfer of IL-10 (Mallat et al., 1999b). Furthermore, transfer of bone marrow from IL-10 transgenic mice to LDLr−/− mice inhibits atherosclerosis by altering the phenotype of the resident lymphocyte and macrophage populations in the atherosclerotic plaque (Pinderski et al., 2002).

We have recently demonstrated that de novo collar-induced atherogenesis in LDLr−/− mice (von der Thüsen et al., 2001b) is inhibited by adenovirus-mediated overexpression of human IL-10 (hIL-10), following both systemic and local transfer (von der Thüsen et al., 2001a) (Fig. 5). Although we found overexpression of hIL-10 to be immunomodulatory, as evidenced by monocyte deactivation, it also resulted in marked serum cholesterol lowering. The anti-atherogenic effect of systemic hIL-10 may therefore be considered to be bipartite in this hypercholesterolemic animal model. Local immunomodulation, however, is thought to be solely responsible for the attenuation of atherosclerotic plaque formation (44.9%, $P < 0.05$) that was observed after in vivo endothelial hIL-10 transduction with the same vector. We have used a similar approach in the evaluation of IL-9 as an atheroprotective agent and found daily injections of IL-9 protein (1 μg/mouse/day i.p.) for 5 weeks to reduce carotid collar-induced atherosclerosis by 65% in LDLr−/− ($P < 0.01$) (Kuiper et al., 2001). An explanation for this finding may lie in the IL-9-mediated up-regulation of inhibitors of interleukin signaling, in addition to its enhancement of IL-10 production (Lejeune et al., 2001).

The atheroprotective nature of IL-10 cannot be considered to be a foregone conclusion, as local injection of an IL-10 expression plasmid inhibits angiogenesis in a

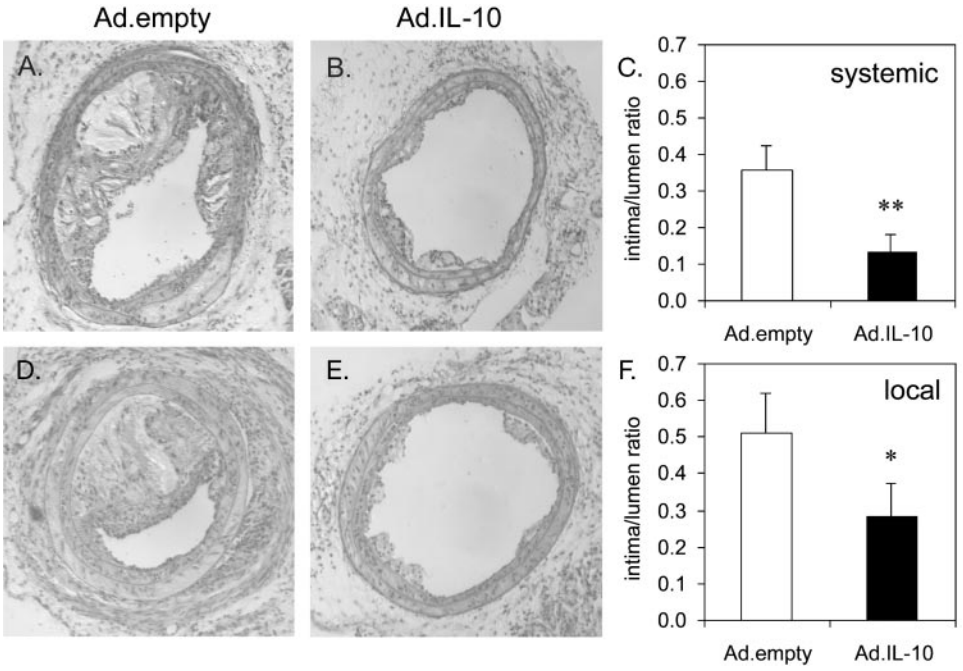

FIG 5. Effects of adenovirus-mediated gene transfer of the anti-inflammatory cytokine IL-10 on atherogenesis in LDLr−/− mice. Both systemic (hepatic) (A–C) and local (endothelial) (D–F) overexpression result in a decrease in atherosclerotic plaque surface area and complexity, which is reflected by a marked attenuation of the degree of stenosis (C+F) *, $P < 0.05$; **, $P < 0.02$. Adapted from von der Thüsen et al., 2001a.

mouse model of hindlimb ischemia (Silvestre et al., 2000), and administration of IL-10 protein augments arterial disease in murine heart transplants (Furukawa et al., 1999). The effect of IL-10 application, as a protein or following gene transfer, may eventually be found to depend on the stage of the disease, the mode of transfer and the dosing regimen. Furthermore, it may be possible to tailor the pleiotropic actions of IL-10 to the use as an anti-atherogenic agent by the use of viral IL-10 homologs. Thus, the Epstein-Barr virus BRCF-1 gene product (vIL-10) has been found to share 84% amino acid sequence identity but only a limited number of the pleiotropic actions of hIL-10. Perhaps most importantly, it lacks the immunostimulatory properties of human IL-10, while sharing its inhibitory activity with respect to cytokine synthesis and macrophage activation (Ding et al., 2000). Furthermore, vIL-10 has been found to lead to augmented and more prolonged expression following adenovirus-mediated transfer in mice in comparison with its human counterpart (Minter et al., 2001), and to effectively reduce endothelial expression of E-selectin, P-selectin, and ICAM-1 in rats following adenovirus-mediated transfer (Henke et al., 2000). The application of vIL-10 may eventually prove to be preferable to hIL-10 if treatment is primarily aimed at providing an anti-inflammatory stimulus, as is the case in the prevention of atherosclerosis.

F. Inhibition of Interleukin Signaling

The effector functions of all interleukins depend on the activation of intracellular signaling cascades involving, *inter alia*, Jaks, Tyks, and STATs (Leonard and Lin, 2000; Touw et al., 2000). These pathways are negatively regulated by endogenous signaling inhibitors, including the SH2-containing phosphatase, SOCS, and protein inhibitor of activated STAT families (Chung et al., 1997; Starr et al., 1997; Liu et al., 1998; Naka et al., 1999), of which the expression is partly controlled by interleukins themselves. These are considered to play a pivotal role in the cross-regulation of interleukin function, as Th2 cytokines have been found to lead to the expression of negative regulators of Th1 cytokines, and vice versa. Moreover, interleukins may also up-regulate inhibitors of their own signaling cascades and are therefore subject to negative feedback loops. Thus, IL-4 activity is controlled by SOCS-1 (SSI-1), which is elaborated in response to interferons as well as IL-4 itself (Naka et al., 1997; Dickensheets et al., 1999; Losman et al., 1999), and the immunosuppressive and autoregulatory effects of IL-9, IL-10, and IL-11 are thought to be partly mediated by the up-regulation of SOCS-3, which inhibits STAT5-mediated signaling (Auernhammer and Melmed, 1999; Cassatella et al., 1999; Donnelly et al., 1999; Lejeune et al., 2001).

The administration of inhibitors of cytokine signaling could have beneficial effects in atherosclerosis. The essential role of tyrosine kinases in cytokine signaling has prompted the evaluation of tyrosine kinase inhibitors as therapeutic agents. In this respect, a group of compounds called “tyrphostins” has been shown to have anti-proliferative and anti-inflammatory properties in vitro and in vivo that are thought to be mediated by tyrosine kinase inhibition (Levitzki, 1990). Platelet-derived growth factor is among the cytokines to be inhib-

ited by the tyrphostins, and these have therefore been speculated to be effective against smooth muscle cell-mediated pathological processes. The latter includes injury-induced neointima formation, and application of the tyrphostin AG-17 by means of a perivascular controlled release implant has been found to inhibit intimal hyperplasia in injured rat carotid arteries (Golomb et al., 1996). In addition, Huynh et al. (1998) have found ex vivo incubation of jugular veins with AG-51 to reduce post-operative intimal hyperplasia by 49%, following their placement as an interposition graft in rabbit carotid arteries. A relative lack of pharmacological and functional selectivity, however, may limit the applicability of these inhibitors as immunomodulatory compounds aimed at diverting the cytokine response from a Th1 to a Th2 expression pattern. SB 203580, for example, in addition to its originally described inhibitory activity for p38 MAPK, also attenuates stress-activated protein kinases and c-Jun N-terminal kinases (Cuenda et al., 1995; Clerk and Sugden, 1998). SB 203580 inhibits TNF and IL-1 expression and protects mice from collagen-induced arthritis (Owens and Lumb, 2000) but also attenuates IL-4, IL-5, and IL-13, and virtually blocks IL-10 production (Koprak et al., 1999). The latter effect, in particular, is considered undesirable in the setting of atherosclerosis. It is conceivable, however, that specificity of protein kinase inhibition may in the future be achieved by the transfer of endogenous inhibitors, including SOCSs by gene therapy or protein administration. As an example, plasmid-mediated overexpression of SOCS-1 has recently been found to inhibit cytokine-induced CD40 expression in macrophages by blocking IFNγ-mediated STAT-1α activation (Wesemann et al., 2002).

G. Inhibition of Interleukin-Induced Gene Expression

Interleukin signaling eventually culminates in the sequence-specific binding of DNA by activated transcription factors and the ensuing up-regulation of target gene transcription. Some of these transcription factors are considered potentially rewarding substrates for immunomodulatory therapy, including NF-κB, AP-1 and the STAT proteins, by virtue of their capacity to integrate converging signals from various proinflammatory cytokines and other inflammatory stimuli (Collins, 1993; Touw et al., 2000; Tedgui and Mallat, 2001). Several methods have been employed in the attenuation of transcription factor activity, based on the characteristic bispecific affinity of these molecules for regulatory proteins and DNA.

The inhibition of vascular NF-κB-regulated transcription, in particular, is presumed to hold anti-atherogenic potential. Activated NF-κB has been identified in smooth muscle cells, macrophages, and endothelial cells in the atherosclerotic lesion (Brand et al., 1996). Functional significance for NF-κB in atherogenesis has been deduced from its colocalization with the expression of NF-κB target genes in plaques (Brand et al., 1996) and the association of its expression in coronary atherosclerotic lesions with unstable angina (Wilson et al., 2002). The role of NF-κB as a causal mediator in atherosclerosis remains unclear, however, which is partly due to the intrauterine lethality associated with p65- and IκBα-deficiency in mice (Collins and Cybulsky, 2001). The regulation of NF-κB activity depends on the extent of binding to its naturally occurring inhibitors, including IκBα, IκBβ, IκBγ, and BCL3 (Ghosh and Baltimore, 1990; Finco and Baldwin, 1995). Phosphorylation of IκB by the IκB kinase (IKK) complex, containing IKKα, IKKβ, and IKKγ (NEMO), leads to IκB ubiquitination and proteasome-mediated degradation. This enables the nuclear translocation of unbound NF-κB and subsequent activation of NF-κB-dependent transcription. In endothelial cells, NF-κB is thought to play an essential role in the regulation of adhesion molecule expression in response to inflammatory stimuli, including cytokines (Collins et al., 1995; De Caterina et al., 2001). The endothelial NF-κB/IκB system is presumed to be primed in endothelial cells in lesion-prone arterial sites, as evidenced by increased expression of the p65 (RelA) NF-κB subunit, IκBα, and IκBβ, prior to plaque development and NF-κB activation (Hajra et al., 2000). The attenuation of IκB activity by IKK up-regulation has been identified as a pivotal step in endothelial activation (Read et al., 1994; Bennett et al., 1996; Johnson et al., 1996), whereas the inhibition of endothelial adhesion molecule expression by nitric oxide has been found to be mediated by IκBα (Spiecker et al., 1997). The recognition of the physiological importance of this inhibitory pathway has prompted the evaluation of the anti-atherogenic properties of IκBα administration. Adenoviral transfer of IκBα has thus been found to effect down-regulation of inflammatory genes in endothelial cells, including VCAM-1, IL-1, IL-6, and IL-8 (Wrighton et al., 1996), and to lead to inhibition of monocyte adhesion and transmigration on TNFα-activated endothelium (Weber et al., 1999). In addition, TNFα-induced endothelial expression of adhesion molecules (E-selectin and ICAM-1) and chemokines (MCP-1) is attenuated by retrovirus-mediated introduction of a proteolysis-resistant IκBα mutant, IκBΔN, and the addition of pharmacological inhibitors of IκBα phosphorylation and proteasome degradation (Cobb et al., 1996; Pierce et al., 1997; Lockyer et al., 1998; Hipp et al., 2002).

NF-κB may also modulate atherogenesis by regulating the transcription of inflammatory genes in monocytes/macrophages and smooth muscle cells (Ghosh and Baltimore, 1990; Bourcier et al., 1997). In macrophages, the LPS-stimulated production of proinflammatory cytokines and inducible nitric-oxide synthase (iNOS) have been found to be reduced by adenoviral overexpression of IκBα and the administration of proteasome inhibitors, respectively (Griscavage et al., 1996; Bondeson et al., 1999). In vascular smooth muscle cells, liposomal deliv-

ery of purified IκBα peptide attenuates TNFα-induced proliferation (Selzman et al., 1999), and overexpression of IκBα diminishes the elaboration of the matrix metalloproteinases MMP-1, MMP-3, and MMP-9, which may have plaque-stabilizing consequences in vivo (Bond et al., 2001). In addition, decoy oligonucleotides to NF-κB binding sites have been used to counteract NF-κB-mediated transcriptional activation and have displayed effectivity in inhibiting graft coronary artery disease of rat cardiac allografts following ex vivo pressure-mediated delivery (Feeley et al., 2000). Other interleukin-activated transcription factors to have been successfully inhibited in vitro by the decoy approach include STAT1 (Ohtsubo et al., 2000), STAT6 (Wang et al., 2000), and AP-1 (Morishita et al., 1998). Inhibition of AP-1-mediated transcription, in particular, effectively reduced joint destruction in a murine model of collagen-induced arthritis (Shiozawa et al., 1997).

Attenuation of NF-κB activity is also presumed to constitute a physiological feedback mechanism in inflammatory homeostasis. Thus, several potentially antiatherogenic interleukins reduce NF-κB activity by variably increasing IκBα transcription (IL-4) (Donnelly et al., 1993; Abu-Amer, 2001), preventing IκB degradation (IL-10 and IL-13) (Lentsch et al., 1997) or increasing the expression of BCL3, a protein with close homology to IκB proteins (IL-4 and IL-9) (Richard et al., 1999). Interestingly, NF-κB inhibition has evolved as a viral strategy of immune response evasion, exemplified by the adenovirus-encoded E1A protein (Kalvakolanu, 1999). The upregulation of IL-6 by TNFα and IL-1 is inhibited by E1A due to its prevention of NF-κB p65-p50 heterodimer formation; although this leaves monomeric p50 to bind to the κB element in the IL-6 promoter, this does not induce transcription (Janaswami et al., 1992). Moreover, E1A negatively regulates Stat1, Stat2, and Stat3 activity, and thereby attenuates IL-6-mediated gene expression (Takeda et al., 1994). An IκB homolog, A238L, is encoded by the African swine fever virus, and this has been shown to inhibit the production of proinflammatory cytokines in macrophages, allowing persistent viral infection (Powell et al., 1996). It may prove possible to exploit these anti-inflammatory traits in the prevention of atherogenesis by overexpression or protein administration of the interleukins or viral proteins concerned.

Synthetic compounds with inhibitory activity for NF-κB have also been described. High throughput cell-based screening has led to the discovery of SP100030, a T cell-specific NF-κB and AP-1 inhibitor (Gerlag et al., 2000). SP100030 attenuates IL-2, IL-8, and TNFα production in T cell lines and alleviates disease progression in a murine model of collagen-induced arthritis. Finally, it has recently transpired that the pharmacological effects of several anti-inflammatory compounds, including salicylates, are partly derived from their inhibition of IκB phosphorylation and degradation (Schwenger et al., 1998; Young, 1998). This knowledge may aid the development of derivatives of these drugs that are specifically targeted toward the inhibition of cytokine-induced inflammation.

Once interleukin-mediated transcription of inflammatory genes has occurred, antisense technology could be employed to interfere specifically with their translation. Interleukin-1 stimulated up-regulation of granulocyte-macrophage and granulocyte colony-stimulating factor gene expression in endothelial cells has been successfully inhibited by antisense ODNs (Segal et al., 1992). Moreover, the expression of endothelial adhesion molecules can be inhibited by the application of phosphorothioate oligonucleotides directed against ICAM-1, VCAM-1, and E-selectin (Bennett et al., 1994). Antisense-mediated down-regulation of endothelial ICAM-1 expression on monocytes reduces endothelial adhesiveness for leukocytes, which may be advantageous in atherogenesis (Steidl et al., 2000). The applicability of ICAM-1 inhibition by means of antisense has been demonstrated in vivo, as it has been shown to be effective in the prevention of cardiac allograft or lung isograft failure in mice and rats, respectively (Stepkowski et al., 1994; Toda et al., 2000). In clinical studies, the phosphorothioate ICAM-1 antisense preparation ISIS 2302 has been found to be well tolerated and to significantly lower the need for steroid treatment in Crohn's disease (Yacyshyn et al., 1998).

The previously mentioned caveats that apply to antisense therapy in general (Lebedeva and Stein, 2001) are evidently also poignant with respect to its use in the inhibition of interleukin-induced gene expression. The doubts that have been raised about the sequence-specific nature of ODN-mediated effects, the poor transfection efficiency, and the short half-life of ODNs in vivo will need to be addressed to warrant their applicability in the prevention of atherosclerosis.

IV. Discussion

Cytokines are being increasingly recognized as a potentially rewarding therapeutic target in a wide variety of diseases. For example, of the over 600 clinical gene therapy trials currently completed, ongoing or pending worldwide, those concerned with the transfer of cytokine genes constitute the largest category (Gene Therapy Clinical Trials, 2002). Most of these involve the application of immunostimulatory cytokines for the treatment of neoplastic and infectious diseases. Of the protocols addressing vascular diseases (51 in total), the overwhelming majority is intended to stimulate revascularization in peripheral and coronary ischemia by cytokine overexpression, largely employing the angiogenic growth factors fibroblast growth factor, PDGF, and vascular endothelial growth factor. While these hold promise for the treatment of atherosclerosis-related ischemia, it will have transpired from the preceding discussion that cytokine-directed therapy in general, and interleu-

kin-based treatment specifically, is still in its infancy as a means for the prevention of the onset and progression of atherogenesis per se. A lack of understanding of their involvement in atherogenesis currently prevents the use of some interleukins as targets for immunomodulation, including the members of the IL-10 family IL-19, IL-20, and IL-22 (Table 1). Other interleukins are overtly pleiotropic in their actions, and attenuating or augmenting their effects may be detrimental or beneficial, depending on the stage of atherosclerosis (IL-4, IL-13). Yet others have been attributed primarily anti- (IL-1ra, IL-9, IL-11, IL-10) or pro-atherogenic (including IL-1, IL-2, IL-6, IL-18) properties, and their modulation could therefore represent the most readily applicable approach to immunotherapy in atherosclerosis. This type of therapy may prove to be an effective alternative to currently used treatment protocols (e.g., lipid-lowering drugs) but could also be useful as an adjunctive to conventional pharmacotherapy. It is possible to conceive of several obstacles that may have impeded the development of such immunomodulatory strategies. Some of these are related to specific pathogenic features associated with atherosclerosis, others to the systemic and local consequences of immunomodulation, and yet others to purely technical aspects of interleukin therapy.

The chronic nature of atherosclerosis has doubtlessly hampered the evolution of adequate disease prevention strategies in general and also remains a significant obstacle to the preventive use of interleukin-based treatments. In considering the relative benefit of long-term use of the latter, one needs to pay attention to its cost, the practicality of its dosing regimen, and, most importantly, potential side effects.

All interleukins possess roles that are certainly not restricted to atherosclerosis, and their actions are frequently pivotal to several aspects of the immune system. Interleukins orchestrate defense mechanisms against a wide range of pathogens and tumor cells, in addition to playing a key role in various forms of nonimmune inflammation, and undiscerning diversions of the interleukin response will therefore invariably compromise one or more of these functions. For instance, whereas the inhibition of signaling by IL-2, IL-6, and IL-12 may be beneficial in the context of atherosclerosis, these factors have been implicated as potent antitumor agents (Maini et al., 1997), and attenuation of IL-2 signaling, in particular, may increase the risk of neoplasia. Conversely, Th2 cytokines are considered to have anti-atherogenic potential, but their role in the pathogenesis of autoimmune diseases is also well documented. Prolonged up-regulation of these factors, although tolerable in the short-term, may have deleterious consequences for the development or progression of *inter alia*, asthma, diabetes mellitus, systemic lupus erythematosus, and rheumatoid arthritis (Lafaille, 1998; Romagnani, 2000). Thus, whereas inhibition of atherogenesis in murine models has been achieved by application of the IL-1 antagonist IL-1ra (Elhage et al., 1998), the anti-inflammatory interleukin IL-10 (von der Thüsen et al., 2001a), and the interleukin-binding protein IL-18bp (Mallat et al., 2001b), these treatments still require long-term toxicological evaluation before beginning clinical trials. This type of untargeted systemic immunomodulation may eventually be limited to short-term treatments aimed at, for instance, the induction of regression or stabilization of existing atherosclerotic plaques. Proof-of-principle data to this effect have been obtained in ApoE−/− mice, in which the administration of antibodies to the cytokine CD40L has been seen to result in a stabilized plaque phenotype (Lutgens et al., 2000; Schonbeck et al., 2000). These studies indicate the potential benefits of short-term immunomodulatory treatment, and could serve as a paradigm for the development of similar strategies in humans.

For prolonged treatment, it may be desirable to restrict the action radius of therapeutic compounds to the atherosclerotic lesion and/or to ensure specificity of action for the atherosclerotic process. This will require the identification of marker molecules and cytokine signaling pathways, which are more or less specific for atherosclerosis, and these efforts may be greatly aided by the advent of DNA array and phage display technology (Faber et al., 2001; Houston et al., 2001; Monajemi et al., 2001). Thus, employing phage display techniques, we have recently identified a peptide sequence that specifically binds human P-selectin (Molenaar et al., 2001). This adhesion molecule is up-regulated on the endothelium of atherosclerosis-prone sites, and high affinity ligands for P-selectin may therefore serve as efficient tools for the targeting of viral and nonviral drug delivery vehicles to the developing atherosclerotic plaque. Such techniques may eventually also be extended to the targeting of specific cellular subsets in the atherosclerotic lesion to enhance therapeutic efficacy and reduce the risk of bystander effects.

Alternatively, site-directed targeting could be achieved by mechanical means. The development of local application catheters has recently been intensified, opening up possibilities for the intravascular instillation of therapeutic compounds. Due to the invasive nature of such techniques, this approach will demand preparations with an extended duration of action or therapeutics that have a lasting effect on atherogenesis or restenosis even with a single dosage regimen. Viral expression vectors may be used in achieving prolonged up-regulation of anti-inflammatory interleukins, such as (v)IL-10 (Kim et al., 2000a; Minter et al., 2001; von der Thüsen et al., 2001a), interleukin antagonists, such as IL-1ra and soluble TNF receptor (Giannoukakis et al., 1999; Kim et al., 2001), inhibitors of NF-κB signaling, such as IκBα (Wrighton et al., 1996; Bondeson et al., 1999; Weber et al., 1999), and antisense oligonucleotides and ribozymes directed against proinflammatory interleukins and interleukin-induced genes. Although ex-

tended transgene expression has been found to occur with some adenoviruses, including Ad-IL-10 (>200 days, unpublished data), the use of AAVs or Ad/AAV hybrids may be preferable in accomplishing this goal (Lynch et al., 1997; Recchia et al., 1999; Monahan and Samulski, 2000).

Barring the development of preparations with an extended duration of action, however, repeated administration will continue to be required to sustain therapeutic efficacy. This may elicit a humoral response to the protein concerned, which could severely compromise its potency and aggravate side effects. A further drawback of repeated administration is the fact that most currently available preparations require parenteral administration, which limits their tolerability and thus the likelihood of patient compliance. Paradoxically, to reduce the need for repeated administration, it may be possible to induce long-term immunomodulation by deliberately opting for active immunization by viral or nonviral means. The possibility of (DNA) vaccination as a method of raising neutralizing antibody responses against inflammatory interleukins has been discussed (Revoltella, 1998; Svenson et al., 2000), as has the possibility of interleukin stabilization and half-life extension by these antibodies (Finkelman et al., 1993). It should be noted, however, that extended duration of effectivity could also be regarded as a disadvantage, due to the relative irreversibility of such therapies in case of the occurrence of deleterious side effects.

The use of smaller synthetic compounds may reduce the need for parenteral administration and could therefore constitute a practical alternative to the transfer of entire interleukin molecules or anti-interleukin (receptor) antibodies. The examples discussed in this review include inhibitors of interleukin processing (Livingston, 1997), tyrosine kinase activity (Golomb et al., 1996; Huynh et al., 1998), proteasome function (Bondeson et al., 1999; Richard et al., 1999), p38 MAPK (Cuenda et al., 1995; Clerk and Sugden, 1998), and NF-κB (Gerlag et al., 2000). A drawback of many of these drugs, however, is their lack of pharmacological and functional specificity, partly due to the involvement of their molecular targets as downstream mediators in convergent signaling cascades, which is perhaps best exemplified by NF-κB. Careful toxicological evaluation will therefore be required before their clinical introduction. The use of (modified) endogenous inhibitors, including SH2-containing phosphatase, SOCS, and protein inhibitor of activated STAT, may eventually provide the required selectivity.

The production of interleukins and most of their inhibitors is currently a rather costly undertaking. Despite recent progress in recombinant protein production technology and therapeutic antibody expression technology (Maini et al., 1997), this situation is unlikely to change in the foreseeable future, making widespread prophylactic protein treatment prohibitively expensive. With a view to these health economic implications and the minimization of potential side effects, it is imperative that treatment be confined to susceptible patients. Accurate tools for the identification of patients who may benefit most from such therapies, are therefore required. Refinement of genetic, biochemical, and radiological markers of predisposition to (complications of) atherosclerosis may provide important prognostic clues. The discovery of correlations between atherosclerotic events and interleukin-related polymorphisms, in particular, including those found for IL-1 (Momiyama et al., 2001), IL-ra (Francis et al., 1999, 2001; Kastrati et al., 2000), and IL-6 (Rauramaa et al., 2000; Georges et al., 2001), may facilitate the identification of suitable patients, whereas improved magnetic resonance imaging and ultrasound imaging of existing plaques will provide an impetus for the noninvasive determination of plaque "vulnerability" to rupture (Fayad and Fuster, 2001; Choudhury et al., 2002).

In summary, the currently available methods of modulation of interleukin-mediated inflammatory pathways are not yet suited to the widespread prevention of atherosclerosis. Substantial investigative efforts are still required with respect to target identification and the definition of suitable patient populations. Technical aspects of compound specificity, duration of action, and mode of transfer await additional improvement, but the first promising signs are looming on the horizon, because several techniques have been successfully validated in animal models. The initial aims of such therapies are likely to include the lasting stabilization of pre-existing plaques by short-term cytokine immunomodulation, which possibly represents the most readily achievable objective in clinical practice in the near future.

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