

Cytokines in Atherosclerosis: Pathogenic and Regulatory Pathways

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I. Introduction	516
A. Historical perspective	516
B. Atherosclerosis as an immunoinflammatory disease	517
II. The Atherosclerotic Cytokine Network	518
A. Cytokine families	518
B. Cytokine-associated signaling pathways	519
III. Inducers of Cytokine Production in Atherosclerosis	526
A. Initial trigger(s)	526
B. Secondary triggers	528
IV. Cytokines and Cytokine Receptors in Human Atherosclerotic Plaques	535
A. Cytokine expression in plaques	535
B. Cellular sources of cytokines	535
C. Biological effects of cytokines	538
V. Cytokine and Cytokine Receptor-Associated Modulation of Plaque Development and Stability	541
A. Proinflammatory cytokines	541
B. Anti-inflammatory cytokines	545
C. Chemokines/chemokine receptors	546
D. Hematopoietic factors/M-CSF	547
E. Platelet-derived factors	548
VI. Cytokines and Adaptive Immunity in Atherosclerosis	548
A. Role of T/B cells in atherosclerosis	548
B. Cytokines and pathogenic immune response in atherosclerosis	549
C. Immunological tolerance and regulatory T cells	551
VII. Cytokines and Cardiovascular Risk	555
A. TNF- α	555
B. IL-2	556
C. IL-6	556
D. IL-7	556
E. IL-8	556
F. IL-18	556
G. sCD40L	556
H. IL-10	557
I. M-CSF	557
VIII. Therapeutic Potential	557
A. Use of anticytokines	557
B. Targetting downstream inflammasome	557
C. Targetting the JAK/STAT pathway	558
D. Activation of the natural anti-inflammatory intracellular pathway (SOCS)	558
E. Stimulation of Treg cells	558
F. Stimulation of macrophage emigration from atherosclerotic lesions	559
IX. Conclusion	559

Tedgui, Alain, and Ziad Mallat. Cytokines in Atherosclerosis: Pathogenic and Regulatory Pathways. *Physiol Rev* 86: 515–581, 2006; doi:10.1152/physrev.00024.2005.—Atherosclerosis is a chronic disease of the arterial wall where both innate and adaptive immunoinflammatory mechanisms are involved. Inflammation is central at all stages of

atherosclerosis. It is implicated in the formation of early fatty streaks, when the endothelium is activated and expresses chemokines and adhesion molecules leading to monocyte/lymphocyte recruitment and infiltration into the subendothelium. It also acts at the onset of adverse clinical vascular events, when activated cells within the plaque secrete matrix proteases that degrade extracellular matrix proteins and weaken the fibrous cap, leading to rupture and thrombus formation. Cells involved in the atherosclerotic process secrete and are activated by soluble factors, known as cytokines. Important recent advances in the comprehension of the mechanisms of atherosclerosis provided evidence that the immunoinflammatory response in atherosclerosis is modulated by regulatory pathways, in which the two anti-inflammatory cytokines interleukin-10 and transforming growth factor- β play a critical role. The purpose of this review is to bring together the current information concerning the role of cytokines in the development, progression, and complications of atherosclerosis. Specific emphasis is placed on the contribution of pro- and anti-inflammatory cytokines to pathogenic (innate and adaptive) and regulatory immunity in the context of atherosclerosis. Based on our current knowledge of the role of cytokines in atherosclerosis, we propose some novel therapeutic strategies to combat this disease. In addition, we discuss the potential of circulating cytokine levels as biomarkers of coronary artery disease.

I. INTRODUCTION

Atherosclerosis is a pathological condition that underlies several important adverse vascular events including coronary artery disease (CAD), stroke, and peripheral arterial disease, responsible for most of the cardiovascular morbidity and mortality in the Western world today. Epidemiological studies indicate that the prevalence of atherosclerosis is increasing all over the world due to the adoption of Western life-style and is likely to reach epidemic proportions in the coming decades (72, 412).

The earliest visible lesion in the development of atherosclerosis is the fatty streak. This comprises an area of intimal thickening composed of macrophages distended by lipid droplets (known as foam cells), lymphocytes, and smooth muscle cells. The American Heart Association (AHA) Committee on Vascular Lesions provided a classification of human atherosclerotic lesions which correlate the histological lesion types, from type I to type VI, with corresponding clinical syndromes (648, 649). This classification should not be understood as an orderly, linear pattern of plaque progression (704). Plaques develop as a result of the accumulation of low-density lipoproteins (LDL) in the subendothelial space, followed by the diapedesis of leukocytes and formation of foam cells, proliferation of smooth muscle cells, and production of connective tissue. The landmark work of Seymour Glagov showed that the arterial wall can remodel itself in response to plaque growth by increasing its external diameter to accommodate the plaque without narrowing of the lumen (234). Thrombosis is the ultimate stage in the disease process that is responsible for clinically observable adverse events implicating coronary, cerebrovascular, and peripheral vascular beds (394). Studies indicate that in patients with atherothrombotic disease plaque formation is likely to be widespread throughout the vasculature, often affecting more than one vascular bed (93).

A. Historical Perspective

Even though atherosclerosis is reaching epidemic proportions nowadays, it is not in any way a disease specific to the modern times; it was already present in antiquity. Sir Marc Ruffer was able to identify in 1911 degenerative arterial changes suggestive of atherosclerosis in the left subclavian artery from an Egyptian mummy (583). Later on, paleopathologist A. T. Sandison, using modern technical methods for tissue fixation, confirmed that Egyptian mummies had histological evidence of atherosclerosis with lipid deposits, reduplication of the internal elastic lamina, and medial calcification in arteries (593).

Atherosclerosis is nowadays recognized as a chronic inflammatory disease of large arteries (235, 265, 395, 417, 578). Remarkably, the very first description of the cause of angina pectoris referred to inflammation. Yet, the belief in this notion was subjected to peaks and troughs from early dates up to recent times.

According to the historian J. O. Leibowitz (381), the Italian surgeon and anatomist Antonio Scarpa (1752–1832) was the first to present an anatomopathological description of arterial wall degeneration in full detail. In his 1804 monograph on aneurysms, Scarpa opposed the view that a dilatation of the aorta was the intrinsic cause of an aneurysm leading to rupture. He emphasizes that "... especially the internal coat is subject, from slow internal cause, to an ulcerated and steatomatous disorganization, as well as to a squamous and earthy rigidity and brittleness," introducing the concept of an underlying metabolic disorder in the process of atherosclerosis, rather than the theory of inflammation that already prevailed at that time, the expression "heart abscess" being frequently used to describe heart pathology (reviewed in Ref. 381).

The term *atheroma*, derived from Greek and meaning "porridge," was first proposed by Albrecht von Haller in 1755 to designate the degenerative process observed in the intima of arteries. London surgeon Joseph Hodgson

(1788–1869) published in 1815 his *Treatise on the Diseases of Arteries and Veins* in which he claimed that inflammation was the underlying cause of atheromatous arteries. But thereafter, most of pathologists of the 19th century following Carl Rokitanski (1804–1878) abandoned the view that inflammation was an etiological factor and considered that atherosclerosis was a degenerative process, with intimal proliferation of connective tissue and calcification, best described by the term *arteriosclerosis* proposed in 1833 by French pathologist Jean Lobstein (1777–1835). However, German pathologist Rudolf Virchow (1821–1902), a leading authority of his day in pathology and the greatest contributor to the notion of thrombosis, considered atheroma as a chronic inflammatory disease of the intima, that he called “chronic endarteritis deformans”. In his opinion, the accumulation of lipids was a late manifestation of atheroma (701). Finally, the Leipzig pathologist Marchand in 1904 first used the term *atherosclerosis*, which since has been widely adopted, instead of *arteriosclerosis*, to designate the degenerative process of the intimal layer of the arteries.

Until the beginning of the 20th century, the theories put forward to explain the pathogenesis of atherosclerosis remained purely descriptive and were based on the anatomical observation of human atherosclerotic vessels. A first revolution in the mechanistic assessment of atherosclerosis was initiated in 1908 when the Russian scientist Alexander Ignatowski showed that experimental atherosclerosis could be induced in rabbits by feeding them a diet of milk and egg yolk (301). Soon thereafter, in 1913, N. Anitschkov and S. Chalotov reproduced experimental atherosclerosis by adding pure cholesterol to rabbit food (21). This gave rise to the lipid theory of atherosclerosis that predominated for most of the 20th century. The next significant leap only came during the 1970s when Brown and Goldstein showed that the LDL receptor that they had discovered, a cell surface protein that binds LDL and removes them from blood (reviewed in Ref. 88), is not involved in macrophage foam-cell formation and proposed that a macrophage receptor that recognized acetylated LDL plays a key role in this process (237). Subsequently, during the 1980s, the central role of oxidized LDL (oxLDL) in the pathogenesis of atherosclerosis was exposed by Daniel Steinberg and his group (650), and a number of scavenger receptors mediating their uptake by macrophages were identified (reviewed in Ref. 387). The model of the Watanabe heritable hyperlipidemic (WHHL) rabbit, introduced in 1980 (726) was particularly useful in establishing the role of oxLDL in atherogenesis. A second revolution occurred at the beginning of the 1990s when mouse models of atherosclerosis, apolipoprotein E (apoE)- and LDL receptor (LDLr)-deficient mice, were derived by homologous recombination techniques (304, 306, 543, 784). In contrast to the previous models, mice

lacking functional apoE or LDLr genes were shown to develop widely distributed arterial lesions that progress from foam cell-rich fatty streaks to fibro-proliferative plaques with lipid/necrotic cores, typical of the spectrum of human lesions (305, 487, 564). The possibility of abolishing the expression of a single gene of interest, or of overexpressing it, in these mouse models opened a new era of atherosclerosis research at a mechanistic level.

B. Atherosclerosis as an Immunoinflammatory Disease

A ripple in the lipid theory appeared in the mid 1970s, when Russel Ross developed his popular “response to injury” hypothesis of atherogenesis, postulating that atherosclerotic lesions arise as a result of focal injury to the arterial endothelium, followed by adherence and aggregation of platelets (580). During the resulting release reaction, platelet-derived growth factor (PDGF) is secreted from the platelets and promotes the proliferative response of smooth muscle cells (SMC). Uncontrolled exuberant SMC proliferation was believed to eventually cause artery occlusion. SMC were considered at that time to be the main promoter of atherosclerotic lesion formation. Instead, it has since been clearly established that SMC proliferation in the plaque is rather modest, and actually tends to be beneficial since it contributes to plaque stabilization (158, 731). In addition, the endothelium actually remains morphologically intact during the development of atherosclerosis (197, 578), although it is activated and directly involved in the immunoinflammatory response. Poole and Florey (547) were the first to observe that soon after initiation of cholesterol feeding in rabbits, monocytes adhere to the endothelium and migrate through the yet intact endothelial monolayer. Michael Gimbrone first proposed the concept of endothelial dysfunction that acknowledged the central role of the normal endothelium in protecting against atherosclerosis while hypothesizing that its cellular functions were altered, “activated” in the disease (232). Ross revisited his “response to injury” theory in 1986 (579) considering that “subtle endothelial injury” was the *primum movens* in atherosclerosis, and published in 1999 in the *New England Journal of Medicine* a remarkable review entitled: “Atherosclerosis: a chronic inflammatory disease” (578). The view that atherosclerosis is indeed a chronic inflammatory disease initiated by monocyte/lymphocyte adhesion to activated endothelial cells (EC) is now widely accepted and substantiated by experimental and clinical observations. Several excellent reviews have been published on the theme of atherosclerosis and inflammation since the founding Ross review (52, 235, 265, 395, 417, 578).

Instrumental in the change of opinion regarding the role of inflammation and immunity, rather than SMC pro-

liferation, in the pathogenesis of atherosclerosis was the precise identification of the cell components of human atherosclerotic plaques using modern immunohistochemical techniques by Göran Hansson and colleagues (316). Histologically, the lipid-laden foam cells of the fatty streak, which characterizes the plaque at an early stage, are derived from macrophages. In time, the lipid/necrotic core is covered with fibrous tissue composed mainly of α -actin positive SMC, and thus forms the fibrolipid plaque. Rather large amounts of T lymphocytes, ~20%, are found as well, surrounding the plaque and in the fibrous cap, pointing to a role of immunity in atherosclerosis (268, 316).

Also determinant in the understanding of the pathogenesis of atherosclerosis were the works by the pathologists Michael Davies (158, 159) and Erling Falk (198), later confirmed and extended by the group of Renu Virmani (704), in their quest for the causes of acute coronary syndromes. Their works emphasized that coronary atherosclerotic plaques exist under two major phenotypes: 1) stable plaques, characterized for the most part by a thick fibrous cap isolating a relatively small lipid core from the lumen, which are associated with a very low risk of thromboembolic complications; and 2) unstable (or vulnerable) plaques, most of which are characterized by a large lipid core covered by a thin fibrous cap prone to rupture and thrombus formation, and which are thought to be associated with a higher risk for thromboembolic complications (218). Analysis of culprit atherosclerotic lesions in patients with acute myocardial infarction revealed that inflammation is crucially determinant in precipitating plaque rupture and some forms of superficial plaque erosion (157, 353, 690).

Virmani uncovered another mechanism of coronary thrombosis occurring in unruptured noninflammatory plaques, described as plaque erosion (199, 703). Eroded plaques differ from ruptured plaques in that they have a base rich in proteoglycans and SMCs. These lesions are more often seen in younger individuals and women, they are associated with less luminal narrowing and less calcification, and they are less likely to have foci of macrophages and T cells compared with ruptured plaque (199). We recently provided experimental evidence that endothelial apoptosis might be a major determinant of plaque erosion (182, 679).

Inflammation, which "is a complex set of interactions among soluble factors and cells that can arise in any tissue in response to traumatic, infectious, postischemic, toxic or autoimmune injury" (493) appears to be involved at all stages of atherosclerosis. It is implicated in the formation of early fatty streaks, when the endothelium is activated and expresses chemokines, including monocyte chemoattractant protein (MCP)-1 and interleukin (IL)-8, and adhesion molecules, including intercellular adhesion molecule (ICAM)-1, vascular adhesion molecule (VCAM)-1, E-

and P-selectin, leading to monocyte/lymphocyte recruitment and infiltration into the subendothelium (265). It also acts at the onset of adverse clinical vascular events, when activated cells within the plaque secrete matrix proteases that degrade extracellular matrix proteins and fragilize the fibrous cap, leading to rupture and thrombus formation (399). Cells involved in the atherosclerotic process include vascular (endothelial and smooth muscle) cells, monocytes/macrophages, lymphocytes (T, B, NKT), dendritic cells, and mast cells. They secrete or are stimulated by soluble factors including peptides, glycoproteins, proteases, and a set of cytokines.

The purpose of this review is to bring together the current information concerning the role of cytokines in the development, progression, and complications of atherosclerosis. Specific emphasis is placed on the contribution of pro- and anti-inflammatory cytokines, in modulating innate, adaptive, and regulatory immunity in the context of atherosclerosis. In addition, we discuss the potential of the circulating cytokine levels as biomarkers of (coronary) artery disease. Finally, we propose some novel therapeutic strategies targeting the cytokine network to combat atherosclerosis.

II. THE ATHEROSCLEROTIC CYTOKINE NETWORK

A. Cytokine Families

Stanley Cohen introduced for the first time the word *cytokine* in 1974 (132, 133). Until then the term *lymphokine*, proposed by Dudley Dumonde in 1969, had been used to designate lymphocyte-derived factors and more generally proteins secreted from a variety of cell sources, affecting the growth or function of many types of cells, collectively (181). At the second International Lymphokine Workshop held in 1979, the name *interleukin* was proposed to characterize proteins with "the ability to act as communication signals between different populations of leukocytes" (473). Later on in 1989, Balkwill and Burke (33) defined cytokine as "one term for a group of protein cell regulators, variously called lymphokines, monokines, interleukins, interferons (we should add "chemokines"), which are produced by a wide variety of cells in the body, play an important role in many physiological responses, are involved in the pathophysiology of a range of diseases, and have therapeutic potential."

Nowadays, the cytokines consist of more than 50 secreted factors involved in intercellular communication, which regulate fundamental biological processes including body growth, lactation, adiposity, and hematopoiesis (77). Cytokines are clustered into several classes: interleukins (33 have been identified to date), tumor necrosis factors (TNF), interferons (IFN), colony stimulating fac-

tors (CSF), transforming growth factors (TGF), and chemokines. They are especially important for regulating inflammatory and immune responses and have crucial functions in controlling both innate and adaptive immunity. The predominant actors in adaptive immunity, helper-T (Th) cells, have been categorized on the basis of the pattern of cytokines that they can secrete, resulting in either a cell-mediated immune response (Th1) associated with IL-2 and IFN- γ secretion, or a humoral immune response (Th2), associated with IL-4, IL-5, IL-10, and IL-13 secretion.

Cytokines are categorized according to the structural homology of their receptors as class I or class II cytokines (77, 369) (Table 1). Most ILs, CSFs, and IFNs belong to one of these two classes of cytokines, which mediate their effects through the Janus kinase-signal transducers and activators of transcription (JAK-STAT) pathway. Three other major cytokine families encompass the IL-1 family (including IL-1 α , IL-1 β , IL-1ra, and IL-18), TNF family, and TGF- β superfamily (Table 1). IL-1 and TNF family members activate the nuclear factor- κ B (NF- κ B) and mitogen-activated protein (MAP) kinase signaling pathways, while TGF- β superfamily members activate signaling proteins of the Smad family.

The TGF- β superfamily is composed of many multifunctional cytokines including TGF- β 1-2-3, activins, inhibins, anti-Müllerian hormone (AMH), bone morphogenetic proteins (BMPs), and myostatin (540). TGF- β family members are secreted as inactive complexes bound to the latency-associated peptide (LAP), a protein derived from the NH₂-terminal region of the TGF- β gene product. The LAP forms covalent bonds with the latent TGF- β binding proteins (LTBPs), high-molecular-weight proteins of which four different isoforms exist (571). The resulting large latent complexes are sequestered within the extracellular matrix. Proteases in the extracellular matrix can digest LTBP, dissociating LAP from TGF- β .

Cytokines share a number of specific features.

1) They show pleiotropic activities: a cytokine can trigger several different cellular responses depending on cell type, timing, and context.

2) They act synergistically: the association of two cytokines (for example, IL-12 and IL-18, TNF- α and IFN- γ , MCP-1 and IL-8) markedly amplifies their activity. This also holds true when a cytokine induces the expression of (an)other cytokine receptor(s).

3) They act in an autocrine, paracrine, or juxtacrine manner: cytokines can stimulate on the cells that produce them, or adjacent cells, or they can intervene through direct cell-cell interaction. This local mode of action sets cytokines apart from classical hormones.

4) They commonly share cytokine receptor subunits: for example, several members of the IL-2 family (IL-7, IL-9, IL-15, IL-21) share the IL-2 receptor γ -chain, the IL-6 family cytokines share the gp130 subunit, and the three

IFN- λ isoforms utilize a heterodimeric receptor composed of its specific receptor subunit IFN- λ R α (or IL-28R α) and the subunit IL-10R2 of the IL-10R, also shared with IL-10 and the IL-10-related cytokines, IL-22 and IL-26.

One must admit that many of these properties are also shared by growth factors. However, one difference is that the production of growth factors, including PDGF, epidermal growth factor (EGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF), tends to be constitutive and is not as tightly regulated as that of cytokines. Also, the target cells of growth factors are mainly nonimmune.

Cytokines are often classified according to their pro- (TNF, IL-1, IL-12, IL-18, IFN- γ) or anti-inflammatory (IL-4, IL-10, IL-13, TGF- β) activities. In light of the data obtained from experimental and clinical studies, described below, regarding the pathophysiological role of cytokines in atherosclerosis, we propose to cluster cytokines as pro- or antiatherogenic (Table 2).

B. Cytokine-Associated Signaling Pathways

1. NF- κ B

The NF- κ B pathway is one of the main signaling pathways activated in response to proinflammatory cytokines, including TNF- α , IL-1, and IL-18, as well as following activation of the Toll-like receptors (TLR) by the pattern recognition of pathogen-associated molecular patterns (PAMPs). Activation of this pathway plays a central role in inflammation through the regulation of genes encoding pro-inflammatory cytokines, adhesion molecules, chemokines, growth factors, and inducible enzymes such as cyclooxygenase-2 (COX2) and inducible nitric oxide synthase (iNOS) (166). NF- κ B is a dimeric transcription factor formed by the hetero- or homodimerization of proteins of the Rel family, including p50 and p65. In its inactive form NF- κ B is bound to inhibitor of κ B (I- κ B α/β) in the cytoplasm. Proinflammatory cytokines and pathogens act through distinct signaling pathways that converge on the activation of an I κ B kinase (IKK) complex containing two kinases IKK1/IKK α and IKK2/IKK β , and the regulatory protein NEMO (NF- κ B essential modifier, also named IKK γ) (762); IKK activation initiates I κ B α/β phosphorylation at specific NH₂-terminal serine residues (782). Phosphorylated I κ B is then ubiquitinated, leading to its degradation by the 26S proteasome. This releases NF- κ B dimers from the cytoplasmic NF- κ B-I κ B complex, allowing them to translocate to the nucleus (Fig. 1). Once in the nucleus, NF- κ B binds to κ B enhancer elements on specific genes promoting transcription. Targets genes of NF- κ B include I κ B α , the synthesis of which ensures that NF- κ B is transiently activated. This negative-feedback regulation gives rise to oscillations in NF- κ B translocation (496).

TABLE 1. *Cytokine classification*

Cytokines	Receptors		Signaling Pathways
<i>Class I cytokines</i>			
<i>IL-6/IL-12 family</i>			
<i>Neuroipoietic cytokines</i>			
CLC	LIFR	} +gp130	JAK1/JAK2/Tyk2
CNTF			
CT-1			
LIF			
OSM			
IL-31	OSMR	} gp130-like receptor (GPL)	JAK1
			JAK1
<i>Hematopoietic cytokines</i>			
G-CSF	gcsfR	} +gp130	JAK1/JAK2/Tyk2
IL-6	IL-6R α		JAK1/JAK2/Tyk2
IL-11	IL-11R α		JAK2/Tyk2
IL-12 α	IL-12R β 2		JAK2
IL-23 α	IL-23R		?
IL-27 α	IL-27R β		
<i>γ-Chain users (IL-2 family)</i>			
IL-2	IL-2R β		JAK1/JAK3
IL-15			JAK1/JAK3
IL-7	IL-7R α		JAK1/JAK3
TSLP			JAK1/JAK3
IL-9	IL-9R α		JAK1/JAK3
IL-21	IL-21R α		JAK1/JAK3
<i>IL-4 family</i>			
IL-4	IL-4R α		JAK1
IL-13			JAK1
IL-3	IL-3R β		JAK2
GM-CSF			JAK2
IL-5			JAK2
<i>Class II cytokines</i>			
<i>IFN family</i>			
<i>Type I</i>			
IFN- α	IFNAR1 + IFNAR2		JAK1/Tyk2
IFN- β			JAK1/Tyk2
IFN- λ 1 (IL-28A)	IFN λ R1(IL-28R α) + IL-10R2		JAK1/Tyk2
IFN- λ 2 (IL-28B)			JAK1/Tyk2
IFN- λ 3 (IL-29)			JAK1/Tyk2
<i>Type II</i>			
IFN- γ	IFN-GR1 + IFNGR2		JAK1/JAK2
<i>IL-10-related cytokine family</i>			
IL-10	IL-10R1 + IL-10R2		JAK1/Tyk2
IL-19	IL-20R1 + IL-20R2		JAK1/Tyk2
IL-20	IL-20R1 + IL-20R2		JAK1/Tyk2
IL-22	IL-22R1 + IL-10R2		JAK1/Tyk2
IL-24	IL20R1 + IL-22R1		JAK1/Tyk2
IL-26	IL-20R1 + IL-10R2		JAK1/Tyk2
<i>TNF superfamily</i>			
TNF- α	TNFR1(p55)/TNFR2(p75)		NF- κ B/JNK/p38/ERK
Lymphotoxin α	TNFR1(p55)/TNFR2(p75)		NF- κ B/JNK/p38/ERK
FasL	Fas		NF- κ B/JNK
CD40L(CD154)	CD40		NF- κ B/JNK
RANKL	RANK		NF- κ B/JNK/p38/ERK
TRAIL	TRAIL-R		NF- κ B/JNK/p38/ERK
<i>TGF family</i>			
TGF- β 1/2/3	TGF- β -R1/ TGF- β -RII		Smad2/Smad3
Activin A	ActRI/ActRII		Smad2/Smad3
<i>IL-1 family</i>			
IL-1	IL-1RI/IL-1RAcP		NF- κ B/JNK/p38/ERK
IL-18	IL-18 R α /IL-18R β		NF- κ B/JNK/p38
IL-32	?		NF- κ B/p38
IL-33	ST2		NF- κ B/p38/ERK

CLC, CT-1-like factor; LIF, leukemia inhibitory factor; CNTF, ciliary neurotrophic factor; CT-1, cardiotrophin-1; OSM, oncostatin M; G-CSF, granulocyte-colony stimulating factor; TSLP, thymic stromal lymphopoietin; RANK, receptor activator of NF- κ B; RANKL, RANK ligand; ActRI, activin type I receptor; IL-1RAcP, IL-1 receptor accessory protein.

TABLE 2. *Pro- and antiatherogenic cytokines*

Proatherogenic Cytokines	Antiatherogenic Cytokines
TNFR family	
TNF- α	
Lymphotoxin	
Osteoprotegerin	
CD40L	
IL-1 family	
IL-1	IL-1ra
IL-18	IL-18BP
Class I cytokines	
IL-2	
IL-4	
IL-6	IL-6
IL-12	IL-9
Class II cytokines	
IFN- γ	IL-10
Hematopoietic factors	
M-CSF	
Chemokines/chemokine receptors	
IL-8/CXCR2	
MCP-1/CCR2	
Fractalkine/CX3CR1	
RANTES	
MIF	
Bone-associated cytokines	
Osteopontin	
TGF- β family	TGF- β

TNF, tumor necrosis factor; IFN, interferon; TGF, transforming growth factor.

NF- κ B is a redox-sensitive transcription factor, and the intracellular redox status of the cell is extremely important in the regulation of NF- κ B activity (reviewed in Ref. 311). Antioxidants, such as aspirin, *N*-acetylcysteine (NAC), and flavonoids can therefore inhibit the activation of NF- κ B. A number of natural constitutive or inducible pathways inhibiting NF- κ B activity also exist (see review in Ref. 669). For example, A1 and A20, two cytoprotective genes, are induced in response to inflammatory stimuli to protect EC from exaggerated activation and from undergoing apoptosis even when NF- κ B is blocked (139). A20 terminates NF- κ B activation by promoting reaccumulation of I κ B through its interaction with proteins involved in TNF- α signaling upstream of I κ B degradation (375). Consequently, A20-deficient mice fail to terminate TNF-induced NF- κ B activity, having a persistently active IKK complex that prevents reaccumulation of I κ B protein, are hypersensitive to TNF- α , and suffer from severe inflammation. The inducible form of the heme oxygenase (HO-1) is another example of endogenous anti-inflammatory pathway induced in response to inflammatory stimuli. HO-1 can be upregulated in human EC by TNF and IL-1 (674), and HO-1 possesses potent antiapoptotic and anti-inflammatory properties (742). HO-1 deficiency in humans is associated with the presence of severe and persistent endothelial damage (761). The anti-inflammatory properties of HO-1 seem to be related to an inhibitory action on P- and E-selectin expression on EC (688).

Activated NF- κ B has been identified in SMC, macrophages, and EC of human atherosclerotic lesions (78, 82, 480). Enhanced endothelial activation of NF- κ B has been shown to occur in LDLr-deficient mice very early on following a high-fat diet, in regions of the proximal aorta with high probability for atherosclerotic lesion development (262). Furthermore, supershift analysis in cells isolated from human carotid atherosclerotic plaques, composed in majority of macrophages and SMC, demonstrate that activated NF- κ B consists of p65, c-Rel, and p50, but not relB or p52 subunits (480). NF- κ B activation in these cells controls the expression of proinflammatory cytokines TNF- α ; IL-6 and IL-8; matrix metalloproteinases (MMP)-1, -3, and -9; and tissue factor (TF), as shown by their selective inhibition following blockade of the NF- κ B pathway by overexpression of I κ B α or dominant-negative IKK-2 (480). Interestingly, in this study NF- κ B inactivation did not affect the expression of the anti-inflammatory cytokine IL-10 or the matrix metalloproteinase inhibitor TIMP-1.

The actual *in vivo* role of the NF- κ B pathway has recently been addressed in experimental models of atherosclerosis. Kanters et al. (324), using LDLr-deficient mice with a cell-specific deletion of IKK2 preventing NF- κ B activation in macrophages, unexpectedly found increased atherosclerotic lesion formation and inflammation in these animals. This result was associated with a significant reduction in the anti-inflammatory and anti-atherogenic cytokine IL-10, suggesting that a certain level of NF- κ B activation is required to modulate the inflammatory reaction and counteract proatherogenic responses (Fig. 2). This finding is in favor of a central role for NF- κ B in the induction of "protective" antiapoptotic and anti-inflammatory genes, critical to the resolution of the inflammatory process (374). However, the detrimental effect of NF- κ B inhibition in atherogenesis is likely to depend on how NF- κ B activity is inhibited. In a subsequent study, Kanters et al. (323) examined the effects of hematopoietic NF- κ B1 (the p50 subunit of NF- κ B) deficiency in the development of atherosclerotic lesions, transplanting bone marrow from mice deficient in NF- κ B1 into irradiated LDLr^{-/-} mice. Instead of promoting the formation of larger inflammatory lesions, as was the case with specific IKK2 deficiency in macrophages, hematopoietic NF- κ B1 deficiency was associated with a significant decrease in lesion size, despite enhanced accumulation of T and B lymphocytes within the lesions. This could be explained, at least in part, by the observation that in contrast to IKK2 deficiency, NF- κ B1 deficiency did not alter the inflammatory balance in favor of a proatherogenic phenotype. Despite increased TNF- α expression by NF- κ B1-deficient macrophages, other major proatherogenic molecules such as MCP-1 were downregulated, whereas critical antiatherogenic factors such as IL-10 were significantly upregulated.

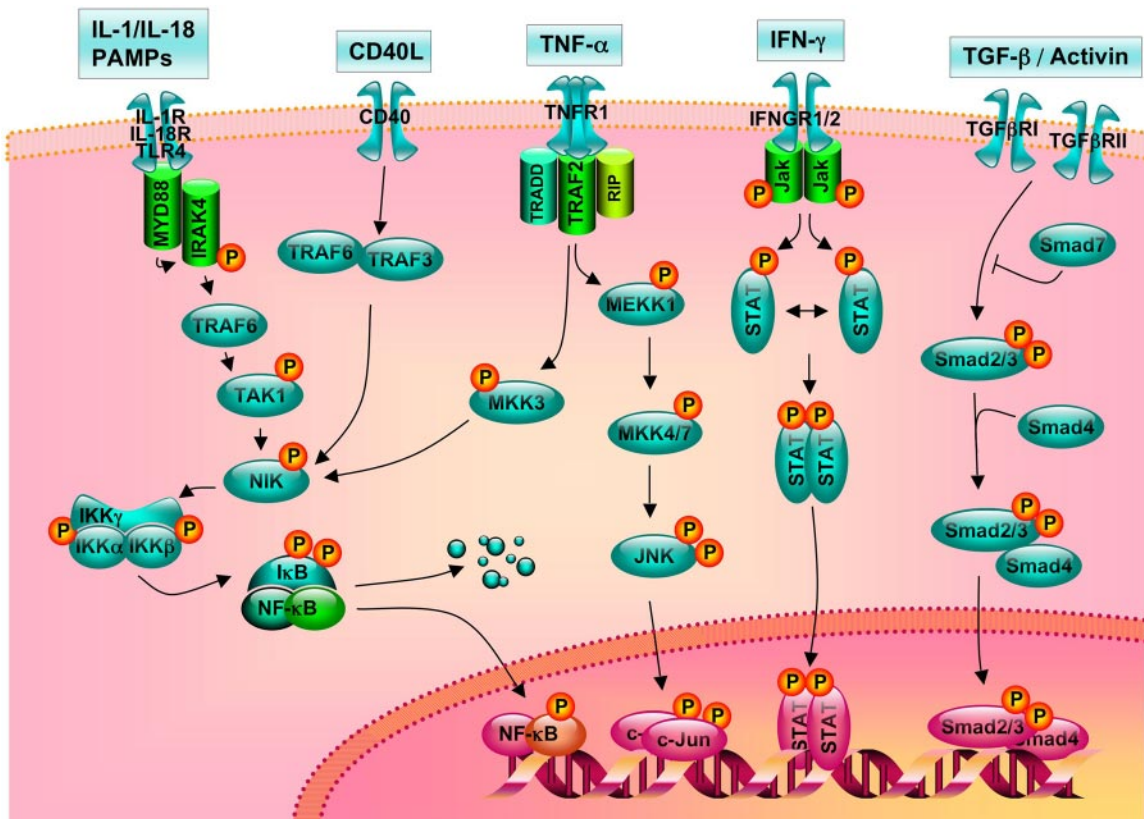


FIG. 1. Principal signaling pathways involved in atherogenesis. Proinflammatory cytokines (IL-1, IL-18) and pathogens (represented as pathogen-associated molecular patterns, PAMP), as well as nonpathogen activators of TLR, act through distinct signaling pathways that converge on the activation of NF- κ B. MyD88 functions as an adaptor between receptors of the TLR or IL-1R families and downstream signaling kinases. Following association of MyD88 with IL-1-associated kinase IRAK-4, IRAK-4 is autophosphorylated, dissociates from the receptor complex, and interacts with TNF-receptor-associated factor-6 (TRAF-6), which also mediates CD40 signaling. Once activated, TRAF6 associates with the MAP3 kinase TAK1 (716). From TAK1, two signaling pathways diverge; one ultimately leads to NF- κ B activation and the other to MAP kinase activation. In its inactive form, NF- κ B is bound to inhibitor of κ B (IKK- β / α) in the cytoplasm and consists of an I κ B kinase (IKK) complex containing two kinases IKK α and IKK β , and the regulatory protein IKK γ (also named NEMO); IKK activation initiates I κ B α / β phosphorylation. Phosphorylated I κ B is then ubiquitinated, leading to its degradation by the 26S proteasome. This releases NF- κ B dimers from the cytoplasmic NF- κ B-I κ B complex, allowing them to translocate to the nucleus. JNK phosphorylation is mediated by two MAPK kinases (MAPKKs), MKK4 and MKK7, that they can cooperatively activate JNK. Both kinases are required for full activation of JNK by environmental stressors, and MKK7 is essential for JNK activation by TNF engagement. Tyrosine phosphorylation activates the cytosolic inactive STATs, resulting in their nuclear translocation and gene activation. This pathway was originally found to be activated by IFNs, but a number of cytokines, growth factors, and hormonal factors also activate JAK and/or STAT proteins. IFN- γ utilizes JAK1 and JAK2, and usually activates STAT1. TGF- β -triggered signals are transduced by proteins belonging to the Smad (for vertebrate homologs of *Sma* and *Mad*) family. The type I receptor recognizes and phosphorylates Smad2 and Smad3, which associates with Smad4, forming complexes that participate in DNA binding and recruitment of transcription factors. Smad3 may also have antagonistic properties, as it plays a critical role in TGF- β -dependent repression of vascular inflammation by inhibiting AP-1 activity. Smad7 inhibits Smad2 and Smad3 phosphorylation.

Decreased MCP-1 production and increased IL-10 expression may have contributed to the limitation of plaque size despite enhanced accumulation of T cells. Another plausible explanation for reduced lesion development in NF- κ B1-deficient animals could be a defect in the uptake of oxLDL by macrophages, as characteristic foam cells were absent in NF- κ B1-deficient lesions. Moreover, both scavenger receptor class A (SR-A) expression and uptake of oxLDL were significantly reduced in NF- κ B1-deficient macrophages stimulated *ex vivo* with lipopolysaccharide (LPS), although *in vivo* relevance of this *in vitro* effect remains to be determined. In summary, NF- κ B appears to be at the

crossroads of the inflammatory response in atherosclerosis, fine-tuning the response of the vessel wall to injury (Fig. 2).

2. JNK/AP-1

AP-1 (activator protein-1) is a transcription factor consisting of homodimers or heterodimers of Fos (c-Fos, FosB, Fra-1 and Fra2), Jun (c-Jun, JunB, JunD), or ATF subunits which recognize either 12-*O*-tetradecanoylphorbol-13-acetate (TPA) response elements or cAMP response elements (CRE) (626). Jun proteins can homodimerize, but Fos proteins can only form stable dimers

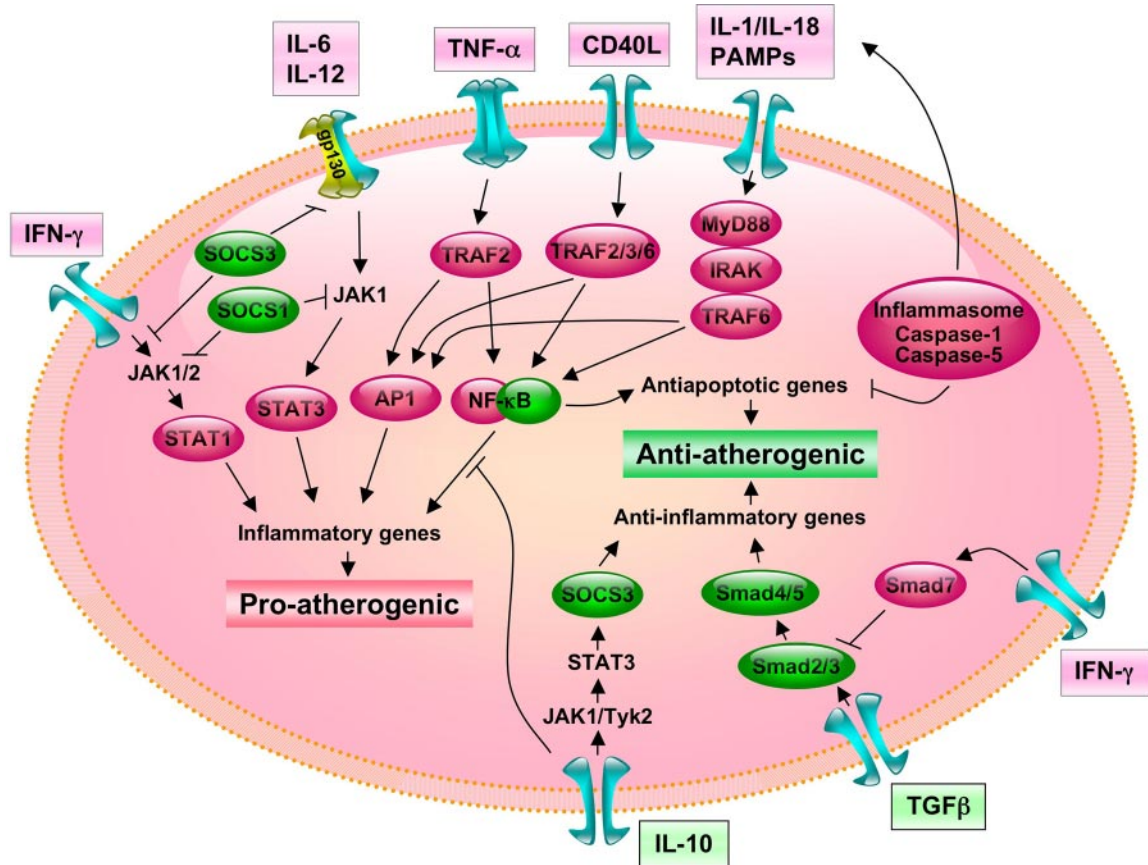


FIG. 2. Cross-talks between proinflammatory/proatherogenic and anti-inflammatory/antiatherogenic signal transduction pathways. Inhibitory Smads such as Smad7 downstream of IFN- γ signaling associate with activated receptors and interfere with Smad2 and Smad3 binding. It is noteworthy that like IFN- γ , the anti-inflammatory cytokine IL-10 also activates JAK and/or STAT proteins. However, the IL-10/IL-10R interaction activates JAK1 and Tyk2, leading to STAT3 and SOCS3 activation, which is central for the anti-inflammatory responses of IL-10 in macrophages. The inflammasome may be a central link between apoptosis and inflammation in pathological conditions. NF- κ B may have a dual role in atherosclerosis, being proatherogenic through its proinflammatory properties, and antiatherogenic through its antiapoptotic activities.

with Jun. Phosphorylation of c-Jun by c-Jun NH₂-terminal kinases (JNKs) results in enhanced transcriptional activity of complexes containing AP-1 dimers (734).

JNK belongs to the family of stress-activated protein kinases that also includes the p38 protein kinases. Three highly related but distinct gene products, JNK1, JNK2, and JNK3, can be expressed as a total of 10 isoforms as a result of variable mRNA splicing (259). JNK1 and JNK2 show a broad tissue distribution, whereas JNK3 is expressed predominantly in neurons but also in cardiac smooth muscle and the testes (770). Targeted deletion of the genes coding for JNK1 or JNK2 results in abnormal thymocyte selection (588) and loss of T-lymphocyte differentiation and effector function (179). JNK3 knockout mice show resistance to neuronal apoptosis, directly implicating JNK in at least some specific instances of programmed cell death (678, 768).

JNK phosphorylation is mediated by two MAPK kinases (MAPKKs), MAP2K4 (or MKK4) and MAP2K7 (or MKK7), that they can cooperatively activate JNK (Fig. 1).

Gene disruption studies in mice demonstrate that both MAP2K4 and MAP2K7 are required for full activation of JNK by environmental stressors and that MKK7 is essential for JNK activation by TNF (677).

Many proinflammatory genes, including those encoding TNF- α , IL-2, IL-6, E-selectin, ICAM-1, VCAM-1, MCP-1, COX2, and MMPs-1, -9, -12, and -13 (500), are regulated by the JNK pathway, through interaction of AP-1 with other *cis*-acting sequences in their promoters and with certain transcription factors that bind to these sequences (Fig. 2).

A recent study showed that atherosclerotic lesions were significantly reduced in JNK2-deficient apoE^{-/-} mice, but not in JNK1-deficient apoE^{-/-} mice, compared with apoE^{-/-} mice (568). JNK2 expression in leukocytes, rather than in vascular cells, appeared to be responsible for this effect. Indeed, transplantation of apoE^{-/-} JNK2^{-/-} bone marrow into apoE^{-/-} mice reduced atherosclerosis to an extent similar to that of apoE^{-/-} JNK2^{-/-} mice transplanted with apoE^{-/-} JNK2^{-/-} bone marrow, whereas apoE^{-/-} JNK2^{-/-} mice transplanted

with apoE^{-/-} bone marrow showed atherosclerotic lesions equivalent to those of apoE^{-/-} mice transplanted with apoE^{-/-} bone marrow (568).

3. JAK/STAT

The class I and II cytokines induce homodimerization and activation of their cognate receptors, resulting in the activation of associated JAK kinases (JAK1, JAK2, JAK3, and Tyk2) (Table 1) (520a). The activated JAKs phosphorylate the receptor cytoplasmic domains, which creates docking sites for SH2-containing signaling proteins. Among the tyrosine phosphorylated substrates are members of the STAT family of proteins (Table 1) (520a). Receptor engagement and tyrosine phosphorylation activate the cytosolic inactive STATs, resulting in their nuclear translocation and gene activation. This pathway was originally found to be activated by IFNs, but a number of cytokines, growth factors, and hormonal factors also activate JAK and/or STAT proteins (Fig. 1). In particular, IL-6 binds to the IL-6 receptor α -chain and gp130, which activate JAK1 and STAT3. IFN- γ utilizes JAK1 and JAK2, and usually activates STAT1. It is noteworthy that the anti-inflammatory cytokine IL-10 also activates JAK and/or STAT proteins (reviewed in Ref. 481). The IL-10/IL-10R interaction activates JAK1 and Tyk2, which are associated with the IL-10R1 and IL-10R2, respectively.

STAT3 can be activated by a number of cytokines, especially those of the IL-6 family, mediating the expression of several acute-phase response genes. Yet, STAT3 appears to play a critical negative role in controlling inflammation, as shown in mice with STAT3 deletion in specific cell types, including keratinocytes (594), T cells (666), macrophages/neutrophils (664), cardiomyocytes (309), or endothelial cells (322), STAT3 deficiency being embryonically lethal. STAT3-deficient T cells show severely impaired IL-6-induced cell proliferation, due to the lack of IL-6-mediated prevention of T-cell apoptosis (666). STAT3 deletion in mice within the macrophage/neutrophil lineage results in chronic inflammation and pathological colitis with age, due to the enhancement of the Th1 response by blockade of IL-10 signaling (664). Removal of STAT3 from hematopoietic progenitors also results in increased proinflammatory cytokine production, inflammatory bowel disease, and an expanded macrophage population (732). Interestingly, STAT3-deficient macrophages and neutrophils show increased production of inflammatory cytokines in response to LPS, which cannot be reduced by IL-10 (664). STAT3 activation by IL-10 is therefore central for anti-inflammatory responses in macrophages and neutrophils (Fig. 2). It is noteworthy that mice with conditional STAT3 deletion in endothelium also show exaggerated inflammation and leukocyte infiltration in multiple organs upon LPS challenge (322). An endothelium-derived soluble factor that is dependent on STAT3 is

likely to control IFN- γ production during LPS-induced inflammation (322).

In terms of immunoregulation, STAT4 and STAT6 are crucially important for the differentiation of Th cells. IL-4 activates STAT6 and promotes the differentiation of Th2 cells (634). Conversely, IL-12 activates STAT4 and drives the differentiation of naive T cells into Th1 cells that produce IFN- γ (325). In atherosclerosis, the Th cell response is of the Th1 type, characterized by abundant secretion of IFN- γ (264). Yet, Th2 profile does not necessarily offer protection against atherosclerosis and might even be proatherogenic (see sect. *viB3*). Therefore, targeting STAT4 and STAT6 could be of use in the treatment of atherosclerosis. Interestingly, statins, which are believed to exert beneficial effects in cardiovascular disease beyond cholesterol lowering (350), have been reported to inhibit Th1-mediated disease and to block activation of STAT4 (386, 492, 778) and induction of major histocompatibility complex (MHC)-II expression by IFN- γ (366). Other drugs, including rapamycin and lisofylline, have also been reported to block STAT4 activation (127, 771). Interestingly, a recent study showed that rapamycin reduces atherosclerosis in apoE^{-/-} mice, with concomitant decreased expression of IL-12p40, IFN- γ and IL-10 mRNA, and enhanced expression of TGF- β 1 (190). Pentoxifylline, a methylxanthine derivative of lisofylline, has been reported to have protective effects against atherosclerosis in apoE^{-/-} mice, associated with a reduced Th1 polarization of Th lymphocytes (373).

Cytokine signaling by the JAK/STAT pathway is regulated, in part, by a family of endogenous JAK kinase inhibitor proteins termed suppressors of cytokine signaling (SOCS) (748). The SOCS family consists of eight members [SOCS-1 to SOCS-7 and cytokine-inducible SH2 proteins (CIS)] all sharing a central SH2 domain and a COOH-terminal SOCS box. Both SOCS1 and SOCS3 inhibit JAK tyrosine kinase activity; SOCS1 directly binds to the activation loop of JAKs through the SH2 domain, while SOCS3 binds to cytokine receptors (Fig. 2). SOCS1 regulates INF γ signaling, and deficiency leads to lethal disease, which is characterized by exaggerated effects of IFN- γ . Interestingly, mice lacking both SOCS-1 and IFN- γ , though saved from the lethal perinatal syndrome observed in SOCS-1-deficient mice, develop a variety of chronic infections or inflammatory lesions as adults (466). In contrast, SOCS2 regulates growth hormone, and SOCS-knockout mice show gigantism. SOCS3 is preferentially expressed in Th2 cells and plays an important role in regulating the onset and maintenance of Th2-mediated allergic immune disease (619).

Very little is known regarding the role of SOCS in atherosclerosis. It has been reported that SOCS-1 inhibits IFN- γ -induced CD40 expression in macrophages by blocking IFN- γ -mediated STAT-1 activation, and in so doing suppressing IFN- γ -induced TNF- α secretion and

subsequent NF- κ B activation (733). Inasmuch as the CD40/CD40L pathway actively participates in plaque development and progression (reviewed in Ref. 605), mimics or inducers of SOCS1 might be useful to attenuate the effects of IFN- γ in the context of atherosclerosis.

4. Smads

TGF- β -triggered signals are transduced by proteins belonging to the Smad (for vertebrate homologs of *Sma* and *Mad*) family. Smads serve as substrates for TGF- β receptors type I and II, in which the cytoplasmic domain possesses serine/threonine kinase activity (453). The type I receptor recognizes and phosphorylates Smad2 and Smad3, which associates with Smad4, forming complexes that participate in DNA binding and recruitment of transcription factors (Fig. 1). Smad3 may also have antagonistic properties, as it plays a critical role in TGF- β -dependent repression of vascular inflammation by inhibiting AP-1 activity (Fig. 2) (200, 201). In addition to these agonistic Smads, inhibitory Smads (I-Smad) such as Smad6 and Smad7, which associate with activated receptors and interfere with Smad2 and Smad3 binding, are present. Expression of Smad7 is induced by IFN- γ as a negative regulator of the TGF- β /Smad pathway (684). Recent advances in the study of atherosclerosis point to an important role of TGF- β signaling in the protection against excessive plaque inflammation, loss of collagen content, and induction of regulatory immunity (see below and reviews in Refs. 243, 444, 445). Immunohistochemistry and RT-PCR analysis of human plaques reveal Smad2, Smad3, and Smad4 expression in macrophages of fibrofatty lesions and in SMC of fibrous caps (320). We also detected phosphorylated Smad2 in the aortic sinus of apoE^{-/-} mice, indicative of TGF- β activity in atherosclerotic lesions (438).

5. TLR/Myd88 signaling pathways

At least 10 TLRs (TLR1–10) recognize different PAMPs associated with different classes of pathogens (review in Refs. 303, 665). For example, TLR4 recognizes LPS, which is unique to Gram-negative bacteria, and TLR2 recognizes peptidoglycan found in Gram-positive bacteria. TLR9 recognizes unmethylated CpG motifs, which are abundant in prokaryotic genomes and virus DNA. TLR3 recognizes double-stranded RNA (dsRNA) produced during viral infections. TLRs are characterized by a 150-amino acid intracytoplasmic domain named TIR (Toll/IL-1R/R), which they share with members of the IL-1 receptor (IL-1R) family and plant disease resistance (R) genes, and by an extracellular domain composed of NH₂-terminal leucine-rich repeats (LRRs) flanked by characteristic cysteine clusters on the COOH-terminal (CF motif) or NH₂-terminal (NF motif) side of the LRRs. Upon stimulation, TLRs and the IL-1R family activate the transcription

factors NF- κ B and AP-1, leading to production of proinflammatory cytokines. TIR domains play a critical role in TLR signaling. They allow homophilic interactions with the cytoplasmic factor MyD88 that also contains a TIR domain (Fig. 1). MyD88, which is recruited to the receptors after stimulation, contains an NH₂-terminal death domain that enables it to bind the death domain-containing serine-threonine kinases of the IL-1R-associated kinases (IRAK) family (reviewed in Ref. 312). As a result, MyD88 functions as an adaptor between receptors of the TLR or IL-1R families and downstream signaling kinases. Following association of MyD88 with IRAK-4, IRAK-4 is autophosphorylated, dissociates from the receptor complex, and interacts with TNF-receptor-associated factor (TRAF)-6. Once activated, TRAF6 activates a heterodimer composed of two ubiquitination proteins called Uev1A and Ubc13, which triggers its association with the MAP3 kinase TAK1 (716). From TAK1, two signaling pathways diverge; one ultimately leads to NF- κ B activation and the other to MAP kinase activation. Studies using MyD88-deficient mice showed that this factor is essential for the NF- κ B-dependent induction of TNF- α and IL-6 in response to TLR agonists (331). Interestingly, analysis of MyD88 mutant mice unexpectedly pointed to the existence of a MyD88-independent pathway downstream of some TLRs. Indeed, TLR4- or TLR3-mediated activation of NF- κ B and AP-1 by LPS and dsRNA, respectively, was not abolished but only delayed in MyD88-deficient mice (13, 331).

Recently, enhanced expression of TLR4 was detected in murine (apoE^{-/-} mice) and human carotid and coronary atherosclerotic plaques (186, 760). TLR1 and TLR2 expression has also been found in human carotid (186) but not in coronary plaques (760). Human epidemiological data demonstrate that an Asp299Gly TLR4 polymorphism, which attenuates receptor signaling, is associated with a decreased risk of atherosclerosis and acute coronary events (18, 64, 335). Functional TLR4 expression has also been correlated with the development of aortic intimal hyperplasia in a mouse model of artery injury (699), and TLR4 activation by LPS increases atherosclerotic plaque formation in the apoE3*Leiden atherosclerotic mouse model (287).

Interestingly, TLR4 appears to be involved in several aspects of the inflammatory response even in the absence of infection, by recognizing endogenous ligands produced during inflammation. Extracellular matrix components, including the type III repeat extra domain A of fibronectin, low-molecular-weight oligosaccharides of hyaluronic acid, and polysaccharide fragments of heparan sulfate, provoke immunostimulatory responses similar to those induced by LPS, via TLR4 (315, 517, 673). Moreover, fibrinogen (642) and minimally modified LDL (mmLDL) (471) are able to induce the production of chemokines and cytokines from macrophages through recognition by

TLR4. Together, these recent findings indicate that TLR4 may exert LPS-independent atherogenic activities (468, 469). Two lines of evidence support this hypothesis: 1) oxLDL enhances TLR4 expression in macrophages (760), and 2) TLR4 or its intracellular adaptor protein, MyD88, reduces atherosclerosis in uninfected apoE-deficient mice, concomitant with a marked reduction in macrophage infiltration and MCP-1 expression in the atherosclerotic lesions (54), and decreased circulating levels of IL-12 and MCP-1 (470).

Remarkably, CD4+CD25+ Treg cells selectively express TLR4-5-7-8 (110). This is of particular importance given the role that Treg cells play in atherosclerosis, as we recently reported (8, 437; see sect. viC).

III. INDUCERS OF CYTOKINE PRODUCTION IN ATHEROSCLEROSIS

A. Initial Trigger(s)

According to the classical view of inflammation, cytokines are produced by cells of the innate immune system (monocytes, neutrophils, NKT cells) in response to microbial infection, toxic reagents, trauma, antibodies, or immune complexes (493). In the host, TLRs and intracellular proteins (NOD1 and NOD2, for “nucleotide-binding oligomerization domain”) act as sensors of the conserved molecular motifs present on a wide range of different microbes, the PAMPs. Hence, cytokines are secondary mediators of inflammation and not the primary triggers. An etiologic role for infectious agents in atherosclerosis, especially *Chlamydia pneumoniae* and cytomegalovirus (CMV), has been repeatedly evoked (396) since the first seroepidemiologic evidence of an association of the chlamydia TWAR strain with acute myocardial infarction and chronic coronary disease was reported in 1988 (589). However, the most recent clinical trials, including Weekly Intervention with Zithromax for Atherosclerosis and its Related Disorders (WIZARD) (511), Azithromycin in Acute Coronary Syndrome (AZACS) (114), Antibiotic Therapy After Acute Myocardial Infarction (ANTIBIO) (781), Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) (108), and Azithromycin and Coronary Events Study (ACES) (250), assessing the potential benefits of antibiotic therapy with the goal of targeting *Chlamydia pneumoniae* showed no effect of treatment in patients with CAD. Moreover, experimental studies showed that infection is not necessary for initiation or progression of atherosclerosis in apoE-deficient mice. Atherosclerosis develops identically in germ-free animals and in animals raised with ambient levels of microbial challenge (749). One must therefore conclude that pathogens do not serve as etiologic agents for atherosclerosis, even though one cannot rule out a role in disease exacer-

ation. Several reports indicate that inoculation of atherosclerosis-prone mice with high doses of *C. pneumoniae* fosters atherosclerosis (292, 475). Yet, the atherogenic effect of *C. pneumoniae* requires elevated serum cholesterol levels (292).

Atherosclerosis clearly does not develop in any animal model without a significant level of plasma cholesterol, and the dominant role of cholesterol is also well established in humans. While hypertension, diabetes, and smoking are factors that dramatically increase the risk of atherosclerosis, it is not rare to have clinically significant atherosclerosis in the absence of these risk factors. In contrast, below a certain level of cholesterol (150 mg/dl), atherosclerosis is practically absent in human populations (106), and risk gradually increases with increased plasma cholesterol levels (647). Moreover, primary and secondary clinical trials have established the efficacy of lowering cholesterol with statins for prevention of cardiovascular disease (256, 694). It is therefore tempting to hypothesize that the primary trigger of cytokine release in atherosclerosis has a link with cholesterol. Atherogenic cholesterol exists mainly in the form of LDL, which are the main culprit in CAD. In fact, several lines of evidence support the hypothesis that oxidized lipids, including oxLDL, are the most likely triggering factors for cytokine production.

Quantitative analysis of atherosclerosis in fetal aorta showed that fatty streaks are already present at this early stage of life, lesions being more abundant in fetus from hypercholesterolemic mothers than from normocholesterolemic mothers (489). Interestingly, qualitative analysis of lesions depicted similar distribution of native LDL, oxLDL, and macrophages in lesions of offspring from both hypercholesterolemic and normocholesterolemic mothers. The presence of macrophages alone, without native LDL or oxLDL, or their association with native LDL, was almost never observed, and most of the lesions contained both oxLDL and macrophages. A few lesions with native LDL or oxLDL without macrophages were also present. This seminal study allows us to describe the exact chronology of events leading to fatty streak formation in humans, starting with native LDL uptake by the arterial intima, followed by LDL oxidation and, finally, monocyte recruitment after endothelial activation by oxLDL.

C3H mice, which do not develop atherosclerotic lesions either when fed an atherogenic diet or when crossed with the atherosclerosis prone apoE^{-/-} mice, do not respond to in vivo administration of oxLDL, in contrast to C57BL/6 mice (391). Their EC are not activated in the presence of oxLDL, whereas cells from C57BL/6 mice express M-CSF, MCP-1, and VCAM-1 in the same conditions. Yet, C3H EC respond perfectly well to activation by the proinflammatory cytokines IL-1 and TNF- α (628, 629).

oxLDL behaves as a potent inflammatory agent. In vivo administration of oxidized LDL to C57BL/6 mice causes rapid induction of circulating M-CSF and upregulation of genes encoding JE (the murine analog of MCP-1) as well as other inflammatory proteins in various tissues (392). OxLDL stimulates the expression of adhesion molecules on EC (337). OxLDL has chemoattractant activity on monocytes, promotes their differentiation into macrophages, but inhibits their mobility (555, 556). Binding of oxLDL to CD36 triggers the release of proinflammatory cytokines in macrophages (310). In addition, incubating human blood mononuclear cells with oxLDL results in T-lymphocyte activation, as assessed by increased expression of IL-2 receptors and HLA-DR antigens on T lymphocytes (215).

Oxidation of LDL generates many “neo-self determinants” that induce an active immune response (288) and may challenge the regulatory pathways responsible for immune homeostasis. Both humoral and cellular immune responses can profoundly affect atherosclerotic development and progression (268).

The amount of lipid retained in macrophages depends on unregulated uptake of oxidized lipoproteins by scavenger receptors, as first identified by Brown and Goldstein (87), counterbalanced by degradation and efflux.

Altogether these findings point to a role of oxLDL as a very early trigger of vascular inflammation. LDL accumulation and modification in the subendothelium trigger monocyte and lymphocyte recruitment. Thereafter, activated macrophages and lymphocytes secrete abundant amounts of cytokines that in turn can activate EC, SMC, and macrophages/lymphocytes to foster cytokine production, leading to a self-perpetuating inflammatory process that becomes less dependent on the presence of oxLDL. This might explain why oxLDL, while instrumental in triggering the early atherosclerotic events, are less critical in upholding the inflammatory environment. This might also explain in part the efficiency of antioxidant therapies in the prevention of atherosclerosis when these therapies are administered at the very beginning of the atherosclerotic process in animal models, but their failure to do so in most secondary or primary prevention clinical trials in humans (reviewed in Ref. 743), where treatment is administered at later stages of the disease when secondary inflammatory mediators become as important as the initial oxidative-related stimulus. It is noteworthy that atherosclerotic plaques do not regress, or regress very slowly, in cholesterol-fed rabbits following short-term withdrawal of cholesterol feeding and normalization of cholesterol plasma levels (2, 155). It is only after a prolonged cholesterol withdrawal period that decrease in plaque size, together with reduced vascular inflammation and plaque stabilization, is observed (7, 347, 697). In humans, aggressive lipid lowering treatment using statins

has been shown to be very effective in limiting plaque development and reducing plaque progression (142, 143, 505, 506, 777). The cytokine network may thus serve as a final common proinflammatory pathway regardless of the initiating event and provides a supplemental therapeutic target, especially in late stages of the disease.

Several oxidized lipids and/or phospholipids are lipid bioactive mediators and may serve as primary triggers of the atherosclerotic process. Bioactive lipids have been identified in the atherosclerotic plaque, including the potent inflammatory mediator platelet activating factor (PAF), PAF-like lipids, oxidized phospholipids (oxPL), and lysophosphatidylcholine (lysoPC) (494). Like oxLDL, PAF induces TNF- α production by monocytes (71, 213) and MHC class II dependent IFN- γ secretion by T lymphocytes (213). Oxidized phospholipids upregulate tissue factor expression in EC (62), as well as in SMC (146). Similarly, lysoPC can enhance IFN- γ secretion and gene expression in human T lymphocytes (503) and stimulate the production of IL-1 β in macrophages (407). It also stimulates ICAM-1 and VCAM-1 expression (362, 793) and induces the release of IL-6 and IL-8 (662) in EC and MCP-1 in EC (663) and SMC (575).

Lipid oxidation products such as lysoPC, 4-hydroxy-2-nonenal (4HNE), and oxysterols are contained in oxLDL (662). Oxidized 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphorylcholine (OxPAPC), which is present in minimally modified LDL, is a PAF-like lipid that is found in atherosclerotic plaques. OxPAPC, but not native PAPC, is able to stimulate EC to bind monocytes and to secrete MCP-1, IL-8, and growth-related oncogene (GRO)- α (376, 565, 773; see review in Ref. 382). Individual lipids identified in OxPAPC include 1-palmitoyl-2-(5-oxovaleroyl)-*sn*-glycero-3-phosphorylcholine (POVPC), 1-palmitoyl-2-glutaroyl-*sn*-glycero-3-phosphorylcholine (PGPC), and epoxy-isoprostane-PC (727, 728). Oxidized 1-palmitoyl-2-linoleoyl-*sn*-glycero-3-phosphorylcholine (PLPC) also promotes monocyte-endothelial interactions (4). Moreover, epoxyisoprostane and epoxy-cyclopentenone phospholipids have been identified in OxPAPC that induce MCP-1 and IL-8 in EC (653). Oxidized phospholipids can upregulate tissue factor both in EC (62) and in SMC (146).

Interestingly, it has been shown that OxPAPC inhibits the binding of LPS to LPS-binding protein and CD14, which are required for presenting LPS to TLR-4 (61). It is therefore likely that upon acute bacterial inflammation oxidized phospholipids exert anti-inflammatory properties by inhibiting NF- κ B pathway, while under conditions of chronic inflammation, the pro-inflammatory activity of lipid oxidation products becomes more pathologically relevant (382).

Eicosanoids are well-known lipid mediators of inflammation. They comprise a variety of compounds [prostaglandins, thromboxanes, leukotrienes (LT), hydroxy-

and epoxy-fatty acids, lipoxins, and isoprostanes] that are derived from arachidonic acid. Leukotrienes are a class of eicosanoids that are derived through the action of the 5-lipoxygenase (5-LO). 5-LO is pivotal for the generation of both proinflammatory (LTB_4 and LTC_4) and anti-inflammatory (lipoxins) mediators. However, in contrast to their inhibitory effects on PMN and eosinophils, lipoxins are potent stimuli for peripheral blood monocytes, stimulating monocyte chemotaxis and adherence (428). Recent biologic and genetic findings implicate the 5-LO pathway in atherosclerosis (162, 279, 461, 552). Mehrabian et al. (461) reported that heterozygotes for the 5-LO gene on the $LDLr^{-/-}$ background had considerably reduced aortic lesions, compared with the advanced lesions observed in $5-LO^{+/+}LDLr^{-/-}$ mice, despite equivalent hypercholesterolemia. 5-LO pathway also promotes pathogenesis of hyperlipidemia-dependent aortic aneurysm (787). Furthermore, clinical findings showed that variant alleles of 5-LO genes were associated with a significant increase of carotid intima thickness (184). Most recently, a significant association was drawn between the gene encoding 5-LO activating protein (FLAP) and myocardial infarction by analysis of single-nucleotide polymorphism haplotype in humans (279).

Another significant recent discovery is the chemotactic activity of LTB_4 on activated $CD4^+$ and $CD8^+$ T cells expressing the LTB_4 receptor, BLT1 (239, 522, 661). It was found that both Th1- and Th2-polarized $CD4^+$ T cells and antigen-specific $CD4^+$ T cells, but not naive T cells, express BLT1 (661). Therefore, the antiatherogenic effects of the blockade of LTB_4 /BLT1 pathway (6, 280) might result in part from decreased Th1/Th2 cells recruitment in the plaque.

B. Secondary Triggers

Once inflammation has been triggered and cytokine release is initiated at the onset of atherosclerotic lesion development, a number of factors that are found in the atherosclerotic plaque can participate in maintaining and amplifying cytokine production (Table 3).

1. HSP

Evidence suggests that the inflammatory component of atherosclerosis might, at least in part, involve immune reactivity to heat shock proteins (HSPs) (446, 544, 737). Animal models of atherosclerosis have shown a very early role for HSP60 in the development of the disease (see review in Ref. 738). HSP60 might be an important autoantigen in atherosclerosis and might play a role similar to that of oxLDL in triggering an autoreactive T-cell response. Rabbits (757, 758) or mice (226) immunized with mycobacterial HSP65, which has a high degree of sequence homology with mammalian HSP60, develop en-

TABLE 3. *Primary and secondary triggers of cytokine release in atherosclerosis*

Primary: bioactive lipid mediators
Oxidized low-density lipoprotein
4-Hydroxy-2-nonenal (4HNE)
Oxysterols
Oxidized phospholipids (oxPL)
Lysophosphatidylcholine (lysoPC)
Oxidized 1-palmitoyl-2-arachidonoyl- <i>sn</i> -glycero-3-phosphorylcholine (oxPAPC)
Platelet activating factor (PAF)
Secondary
Heat shock proteins
Immune complexes
Infectious agents
Defective clearance of apoptotic cells
Matrix metalloproteinases
Inflammasome
Oxygen radicals
Angiotensin II
Advanced glycated end products
Proinflammatory cytokines
Toll-like receptor endogenous ligands
Mechanical factors
Hypertension
Disturbed flow
Adipokines
Leptin
Resistin
Platelet products

hanced early atherosclerotic lesions. High levels of autoantibodies specific for human HSP60 have been reported to be associated with CAD (792).

Besides their role as autoantigens, HSPs can act as an amplifier of the cytokine production. Although HSPs are typically regarded as intracellular proteins, HSP60 and HSP70 are present in the sera of clinically normal individuals (546, 759), and enhanced levels of circulating HSP60 are associated with early atherosclerosis in clinically normal subjects (546, 759), as well as with peripheral vascular disease (749). Elevated HSP60 levels also predict the progression of atherosclerosis in hypertensive patients according to the European Lacidipine Study on Atherosclerosis (ELSA) (545). HSP60, HSP70, HSP90, and gp96 are capable of inducing the production of proinflammatory cytokines by macrophages, and they can stimulate the activation and maturation of dendritic cells as well, via CD14/TLR2 and CD14/TLR4 receptor complex-mediated signal transduction pathways, in a manner similar to the effects of LPS and bacterial lipoprotein (714). In particular, chlamydial and human HSP60 induce $TNF-\alpha$ and MMP production by macrophages (351) and stimulate E-selectin, ICAM-1, and VCAM-1 expression on EC (349). HSP60 also markedly enhances IL-6 production by EC, SMC, and macrophages (349). However, recent evidence suggests that the reported cytokine-inducing effects of HSPs may in part be due to contaminating LPS and LPS-associated molecules (see review in Ref. 680).

2. Immune complexes

OxLDL is a major autoantigen involved in atherosclerosis (reviewed in Ref. 52), and both oxLDL and anti-oxLDL antibodies are present in atherosclerotic lesions (526, 775). Immune complexes consisting of oxLDL and anti-oxLDL may be ingested by macrophages via Fc- γ receptors, leading to their activation and subsequent release of inflammatory cytokines, oxygen-activated radicals, and MMPs (702). Immune complexes may also induce dendritic cell maturation and the production of immunostimulatory cytokine via ligation of the Fc- γ receptors.

3. Infectious agents

We have previously indicated why infectious agents are unlikely to be etiological factors in atherogenesis. However, they may participate in exacerbating the inflammatory process associated with atherosclerosis. *Chlamydia pneumoniae* can infect EC, SMC, and macrophages, resulting in the production of large amounts of chlamydial HSP60 during chronic, persistent chlamydial infections. *Chlamydia pneumoniae* induces the expression of the adhesion molecules E-selectin, ICAM-1, and VCAM-1 in EC (329, 349) and stimulates the production of TNF- α , IL-1 β , IL-6, MMP-2, and MMP-9 in macrophages (330, 349, 351, 499). In addition, *Chlamydia pneumoniae* is a potent inducer of IL-18 and IFN- γ production in peripheral blood mononuclear cells, the latter depending on the release of endogenous IL-18, IL-12, and IL-1 β but not on TNF- α (499). *Chlamydia pneumoniae*-induced synthesis of TNF- α and IL-1 β involves TLR2-mediated signals, whereas stimulation of IL-18 production is mediated through MyD88-dependent pathways independent of TLR2 or TLR4 (498, 499).

A role for viruses in atherosclerosis was proposed in the 1970s by Catherine Fabricant showing that Marek's disease virus induces atherosclerosis in hypercholesterolemic chickens (196). Other herpes viruses such as herpes simplex virus (HSV) and CMV can contribute to atherosclerosis (90). In the human aorta, EC and SMC appear to be a primary site of infection with CMV, suggesting that the vasculature may serve as a reservoir for CMV (527). Interestingly, the production of IL-6 and IL-8 has been shown to be enhanced in CMV-infected SMC and EC (14, 172). Likewise, infection of SMC with human CMV induces strong production of chemokines, RANTES (regulated upon activation, normal T expressed and presumably secreted), and IP-10 (IFN-inducible protein 10) (249). One of the most relevant contributions of herpes viruses to atherosclerosis could be through their potential to initiate the generation of thrombin by having essential phospholipids and TF activities on their surface (656).

4. Defective clearance of apoptotic cells

A variety of mechanisms are involved in apoptotic cell recognition by phagocytes. Innate recognition of non-self involves CD91-calreticulin complex (binding to C1q or to mannose binding lectin which recognizes apoptotic cell-associated molecular patterns by phagocytes), CD14 and β_2 -integrins (which bind the inactivated complement fragment iC3b) (reviewed in Ref. 596). Recognition of altered self (oxidized epitopes) is achieved through scavenger receptors, or ligation to bridging proteins, like Gas6 and milk fat globule epidermal growth factor 8 (MFG-E8), which bind Mer kinase receptor and $\alpha_v\beta_3$ -integrin, respectively, on phagocytes (596). Apoptosis is a mechanism of cell death that does not generate an inflammatory response, since appropriate clearance of apoptotic bodies by professional phagocytes induces the release of the anti-inflammatory cytokines IL-10 and TGF- β (596). However, intrinsic defects in the clearance of apoptotic cells are associated with spontaneous and persistent tissue inflammation and autoimmunity. This may be due to reduced production of immunoregulatory cytokines due to defective phagocytosis and/or to the immunogenic and proinflammatory potential of the unremoved apoptotic cells (53). For instance, impaired clearance of apoptotic cells has been described in patients with cystic fibrosis and bronchiectasis (691) and has also been linked to the pathogenesis of systemic lupus erythematosus (SLE) (668). Interestingly, a recent study by Grainger et al. (246) provided evidence that apoE deficiency results in impaired clearance of apoptotic cell debris. This in turn was associated with a systemic increase in proinflammatory markers in apoE^{-/-} mice, including TNF- α and fibrinogen, which was independent of lipoprotein metabolism (246). With regard to atherosclerotic plaques, we have shown that apoptotic microparticles accumulate in the lipid core (442), most likely as a result of reduced capacities of clearance of apoptotic cells by foam macrophages that are in an oxidant-rich environment (443, 592). Defect in the clearance of apoptotic cells/microparticles may promote and perpetuate proinflammatory cytokine production.

5. Cellular microparticles

Microparticles (MPs) are plasma membrane-derived vesicles shed from the plasma membrane of stimulated or apoptotic cells. They are now acknowledged as cellular effectors involved in fundamental physiological processes including intercellular communication, hemostasis, and immunity (reviewed in Refs. 296, 482). MPs are ideal links between inflammation, thrombosis, and atherosclerosis. MPs express a number of proinflammatory and prothrombotic molecules and could play an important role in the dissemination of these factors to sites remote from the site of their production. MPs are a source for IL- β secre-

tion (427) and are rich in aminophospholipid substrates of secretory phospholipase A₂ for the generation of lysophosphatidic acid, a potent proinflammatory mediator and platelet agonist (209). Platelet-derived MPs enhance monocyte arrest on activated endothelium or atherosclerotic carotid arteries, through P-selectin, GPIIb/IIIa, and JAM-A-dependent deposition of RANTES (457, 604), and/or increased endothelial expression of ICAM-1 and monocyte expression of CD11a/CD18 and CD11b/CD18 (36). The induction of monocyte-endothelial adhesion could also be mimicked by arachidonic acid isolated from MPs, suggesting a role for MP-associated bioactive lipids in transcellular communications. These effects of MPs may have contributed to the accelerated atherosclerosis in mice injected with activated platelets (604). P-selectin/PSGL-1 also enhances the production of leukocyte-derived MP and the recruitment of these MPs to thrombi (reviewed in Ref. 711). In addition, platelet-derived MPs express CD40L, which has been involved in thrombus stabilization (19). Others have shown that leukocyte MP formation was enhanced by inflammatory stimuli (464). Purified leukocyte-derived MPs in turn induced EC IL-6 and IL-8 release, MCP-1, and tissue factor expression (465), suggesting a potential role in the perpetuation of endothelial cell activation. MMPs have been observed in endothelium, platelet, monocyte, and T lymphocyte-derived MPs (177) and may contribute, in conjunction with other factors such as tissue factor, to the proangiogenic potential of these cell fragments. MPs are abundantly present in the lipid core of human atherosclerotic plaques (442) where they are responsible for tissue factor activation and may contribute to plaque inflammation. MPs also circulate at high levels in the peripheral blood of patients with acute coronary syndromes (433) and are suggested to play an important role in endothelial dysfunction (76) in addition to their potential role as carriers of blood-borne tissue factor (231), involved in blood thrombogenicity.

6. MMPs

Several studies have indicated that MMPs can directly or indirectly affect the activity of various cytokines that participate in inflammation and repair processes, including IFN- β , VEGF, EGF, FGF (see review in Ref. 532). Of particular interest in the context of atherosclerosis are the effects of MMPs on TGF- β , IL-1 β , and TNF- α . Proteolysis of extracellular matrix by MMPs is one of the mechanisms that can release active TGF- β from inactive complexes. In both cells and tissue explant models, MMP-3 (429), MMP-9 (779), and MMP-14 (328) have been shown to activate TGF- β . By activating TGF- β in vivo, MMPs would restrain, rather than augment, inflammation. This might, at least in part, account for reduced macro-

phage infiltration in atherosclerotic lesions of MMP-3-deficient apoE^{-/-} mice (637).

IL-1 β also requires caspase-1-dependent proteolytic processing for activation. MMP-2, MMP-3, and MMP-9 can cleave and activate the IL-1 β precursor (606). Furthermore, beyond activating IL-1 β , MMP-3 can actually degrade the biologically active cytokine (606), which can also be inactivated in vitro by MMP-1, MMP-2, and MMP-9 (308). Altogether, these data indicate a potential dual role for MMPs in the modulation of cytokine activity, being involved in both activation and inactivation processes.

Similarly, TNF- α is regulated by MMP activity. TNF α , which is produced as a 26-kDa membrane-associated protein, is cleaved by TNF- α converting enzyme (TACE) into a soluble 17.5-kDa cytokine. TACE is a member of the disintegrin family of metalloproteinases (ADAM17) (55, 483), and the release of active TNF- α is dramatically reduced in cells derived from ADAM17-deficient mice, indicating that ADAM17 plays a key role as a TNF- α convertase in vivo (788). However, even if ADAM17 is the main modulator of the generation of TNF- α activity, MMP1 and MMP-9 are able to cleave proTNF even though they do not produce active TNF- α (477).

7. Inflammasome

Caspases are a family of cysteine proteases that fulfill a critical role in the execution of apoptosis. Moreover, a subfamily of caspases, known as inflammatory caspases, is involved in innate immunity, caspase-1 being the prototypic member. Other members include human caspase-4 and -5, and mouse caspase-11 and -12, all of which contain an NH₂-terminal caspase recruitment domain (CARD). Activation of the inflammatory caspases requires the assembly of a unique intracellular complex, designated the inflammasome, that proceeds to cleave and activate IL-1 β and IL-18 (452, 681). Of note, caspase-1^{-/-} mice have defects in the production of IL-1 β and IL-18 but only subtle defects in apoptotic pathways (358, 390). Evidence is now accumulating that members of the CATERPILLER [CARD, transcription enhancer, R (purine)-binding, pyrin, lots of leucine repeats] gene family, and, in particular, of the NALP subfamily, are important players in this signaling process. When NALP1 is activated by factors that are yet unknown, it interacts with an adaptor protein ASC (apoptosis-associated specklike protein containing a CARD) through homologous pyrin domain (PYD) to induce the assembly of a complex composed of NALP1, ASC, caspase-1, and caspase-5. This brings the caspases in close proximity to each other, thereby inducing their activation (681). Upon activation of caspase-1, the 31-kDa IL-1 β precursor and the active caspase-1 colocalize to the inner surface of the cell membrane and caspase-1 cleaves the precursor (640). The active 17-kDa IL-1 β is then released into the extracellular

compartment. Caspase-1-dependent processing of the 24-kDa IL-18 precursor is believed to be similar to that of IL-1 β (176). Interestingly, a single amino acid mutation in the NALP-3 gene has been reported in humans with Muckle-Wells syndrome, a rare autosomal dominant disease characterized by recurrent fevers, neutrophilia, elevated acute-phase proteins and arthritis (3). This mutation in NALP-3 results in a high state of activation of caspase-1 in LPS-stimulated monocytes and increased release of IL-1 β compared with cells from patients without the mutation. Inflammasome-related proteins might represent novel pharmacological targets to prevent exaggerated production of IL-1 and/or IL-18, and thereby combat inflammatory diseases.

8. Oxygen radicals

Cells present in the atherosclerotic plaque can produce reactive oxygen species (ROS) such as O₂⁻, H₂O₂, and \cdot OH in response to activation by a number of molecular actors of atherosclerosis, including cytokines (TNF- α , IL-1), growth factors (PDGF), vasoactive peptides (angiotensin II), platelet-derived products (thrombin, serotonin), and mechanical factors (cyclic stretch, laminar and oscillatory shear stress) (252). Major sources of ROS include normal products of mitochondrial respiration, NADPH oxidases, NO synthases, cyclooxygenases, lipoxygenases, cytochrome *P*-450 monooxygenase, and xanthine oxidase. These enzymes are all expressed in the atherosclerotic plaque, but evidence suggests that NADPH oxidase-like activity appears to be the major contributing enzymatic source of ROS in the vascular wall, generating superoxide anion in endothelial and smooth muscle cells (41, 253). The production of ROS activates reduction-oxidation (redox)-sensitive signaling pathways that regulate inflammatory gene expression.

ROS have been viewed previously as general messengers for signal-induced NF- κ B activation (612). However, recent evidence supports the notion that ROS themselves are not direct activators of NF- κ B (273). In fact, ROS may oxidize NF- κ B subunits and thus impair the DNA binding and transcriptional activities of NF- κ B (504). At the activation level, the ubiquitination and degradation of NF- κ B inhibitor, I κ B α , is dependent on the kinase activity of IKK complexes. IKK α and IKK β contain a redox-sensitive cysteine residue (Cys-179) that may be sensitive to oxidative modification by ROS (582). This would explain the oxidative inactivation of IKK β kinase activity observed in cells exposed to ROS (354). In contrast, ROS are potent activators for JNK through oxidative inactivation of the endogenous JNK inhibitors, such as JNK phosphatases and glutathione *S*-transferase (124). Thus ROS may act as unfair brokers between NF- κ B and JNK, inhibiting one but promoting the other, and creating a new form of

cross-talk between these two important stress-responsive systems (785).

9. Angiotensin II

A large body of evidence indicates that angiotensin II (ANG II) has significant proinflammatory activity in the vascular wall, inducing the production of ROS, inflammatory cytokines, and adhesion molecules. ANG II stimulates ICAM-1 and VCAM-1 expression in EC and SMC (144, 535, 553, 682), as well as E- and P-selectin expression in EC (15, 242). ANG II also enhances the functional adhesion of monocytes to EC (1, 336) and stimulates MCP-1 production in SMC and monocytes (122, 217, 283, 584). Furthermore, ANG II participates in the vascular synthesis of IL-8 and its homologs macrophage inflammatory protein (MIP)-2 and KC, as well as IP-10 (178, 284, 520, 658). Interestingly, one study, that needs to be confirmed, reported that ANG II can elicit the synthesis of MCP-1 and RANTES in rat glomerular EC via AT₂ rather than AT₁ receptors (745).

The proinflammatory effects of ANG II are generally considered to be AT₁ receptor dependent and are mediated, at least in part, through NF- κ B and AP-1. A number of studies clearly indicated that inhibition of NF- κ B blocks ANG II-induced expression of inflammatory agents including MCP-1 (283), IL-6 (263), and VCAM-1 (553). NF- κ B activation appears to be downstream of the NAD(P)H oxidases, inasmuch as antioxidant treatment interferes with its activation by ANG II (163). Moreover, angiotensin IV, a NH₂-terminal degradation product of ANG II, has recently been found to activate, via AT₄ receptors, the NF- κ B pathway in cultured vascular SMC, and to upregulate proinflammatory genes, such as ICAM-1, IL-6, TNF- α , MCP-1, and PAI-1 (195).

In agreement with *in vitro* observations, *in vivo* studies clearly indicate that ANG II can stimulate proinflammatory cytokine expression and promote inflammation and atherosclerosis. Chronic infusion of ANG II in apoE^{-/-} mice enhances the vascular expression of TNF- α , IL-6, and IL-1 β as well as chemokines and chemokine receptors including RANTES, MCP-1, CCR1 (C-C chemokine receptor 1), CCR2, and CCR3 (501). In addition, ANG II treatment increases atherosclerotic lesion size and promotes unstable plaque phenotype (501). Even though these effects might partly be attributed to ANG II-induced blood pressure elevation, it is noteworthy that blockade of MCP-1, by transfection with a dominant negative of the MCP-1 gene into skeletal muscles, limited ANG II-induced progression and destabilization of atherosclerotic plaques and suppressed the induction of proinflammatory genes (501). Interestingly, genetic disruption of the AT₁ receptor in apoE^{-/-} mice leads to inhibition of atherosclerotic lesion formation, irrespective of blood pressure or plasma cholesterol levels (724), and treatment

of apoE^{-/-} mice with an AT₁ antagonist inhibits MCP-1 and MIP-1 expression, together with monocyte/macrophage infiltration (178). In humans, it has been shown that elevated plasma levels of MCP-1 in patients with cardiovascular disease are reduced by an ACE inhibitor or an AT₁ antagonist (356, 557). Remarkably, hypertensive patients display an enhanced ANG II-dependent monocyte activation and adhesion to EC compared with normotensive subjects (180).

Besides its inflammatory effects on vascular cells, ANG II can also modulate adaptive immunity. ANG II triggers the proliferation of splenic lymphocytes through AT₁ receptor activation (491) and promotes an immune switch toward a Th1 response. Rats infused with ANG II show an increased IFN- γ and decreased IL-4 expression in splenocytes (625). Similarly, splenocytes from hypertensive apoE^{-/-} mice with high ANG II produce more IFN- γ than those from hypertensive mice with normal ANG II or normotensive apoE^{-/-} mice (459).

Recently, hyperresponsive cross-linked ANG II-induced AT₁ receptor homodimers have been identified, which are covalently bound by the transglutaminase activity of intracellular factor XIIIa (1). High levels of cross-linked AT₁ dimers were present on monocytes of hypercholesterolemic apoE-deficient mice, and inhibition of ANG II generation or of intracellular factor XIIIa activity suppressed both the appearance of cross-linked AT₁ receptor dimers and symptoms of atherosclerosis. Intriguingly, levels of factor XIIIa activity and AT₁ receptor dimers are significantly higher in monocytes derived from hypertensive patients than in monocytes derived from normal subjects and correlate with an enhanced ANG II-dependent monocyte adhesion to EC (1). Furthermore, factor XIIIa activity and the levels of AT₁ dimers in hypertensive patients could be reduced or normalized by chronic treatment with an ACE inhibitor. These findings point to a significant contribution of covalent dimerization of AT₁ receptors in pathogenic events that drive lesion formation.

10. AGEs

Advanced glycation end products (AGEs), the products of nonenzymatic glycation and oxidation of proteins and lipids, accumulate in the vessel wall especially in diabetes but also in euglycemia, in the latter case driven by oxidant stress (767). AGEs may exert their pathogenic effects by engaging cellular binding sites/receptors. A number of cell surface interaction sites for AGEs have been identified, including macrophage scavenger receptors type II, OST-48, 80K-H, galectin-3, CD36, and receptor for AGE (RAGE) (see review in Ref. 767). The interaction of AGEs with macrophages has been shown to activate macrophages in an NF- κ B-dependent fashion, leading to

the induction of PDGF, insulin-like growth factor (IGF)-I, and proinflammatory cytokines, such as IL-1 β and TNF- α (286, 706). Binding of AGEs to endothelial RAGE results in the depletion of cellular antioxidant defense mechanisms (e.g., glutathione, vitamin C) (51) and the generation of ROS (767). As a consequence of the increased cellular oxidative stress, AGE-activated EC express the procoagulant tissue factor and adhesion molecules such as E-selectin, ICAM-1, and VCAM-1 (38, 39, 51, 194).

In addition to AGEs, RAGE is a signal transduction receptor for S100/calgranulins that can also activate EC, SMC, and peripheral blood mononuclear cells (PBMC), including T cells, and trigger the generation of proinflammatory cytokines and adhesion molecules (286, 767). For example, incubation of EC with EN-RAGE (extracellular newly identified RAGE-binding protein) or S100B also causes VCAM-1 induction (286). Atherosclerotic lesions in diabetic apoE^{-/-} mice display accelerated accumulation of AGEs and S100/calgranulins and enhanced expression of RAGE compared with nondiabetic apoE^{-/-} mice (343). Administration of murine soluble RAGE (sRAGE) suppresses the increased lesion area and complexity associated with diabetes (92, 531). In parallel, the treatment induces a reduction in the levels of tissue factor, VCAM-1, AGEs/S100/calgranulins, and nuclear translocation of NF- κ B in the aorta of sRAGE-treated mice compared with untreated diabetic animals (343, 531).

11. Proinflammatory cytokines

The fact that cytokines favor their own production is a well-recognized phenomenon. Not only does IL-1 induce IL-1 (175) and TNF- α induce TNF- α (168), but these main directors of the inflammatory process induce a large panel of cytokines and other inflammatory mediators acting in a signaling cascade on target cells, as well as within auto-crine loops (164, 720). Negative regulatory loops have also been described with IL-10 (170). In the late 1980s and early 1990s, observations made in experimental models of endotoxemia led to the conclusion that TNF- α was a prerequisite for the induction of many other inflammatory cytokines (see review in Ref. 113). Injection of LPS in experimental animal models or in human volunteers led to the appearance of TNF- α in the bloodstream before any other cytokines could be detected. Moreover, experiments conducted with anti-TNF- α antibodies indicated that blocking TNF- α in bacterial or endotoxin-induced shock models led to a dramatic decrease in the levels of other cytokines measured in the bloodstream. However, while TNF- α may help in perpetuating sustained levels of proinflammatory cytokines, it does not appear to be a prerequisite for their induction in atherosclerosis. Even though the expression of proinflammatory cytokines is significantly decreased in apoE^{-/-} mice deficient in

TNF- α compared with apoE^{-/-} mice, it is not totally abolished (515).

Of importance, the immunoinflammatory pathway related to CD40 and its ligand (CD40L) mediates proatherogenic biological responses, such as the expression of cytokines, chemokines, growth factors, matrix metalloproteinases, and procoagulants on EC, SMC, and macrophages, suggesting a major role in atherosclerosis (see sect. vA).

12. TLR endogenous agents

As discussed above, TLRs have been involved in the development of atherosclerosis. Activation of TLRs through PAMPs is a well-recognized pathway that leads to the production of cytokines by macrophages and vascular cells. For instance, LPS-associated TLR4 signaling promotes a proinflammatory phenotype in vascular SMC, inducing the release of MCP-1 and IL-6 and the expression of IL-1 α (769). Dendritic cells are also present in the atherosclerotic plaque (59), and after TLR activation, CD1b+ dendritic cells secrete high levels of IL-12p40, TNF- α , and IFN- γ , but no IL-10 (355). However, in the context of atherosclerosis, it is important to envision the potential role of TLR activation by nonpathogenic endogenous agents. Accordingly, a recent study reported that mmLDL is able to stimulate early gene and protein expression of TNF- α , IL-6, MCP-1, and MIP-2 in macrophages through the TLR4/MyD88, PI3K/Akt, and ERK1/2 pathways, and in the absence of NF- κ B activation (471). Also, ox-PAPC, a bioactive component of oxidized lipoproteins, interacts with TLR4 to induce IL-8 in EC through interaction with CD14 (715).

13. Mechanical factors

A) SHEAR STRESS. Blood flow-induced shear stress has long been recognized as critically important in atherogenesis (111, 148). Atherosclerotic lesions preferentially develop in areas of disturbed or oscillatory flows, including arterial bifurcations, branch ostia, and curvatures. The vascular endothelium is extremely sensitive to changes in blood flow (160, 380); *in vitro* experiments suggest that physiological levels of shear stress are anti-inflammatory and antiadhesive, while low or oscillatory shear stress promotes oxidative and inflammatory transformations in EC, with enhanced monocyte adhesion, VCAM-1, ICAM-1, and E-selectin expression (116, 478). Flow is able to block TNF-mediated endothelial VCAM-1 expression by inhibiting JNK and p38 MAP kinases (765), a process that involves decreased expression of thioredoxin-interacting protein (766). Also, transcriptional profiling studies identified the Kruppel-like factor (KLF)-2 as a flow-induced anti-inflammatory transcription factor, being inhibited by IL-1 β and induced by laminar shear stress in cultured EC

(620). *In vivo*, lesion-prone areas of disturbed flow show constitutive activation of NF- κ B (262) and a greater propensity for LPS-induced VCAM-1 and E-selectin expression than areas of laminar flow.

B) HYPERTENSION. Epidemiological investigations clearly pointed out that hypertension is a powerful cardiovascular risk factor. Besides being associated with exaggerated atherosclerosis, elevated blood pressure levels have been found to be highly predictive of atherosclerosis-associated cardiovascular events, including ischemic coronary disease, stroke, and peripheral arterial disease (321). In human subjects, carotid artery intima-media thickness, measured with high-resolution B-mode ultrasound, is highly correlated with blood pressure levels and accurately reflects cardiovascular risk (517a). Experimental studies have demonstrated that hypertension increases the rate of atherosclerotic plaque development in hypercholesterolemic rabbits (128), monkeys (755), and, as shown more recently, in mouse models of atherosclerosis (345, 459). Hypertension occurs under several conditions, some linked to the activation of the renin-angiotensin system and characterized by elevated circulating ANG II, some with normal ANG II levels. Interestingly, by using hypertensive apoE^{-/-} mice with either elevated plasma ANG II levels (two-kidney, one-clip model of renal hypertension), or normal plasma ANG II levels (one-kidney, one-clip renal hypertension), Mazzolai et al. (459) found that both forms of hypertension led to a similar increase in atherosclerotic plaque size compared with normotensive animals. However, the atherosclerotic plaques of hypertensive animals with high ANG II showed signs of instability, including higher macrophage content, lower collagen and SMC accumulation, and larger lipid core than plaques from hypertensive apoE^{-/-} mice with normal ANG II, which were of a comparatively more stable phenotype (thicker fibrous cap, less inflammatory cell infiltration, and smaller lipid core). In addition, hypertensive apoE^{-/-} mice with high ANG II showed enhanced systemic inflammation compared with hypertensive mice with normal ANG II, as evidenced by increased serum IL-6 levels and white blood cell counts.

Several mechanisms can account for hypertension-induced atherosclerosis. Pressure-induced stretch of the vessel wall increases endothelial permeability to LDL and accentuates LDL accumulation in the intima, which is central to the atherogenic process (467). In addition, hypertension may promote or aggravate vascular inflammation. Indeed, mechanical strain stimulates the expression of ICAM-1 in EC (126) and MCP-1 in SMC (109), which is in good agreement with *in vitro* studies in organ culture of mouse carotid artery showing that high intraluminal pressure activates NF- κ B (383). Moreover, high blood pressure *in vivo* upregulates the arterial expression of MCP-1 (109), ICAM-1, and P-selectin (717).

14. Adipokines

A large body of evidence links obesity with accelerated atherosclerosis (460). Adipose tissue is an active endocrine and paracrine organ that releases a large number of cytokines and bioactive mediators, designated adipokines. These products influence not only body weight homeostasis but also inflammation, coagulation, and fibrinolysis, which ultimately affects atherosclerosis and its clinical complications. Adipokines with proinflammatory activities include TNF- α , IL-6, plasminogen activator inhibitor-1 (PAI-1), angiotensinogen, leptin, and resistin (372). Increased production of these proteins by adipose tissue in obesity is likely to raise circulating levels of acute-phase proteins and inflammatory cytokines leading to a state of chronic low-grade inflammation that characterizes the obese.

Leptin, which shares structural and functional similarities with the IL-6 family of cytokines (783), enhances the production of TNF- α , IL-6, and IL-12 from LPS-stimulated monocytes/macrophages (411). Leptin also plays an important role in the regulation of adaptive immunity. Leptin alters the Th1/Th2 balance in favor of a Th1 response associated with increased IL-2 and IFN- γ as well as decreased IL-4 production (414). Moreover, recent observations provided evidence that serum leptin levels are negatively correlated with the percentage of circulating CD4+CD25+ regulatory T cells in patients with autoimmune disease such as multiple sclerosis (454). This *in vivo* observation is substantiated by experimental findings showing that the number of Treg is increased in leptin-deficient (*ob/ob*) and leptin receptor-deficient (*db/db*) mice (454). However, *ob/ob* LDLr^{-/-} mice have been shown to develop more atherosclerotic lesions than wild-type LDLr^{-/-} mice (271, 463). Yet, leptin deficiency causes marked hypercholesterolemia and lesions of *ob/ob* LDLr^{-/-} mice appear to be much smaller than those usually observed in mice of similar age (22–26 wk old) having equivalent cholesterol levels (~10–12 g/l) (personal observation). It would be important to examine whether this finding could be attributed to a better regulatory T-cell response in the leptin-deficient mice. This interpretation is consistent with the recent finding that leptin administration enhances atherosclerotic lesion development in apoE^{-/-} mice (63).

Resistin is another adipokine with potent inflammatory activities. Resistin seems to be expressed at much higher levels in mononuclear leukocytes, macrophages, and bone marrow cells than in human adipose cells (536). Resistin stimulates the production of TNF- α , IL-6, and IL-1 in human PBMC (70). It is noteworthy that plasma resistin levels are correlated with markers of inflammation [soluble TNF receptor (sTNFR)-2 and IL-6] and are predictive of coronary atherosclerosis in humans (567). Taken together, these data indicate that

leptin and resistin may represent a novel link between metabolic signals, inflammation, and atherosclerosis.

On the contrary, adiponectin exerts potent anti-inflammatory properties. It inhibits TNF-induced expression of adhesion molecules in vascular EC (523), blocks lipid accumulation in macrophages, and suppresses the expression of class A scavenger receptors (524). Adiponectin also upregulates the expression of IL-10 in human monocyte-derived macrophages and increases TIMP-1 expression through IL-10 induction (361). Plasma adiponectin levels are reduced in patients with CAD (523), and overexpression of adiponectin in apoE^{-/-} mice inhibits the progression of atherosclerosis (764), an effect that appears to be mediated by adiponectin-induced IL-10 production (361).

15. Platelet products and coagulation factors/others

Thrombin is a serine protease that has a central role in hemostasis and thrombosis. It is generated in the process of activation of the coagulation cascade. Once formed, thrombin cleaves fibrinogen to produce the fibrin mesh of the blood clot. Thrombin also acts on cells through cleavage of specific receptors, which belong to the family of protease-activated receptors (PARs), including PAR-1 and PAR-3. In addition to these procoagulant effects, thrombin participates in inflammation and repair of injured tissues. It stimulates the secretion of other inflammatory mediators. It causes mast cell degranulation and release of histamine (562) and promotes production of IL-1 by activated macrophages (318). Thrombin can also induce, in a PAR-1-dependent way, the expression of E-selectin, ICAM-1, and VCAM-1 and enhances neutrophil and monocyte adhesion to the endothelium (247, 326, 327). In addition, thrombin stimulates endothelial production of IL-6 (449), IL-8 and MCP-1 (134, 247), and macrophage migration inhibitory factor (MIF) expression (633).

5-Hydroxytryptamine (5-HT), known as serotonin, is a well-characterized neurotransmitter and vasoactive amine. 5-HT is synthesized and released by mast cells, basophils, platelets, and enterochromaffin cells. Enhanced extracellular levels of this amine during inflammation and platelet activation are well documented (456). 5-HT inhibits TNF- α production but increases the secretion of IL-1 β , IL-6, IL-12p40, and IL-8 in LPS-stimulated monocytes (131, 183).

Mast cells have been reported to likely play a role in the progression of heart failure, atherosclerosis, and plaque rupture of atheroma (367, 537). Mast cell tryptase can stimulate the production of MCP-1 and IL-8 (136, 341).

IV. CYTOKINES AND CYTOKINE RECEPTORS IN HUMAN ATHEROSCLEROTIC PLAQUES

A. Cytokine Expression in Plaques

The first evidence that cytokines are expressed in the atherosclerotic plaque stems from the observation in the mid 1980s by Hansson and co-workers (317) that most of the cells present in the plaque express the MHC class II antigen HLA-DR, indicating that IFN- γ must be produced in the vicinity of these cells. This was demonstrated later on by the same group (214, 267). By the late 1980s, immunohistochemistry, in situ hybridization, or RT-PCR techniques had been used to identify in human atherosclerotic plaques, mainly from carotid endarterectomy specimens, a number of growth factors and cytokines: PDGF (581, 740), TNF- α (26, 35, 585, 676), IL-1 (611), MCP-1 (CCL2) (495, 774), IFN- γ (267), and M-CSF (130). Thereafter, as novel cytokines were gradually discovered, their expression in human atherosclerotic plaques was studied and reported (Table 4).

In 1999, Hansson and colleagues (214) determined the expression profiling of Th1 and Th2 cytokines in advanced human atherosclerotic plaques. They found that

TABLE 4. *Cytokines expressed in human atherosclerotic plaques*

TNF- α (26, 35, 585, 676)
IL-1 (611)
IL-2 (214)
IL-3 (mRNA expression) (86)
IL-6 (586, 618)
IL-8 (CXCL8) (22, 586, 718)
IL-10 (441, 687)
IL-12 (687)
IL-15 (289, 750)
IL-18 (228, 435)
IFN- γ (214, 267)
Oncostatin M (476)
TGF- β 1, TGF- β 2, TGF- β 3 (58, 214)
Activin A, a member of the TGF- β superfamily (191)
Cyclophilin A, a potent chemoattractant for leukocytes (140, 314)
M-CSF (130)

Chemokines

MCP-1 (CCL2) (495, 774)
IFN- γ -inducible CXC chemokines
Monokine induced by IFN- γ (Mig/CXCL9) (424)
IFN-inducible protein 10 (IP-10/CXCL10) (424)
IFN-inducible T-cell α -chemoattractant (I-TAC/CXCL11) (424)
CXCL16/SR-PSOX (751)
MIP-1 α (CCL3) (274, 739)
RANTES (CCL5) (274, 739)
Fractalkine (CX3CL1), the ligand of CX3CR1 (746)

Bone-associated cytokines

Osteopontin (OPN) (230, 508)
Osteoprotegerin (OPG) (173)
Receptor activator of NF- κ B ligand (RANKL) (238)

Reference numbers are given in parentheses.

IL-2 was present in 50% of plaques, and IFN- γ was detected in some but not all of the IL-2-positive plaques. In contrast, the expression of IL-4 and IL-5, Th2 cytokines, and TNF- β (lymphotoxin- α), expressed by both Th1 and Th2 cells, was very scarce, and IL-10 was not detected at all. However, we (441) and others (687) have found that IL-10 is produced in atherosclerotic lesions and correlates with diminished expression of inflammatory mediators. TGF- β was expressed abundantly in all plaques as previously reported (502). Comparisons between sections stained for TGF- β and for cell type-specific antigens implied that macrophages, T cells, and smooth muscle cells expressed this group of cytokines. Among isoforms, TGF- β 2 was detected in high frequency and exhibited stronger intensity of staining than TGF- β 1 or TGF- β 3. The distribution of TGF- β overlapped with that of its transport protein, LTBP. This suggested that TGF- β is actively secreted. Subsequent experiments in murine models of atherosclerosis analyzing the role of IL-10 (104, 434, 542) and TGF- β (236, 245, 420, 572) in this setting led to the conclusion that the balance between proinflammatory and anti-inflammatory cytokines is decisive for disease development and progression.

A group of noncollagenous matrix proteins originally identified as important in bone mineralization, including osteopontin (OPN), osteoprotegerin (OPG), and receptor activator of NF- κ B ligand (RANKL), are expressed by macrophages, EC, and SMC in plaques (173, 230, 238, 508). They have pleiotropic effects that influence matrix turnover, cell migration, and inflammation (248, 609). OPN and OPG expression is greater in symptomatic than in asymptomatic carotid atherosclerotic plaques, whereas RANKL expression is similar (238). Remarkably, OPN, also called early T-lymphocyte activation protein-1 (Eta-1), is needed for Th1 responses and promotes IL-12 expression (29).

Better understanding of the time course of cytokine gene expression is important for successful prevention of plaque development and progression. However, this information cannot be easily obtained in humans. A recent study has addressed this issue in apoE^{-/-} mice (695). After 4 wk of a cholesterol-rich diet, the expression of the proinflammatory cytokines was much more pronounced than anti-inflammatory cytokines. This imbalance between pro- and anti-inflammatory cytokines might account for the progression of atherosclerosis.

B. Cellular Sources of Cytokines

1. Vascular cells

All cells present in the atherosclerotic plaques are potentially able to elaborate a set of cytokines (Table 5; Fig. 3). By the end of the 1980s, Peter Libby and his group identified for the first time the capacity of human vascular

TABLE 5. *Cellular sources of cytokines with potential activities in atherosclerosis*

Cytokine	Cell Source	Cell Target	Function
IL-1 α	Macrophages, lymphocytes, EC, SMC	Many cell types	Proinflammatory, stimulates endothelial and SMC activation
IL-1 β			
IL-2	Activated T cells	Macrophages, T & B cells, NK cells	T-cell growth factor, stimulates NK activity, stimulates Treg cells
<i>IL-3</i>	<i>T cells, mast cells</i>	<i>Mast cells, hematopoietic progenitors</i>	<i>Promotes proliferation and differentiation of mast cell and hematopoietic cell lineages (granulocytic, monocytic, megakaryocytic)</i>
IL-4	Th2 cells, mast cells	T & B cells, mast cells, macrophages, hematopoietic progenitors	Proliferation and differentiation of B cells (Ig switching to IgG ₁ and IgE) and Th2 cells (anti-inflammatory by inhibiting Th1 immune responses); stimulates VCAM-1
IL-5	T cells, mast cells, EC	B cells	Stimulates growth and differentiation of B cells, Ig switching
IL-6	Macrophages, EC, SMC, T cells	T & B cells, hepatocytes, EC, SMC	Differentiation of myeloid cells, induction of acute phase proteins, SMC proliferation
<i>IL-7</i>	<i>Platelets</i>	<i>Monocytes, T & B cells</i>	<i>Proinflammatory</i>
IL-8	Monocytes, EC, T cells	Neutrophils, T cells, monocytes	Proinflammatory, promotes leukocyte arrest
IL-9	Th2 cells	T cells, B cells, mast cells, eosinophils, neutrophils, and epithelial cells	Promotes proliferation and differentiation of mast cells, stimulates IgE production, inhibits monocyte activation, stimulates TGF- β in monocytes
IL-10	Macrophages, Th2, Treg and B cells, mast cells	Macrophages, T & B cells	Anti-inflammatory, inhibits Th1 responses, promotes proliferation and differentiation of regulatory T cells
<i>IL-11</i>	<i>EC</i>	<i>Hematopoietic progenitor cells</i>	<i>Hematopoiesis</i>
IL-12	Th1 cells	T cells, macrophages	Proinflammatory; promotes NK and cytotoxic lymphocyte activity; induces IFN- γ
<i>IL-13</i>	<i>Th2 cells</i>	<i>B cells</i>	<i>Activation of Ig transcription</i>
<i>IL-14</i>	<i>EC, lymphocytes</i>	<i>B cells</i>	<i>B-cell growth factor</i>
<i>IL-15</i>	<i>EC, macrophages</i>	<i>T & B cells, NK cells, monocytes</i>	<i>Enhances neutrophil chemokine production, cytoskeletal rearrangements, phagocytosis; delays apoptosis</i>
<i>IL-16</i>	<i>Mast cells, CD4⁺ and CD8⁺ cells</i>	<i>CD4⁺</i>	<i>CD4⁺ T-cell growth factor; proinflammatory; enhances lymphocyte chemotaxis, adhesion molecule, and IL-2 receptor and HLA-DR expression</i>
<i>IL-17</i>	<i>Human memory T cells, mouse $\alpha\beta$TCR⁺ CD4⁻ CD8⁻ thymocytes</i>	<i>Fibroblasts, keratinocytes, epithelial and EC</i>	<i>Secretion of IL-6, IL-8, PGE₂, MCP-1 and G-CSF, induces ICAM-1 expression, T-cell proliferation</i>
IL-18	Macrophages	T cells; NK cells; myeloid, monocytic, erythroid, and megakaryocytic cell lineages	Proinflammatory, induces IFN- γ and other Th1 cytokines, promotes Th1 development and NK activity
<i>GM-CSF</i>	<i>Macrophages, EC, lymphocytes</i>	<i>Hematopoietic stem cells, neutrophils, macrophages</i>	<i>Growth and differentiation of granulocytes, macrophages</i>
M-CSF	Macrophages, EC, lymphocytes	Hematopoietic stem cells, neutrophils, macrophages	Growth and differentiation of macrophages
TNF- α	Macrophages, T & B cells, NK cells, SMC	Many cell types	Proinflammatory, fever, neutrophil activation, bone resorption, anticoagulant, tumor necrosis
TGF- β	Platelets, macrophages, Th3, Treg & B cells, SMC	Many cell types	Anti-inflammatory; profibrotic; promotes wound healing, angiogenesis; suppresses Th1 & Th2 immune responses
IFN- γ	Th1 cells, NK cells, SMC (?)	Macrophages, lymphocytes, NK cells, EC, SMC	Proinflammatory, promotes Th1 immune responses/secretion of Th1-associated cytokines, inhibits extracellular matrix synthesis by SMC
CD40L	Platelets, T cells, NK cells, EC, SMC	Macrophages, lymphocytes, NK cells, EC, SMC	Proinflammatory, promotes Th1 immune responses/secretion of Th1-associated cytokines, stimulates MMP secretion

Cytokines in italics have a yet unknown role in atherosclerosis.

cells to be both source and target of cytokines, showing that IL-1 α and IL-1 β induced IL-1 β production by human SMC and EC (721, 722) and that TNF- α induced TNF- α production by SMC (723). Of note, TNF- α is not expressed by EC. IL-6 is constitutively released by SMC in culture, and its production can rise to the point of representing ~4% of newly synthesized proteins in activated cells (413). The proinflammatory repertoire of vascular cells includes TNF- α , IL-1 β , IL-6, IL-8, and IL-15 while the anti-

inflammatory repertoire is represented predominantly by TGF- β . EC also express low levels of IL-1ra (171). Vascular cells do not seem to be able to express the anti-inflammatory cytokines IL-10, IL-4, or IL-13. Moreover, the response of EC to IL-4 and IL-13 favors inflammation, with sustained expression of VCAM-1 (85, 601, 602) and P-selectin (772).

EC are also important sources of hematopoietic growth factors including stem cell factor (SCF), IL-3,

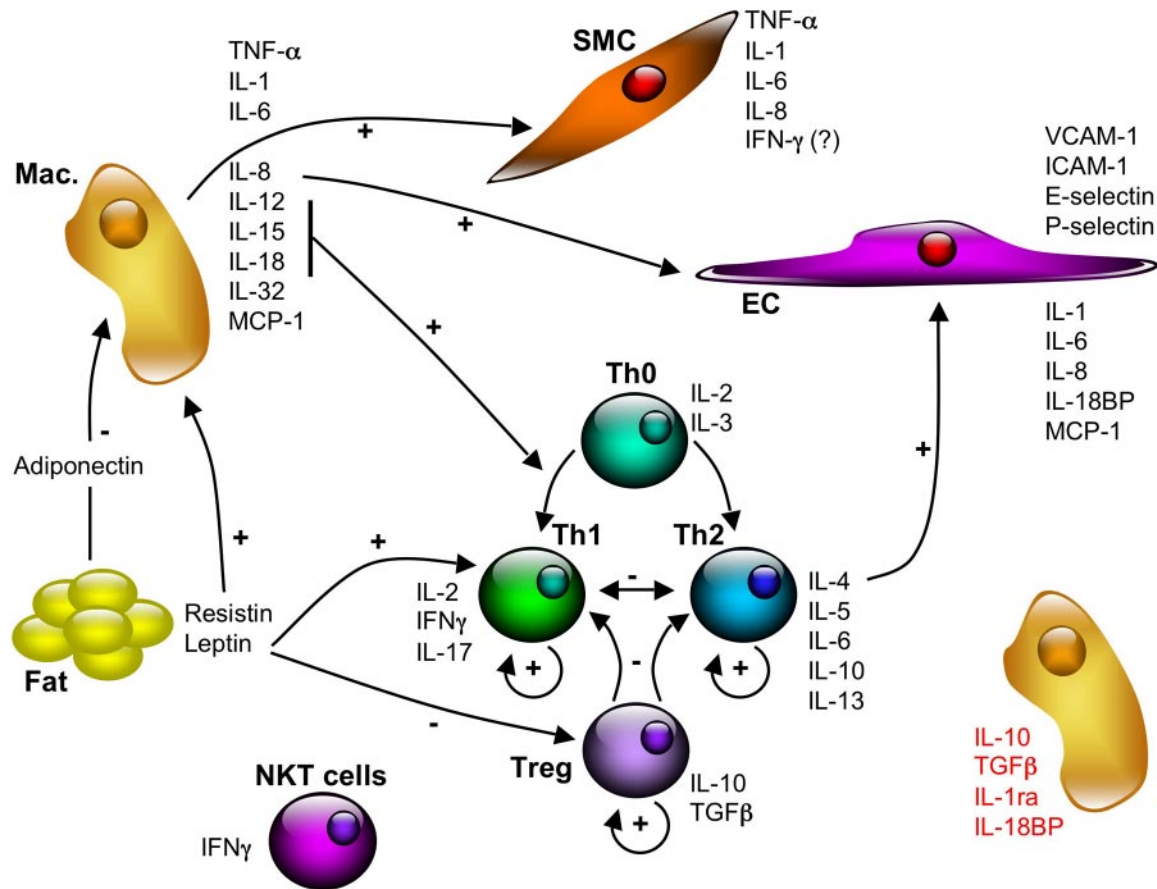


FIG. 3. Cytokines involved in atherogenesis. Cytokines are produced by several cell types, including inflammatory and vascular cells, as well as adipocytes. IL-12 and IL-18 produced by macrophages are potent inducers of IFN- γ and promote the differentiation of naive T cells into proatherogenic Th1 cells. Macrophage or macrophage-derived cytokines also activate smooth muscle cells (SMC) and endothelial cells (EC) to produce an array of proinflammatory mediators. On the other hand, the anti-inflammatory cytokines IL-10 and TGF- β , also produced by macrophages, promote antiatherogenic Treg cell differentiation. Other anti-inflammatory mediators with potent antiatherogenic properties include IL-1 receptor antagonist (IL-1ra) and IL-18 binding protein (IL-18BP). Interestingly, IL-4, the prototype of Th2 cells, has proinflammatory properties on EC. Adipocytes produce both pro- and anti-inflammatory mediators. Leptin activates Th1 cells but inhibits Treg cell function. Adiponectin has been shown to dampen macrophage activation.

GM-CSF, G-CSF, and M-CSF (447). IL-15, a cytokine implicated in T-cell migration, has been shown to be produced by EC in response to IFN- γ (519). In addition, EC express the chemokines I-309/CCL1, MCP-1/CCL2, MCP-4/CCL13, monokine induced by IFN- γ (Mig)/CXCL9, IFN-inducible T-cell chemoattractant (I-TAC)/CXCL11, and MIF (reviewed in Ref. 729). Chemokines produced by SMC include MCP-1/CCL2, Eotaxin/CCL11, Mig/CXCL9, stromal cell-derived factor (SDF)-1/CXCL12, (scavenger receptor that binds phosphatidylserine and oxidized lipoprotein) SR-PSOX/CXCL16, Fractalkine/CX3CL1, and MIF (reviewed in Ref. 729). SMC constitutively express mRNA for the chemokine receptors CCR1 and CCR2, but not CCR3, CCR4, CCR5, or CXCR1 (C-X-C chemokine receptor 1) or CXCR2 (274).

2. Leukocytes

Macrophages are certainly the main source of cytokines in the atherosclerotic plaque. Their repertoire is

huge, including the proinflammatory cytokines TNF- α , IL-1, IL-6, IL-12, IL-15, and IL-18, as well as the anti-inflammatory cytokines IL-10 and TGF- β . IL-32, a recently discovered cytokine that activates typical cytokine signal pathways of NF- κ B and p38 MAP kinase (338), can be added to this list. Macrophages have also been reported to produce IFN- γ after stimulation by a combination of IL-12 and IL-18, suggesting the possibility of an autocrine activation loop in macrophages (484). However, these results were recently questioned by Schleicher et al. (600) who showed that conventional techniques used to generate peritoneal and bone marrow-derived macrophages in fact contain small quantities of natural killer (NK) cells or CD8+ T cells, respectively, that are fully responsible for the production of IFN- γ . In the atherosclerotic plaque, IFN- γ can be produced by CD4+ Th1 cells, CD8+ T cells, and NKT cells.

Macrophages express a number of chemokines: MCP-1/CCL2, MCP-4/CCL13, IL-8/CXCL8, GRO- α /KC/CXCL1, Mig/

CXCL9, I-TAC/CXCL11, SDF1/CXCL12, SR-PSOX/CXCL16, and MIF, whereas lymphocytes express RANTES/CCL5, MIP1 α /CCL3, MIP β /CCL4 (reviewed in Ref. 729). It is noteworthy that chemokines may share a close evolutionary relationship with scavenger receptors in that chemokines generally have scavenger receptor-like activity, binding oxLDL through their receptor-binding domain (631). This is especially the case for the transmembrane protein SR-PSOX that is identical to the chemokine CXCL16 (455, 630).

A variety of chemokine receptors have been found to be differentially associated with Th cell subpopulations. CCR5 and, to a lesser degree CXCR3, are preferentially found on Th1 cells, whereas CCR4 is preferentially found on Th2 cells (105). CCR4 and CCR8 seem to be specifically expressed by CD4⁺CD25⁺ Treg cells (211, 300).

3. Platelets

Platelets have inflammatory actions and are a rich source of chemokines, cytokines, and growth factors. These factors are preformed and packaged in storage granules and, when released, may participate in atherosclerosis. While IL-1 β cannot be detected in resting platelets, it is shed in its active form in microvesicles, after activation with thrombin (402). Platelets are the main source of circulating CD40L (551), and following ligation with the CD40 receptor might be involved in inflammatory cellular cross-talks (281).

From their α -granules, platelets secrete CXC chemokines, such as platelet factor 4 (PF4/CXCL4) or epithelial cell-derived neutrophil-activating peptide (ENA-78/CXCL5), and precursors for the CXCR2 ligand neutrophil attracting peptide (NAP)-2 (CXCL7), such as CTAP-III or β -thromboglobulin, as well as CC chemokines, such as MIP-1 or RANTES (see review in Ref. 729). The deposition and immobilization of platelet-derived RANTES have been shown to trigger enhanced recruitment of monocytes on activated aortic endothelium (604, 710). RANTES was revealed on the luminal surface of carotid arteries with early atherosclerotic lesion in apoE^{-/-} mice (710). In fact, activated platelets can deliver RANTES and PF4 to the endothelial lining of early atherosclerotic lesions, as well as to the surface of monocytes via a mechanism involving the platelet P-selectin (298, 604). The important observation that the intermittent injection of activated, but not P-selectin-deficient, platelets exacerbates lesion formation in apoE^{-/-} mice strongly suggests that mechanisms of P-selectin-mediated chemokine delivery participate in the in vivo pathogenesis of native atherosclerosis (298).

4. Mast cells

Mast cells are inflammatory cells best known for their pivotal role in allergic diseases. They are also

present in the arterial wall, where they form part of the inflammatory cell infiltrate and may contribute to atherosclerosis (319, 384, 404). Mast cells might be an additional source of inflammatory cytokines within the plaque. They are able to produce copious amounts of presynthesized TNF- α within their granules, in addition to de novo synthesis and secretion of TNF- α following stimulation (240).

C. Biological Effects of Cytokines

1. Effects on endothelial permeability

Alteration of endothelial permeability is an important feature during inflammatory conditions and is associated with leukocyte transendothelial migration and accumulation within the tissues (see Table 6). The intercellular junction complex and its interactions with the cytoskeleton are important for the maintenance of endothelial permeability (43). A number of proinflammatory cytokines, such as TNF- α and IFN- γ , have been shown to alter the distribution of adhesion receptors involved in cell-cell adhesion, namely, vascular endothelial (VE)-cadherin-catenin complexes, and prevent the formation of F-actin stress fibers (744). This results in restructuring of the intercellular junction leading to loss of endothelial permeability and favoring leukocyte transmigration. Complete alteration in intercellular junction organization during inflammatory conditions may require the interplay between inflammatory cell adhesion and secretion of proinflammatory mediators (185).

2. Activation of adhesion molecule and chemokine expression

Since the initial discovery that cytokines induce ELAM and VCAM-1 expression on EC (47, 150), many

TABLE 6. *Biological effects of cytokines*

Effects on endothelial permeability (185, 744)
Activation of adhesion molecule expression (47, 150)
Induction of chemokine release (424)
Modulation of scavenger receptor expression (291, 363, 388)
Modulation of lipid metabolism (472, 751)
Activation of 15-lipoxygenase expression in cultured macrophages (621, 754, 756)
Effect of SMC migration/proliferation (266, 267, 400, 670, 723, 776)
Regulation of immune response (Th1/Th2/Treg) (34, 145, 431)
Conversion of CD4 ⁺ naive T cells into CD4 ⁺ regulatory T cells (120, 207, 251, 707)
Oxidation of LDL (induction cell oxidant stress) (204, 458)
Stimulation of MMP expression (500)
Modulation of extracellular matrix expression (17)
Modulation of endothelial of SMC progenitor differentiation (370, 389, 686)
Regulation of neovessel formation (63, 69, 192, 423)
Promotion of intraplaque neovascularization (705)
Induction of apoptosis (79, 80, 222, 223)
Stimulation of microparticle release (464)
Modulation of endothelial procoagulant activity (193, 216, 451)
Modulation of fibrinolysis (PAI-1) (597)

cytokines, including, IL-1, TNF- α , and IFN- γ , have been implicated in the induction of an array of adhesion molecules and chemokines in the vascular wall. IL-1 and TNF- α stimulate membrane expression of leukocyte adhesion molecules ICAM-1, ICAM-2, VCAM-1, E-selectin, and P-selectin by EC. These molecules interact with specific ligands expressed by neutrophils, lymphocytes, and circulating monocytes. VCAM-1 plays an important role in atherogenesis (151). It selectively promotes the adhesion of mononuclear cells on the vascular endothelium that constitutively express its ligand very late antigen (VLA)-4. VCAM-1 is present in human advanced coronary atherosclerotic lesions but is barely expressed by EC being more prevalent in intimal SMC and plaque microvessels (397, 509, 510). Cytokines also play an important role in the induction of chemokines by vascular cells, particularly, IL-8 and MCP-1 that are involved in monocyte adhesion and migration into the inflamed vessel wall in atherosclerosis. Other chemokines, such as IP-10, Mig, and I-TAC, are IFN- γ inducible and potently chemoattract activated T lymphocytes. These chemokines are expressed in atherosclerotic plaques (424) and may play an important role in T-lymphocyte infiltration and activation in atherosclerosis.

3. Modulation of scavenger receptor expression and lipid metabolism

Proinflammatory cytokines have contrasting effects on the expression of the various scavenger receptors. Lectin-like oxidized LDL receptor (LOX)-1, which is detectable in EC, intimal macrophages, and SMC of advanced atherosclerotic plaques, can be induced by proinflammatory stimuli such as TNF- α , in addition to its induction by oxidized LDL and other stimuli (363). TNF- α and IFN- γ have been shown to increase scavenger receptor expression and function in cultured rabbit aortic SMC (388). However, TNF- α and IFN- γ appear to inhibit scavenger receptor SR-A surface expression in macrophages, principally by destabilization of scavenger receptor mRNA (291). This effect of TNF- α may account for the increased scavenger receptor activity, as assessed by acetylated LDL uptake by peritoneal macrophages, in mice deficient for TNF p55 receptors (613). Regarding IFN- γ , recent studies confirmed and extended its role in lipid metabolism. IFN- γ induced foam cell formation through upregulation of SR-PSOX (751), the scavenger receptor for phosphatidylserine and oxLDL, which has been involved in Ox-LDL uptake and subsequent foam cell transformation in macrophages (472). Interestingly, SR-PSOX is identical to the chemokine, CXCL16 that ligates CXCR6, expressed in intimal macrophages of human atherosclerotic plaques (751). IFN- γ inhibits apoE (81) and the ATP-binding cassette transporter A1 (ABCA1) (530), resulting in decreased cholesterol efflux from macro-

phages (530). Thus IFN- γ could serve as a molecular link between lipid metabolism and immune activity (751). In contrast, TGF- β enhances cholesterol efflux through upregulation of ABCA1 (27) and apoE (794). NF- κ B activity has also been reported to affect scavenger receptor expression and function, as suggested by studies in p50 (NF- κ B1)-deficient mice showing reduced uptake of oxLDL in macrophages from these mice, associated with a reduction in the expression of SR-A (323). IL-4 and IL-13 are activators of 15-LO expression in cultured macrophages (621) through phosphorylation of protein kinase C (PKC)- δ and p38 MAPK acting on STAT1 and STAT3 (754, 756), which may affect lipid oxidation. IL-4 augments acetylated LDL-induced cholesterol esterification in macrophages through SR-A (141).

Interestingly, adipokines may significantly modulate scavenger receptor expression. Treatment of apoE^{-/-} mice with adiponectin (516) or overexpression of globular adiponectin in apoE^{-/-} mice (764) was associated with decreased expression of SR-A and TNF- α , which may have contributed to the reported reduction of atherosclerosis in mice with elevated adiponectin levels (516, 764). Thus modulation of scavenger receptor expression and function by various cytokines may greatly affect lipid metabolism in an inflammatory context.

Besides their effects on scavenger receptor expression and lipid transport in macrophages, cytokines modulate the ability of monocytes/macrophages to oxidize LDL. IFN- γ inhibits the macrophage-induced oxidation of LDL (129, 206), whereas TNF- α (458), IL-4, and IL-13 (204) enhance the ability of cell-mediated oxidation.

4. Effect of SMC migration/proliferation

In addition to classic survival and growth factors such as PDGF, cytokines have been shown to differentially affect SMC migration and proliferation. One of the first cytokines to be studied in this context was IL-1. IL-1 is a potent mitogen for human SMC, even though it also induces in the short term the production of endogenous prostanoids with growth-inhibitory properties, suggesting both positive and negative, temporally distinct, effects on SMC proliferation (400). An important debate occurred regarding the role of IFN- γ on SMC proliferation. Initial *in vitro* and *in vivo* studies using models of mechanical injury in T-cell competent or deficient animals reported a cytostatic effect of this T cell-derived cytokine on SMC (266, 267, 723). In contrast, others have reported a promoting effect of IFN- γ on SMC in culture (776) and a lack of effect of T-cell deficiency on injury-induced neointima formation using athymic *rmu/rnu* rats (202). A carefully conducted study has shown that IFN- γ indeed elicits SMC proliferation and intimal hyperplasia in a model of transplantation of pig or human arteries into the aorta of immunodeficient mice (670). IFN- γ was not found to be

directly mitogenic, but potentiated the proliferative effect of PDGF-BB under low-serum conditions and upregulated PDGF- β receptors (670).

5. Modulation of extracellular matrix remodeling

Pro- and anti-inflammatory cytokines produced during atherosclerosis significantly affect the expression of MMPs and their inhibitors TIMPs, acting synergistically with other cytokines, growth factors, or oxidized lipids to induce substantial remodeling of many components of the extracellular matrix (see Ref. 500 for review). The production of type I and III collagen by SMC is slightly increased by IL-1 and TNF- α , whereas TGF- β is a potent inducer of collagen synthesis. In contrast, IFN- γ inhibits collagen synthesis (17). The proinflammatory IL-1 and TNF- α induce a broad range of MMPs in vascular cells, including MMPs-1, -3, -8, and -9. Cell contact with T-lymphocyte membranes and addition of recombinant CD40 ligand further upregulates a broad spectrum of MMPs in EC and SMC. Proinflammatory cytokines, including IL-1 and TNF- α , upregulate macrophage metalloelastase MMP-12, which favors monocyte migration, and MT1-MMP (MMP-14) and MT3-MMP (MMP-16) expression, which could lead to significant basement membrane turnover through activation of constitutive vascular MMP-2. Of note, the Th2-type cytokine IL-4 induces the elastolytic MMP-12 (632). MMP-9 expression in macrophages can be further upregulated by IL-18 and TNF- α . As in vascular cells, CD40 ligation further upregulates MMP expression in macrophages. In contrast, anti-inflammatory cytokines inhibit MMP expression. IL-10 and TGF- β , the most relevant anti-inflammatory cytokines in atherosclerosis, inhibit an array of MMPs, including MMP-9 and MMP-12. The activity of MMPs is negatively regulated by endogenous TIMPs, including TIMP-1, -2, and -3 constitutively expressed by SMC (reviewed in Ref. 500). Even though TIMP-1 is upregulated in response to CD40 ligation, TIMP-1 and -2 are unaffected by IL-1 or TNF- α (220, 425). In addition, TIMPs may be upregulated by IL-10 and TGF- β . Therefore, in plaque areas in which proinflammatory cytokine expression prevails over that of IL-10 and TGF- β , an imbalance between matrix degradation and synthesis might compromise fibrous cap structure and precipitate its rupture.

6. Mobilization of vascular progenitor cells

Since the initial isolation and characterization of putative progenitor endothelial cells (28), a number of growth factors and cytokines have been shown to affect their mobilization, homing to injured tissues, proliferation, and function (389). Cytokines play a critical role in stem cell mobilization (reviewed in Refs. 370, 686). One of the most important and clinically relevant molecules for

mobilization of CD34+ T cells is G-CSF. It induces proteinase production by leukocytes, allowing disengagement of stem cells from the stromal bone marrow. Moreover, SDF-1 is released into the circulation leading to attraction and exit of CXCR4+ cells from the bone marrow (272). VEGF, SDF-1, and placenta growth factor (PlGF)-induced stem cell mobilization is dependent on MMP-9 (278), which is required for the cleavage of membrane-bound Kit ligand (278). Lack of endothelial nitric oxide synthase (eNOS) in the stromal bone marrow microenvironment leads to defective mobilization. The phenotype of eNOS-deficient mice recapitulated that of MMP-9-deficient mice and was rescued by exogenous administration of soluble Kit ligand, which bypasses the requirement for MMP-9-mediated cleavage of mKit (5).

7. Regulation of neovessel formation/promotion of intraplaque neovascularization

EC, SMC, as well as inflammatory cells (monocytes/macrophages and T lymphocytes) fully participate in the angiogenic process by expressing or inducing the production of cytokines, chemokines, and adhesion molecules that may affect endothelial cell survival, proliferation, migration, and activation. As in atherosclerosis, positive and negative regulators of the inflammatory response greatly affect neovascularization. It appears that (unfortunately?) most proinflammatory and proatherogenic mediators enhance neovessel formation, and vice versa, particularly in a postischemic setting. On the other hand, most anti-inflammatory and antiatherogenic mediators inhibit the neovascularization process. This tradeoff has been referred to as the Janus phenomenon (192) and may have important clinical implications given the risk of compromising postischemic tissue repair while inducing plaque stabilization (by inhibiting the inflammatory/angiogenic mediators), or the risk of favoring plaque progression/destabilization while promoting tissue functional recover after ischemia (by promoting proangiogenic but also proatherogenic pathways). This could be the case for the growth factors VEGF, PlGF, FGF-2, the cytokines IL-1 β and TNF- α , the chemokines CCL2 and CXCL8, or even leptin, which all have proinflammatory, proatherogenic, and proangiogenic properties (63, 69, 192, 423). On the other hand, IL-10, CXCL9 (Mig), CXCL10 (IP-10), or adiponectin are anti-inflammatory, antiatherogenic, and antiangiogenic mediators. However, CXCL9 and CXCL10 may also recruit high numbers of lymphocytes to the ischemic tissue, which may promote neovascularization. Interestingly, exceptions to the Janus phenomenon have been reported. eNOS is a potent proangiogenic mediator (5), previously shown to limit atherosclerosis development (346). However, the promotion of superoxide production rather than NO by eNOS under certain pathological conditions may exaggerate atherosclerosis (357). In

our view, an important exception to the fact that proinflammatory cytokines are also proangiogenic is the IL-18 (and potentially IL-12) pathway. As discussed below, IL-18 is a major proinflammatory/proatherogenic cytokine. Inhibition of endogenous IL-18 significantly reduced atherosclerosis in mice (436). Interestingly, the same therapeutic strategy resulted in the stimulation of postischemic neovascularization, identifying an important target for modulation of atherogenesis while promoting post-ischemic tissue repair.

Pathological examination of coronary lesions made by the group of Renu Virmani (352) revealed that intraplaque hemorrhage is an important process in the evolution of the plaques from a stable phenotype to high-risk unstable lesions. The source of red blood cells within the plaques is believed to be leaky immature microvessels that are present around and within the plaque (352). Areas of intraplaque neovascularization are infiltrated with T lymphocytes (705), suggesting a major role for T-cell-derived cytokines in plaque angiogenesis.

8. Induction of apoptosis

Apoptotic cell death occurs during the development and progression of the atherosclerotic plaque. All cell types are involved, with a high predominance of apoptotic macrophages in the lipid core. Macrophage apoptosis may contribute to enlargement of the lipid core, whereas plaque SMC apoptosis may induce a thinning in the fibrous cap, favoring its rupture (348, 405, 443). The distribution of apoptosis is heterogeneous within the plaque, being more frequent in regions rich in inflammatory cells and proinflammatory cytokines and much less abundant in regions characterized by a significant production of anti-inflammatory cytokines (441). A number of proinflammatory cytokines have been shown to induce SMC and macrophage apoptosis in culture, particularly the association of IL-1, TNF- α , and IFN- γ and promotion of Fas-FasL killing (222, 223). Also, macrophages themselves induce SMC apoptosis through direct and autocrine mechanisms involving TNF- α , inducible NO, and Fas/FasL interactions (79, 80). Importantly, although physiological programmed apoptosis is essentially a noninflammatory process, apoptosis induced during pathological conditions might per se contribute to disease progression through its inflammatory potential. This could be the case of apoptosis induced through caspase-1 activation, which also releases the active forms of the proinflammatory cytokines IL-1 β and IL-18 (339, 667). Other proinflammatory caspases include caspase-4, -5, and -13. Caspase-1 and caspase-5 associate with PYCARD/ASC and NALP1 and together form the inflammasome, which results in the activation and processing of IL-1 β and IL-18.

9. Modulation of procoagulant activity and fibrinolysis

The antithrombotic properties of EC are deeply altered by IL-1 and by TNF- α and endotoxin (193, 216, 451). They can increase the tissue procoagulant activity and suppress the anticoagulant activity mediated by the thrombomodulin-protein C system, by decreasing gene transcription of thrombomodulin and protein C receptor. Downregulation of protein C pathway limits protein C activation and thus promotes thrombus formation. In addition, vascular heparin-like molecules are reduced by inflammatory cytokines (344). Downregulation of anticoagulant mediators may in turn affect inflammation. Thrombomodulin has direct anti-inflammatory activities on the endothelium, inhibiting MAPK and NF- κ B pathways (138), and activated protein C has been shown to inhibit NF- κ B in monocytes. On the other hand, proinflammatory cytokines modify the fibrinolytic properties of EC; they decrease the production of tissue plasminogen activator (tPA), and they increase the production of the inhibitor of tissue plasminogen activator (PAI-1). PAI-1 levels rise substantially in response to an inflammatory challenge (597). The increased PAI-1 levels severely impair the ability to remove the thrombus. In addition, inflammatory mediators like IL-6 increase platelet production and thrombogenicity (99).

10. Regulation of immune response

For dendritic cell maturation and Th1/Th2/Treg development/maintenance, see section VI.

V. CYTOKINE AND CYTOKINE RECEPTOR-ASSOCIATED MODULATION OF PLAQUE DEVELOPMENT AND STABILITY

The generation of a number of mouse models of experimental atherosclerosis using apoE^{-/-} or LDLr^{-/-} mice crossed with mice deficient in genes encoding cytokines or cytokine receptors has been instrumental in our understanding of their role in atherosclerosis development and progression (Table 7) (see review in Refs. 521, 709).

A. Proinflammatory Cytokines

1. TNF- α

Experimental studies using TNF-deficient apoE^{-/-} mice showed that atherosclerotic lesion size in the aortic sinus of TNF- α ^{-/-}apoE^{-/-} mice is significantly smaller than that of apoE^{-/-} mice, associated with decreased expression of ICAM-1, VCAM-1, and MCP-1 (515). Surprisingly, antiatherogenic property of TNF- α

TABLE 7. *Effect of cytokine deletion on atherosclerosis in murine models of atherosclerosis*

Cytokine	Age(w)	Sex	Chol.	Lesion Size	Mac	T Cells	SMC	Collagen	Reference Nos.
IL-1β									
IL-1 β ^{-/-} apoE ^{-/-}	12	?	NC	-33%	ND	ND	ND	ND	342
IL-1 β ^{-/-} apoE ^{-/-}	24	?	NC	-32%	ND	ND	ND	ND	342
IL-1ra									
IL-1ra ^{+/-} apoE ^{-/-}	16	M	NC	+30%	NC	ND	NC	ND	307
IL-1ra ^{+/-} apoE ^{-/-}	32	M	NC	NC	+90%	ND	-15%	ND	307
TgIL-1raxLDLr ^{-/-} HFD	14(4 + 10)	?	+40%	NC	ND	ND	ND	ND	169
IL-1ra ^{+/-} (cholate)	16(4 + 12)	?	-25%	+50%	ND	ND	ND	ND	169
IL-1ra ^{-/-} (cholate)	16(4 + 12)	?	-60%	+180%	ND	ND	ND	ND	169
ReIL-1ra>apoE ^{-/-}	12	M/F	NC	-74%/-56%	ND	ND	ND	ND	189
TgIL-1raxapoE ^{-/-} HFD	20(10 + 10)	M	+70%	-53%	ND	ND	ND	ND	462
TgicIL-1raxapoE ^{-/-} HFD	20(10 + 10)	M	+90%	-67%	ND	ND	ND	ND	462
IL-2									
RecIL-2>apoE ^{-/-}	?	?	?	+24%	?	?	?	?	685
Anti-IL-2>apoE	?	?	?	-43%	?	?	?	?	685
IL-4									
IL-4 ^{-/-} (cholate)	20(5 + 15)	F	NC	NC	NC	NC	ND	ND	227
IL-4 ^{-/-} apoE ^{-/-}	30	M/F	NC	-34%/-23%	NC	NC	ND	ND	156
IL-4 ^{-/-} apoE ^{-/-}	45	M/F	NC	NC/NC	NC	NC	ND	ND	156
BMT IL-4 ^{-/-} >LDLr ^{-/-}	46(42 + 4)	F	NC	NC(AS) -67%(aorta)	NC	NC	ND	ND	340
IL-5									
BMT IL-5 ^{-/-} >LDLr ^{-/-}	28(12 + 16)	F	NC	+18%(AS) +54%(aorta)	ND	ND	ND	ND	53
IL-6									
RecIL-6>C57BL6	24(3 + 21)	M	NC	+400%	ND	ND	ND	ND	294
RecIL-6>apoE ^{-/-}	9(3 + 6)	M	NC	+89%	ND	ND	ND	ND	294
RecIL-6>apoE ^{-/-}	24	M	NC	+138%	ND	ND	ND	ND	294
IL-6 ^{-/-} apoE ^{-/-}	53	F	NC	+85%	ND	ND	ND	ND	187
IL-6 ^{-/-} apoE ^{-/-}	53 ± 4	M	+64%	+87%(aorta)	-67%	-50%	ND	-20%	598
IL-9									
RecIL-9 > LDLr ^{-/-}	?	?	NC	-65%	ND	ND	ND	ND	359
IL-10									
IL-10 ^{-/-} (C57BL6) (cholate)	24(8 + 16)	F	NC	+200%(SPF) +3000%(CONV)	ND NC	ND +350%	ND ND	ND -75%	434 434
IL-10 ^{-/-} (C57BL6) (cholate)	15	?	NC	+150%(SPF)	ND	ND	ND	ND	542
IL-10TgC57BL6 (cholate)	15	?	NC	-60%	ND	ND	ND	ND	542
IL-10 ^{-/-} apoE ^{-/-}	16	M/F	NC	NC/+180%	NC	NC	NC	NC	104
IL-10 ^{-/-} apoE ^{-/-}	48	M/F	-36%	NC/NC	NC	NC	NC	NC	104
BMT IL10Tg>LDLr ^{-/-}	30(10 + 20)	M	NC	-47%	+50%	No T cell	ND	+30%	541
BMT IL-10 ^{-/-} >LDLr ^{-/-}	32(18 + 14)	F	NC	+35%	+61%	+116%	NC	-49%	548
AdIL-10syst>LDLr ^{-/-}	20(12 + 8)	F	-40%	-56%	-	ND	ND	ND	708
AdIL-10local>LDLr ^{-/-}	20(12 + 8)	F	NC	-50%	-	ND	ND	ND	708
AdIL-10>apoE ^{-/-}	13	M	NC	-61%	NC	+89%	No SMC	NC	488
IL-12									
IL-12 ^{-/-} apoE ^{-/-}	30	M/F	NC	-48%/-59%	-40%	NC	ND	ND	156
IL-12 ^{-/-} apoE ^{-/-}	45	M/F	NC	NC/NC	NC	NC	ND	ND	156
RecIL-12>apoE ^{-/-}	21	M	NC	+100%	ND	+	ND	ND	377
Apobec1 ^{-/-} LDLr ^{-/-} 12/15Lox ^{-/-} (IL-12 deficient)	15	M/F	NC	-39%/NC	ND	ND	ND	ND	786
	34	M/F	NC	-43%/-48%	ND	ND	ND	ND	786
IL-18									
IL-18 ^{-/-} xapoE ^{-/-}	24	M	+50%	-35%	-	-38%	+160%	ND	188
RecIL18bp>apoE ^{-/-}	23	M	NC	-25%	-50%	-67%	+100%	+85%	436
RecIL-18>apoE ^{-/-}	16	M	NC	+120%	+	+350%	ND	ND	735
RecIL-18>apoE ^{-/-} /IFN ^{-/-}	16	M	NC	NC	ND	NC	ND	ND	735
AdIL-18>apoE ^{-/-} (carotid collar model)	18	F	NC	NC	-23%	ND	NC	-44%	167
RecIL-18>apoE ^{-/-} /SCID	14	F	NC	+187%	+	ND	ND	ND	672
TNF-α									
TNF- α ^{-/-} (cholate)	22(6 + 16)	F	+46%	NC	ND	ND	ND	ND	614
TNFRp55 ^{-/-} (cholate)	24(6 + 18)	F	NC	+130%	ND	ND	ND	ND	613, 614
TNFRp75 ^{-/-} (cholate)	24(6 + 18)	F	NC	NC	ND	ND	ND	ND	614
TNFR p55 ^{-/-} p75 ^{-/-} (cholate)	24(6 + 18)	F	NC	+130%	ND	ND	ND	ND	614
TNFbp>apoE ^{-/-} HFD	13(8 + 5)	M/F	NC/NC	NC/-30%	NC	ND	NC	ND	189
TmTNF \times C5BL/6 (cholate)	29(9 + 20)	M	NC	-44%	-81%	ND	+	ND	107
TNF- α ^{-/-} diet	29(9 + 20)	M	NC	-94%	-	ND	ND	ND	107
TNF- α ^{-/-} apoE ^{-/-} HFD	14(4 + 10)	?	+40%(NS)	-50%(aorta)	NC	-50%(NS)	ND	ND	83
TNF- α ^{-/-} apoE ^{-/-} HFD	44(4 + 40)	?	NC	-60%(aorta)	NC	-50%(NS)	ND	ND	83

TABLE 7—Continued

Cytokine	Age(w)	Sex	Chol.	Lesion Size	Mac	T Cells	SMC	Collagen	Reference Nos.
rec sTNFR1>apoE ^{-/-}	32(7 + 25)	M	+62%(NS)	-75%	NC	+240%	ND	ND	83
BMT TNF>apoE HFD	35(10 + 25)	M > F	NC	-83%	ND	ND	ND	ND	83
TNF- α ^{-/-} apoE ^{-/-}	12	M/F	NC/NC	-20%/-32%	ND	ND	ND	ND	515
TNF ^{-/-} apoE*3Leiden HFD	28(8 + 20)	F	NC	NC	NC	NC	NC	NC	67
TNF- β									
Lymphotoxin α ^{-/-} (cholate)	22(6+16)	F	-20%(NS)	-63%	ND	ND	ND	ND	614
IFN- γ									
IFN- γ R ^{-/-} xapoE ^{-/-} HFD	17(5 + 12)	F	+	-60%	-	-	ND	+	260
recIFN- γ >apoE ^{-/-} HFD	23(16 + 7)	M	NC	+100%	+	+170%	ND	+	736
IFN- γ ^{-/-} xapoE ^{-/-} HFD		M	NC	-	-	-	ND	-	735
IFN- γ ^{-/-} xapoE ^{-/-} HFD		F	NC	NC	NC	NC	ND	-	735
INF γ ^{-/-} xLDLr ^{-/-}	8	M/F	NC	-75%	-	-	ND	-(?)	95
INF γ ^{-/-} xLDLr ^{-/-}	20	M/F	NC	-43%	NC	NC	NC	NC	95
BMT IFN- γ ^{-/-} >LDLr ^{-/-} HFD	15(9 + 6)	M/F	NC	+80%	NC	NC	NC	+	507
BMT IFN- γ ^{-/-} >LDLr ^{-/-} HFD	21(9 + 12)	M/F	NC	NC	NC	NC	NC	+	507
TGF- β									
TGF- β 1 ^{+/-} (cholate)	20(8 + 12)	F	NC	+500%	+	ND	-	ND	245
AbTGF- β >apoE ^{-/-} HFD	15(6 + 9)	M	NC	+82%	+30%	NC	NC	-54%	438
sTGF- β RII>apoE ^{-/-}	17(5 + 12)	M	NC	NC	-15%	+177%	NC	NC	421
sTGF- β RII>apoE ^{-/-}	29(17 + 12)	M	NC	-37%	NC	+145%	NC	-50%	421
BMT CD2-dnTGF-RII>LDLr ^{-/-}									
- HFD	22(12 + 10)	M	NC	-29%	NC	+75%	-33%	-29%	236
CD2-dnTGF-RIIxapoE ^{-/-}	12	F	-26%	+300%	+	+	NC	-	572

NC, no change; ND, not determined; SPF, specific-pathogen free; CONV, conventional environment; Tg, transgenic; icILra, intracellular IL-1ra; HFD, high-fat diet: in the age column, first is age of animals at death; in parentheses, age at the start of diet + duration of diet. Cholate indicates HFD containing cholate. BMT, bone marrow transplantation: in the age column, first is age of animals at death; in parentheses, age at the start of diet + duration of diet. AS, aortic sinus; NS, not statistically significant; Mac, macrophage.

has also been reported. It has been shown that TNF-R1(p55)-deficient C75BL/6 mice fed an atherogenic diet developed larger lesions than did wild-type C75BL/6 mice, suggesting that TNF-R1 signaling has protective action against atherosclerosis (613, 614). In contrast, the same group found that deficiency in TNF- α or in TNFR2(p75) did not affect lesion development, whereas deficiency in lymphotoxin- α (TNF- β) was associated with smaller lesions (613, 614). One possible explanation for a favorable effect of TNF- α on atherosclerosis is that TNF- α downregulates scavenger receptor gene and protein expression in macrophages (291, 692), leading to decreased LDL uptake by macrophages and foam cell formation. However, it is noteworthy that the lack of effect of TNF- α deficiency was observed despite a significant 46% increase in cholesterol levels in TNF- α ^{-/-} mice compared with wild-type animals (614). In these conditions of increased cholesterol levels, an absence of effect of TNF- α on the atherosclerotic process should have resulted in enhanced lesion development. The most likely reason for the discrepancy between previous studies analyzing the role of TNF- α on experimental atherosclerosis in mice is the difference in the underlying mechanism of atherogenesis between apoE^{-/-} mice fed a normal chow diet and C57BL/6 mice fed an atherogenic diet containing cholate. Schreyer et al. (613) employed TNFR1^{-/-} C57BL/6 mice fed an atherogenic diet, whereas Ohta et al. (515) used TNF- α ^{-/-} apoE^{-/-} mice fed a normal

chow diet. In support of a deleterious effect of TNF- α in atherosclerosis, Canault et al. (107), exploring the role of a noncleavable transmembrane form of TNF- α (tm TNF- α) in the development of early atherosclerotic lesions, found that the order of the severity of atherosclerotic lesions in C57BL/6 mice fed a cholate-containing high-fat diet was wild-type mice > tm TNF- α mice > TNF- α ^{-/-} mice.

2. IL-1

The pathogenic role of IL-1 has been investigated in apoE^{-/-} mice fed a cholesterol-rich diet receiving subcutaneous administration of recombinant human IL-1ra (189), and in LDLr^{-/-} mice (169) or apoE^{-/-} mice (462) crossed with transgenic mice expressing high levels of IL-1ra. Overexpression of IL-1ra increased total cholesterol levels by ~50%, and in spite of this decreased the size of atherosclerotic lesions by 50–70%. In contrast, IL-1ra knockout C57BL/6J mice fed a cholesterol/cholate diet had a threefold decrease in non-HDL cholesterol and a trend toward increased foam-cell lesion area compared with wild-type littermate controls (169). Taken together, these results clearly indicate that IL-1 contributes to atherosclerosis in mice. Further evidence for an important role of IL-1 β in atherosclerosis is provided by experiments showing that IL-1 β deficiency in apoE^{-/-} mice hampers lesion development (342).

3. *IL-2*

IL-2 has long been recognized as a T-cell growth factor, but deficiency of IL-2 has surprisingly no consequences. Mice lacking either IL-2 (610) or its receptors (IL-2R α /CD25 and IL-2R β) have normal development of T cells but show severe lymphoproliferative disease (364). These data have been interpreted to indicate that IL-2 has an essential role in controlling self-tolerance. Indeed, a crucial function of IL-2 is to act as the primary growth factor for Treg cells (432, 623). Even though IL-2 is expressed in atherosclerotic plaques, its direct role in atherogenesis has not been studied. Only one study reported that intraperitoneal injections of IL-2 or anti-IL-2 antibody in apoE^{-/-} mice fed an atherogenic diet increased or decreased, respectively, lesion size (685). These results would indicate that IL-2 is an atherogenic cytokine in apoE^{-/-} mice. However, in the absence of information on the effect of IL-2 on lipid profiles and on the composition of atherosclerotic lesions, it is premature to conclude on the definitive role of IL-2 in atherosclerosis, given the function of IL-2 in immune tolerance.

4. *IL-6*

IL-6 has been shown to enhance fatty lesion development in mice (294). IL-6 treatment of C57Bl/6 mice at supraphysiological concentrations resulted in an about fivefold increase in fatty streak size, whereas treatment of apoE^{-/-} mice on low- or high-fat diets resulted in about twofold increases (294), suggesting that IL-6 is a proatherogenic cytokine. However, 1-yr-old IL-6^{-/-}apoE^{-/-} mice show enhanced plaque formation (187, 598). Serum cholesterol levels were found increased in one study (598), but not in the other (187). Increased atherosclerosis in IL-6^{-/-}apoE^{-/-} mice was associated with reduced collagen content in the plaques, blunted synthesis, and release of IL-10 and diminished recruitment of inflammatory cells into the atherosclerotic plaque (598). At 1 yr of age, mice showed more calcified lesions (187). In younger 16-wk-old IL-6^{-/-}apoE^{-/-} mice, no significant difference in fatty streaks was detected compared with IL-6^{+/+}apoE^{-/-} mice. Therefore, the role of IL-6 in atherosclerosis appears ambivalent. Similarly, IL-6 can be viewed as a proinflammatory cytokine but may also be regarded as an anti-inflammatory cytokine as it induces the synthesis of IL-1ra and release of soluble TNFR leading to reduced activity of proinflammatory cytokines (37, 675, 753). It also inhibits macrophage SR-A (393).

5. *IL-12/IL-18/IFN- γ*

Previous studies have shown that IFN- γ plays a major role in atherosclerosis. IFN- γ receptor deficiency was associated with a reduction in atherosclerotic lesion size in apoE^{-/-} mice (260), and cholesterol diet-induced ath-

erosclerosis in LDLr^{-/-} mice was significantly reduced in the absence of IFN- γ (95). Moreover, IFN- γ administered intraperitoneally promoted atherosclerosis in apoE^{-/-} mice (736). It has been suggested that IFN- γ may affect atherosclerosis in a gender-specific manner, IFN- γ being proatherogenic only in males (735). However, two studies show conflicting results showing effects of IFN- γ on atherosclerosis in female mice (95, 260).

IFN- γ is a Th1 cytokine that is produced by T and NK cells following synergistic activation by IL-12 and IL-18. Interestingly, IL-12 and IL-18 have both been shown to be pro-atherogenic. IL-12 appears to intervene in the atherosclerotic process during the early phase of the disease in apoE^{-/-} mice (156). Thirty-week-old IL-12^{-/-}apoE^{-/-} mice showed increased lesions, while 40-wk-old mice had lesions of equivalent size compared with wild-type apoE^{-/-} mice (156). Also, a selective defect of IL-12 synthesis by macrophages due to 12/15-lipoxygenase deficiency reduced plaque formation in Apobec1^{-/-}LDLr^{-/-} (786), and injection of IL-12 in apoE^{-/-} mice promoted lesion development (377). IL-18 administration increased lesion size in apoE^{-/-} mice (735), and overexpression of its endogenous inhibitor IL-18 binding protein (IL-18BP) reduced atherosclerosis with profound changes in plaque composition leading to a more stable plaque phenotype (436). Furthermore, IL-18-deficient apoE^{-/-} mice reproduced findings observed in apoE^{-/-} mice in which IL-18 signaling was blocked by overexpression of IL-18BP, with smaller and more stable lesions compared with apoE^{-/-} mice (188). It has been suggested that the proatherogenic effect of IL-18 is in fact mediated by IFN- γ because the promotion of atherosclerosis by exogenous IL-18 administration was ablated in IFN- γ -deficient apoE^{-/-} mice (735). However, the proatherogenic effect of IL-18 can occur in the absence of T cells (671). Intraperitoneal injection of IL-18 in SCID/apoE^{-/-} mice led to larger lesions and increased circulating IFN- γ compared with mice injected with saline solution. NK cells were the most likely source of IFN- γ since the possibility that it was produced by macrophages has been recently questioned (600), and the production of IFN- γ by SMC activated with a combination of IL-12 and IL-18 appears to be low and occasional (228).

6. *CD40/CD40L*

CD40 is widely expressed on several cell types including leukocytes and vascular cells. The CD40 receptor is activated following ligation with CD40L (CD154). A large variety of immunological and vascular cells express CD40 and/or CD40L (reviewed in Ref. 605). Both CD40 and CD40L are present in human atherosclerotic plaques. Platelets are a major source of CD40L. CD40L is cryptic in resting platelets but rapidly translocates to the platelet surface after stimulation by agonists, including ADP,

thrombin, or collagen. CD40L, expressed at the platelet membrane, is cleaved and shed from the platelet surface in a time-dependent manner, over a period of minutes to hours, generating a soluble fragment, soluble CD40L (sCD40L). Although it may also be shed from stimulated lymphocytes, it is estimated that >95% of circulating CD40L is derived from platelets (19). Interestingly, only membrane CD40L on the surface of platelets (281) but not platelet-derived sCD40L (282) can activate EC and up-regulate adhesion molecules, proinflammatory cytokines and chemokines *in vitro*. This might limit vascular inflammation following the cleavage of CD40L from the surface of activated platelets (282). However, the important role for CD40/CD40L interactions in the atherosclerosis has been clearly established in apoE^{-/-} and LDLr^{-/-} mice. Administration of antibody to CD40L, when given early in the development of atherosclerosis, was shown to inhibit atherosclerotic lesion initiation in LDLr^{-/-} mice (426). However, in CD40L^{-/-}apoE^{-/-} mice, advanced plaques, but not initial lesions, were markedly reduced and displayed a more stable phenotype, associated with a reduced macrophage and T-lymphocyte content, compared with plaques in wild-type apoE^{-/-} mice (421). Recent studies aimed at evaluating the respective role of vascular and leukocyte CD40L in promoting atherosclerosis showed that CD40L deficiency on hemopoietic cells did not affect atherosclerosis, suggesting that CD40L expression on nonhematopoietic cell types could be responsible for the proatherogenic effects of CD40L (40, 644).

7. *Osteopontin*

OPN, also known as Eta-1 (early T lymphocyte activation 1), is a pleiotropic cytokine critical for the generation of Th1 immunity (29). It can be categorized as a proinflammatory proatherogenic cytokine. With the use of OPN-deficient apoE^{-/-} mice infused with ANG II, it has been shown that OPN promotes the development of atherosclerosis and abdominal aortic aneurysms (89). OPN appears to specifically promote early inflammatory mechanisms associated with macrophage recruitment in atherosclerotic lesions.

8. *MIF*

MIF plays an important role in both innate and adaptive immunity (100). It is an integral component of the host antimicrobial alarm system and stress response that promotes the proinflammatory functions of immune cells. Recent *in vivo* studies applying neutralizing MIF antibodies in models of injury-induced carotid manipulation in apoE^{-/-} and LDLr^{-/-} mice have provided evidence for a role of MIF in atherosclerosis and restenosis (125, 603). Moreover, deficiency of MIF in LDLr^{-/-} mice reduced atherosclerosis, associated with reduced SMC prolifera-

tion, cysteine protease expression, and elastolytic and collagenolytic activities. (528).

B. Anti-inflammatory Cytokines

The concept of a cascade of proinflammatory cytokines followed by production of anti-inflammatory cytokines has contributed to the dissemination of the idea that the inflammatory process can be separated into a first set of events linked to the inflammatory response and a second one later on, linked to the anti-inflammatory response involved in the resolution of inflammation. Because atherosclerosis is a chronic inflammatory disease, we have put forward the idea that endogenous anti-inflammatory cytokines should intervene in the atherosclerotic process to dampen inflammation.

1. *IL-10*

IL-10 is a pleiotropic cytokine produced by Th2-type T cells, B cells, monocytes, and macrophages that inhibits a broad array of immune parameters including Th1 lymphocyte cytokine production, antigen presentation, and antigen-specific T-cell proliferation (712). IL-10 has also potent anti-inflammatory properties on macrophages (68) and plays an active role in limiting the inflammatory response in the vessel wall (669). The role of endogenous IL-10 has been clearly established in mouse models of atherosclerosis. We and others have shown that IL-10 deficiency in C57BL/6 mice fed an atherogenic cholate-containing diet promotes early atherosclerotic lesion formation, characterized by increased infiltration of inflammatory cells, particularly activated T cells, and by increased production of proinflammatory cytokines (434, 542). Similar results have been reported in IL-10^{-/-}apoE^{-/-} mice fed a chow diet (104). Consistent with a protective role of IL-10 in atherosclerosis, systemic or local overexpression of IL-10 by adenoviral gene transfer in a model of collar-induced carotid atherosclerosis in LDLr^{-/-} mice was found highly efficacious in preventing atherosclerosis (708), and overexpression of IL-10 by activated T lymphocytes reduced atherosclerosis in LDLr^{-/-} mice (541). More recently, using a model of chimeric LDLr^{-/-} mice in which bone marrow cells were deficient for IL-10, we provided evidence that leukocyte-derived IL-10 is instrumental in the prevention of atherosclerotic lesion development and in the modulation of cellular and collagen plaque composition, at least in part, through a systemic immune response modulation (548).

2. *IL-4/IL-13*

IL-4 is produced by Th2 lymphocytes, eosinophils, basophils, and mast cells. It promotes synthesis of IgE and allergic response. The effects of IL-4 are generally

considered as anti-inflammatory. However, a growing body of evidence indicates that IL-4 may play a role in atherosclerosis through induction of inflammatory responses, such as upregulation of VCAM-1 (219, 379, 416) and MCP-1 (378, 573). Consistent with this hypothesis, transplantation of bone marrow stem cells from IL-4-deficient mice in LDLr^{-/-} mice decreased atherosclerotic lesion formation in a site-specific manner (340). Similarly, IL-4^{-/-}apoE^{-/-} mice had reduced atherosclerosis in the aortic arch, but not in the aortic sinus, compared with apoE^{-/-} mice (156). In contrast, IL-4 deficiency in C57BL/6 mice fed an atherogenic diet did not affect the development of early lesions (225). However, the same group found that fatty streak formation in IL-4^{-/-} mice immunized with HSP65 or *Mycobacterium tuberculosis* was significantly reduced compared with lesions in wild-type C57BL/6 mice (227).

IL-4 and IL-13 share a common predominant receptor signaling chain IL-4R α . As a result, it is expected that IL-13 affects atherosclerosis in a similar way as does IL-4. However, no studies are currently available to confirm this hypothesis.

3. TGF- β

TGF- β is a potent anti-inflammatory, immunosuppressive and pro-fibrotic cytokine, with major effects on the biology of SMC (see review in Ref. 243). TGF- β 1-deficient mice die in utero or in the perinatal period because of widespread uncontrolled inflammation (360, 636). The anti-inflammatory and profibrotic properties of TGF- β are highly suggestive of a potential antiatherogenic role for this cytokine. Indeed, Grainger et al. (244) first showed that serum active TGF- β is markedly depressed in patients with advanced atherosclerosis (244), and that TGF- β 1 heterozygous mice fed a cholate-supplemented atherogenic diet displayed increased endothelial activation and macrophage infiltration in the aortic sinus (245). The critical role of TGF- β for SMC matrix production and plaque stability in atherosclerosis was thereafter demonstrated by studies using apoE^{-/-} mice. We have shown that treatment of apoE^{-/-} mice with neutralizing antibodies to TGF- β 1, TGF- β 2, and TGF- β 3 accelerates the development of atherosclerosis, with lesions displaying increased inflammatory cells and decreased collagen content (438). TGF- β may therefore reduce inflammation but also contributes to matrix production within lesions. In agreement with this hypothesis, treatment of apoE^{-/-} mice with a soluble TGF- β -receptor II protein (TGF-RII:Fc) that inhibits TGF- β signaling resulted in larger plaques, with an increased frequency of macrophages and T cells and decreased collagen content in the atherosclerotic lesions (419, 420). Moreover, intraplaque hemorrhages were frequently observed. We and others established later on that specific inhibition of TGF- β signaling

in T cells leads to the development of atherosclerotic plaques with a phenotype that may potentially increase plaque vulnerability to rupture, strongly suggesting an important protective role of endogenous T-cell TGF- β activity against vulnerability to atherosclerosis (236, 572). Bone marrow transplantation from transgenic mice that express a dominant negative TGF- β receptor type II under a T-cell-specific promoter into LDLr^{-/-} mice resulted in increased differentiation of spleen-derived T cells toward both Th1 and Th2 phenotypes (236). Moreover, atherosclerotic plaques of these mice showed increased T-cell infiltration and expression of MHC class II, along with a decrease in SMC and collagen content. Consistent with these findings, apoE^{-/-} mice with disrupted TGF- β signaling in T cells exhibited markedly larger atherosclerotic lesions, with a >100-fold increase in aortic IFN- γ expression compared with apoE^{-/-} littermates (572). The important role of T-cell-TGF- β signaling in atherosclerosis suggests that regulatory pathways in adaptive immunity are essential in modulation of the development and progression of the disease (see sect. VI C).

C. Chemokines/Chemokine Receptors

Recruitment of inflammatory cells in the intima is an essential step in the development and progression of atherosclerosis. This process depends on the local production of chemokines where inflammatory cells are attracted and on the expression of chemokine receptors by these cells.

1. MCP1/CCR2

One of the earliest studies to link chemokines with atherosclerosis in vivo showed that mmLDL injected into mice increased production of JE, the mouse homolog of MCP-1 (392). LDLr^{-/-} and apoE^{-/-} mice have since been used to confirm this link showing increased expression of MCP-1/JE and/or its receptor, CCR2 (560). Other studies, in CCR2-deficient apoE^{-/-} mice, showed a reduction in aortic lesion area compared with apoE KO alone, even though lipid levels remained high (74, 161). In another model of atherosclerosis, using mice overexpressing apolipoprotein B, deletion of the MCP-1 gene protected against monocyte recruitment (241). MCP-1-deficient LDLr^{-/-} mice also showed reduced macrophage recruitment, suggesting that the role of MCP-1 in atherosclerosis is to attract CCR2-bearing monocytes into the vessel wall (258). These studies therefore indicate a proof of principle for the role of MCP-1 in atherosclerotic lesions.

2. Fractalkine/CX3CR1

Fractalkine (CX3CL1) is the unique member of the CX3C subfamily and is expressed in both a soluble and

membrane-bound form on the surface of inflamed endothelium, which confers to it special properties among the other members of the chemokine family (42). Interestingly, whereas soluble CX3CL1 was reported to recruit lymphocytes and monocytes (42, 529), immobilized forms of CX3CL1 and CX3CL1-expressing human umbilical vein EC have been shown to directly mediate the rapid capture and firm adhesion of leukocytes expressing its receptor CX3CR1 under physiological flow conditions (205, 302). In contrast to cell adhesion mediated by the chemokine KC (murine CXCL1) through its receptor CXCR2, the CX3CL1-induced firm adhesion is uniquely mediated by direct binding of the chemokine to CX3CR1 and does not require the upregulation and activation of integrins, suggesting that CX3CL1 and CX3CR1 mediate a novel pathway for leukocyte trafficking (205, 302). Studies in our group and others suggested that CX3CR1 plays a central role in atherogenesis (135, 385). CX3CR1 deficiency in apoE^{-/-} mice, even when restricted to one allele, decreased the development of atherosclerosis with a marked reduction in macrophage accumulation (135).

3. IL-8/CXCR2

While high levels of circulating chemokines are associated with poor outcome, they contribute towards deactivating circulating leukocytes and limiting their recruitment towards inflammatory foci. This was first illustrated when Gimbrone et al. (233) showed that IL-8 inhibits neutrophil adhesion to cytokine-activated EC and protects these cells from neutrophil-mediated damage. Neutrophil migration into inflamed compartments is severely impaired in transgenic mice showing high levels of circulating IL-8 (639), and a similar observation was reported for monocyte deactivation to chemoattraction in MCP-1 transgenic mice showing high levels of circulating MCP-1 (587). Injection of IL-8 in rabbits and rats significantly reduced in vivo neutrophil migration towards inflammatory foci (275). Similarly, an altered response of neutrophils to IL-8 was reported in human endotoxemia (18), and an altered chemotaxis to GRO- α , GRO- β , GRO- γ and ENA-78, but not to IL-8 of neutrophils was reported in septic subjects and associated with a decreased expression CXCR2 (147). Boisvert et al. (69) showed that the murine homolog of the IL-8 receptor also participates in monocyte/macrophage accumulation in LDL receptor KO mice.

4. RANTES/CCR5

RANTES is a chemokine that mediates the trafficking and homing of T lymphocytes, monocytes, basophils, eosinophils, and NK cells via different chemokine receptors (CCR1, -3, -4, and -5). It has been implicated in cardiac inflammatory disorders after organ transplantation or arterial injury (710, 780). Its role in atherosclerosis has been

suggested by studies showing that treatment of LDLr^{-/-} mice with *N*-methionylated RANTES (Met-RANTES), a functional CC chemokine antagonist, reduced the extent of atherosclerotic lesions, associated with decreased leukocyte infiltration (695). Of note, levels of CCR5 and CCR2 were significantly decreased in Met-RANTES-treated mice. Therefore, the effects of Met-RANTES could not be solely attributed to the functional inhibition of RANTES activity, but possibly to blockade of CCR2 and CCR5 activities. The latter is however unlikely since CCR5 deficiency in apoE^{-/-} mice does not seem to be protective in the early stages of atherosclerosis (365).

5. MIF

It has recently been proposed to group mediators with similar functional patterns, which cannot be structurally classified into the known chemokine subfamilies, as a family termed "chemokine-like" (165). MIF, a pleiotropic inflammatory T cell and macrophage cytokine, belongs to this subfamily. MIF is involved in immune-mediated diseases, including septic shock and chronic inflammation (reviewed in Ref. 100). A key regulatory role for MIF has been shown in the pathogenesis of immunologically induced kidney disease, suggesting that MIF may be important in immune-mediated disease (368). Consistent with this hypothesis, an upregulation of MIF has been observed in EC, SMC, and macrophages during progression of atherosclerosis in humans (98) and in hypercholesterolemic rabbits (401). Moreover, inhibition of MIF in apoE^{-/-} mice by treatment with neutralizing MIF antibodies resulted in a shift in the cellular composition of neointimal plaques toward a more stable phenotype with reduced macrophage and increased SMC content (603), as well reduced circulating levels of inflammatory markers such as fibrinogen, MIF and IL-6 (97).

D. Hematopoietic Factors/M-CSF

Macrophages are the predominant cells in atherosclerotic plaques. They are derived from circulating monocytes that adhere to the endothelium and then migrate to the subendothelial space. Macrophages are involved in the formation of the plaque, as evidenced by the decreased atherosclerosis in apoE^{-/-} mice deficient in macrophage-stimulating factor (*op/op* mice), which have decreased blood monocyte differential count (643). It is thus likely that macrophages that enter the intima following primary LDL accumulation to scavenge cholesterol overload, activate EC through cytokine release, which in turn increase endothelial permeability to LDL, triggering a vicious circle.

One important finding is that macrophages in the plaque can multiply in situ in the vessel wall (576). Monocyte-colony stimulating factor (M-CSF), a factor of differ-

entiation and proliferation of stem cells into monocytes, is locally produced by the endothelial and smooth muscle cells from the human atheromatous plaque (577).

E. Platelet-Derived Factors

Platelets were first believed to participate in atherogenesis because they can promote the proliferative response of SMC through the release of PDGF after adherence and aggregation at focal sites endothelial denudation (580). This turned out to be an erroneous view of atherogenesis. The role of platelets in the initiation of plaque formation has since been revisited, and a large body of evidence indicates that platelets participate in vascular inflammation and may promote atherosclerotic plaque formation. Circulating activated platelets bind to monocytes to form platelet monocyte aggregates. The interactions of activated platelets with monocytes and atherosclerotic arteries lead to the delivery of the platelet-derived chemokines RANTES (CCL5) and PF4 (CXCL4) to the monocyte surface and endothelium of atherosclerotic arteries (298). In addition, activated platelets injected into apoE^{-/-} mice enhance the development of atherosclerotic lesions compared with mice injected with the supernatant of activated platelets (298). The effect of activated platelets on atherosclerosis is shown to require platelet P-selectin, as the development of atherosclerotic lesions is not affected by the injection of activated platelet lacking P-selectin. P-selectin is also expressed by the activated EC and allows leukocyte adhesion to EC (298). However, the main circulating mass of P-selectin is carried in the platelets and is stored in platelet α -granules. When the platelets become activated, P-selectin is expressed at the outer membrane of the platelets, and this allows formation of platelet-leukocyte complex. P-selectin can be shed and released in the plasma from both sources. The role of platelet versus endothelial P-selectin in the development of atherosclerotic plaques has been investigated by using chimeric mice with bone marrow of P-selectin^{-/-} apoE^{-/-} mice or wild-type apoE^{-/-} mice transplanted to the recipient from either genotype (96). Endothelial P-selectin is crucial for the promotion of atherosclerotic lesion growth because in its absence only relatively small lesions developed. However, platelet P-selectin also contributed to the lesion development because lesions in wild-type recipients receiving transplants with wild-type platelets were 30% larger than those receiving P-selectin-deficient platelets and were more frequently calcified (96).

In addition to their effects in early atherosclerosis, as shown above by experimental studies, platelets contribute to the progression of late atherosclerosis. The endothelium over established human plaques often shows focal endothelial loss, with adhesion of a platelet monolayer

(137, 157). Incorporation of platelets in plaques after rupture or erosion participate in their episodic expansion.

VI. CYTOKINES AND ADAPTIVE IMMUNITY IN ATHEROSCLEROSIS

A. Role of T/B Cells in Atherosclerosis

Adaptive immunity develops when specific molecular epitopes on antigens are recognized by antigen receptors with high specificity and affinity, such as T-cell receptors (TCR) and B-cell receptors (BCR), generated by somatic rearrangements in blast cells. A number of data from humans and mice showed oligoclonal expansion of T cells within atherosclerotic lesions owing to the preferential expression of a limited number of TCR-variable gene segments (103, 652). This suggests that a limited set of candidate antigens mediates the specific T-cell proliferation, the most likely immunodominant antigen being ox-LDL. Further studies aimed at the elucidation of the direct role of T and B cells in atherosclerosis. There is now ample evidence from experimental studies that the adaptive immune system affects the development of atherosclerosis. The net effect of a deficiency in both T and B cells is a 40–80% reduction in atherosclerotic lesion development, as shown in apoE^{-/-} or LDLr^{-/-} crossed into a recombination activating gene (Rag)-deficient background (153, 154, 563, 646) or crossed with severe combined immunodeficiency (SCID) mice (790). The protective effect is observed when the mice are examined at the early stages of plaque development (646), but also at later stages in the absence of severe hypercholesterolemia (153). The effect may vary according to the site of the lesion, immunodeficiency being protective in the aortic root but not in the thoracic and abdominal aorta (153, 154) or in the brachiocephalic trunk (563). Transfer of CD4+ T cells from atherosclerotic apoE^{-/-} mice into apoE^{-/-} x SCID^{-/-} mice enhances atherosclerotic lesion development to a level similar to that of immunocompetent controls (790), indicating a proatherogenic role for T cells.

Natural killer T (NKT) have also been shown to enhance fatty streak development (30, 430, 486, 683). NKT cells can recognize lipid antigens presented by CD1 molecules. CD1 deficient mice on apoE^{-/-} or LDLr^{-/-} background showed significant reduction in early fatty streak development, whereas treatment with α -galactosylceramide, a potent and specific NKT cell activator, resulted in an increase in lesion size associated with increased IFN- γ and IL-4 production. The influence of CD1d-restricted NKT cells on lesion size was transient, suggesting that these cells contribute to early fatty streak development but are dispensable for plaque progression.

On the other hand, B cells appear to exert a protective effect. Induction of humoral immunity by immuniza-

tion of hypercholesterolemic apoE^{-/-} mice with oxLDL reduces lesion size in association with the production of high levels of IgM type anti-oxLDL antibodies, probably from B1 cells (16, 212, 224, 525, 789). These cells appear to be stimulated by IL-5 produced by MDA-LDL-specific Th2 cells, generated in response to immunization. The group of Joseph Witztum (627) has shown that the IgM type anti-oxLDL antibodies recognize similar oxidation-specific epitopes on apoptotic cells and are structurally and functionally identical to classic "natural" antiphosphorylcholine antibodies that provide protection against pneumococcal infection (627). Immunization of LDLr^{-/-} mice with *Streptococcus pneumoniae* induces high circulating levels of oxLDL-specific T15 IgM, indicating molecular mimicry between epitopes of ox-LDL and *S. pneumoniae* and leads to a reduction in the extent of atherosclerosis, confirming the protective role of this humoral immune response in murine cholesterol-induced atherosclerosis. Splenectomy-induced increase in atherosclerosis in cholesterol-fed apoE^{-/-} mice is abrogated by the transfer of purified B cells from the spleens of atherosclerotic apoE^{-/-} (but not from the spleens of nonatherosclerotic mice), suggesting a protective immunity provided by splenic B cells that were "educated" by prior in vivo exposure to atherosclerotic antigens (102).

Besides the possibility of direct B-cell stimulation by thymus-independent antigens leading to IgM-dominated responses, adaptive immunity requires the presentation of antigen by an antigen presenting cell (dendritic cell and macrophage) to the antigen-specific TCR (signal 1) and typically additional costimulatory signals (signal 2), such as the interaction between CD40L with CD40 or that of CD80/CD86 (B7-1/2) with CD28 (Fig. 4). These costimulatory molecules are present in regions of atherosclerotic plaques of mice and humans (66, 377) and are required, at least for initial development of atherosclerotic lesions (94, 421, 426), and in the case of CD40/CD40L, for the perpetuation of plaque inflammation (418, 605) in mouse models of atherosclerosis. The role of costimulators in the human atherosclerosis is unknown. The best-established role for costimulators is in the activation of naive T cells, in which they function to reduce the threshold antigen concentration that can activate them (700). Prolonged exposure to higher doses of antigen, as could be the case in the extended course of atherosclerosis development in humans, may well override the need for costimulation. It is therefore tempting to speculate that while costimulation may be necessary for the initiation of pathogenic immune responses in atherosclerosis, this role may become dispensable during disease progression. We believe that it will be important to examine whether at this stage of disease development, other critical roles of costimulators prevail, such as the contribution to regulatory T-cell function (see below).

B. Cytokines and Pathogenic Immune Response in Atherosclerosis

1. Cytokines and DC maturation

Dendritic cells (DCs) are specialized antigen presenting cells (APCs) that are potent stimulators of both T and B cell-mediated immune responses. DC maturation requires the coordinated action of a number of cytokines and growth factors (reviewed in Ref. 34). Several molecules including CD40, TNFR, and IL-1R have been shown to activate DCs and to trigger their transition from immature antigen-capturing cells to mature APCs. The balance between proinflammatory and anti-inflammatory signals in the local microenvironment, including TNF, IL-1, IL-6, IL-10, and TGF- β , greatly affect DC maturation, and CCR7 plays a critical role in the homing of DCs to lymph nodes (208, 554). Distinct subsets of DCs elicit distinct T-helper responses (34). IL-12 production by DCs plays a critical role in Th1 differentiation as DCs from IL-12^{-/-} mice fail to induce Th1 responses (431). IL-6, IL-13, and OX40-ligand (OX40-L), a cell surface molecule belonging to the TNF superfamily (TNFSF) also known as TNFSF4 (719), may play a role in DC-induced Th2 differentiation (34). However, DCs exhibit considerable plasticity. Particularly, the anti-inflammatory cytokines IL-10 and TGF- β can convert DCs from cells inducing Th1 to cells inducing Th2 or regulatory T cells (see below). DCs have been identified in atherosclerotic plaques and may cluster with T cells within the lesions (60). DCs showed impaired migratory function in hypercholesterolemic mice due to inhibitory signals generated by PAF and oxLDL (410). Whereas these abnormal migratory properties directly affect the atherosclerotic process is still unknown.

2. Cytokines and Th1 differentiation

Following the demonstration of a pathogenic role for T cells in atherosclerosis, several groups have been involved in the characterization of the pathogenic T-cell subsets. Most of the T cells in atherosclerotic plaques are of the CD4⁺ T cells expressing $\alpha\beta$ -TCR, which interacts with MHC class II molecules. The CD4⁺ T cells are the main cytokine-secreting T cells, although the cytotoxic CD8⁺ killer cells may also produce cytokines, such as TNF- α , lymphotoxin, and IFN- γ . Characterization of the Th cell type in atherosclerosis was based on the cytokines secreted by the T cells, which are traditionally divided into Th1 cells, responsible for cell-mediated immunity and secreting IFN- γ and IL-2, and Th2 cells, which secrete IL-4, IL-5, IL-10, IL-13, and provide help for antibody production by B cells. Th1 and Th2 cells have a common precursor, and cytokine microenvironment is one of the primary determining factor for Th-cell lineage development. IL-12 and TCR activation are required for the induction of Th1 cells, whereas IL-4 is essential for the induc-

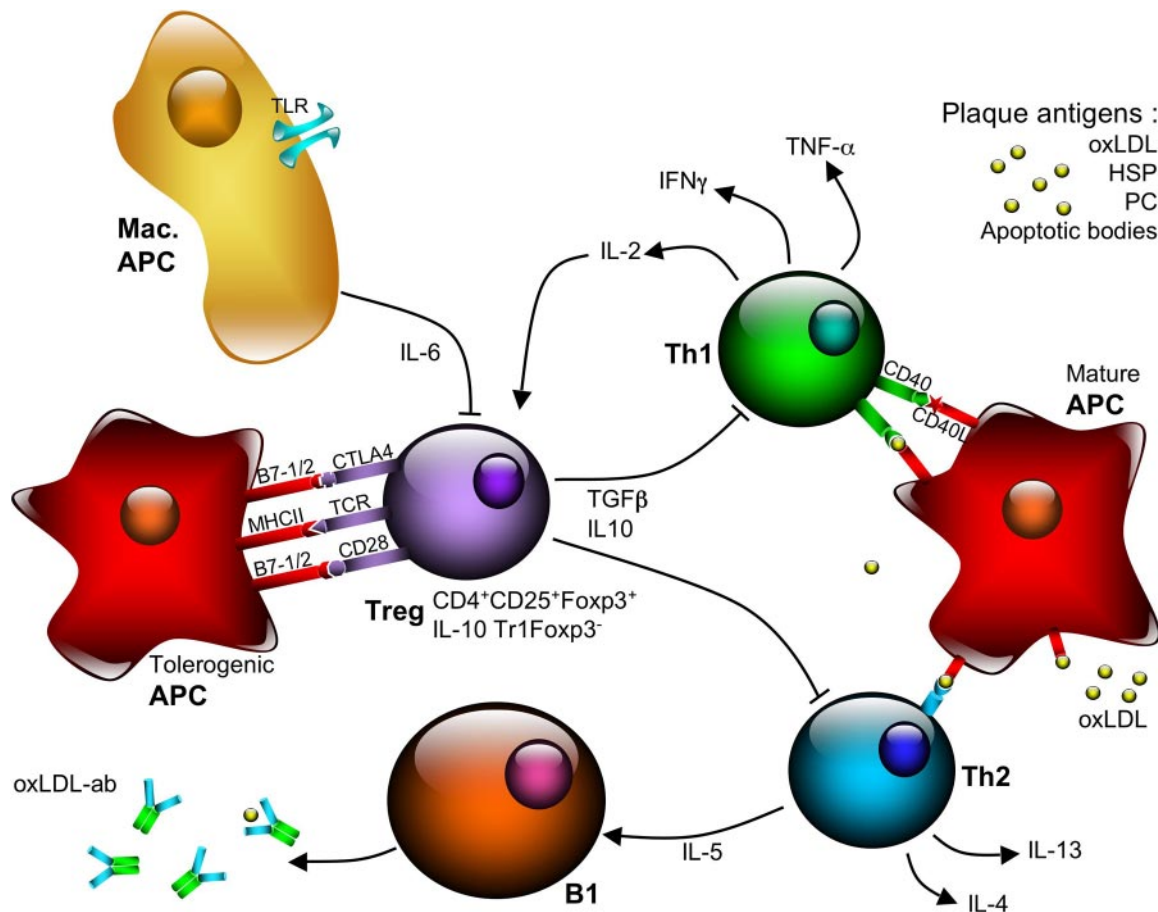


FIG. 4. Development and maintenance of pathogenic and regulatory immunity in atherosclerosis. Candidate antigens [oxidized lipoproteins (oxLDL), heat shock proteins (HSP), phosphorylcholine (PC), apoptotic bodies. . .] may induce Th1, Th2, or both Th1 and Th2 pathogenic responses. Maturation of the antigen presenting cell (APC) is necessary for T-cell priming. The CD40/CD40L pathway is critical for Th1 differentiation. IL-6 and IL-13 contribute to the induction of Th2 cell type. Both IFN- γ (Th1) and IL-4 (Th2) have been shown to promote atherosclerosis. Production of IL-5 by Th2 cells is important for protective antibody production by B lymphocytes in response to immunization with oxLDL. Distinct subsets of APCs, called "tolerogenic" cells, induce the differentiation of the regulatory T-cell subset (Treg). The development of CD4⁺CD25⁺Foxp3⁺ Treg cells occurs in the thymus and requires TCR and CD28 engagement among other yet unknown factors. Interestingly, production of IL-2 by pathogenic Th1 cells is essential for the survival and maintenance of this Treg subset in the periphery. Other Treg cells of the Tr1 type may not express Foxp3 and are mainly induced in the periphery in response to antigen stimulation. Both types of Treg cells use IL-10 and/or TGF- β to suppress the proliferation of pathogenic T cells in vivo. IL-6, produced in response to TLR stimulation, may contribute to the inhibition of Treg function.

tion of antigen-specific Th2 cells. IL-12 originates from macrophages and dendritic cells of the innate immune response, but the initial sources and mechanisms of IL-4 production remain poorly understood. IL-12 activates the transcription factor STAT4 and a unique Th1 transcription factor, T-box expressed in T cells (T-bet), leading to upregulation of IFN- γ and downregulation of IL-4 and IL-5 expression in T cells. IL-4 drives Th2 cell differentiation through STAT6, which activates the transcription factor Gata3, leading to upregulation of IL-4 and IL-5 and downregulation of IFN- γ . Counterregulation between T-bet and Gata3 has been suggested, resulting in inhibition of development of the other T-cell subset (660). Based on these T-cell subset specificities, most CD4⁺ T cells of atherosclerotic plaques of mice and humans have been shown to be of the Th1 cell type, producing IL-2 and IFN- γ (reviewed in Ref. 751), which is consistent with the high

levels of IL-12 expression within the plaques. Subsequent studies have clearly shown a critical pathogenic role for the Th1 response in atherosclerosis at the cell-type level (transfer of Th1 cells) (790), the cytokine production level (IL-12, IL-18, and IFN- γ) (260, 377, 436, 735, 736), and even at the level of Th1 cell commitment, as shown more recently using the LDLr^{-/-} \times T-bet^{-/-} mice (94). These results provide convincing elements to incriminate Th1 responses in the promotion of plaque development.

3. Cytokines and Th1/Th2 paradigm

Because of the crucial roles of Th1 and Th2 in the modulation of the immune response in many immunoinflammatory diseases, a model has emerged in which Th2-biased responses were proposed to antagonize proatherogenic Th1 effects and thereby confer atheroprotection.

Data supporting an antiatherogenic effect of Th2 responses are based on several, seemingly convincing findings: 1) IL-10, one of the Th2-related cytokines, is expressed in atherosclerotic plaques (441, 687) and inhibits oxLDL-induced production of IL-12 by human monocytes *in vitro* (687); 2) endogenous IL-10 is protective against atherosclerosis in several experimental models (434, 542, 708); 3) mice producing T cells that were engineered to overexpress IL-10 under the control of the IL-2 promoter show a reduction in IFN- γ production and a switch in IgG production toward a Th2-related IgG1 phenotype, associated with a significant decrease in atherosclerotic lesion formation (541); and 4) mice in which Th2 responses prevail over Th1 may show reduction in early fatty streak formation (295).

However, these data are not as straightforward as they may seem to be, and may be opposed by several other findings. 1) Even though IL-10 is a Th2-related cytokine, it is not specific of Th2 cells and has even been shown to inhibit Th2 responses (145, 257). 2) Mice overexpressing IL-10 under the IL-2 promoter, discussed above, have been previously shown to be unable to mount Th2 responses (261). 3) Deficiency in IL-4, the prototypic Th2-related cytokine, has been associated with a decrease in atherosclerotic lesion formation (340), suggesting a proatherogenic role of Th2. 4) Prolonged hypercholesterolemia in animal models of atherosclerosis is associated with a switch of the autoimmune response toward a Th2 cell type, producing IL-4 (795), which contribute to plaque progression, since deficiency in IL-4 at these advanced stages greatly hampers plaque progression (156). 5) With the use of apoE^{-/-} \times IL-12^{-/-} and apoE^{-/-} \times IL-4^{-/-} mice, it has been clearly shown that both Th1 and Th2 play roles throughout the development of atherosclerosis, Th1 being predominant during the initiation of lesion formation with a switch toward a proatherogenic Th2 response in the chronic phase of plaque development (156). Therefore, even though atherosclerosis occurs mostly in a Th1-related pathogenic context, no direct and solid evidence is available suggesting that promotion of Th2 responses would invariably lead to limitation of disease progression. The attractive concept of Th1 and Th2 controlling in a Yin-Yang fashion the development of atherosclerosis may be, at least in some circumstances, overly simplistic. However, this does not exclude a certain level of counterregulation between Th1 and Th2 in atherosclerosis, which may vary with the stage of disease development and the vascular sites. For example, in the study by Davenport et al. (156), while deficiency in IL-4 (and hence Th2 response) was associated with a decrease in lesion size in the advanced stage of lesion development, deficiency in IL-12 was associated with a trend toward larger lesions in certain vascular sites, suggesting a potential regulatory role for Th1 response at this advanced disease stage. Given the available data, we would caution

about the extreme hazard associated with the promotion of either a Th1 or a Th2 response to modulate atherosclerosis, especially in humans. Indeed, a careful look at the disease in humans shows that Th1- and Th2-related diseases develop and perpetuate in the same patient. A substantial proportion of patients are affected both by coronary atherosclerosis, a Th1-predominant disease, and atherosclerotic aortic aneurysm, a Th2-predominant process (149, 607, 633). In addition, the development of a Th2-related disease (allergic asthma, for example) in a given patient does not protect from the development of a Th1-related disease (coronary atherosclerosis, for example). A substantial proportion of patients, especially obese patients, frequently develop both allergic asthma and coronary atherosclerosis. An objective interpretation of the available data suggests that Th1- and/or Th2-mediated responses may contribute to the development and progression of atherosclerosis. Therefore, we believe that rather than focusing on a supposedly Th1/Th2 Yin-Yang in atherosclerosis, we should aim at the identification of the causes of Th1/Th2 dysregulation, which we believe could be better explained by a dysfunction in the regulatory arm of the immune response that controls both Th1 and Th2. Our hypothesis is that in the context of atherosclerosis, an imbalance exists between pathogenic T cells (Th1 and/or Th2) and so-called "regulatory T cells" in response to "altered" self-antigens, leading to reciprocal and mutual amplification of the innate and adaptive immune responses, responsible for plaque development and progression.

C. Immunological Tolerance and Regulatory T Cells

1. Development and function of natural regulatory T cells

The adaptive immune system of higher vertebrates allows individual organisms to mount more efficient and specific defensive immune reactions against unanticipated microbial antigens by the random generation, in developing lymphocytes, of a diverse repertoire of clonally distributed antigen receptors capable of recognizing a multitude of antigens. This occurs through a process of somatic cell gene rearrangement mediated by the recombination-activating gene recombinase. However, due to the diversity of antigen recognition afforded by the system, there is a considerable risk of self-antigen recognition by self-reactive receptors, posing a concrete risk of autoimmunity. Most solutions to this threat involve the deletion or functional inactivation of autoreactive lymphocytes (clonal deletion and anergy, respectively) in the primary lymphoid organs or in the periphery. These mechanisms are called "cell-intrinsic," since they do not affect other self-reactive clones. In addition to this "reces-

sive" suppression, a unique "dominant" self-tolerance mechanism has been identified over the past few years and related to the generation of a population of T cells with regulatory properties, the so-called "regulatory T cells," which actively suppress immune activation and maintain immune homeostasis.

Most if not all naturally arising Treg cells are CD4⁺ single-positive cells and constitutively express the CD25 molecule (IL-2R α). They are produced in the normal thymus where unique interactions between their TCRs and self-peptide/MHC complexes expressed on the thymic stromal cells are required for their development. CD25 expression on Treg cells is crucial for their generation, survival, and function. Mice deficient in IL-2 or CD25 develop a lymphoproliferative disease with autoimmune manifestations, a syndrome that can be rescued by IL-2 administration in IL-2-deficient mice. Interestingly, the responder non-Treg cells are the main source of IL-2 production and are required for the activation and maintenance (and proliferation) of Treg cells. These in turn suppress the pathogenic T cells by targeting the transcriptional control of IL-2, leading to inhibition of IL-2 production. Thus IL-2 mediates a feedback control mechanism between pathogenic and Treg cells.

Costimulatory signals mediated by engagement of CD28 by CD80/CD86 (B7) are essential for the development and homeostasis of Treg cells (Fig. 4). Mice deficient in CD28 or B7 molecules lack Treg cells and are at increased risk of autoimmune diabetes (591). In turn, CD28 engagement promotes IL-2 production by nonregulatory conventional T cells, maintaining a stable pool of Treg (Fig. 4).

Even though IL-2 is a vital cytokine for Treg, recent studies suggest that expression of the forkhead transcription factor Foxp3, irrespective of CD25 expression or MHC restriction, defines the naturally occurring Treg cell lineage (207). The critical role of Foxp3 in the control of autoimmune diseases is reflected by the observations that Foxp3 is the mutated gene in the fatal human autoimmune disorder "immune dysregulation, polyendocrinopathy, enteropathy, X-linked" (IPEX) and in the mouse, scurfy, which develops a similar autoimmune syndrome (45, 741). Foxp3 appears to be crucial for both the development and function of Treg cells and controls genes encoding Treg cell-associated molecules, such as CD25, cytotoxic T-lymphocyte antigen-4 (CTLA-4), and glucocorticoid-inducible tumor necrosis factor receptor (GITR) (334). Transduction of Foxp3 in CD25⁻ cells led to the acquisition of Treg cell properties and CD25 expression in some of the transduced cells, suggesting a central, but probably not sufficient, role for Foxp3 in the development and programming of Treg cell function. The current understanding is that Foxp3 is required for the development of the Treg cell lineage, whereas production of IL-2 by peripheral T cells expands the Treg cell population. The

precise molecular mechanisms behind the induction of Treg cells by Foxp3 and the potential role of Foxp3 in the maintenance of Treg cell function remain to be addressed.

Specific subsets of dendritic cells may be critical to the generation of defined populations of Treg (23). Aberrant expression of T-cell receptor agonists by nonactivated hematopoietic cells produces mostly CD4⁺CD25⁻ regulatory T cells, whereas expression on thymic stroma yields predominantly antigen-specific CD4⁺CD25⁺ Treg. Interestingly, expression of thymic stromal lymphopoietin (TSLP) in the human thymus induces tolerogenic thymic dendritic cells with high expression of CD80 and CD86, leading to the proliferation and differentiation of CD4⁺CD25⁻ thymic T cells into CD4⁺CD25⁺ Foxp3⁺ regulatory T cells (725).

2. Cytokines and regulatory T cells

Besides the role of IL-2 in the Treg cell development and maintenance, two immunosuppressive cytokines, TGF- β and IL-10, have been shown to mediate, at least in part, Treg function in vivo. In fact, Treg cells appear to use various modes of suppression in vivo. Depending on the microenvironment and the immunopathology to be suppressed, Treg cells may act through cell-cell contact-dependent mechanisms, particularly engagement of CTLA-4 on B7 molecules, through production of immunosuppressive mediators or both (707).

Recent studies have shown that at least part of the in vivo regulatory function of natural Treg may be due to the induction of IL-10 production in responder CD4⁺CD25⁻ T cells, which in turn become immunoregulatory cells able to suppress certain forms of immunopathology (32, 174, 655). TGF- β mediates, at least in part, the suppressive function of natural Treg in vivo and under certain culture conditions in vitro (44, 120, 251). This TGF- β -dependent suppressive activity of CD4⁺CD25⁺ Treg cells is required to inhibit pathogenic CD8⁺ T cells in models of autoimmunity or tumor rejection (120, 251), as shown in models with defective TGF- β receptor II signaling in CD8⁺ T cells. TGF- β -dependent CD4⁺CD25⁺ Treg cells are induced in vivo after treatment by antibodies to CD3 and mediate the restoration of self-tolerance in overt autoimmune diabetes (44), leading to limitation of disease progression (333). Whether TGF- β -dependent suppressive function is also required for inhibition of CD4⁺ T cell-dependent immunity in particular settings remain to be determined.

In addition to their role in mediating the suppressive properties of naturally arising Treg cells, TGF- β and IL-10 mediate the development and function of adaptive Treg cells induced in the periphery in response to antigen stimulation. These Treg do not express CD25 and have lower Foxp3 expression compared with natural CD4⁺CD25⁺ Treg cells (Fig. 4). The IL-10 producing Treg

are known as Tr1 cells (255, 512, 698). These cells can be generated by chronic antigenic stimulation or mucosal administration of antigen (9, 654) *in vivo* or under certain culture conditions *in vitro* (see below) (255, 512, 698). Tr1 cells also produce a significant amount of TGF- β in addition to IL-10. Other antigen-induced Treg cells, Th3 cells, arise after oral administration of antigen *in vivo* and suppress immune pathology in several animal models through the production of high concentrations of TGF- β (123, 730).

The development of these regulatory cells may be promoted *in vitro* and *in vivo* by a specific set of antigens and under particular conditions (254). Particularly, administration of antigens via the nasal route leads to IL-10-dependent Treg (9, 654), whereas oral administration induces the generation of TGF- β -dependent Treg (123). *In vitro* culture of bone marrow cells in the presence of IL-10 induces the differentiation of a distinct subset of dendritic cells (CD11c^{low}CD45RB^{high}) that display plasmacytoid morphology and an immature-like phenotype, secrete high levels of IL-10 after activation, and induce tolerance through the differentiation of Tr1 cells *in vitro* and *in vivo* (713). TGF- β and IL-10 production by apoptotic cells or upon ingestion of these cells by macrophages leads to cell deactivation and inhibition of self-reactive T cells (121, 221, 293, 299, 651). Apoptotic cells may also induce the generation of tolerogenic dendritic cells (10–12, 595, 596), potentially leading to the development of defined populations of Treg. Engulfment of apoptotic cells by dendritic cells in a proinflammatory microenvironment suppressed the upregulation of the costimulatory molecule CD86 and inhibited IL-12 production, leading to a reduced ability to stimulate T cells. Opsonization of apoptotic cells by the complement C3 activation product iC3b induces tolerant dendritic cells that are able to migrate to lymph nodes (696). The ligation of iC3b to complement receptor type 3 (the iC3b receptor) on antigen-presenting cells results in the sequential production of TGF- β and IL-10, which is essential for the induction of tolerance (645). Moreover, coengagement of CD3 and the complement regulator CD46 in the presence of IL-2 induces a Tr1-specific cytokine phenotype in human CD4⁺ T cells (332), and transgenic expression of human CD46 in mice promotes a regulatory T-cell response (448).

3. Regulatory T cells in atherosclerosis

The findings by several independent groups that two of the major counterregulatory cytokines in atherosclerosis, IL-10 and TGF- β , are those required for the immunoregulatory functions of either natural or adaptive antigen-induced Treg cells, led to the hypothesis that adaptive or natural regulatory cells may play an important role in the control of the atherosclerotic process (Fig. 5).

Given that immunization of mice with mHSP65 aggravates the development of atherosclerosis, two studies addressed the role of mucosal tolerance to HSP-65 (expected to induce Treg cells) in the development of experimental atherosclerosis (269, 450). Harats et al. (269) showed a reduction in lesion size after oral administration of HSP-65 in LDLr^{-/-} mice immunized with *M. tuberculosis* or fed an atherogenic diet (269), suggesting that tolerance induction toward HSP may be protective against atherosclerosis. Although oral feeding with HSP-65 induced a specific immune suppression, the reduction in atherosclerosis could also be obtained with nonsuppressive doses of oral HSP (269). The mechanisms leading to lesion reduction have not been clearly delineated, but the T-cell cytokine profile was switched toward a Th2 phenotype with high production of IL-4. Maron et al. (450) also showed a reduction in atherosclerosis after nasal or oral feeding of HSP-65 while only nasal feeding resulted in significant changes in the T-cell phenotype. No HSP-specific IL-10 responses were detected in splenocytes, but significant IL-10 production was observed following anti-CD3 stimulation *in vitro*. IL-10 production was attributed to a switch toward a Th2 phenotype and could not be related to changes in IFN- γ production by T cells (450). Taken together, the results of these two studies suggest that mucosal administration of antigen reduces plaque development. However, the mechanisms behind this effect are not fully understood. Additional mechanistic work is required to understand the potential role of the regulatory immune response in this process.

We have recently used a different approach to address the role of the regulatory immune response in atherosclerosis. As our hypothesis implies that an imbalance exists between the effector (Th1/Th2) and the regulatory arms of the immune response, we suggested that supplementation with Treg cells may lead to the induction of immune suppression and a reduction in pathogenic T-cell-mediated responses, ultimately altering plaque development and/or composition. In a first step, we attempted to provide a proof of concept that Tr1 cell therapy could induce immunomodulation *in vivo* and limit plaque development in a model of humanlike atherosclerosis. Therefore, we generated *in vitro*, as previously described (255), ovalbumin (OVA)-specific Tr1 cells and administered these cells to apoE^{-/-} mice. These antigen-specific clones of Tr1 cells have been shown to induce both antigen-specific and nonspecific bystander immune suppression *in vitro*, and when introduced *in vivo* (255). We showed that the clone of Tr1 cells, when transferred into mice with their cognate antigen, induced a significant suppression of Th1 (and Th2)-mediated responses and led to an increase in IL-10 production by stimulated peripheral T cells (437). Interestingly, the induction of Tr1 responses was associated with a significant reduction in atherosclerotic plaque development and a marked reduction in the

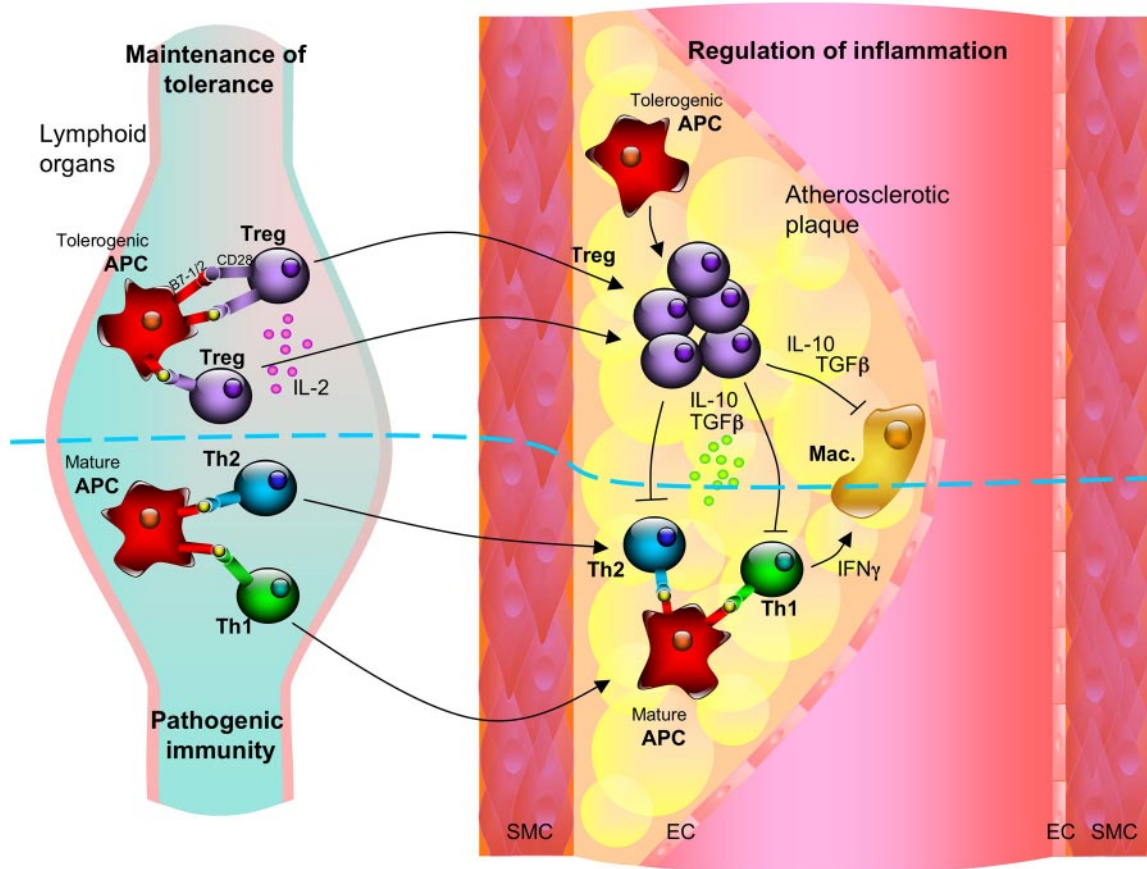


FIG. 5. Local and systemic effects of pathogenic and regulatory cells in atherosclerosis. Lymphoid organs are specialized in antigen presentation and may be the major site of pathogenic or tolerogenic antigen presentation and T-cell priming in atherosclerosis. Antigen presentation may also occur within the atherosclerotic plaque, which is rich in cells with antigen-presenting capacity (macrophages and dendritic cells). Continuous trafficking of immune cells between the inflamed atherosclerotic artery and the lymphoid organs may be necessary to mount an adaptive immune response. CD28 engagement and IL-2 production by pathogenic T cells are required for Treg cell survival and maintenance in the periphery. Treg cells suppress the pathogenic response through IL-10, TGF- β , and/or cell-cell contact-dependent mechanisms. The precise mechanisms that drive a pathogenic or a regulatory immune response in atherosclerosis are currently unknown.

relative accumulation of inflammatory macrophages and T lymphocytes with a preservation of SMC and collagen contents. These results showed that modulation of the peripheral immune response is achievable by transfer of Tr1 cells with no specificity to a known plaque antigen and leads to limitation of plaque development in apoE-deficient mice. Many issues remain to be addressed, particularly those regarding the precise site(s), mode(s) of action, and molecular mechanisms responsible for the regulatory functions of the transferred Tr1 cells in this setting, and whether specific and local immune suppression could be achievable by the development and transfer of Tr1 cells specific for a known plaque antigen.

An important question that has not been addressed in the above-mentioned experiments concerns the role of endogenous natural Treg in the control of atherosclerosis. A number of endogenous self- or altered self-antigens (oxidized epitopes on apoptotic cells or ox-LDL, HSP, for example) may induce the development of Treg cells with atheroprotective properties. We have recently tested the

hypothesis that the natural repertoire of Treg cells, which is responsible for the maintenance of immune homeostasis, also limits the development of atherosclerosis. Atherosclerosis in apoE^{-/-}RAG-2^{-/-} mice is exacerbated after transfer of splenocytes with Treg deficiency (from CD28- or B7-deficient mice) compared with the transfer of wild-type splenocytes, a process that is abrogated after the reconstitution of a normal CD4⁺CD25⁺ Treg cell compartment (8). Protection is associated both with enhanced IL-10 production by CD4⁺ T cells and TGF- β -dependent Treg suppressive function, consistent with the critical roles of these immunosuppressive cytokines in atheroprotection. We believe that innate or acquired impairment of natural Treg cell function may promote atherosclerosis.

Defective clearance of apoptotic cells has been described in atherosclerosis (25, 243, 615). Such a defect may break immunological tolerance and alter both specific and bystander immune suppression, leading to exacerbation of plaque development. Impaired clearance of dying cells appears to play a pathogenic role in the devel-

opment of autoimmunity (75, 549, 617, 668). Methods aiming at the promotion of endogenous natural Treg cell activity against atherosclerosis-related antigens or methods based on the transfer of antigen-specific Treg cells hold great promise for the control of plaque development and progression through the induction of a regulatory atheroprotective immunity.

Cells other than CD4⁺ T lymphocytes, such as CD8⁺, NKT and B cells, may prove to exert potent regulatory properties in atherosclerosis. An IL-10-producing regulatory B-cell subset characterized by CD1d upregulation has been shown to be essential for the dampening of the inflammatory response in a model of chronic intestinal inflammation mediated by a Th2 pathway (474). It is noteworthy in this regard that the protective role of B cells in atherosclerosis has been shown to occur in a Th2 context (52, 102, 268).

VII. CYTOKINES AND CARDIOVASCULAR RISK

Once produced, cytokines are rapidly trapped by neighboring cells via their high-affinity receptors. Accordingly, measuring the levels of circulating cytokines is not necessarily a perfect surrogate end point reflecting the actual activity of the cytokine. Nevertheless, a variety of plasma inflammatory markers have been shown to well predict future cardiovascular risk. They can be useful for risk stratification and also to identify those patients who might benefit from targeted interventional therapy. Of these markers, C-reactive protein (CRP), an acute-phase protein, has been the most extensively studied, and there is now robust evidence from primary prevention cohorts and among patients presenting with ACS that elevated CRP levels predict future cardiovascular events (see review in Ref. 398). The production of CRP occurs almost exclusively in the liver by the hepatocytes as part of the acute phase response upon stimulation by IL-6, and to a lesser degree by TNF- α and IL-1 β , originating at the site of inflammation. CRP activates the classical complement cascade and mediates phagocytosis. In the 1990s, Berk, Weintraub, and Alexander (46) showed that plasma CRP levels are elevated in patients with "active" CAD compared with those with stable CAD. In 1994, Attilio Maseri and his group (408) established a link between CRP elevation and cardiovascular events in patients with unstable angina (UA). In the late 1990s, several studies linked elevated high-sensitivity CRP (hsCRP) levels with future cardiovascular events in different populations (reviewed in Ref. 56). It is believed that classical cardiovascular risk factors including LDL cholesterol, hypertension, smoking, and diabetes can instigate the vascular release of proinflammatory cytokines and subsequent promotion of low-grade inflammation. These proinflammatory cytokines increase serum levels of CRP, supporting the concept that

CRP acts as an integrator for many inflammatory stimuli, which in association with plasma LDL-cholesterol levels can predict the cardiovascular risk (569). Of potential clinical interest, the combination of an inflammatory marker (CRP, SAA, sICAM-1, or IL-6) with lipid testing improved upon risk prediction based on lipid testing alone. Thus lipid and inflammatory parameters appear to be assessing different biological pathways that carry separate prognostic value. In support of this hypothesis, the PROVE-IT-TIMI 22 study recently established that the risk of recurrent myocardial infarction (MI) or death from coronary causes among patients with acute myocardial syndromes (ACS) is best predicted by the combination of LDL cholesterol and CRP levels (569).

A number of in vitro studies aimed at investigating the direct inflammatory effects of CRP on vascular cells emphasized the potential importance of CRP as an etiological factor in inflammation and atherosclerosis (see review in Ref. 313). Among other effects, recombinant CRP has been shown to enhance the expression of ICAM-1, VCAM-1, E-selectin, and MCP-1 in EC (533, 534). However, several recent papers have clearly demonstrated that most, if not all, of the in vitro effects of recombinant CRP previously reported in the literature were most likely artifactual and due to the presence of sodium azide (406, 659, 689) or contamination by bacterial products (539) in the commercial CRP preparation used in the experiments. Moreover, in vivo experiments assessing the direct role of CRP on atherosclerosis in CRP transgenic apoE^{-/-} mice failed to observe any effect (285, 566), or reported a very small effect in male but not female mice (538). There is even some evidence that CRP might be protective against atherosclerosis (48, 616) and has a clear anti-inflammatory activity that protects mice from lethality due to LPS challenge (752). The protective effect of CRP appears to be mediated by binding to Fc γ RI and Fc γ RII resulting in enhanced secretion of IL-10 and downregulation of IL-12 (479). It is therefore unlikely that CRP is a mediator of atherosclerosis and its complications, even though it appears to be a strong independent predictor of cardiovascular events.

A. TNF- α

In a study from the secondary prevention cholesterol and recurrent events (CARE) trial, TNF- α has been associated with an elevated risk of recurrent MI and cardiovascular death after a first MI (570). TNF- α levels are correlated with ankle-brachial index, used to predict the severity of peripheral arterial disease (91) and also correlate with the burden of atherosclerosis as assessed by carotid ultrasound among healthy middle-aged men (641). However, other investigators have suggested that sTNFR levels may be a better marker of atherosclerotic burden

than TNF- α itself. A study that sought to determine whether TNF- α and TNFR levels were associated with carotid plaque thickness concluded that relative elevation in TNFR levels, but not TNF- α , was associated with carotid atherosclerosis among individuals aged <70 yr (112).

B. IL-2

A transient burst of T-cell activation has been detected in patients with UA (101, 103, 497). Furthermore, patients with UA are characterized by a perturbation of the functional T-cell repertoire with a bias toward IFN- γ production (409). In an attempt to determine the relationship between T-lymphocyte activation and CAD, plasma levels of IL-2 have been measured in coronary patients. Surprisingly, high levels of IL-2 and soluble IL-2 receptor were found in those with stable but not UA (638).

C. IL-6

IL-6 levels appear to be predictive of future CAD (270) and are elevated in patients with UA compared with those with stable angina (50). Patients with persistently elevated IL-6 levels demonstrate a worse in-hospital outcome following admission with UA (49). Raised levels of IL-6 are often found correlated to CRP levels, consistent with IL-6 being the main stimulant for the hepatic production of CRP (reviewed in Ref. 747).

In the fast revascularization during instability in coronary artery disease (FRISC) II trial, IL-6 was an independent predictor of mortality among patients presenting with ACS, even when measurements with a hsCRP method were included in the analysis (403). Interestingly, elevated IL-6 levels appeared to have utility in terms of directing subsequent care. Early invasive strategy in patients with elevated IL-6 levels led to a dramatic 65% relative reduction in mortality at 1 yr (403). In contrast, among patients with lower levels of IL-6, randomization to an early invasive strategy did not confer any benefit over a conservative strategy. This illustrates how inflammatory biomarkers can be used for risk stratification and also to identify those patients who might benefit from targeted interventional therapy.

D. IL-7

A role for IL-7 has been suggested in the promotion of clinical instability in CAD (152). This is based on the fact that IL-7 plasma levels were significantly increased in patients with stable angina and UA compared with healthy controls. Increased release from activated platelets appeared to be a major contributor to raised IL-7

levels in patients with CAD. In addition, IL-7 enhanced the expression of several inflammatory chemokines in peripheral blood mononuclear cells in both healthy subjects and patients with CAD, and aspirin reduced both spontaneous and stimulated release of IL-7 from platelets (152).

E. IL-8

The prospective EPIC-Norfolk population study provided evidence that elevated plasma levels of IL-8 were associated with an increased risk of CAD in apparently healthy individuals (65). This relationship was independent of traditional cardiovascular risk factors and also independent of CRP levels. An earlier study also showed that IL-8 levels may be useful clinical predictors of unstable CAD (574).

F. IL-18

Consistent with a role of IL-18 in plaque instability (435), several observational studies showed that IL-18 levels are higher among patients with UA or MI than among patients with stable angina or normal controls (439, 490, 622, 763). Of note, ratio of IL-18 to its natural inhibitor IL-18 BP were significantly higher among patients who had recent MI than among those who did not, suggesting a relation between unopposed IL-18 activity and recent MI (490). IL-18 was also identified as a strong independent predictor of death from cardiovascular causes in patients with CAD with stable or unstable angina (57). Diabetic patients with high IL-18 had a greater carotid intima-media thickness than those with normal IL-18 (31). Furthermore, numbers of carotid plaques were higher in diabetic patients with high IL-18 than in those with normal IL-18. Moreover, IL-18 is raised in heart failure patients, in whom elevations correlate with poorer cardiac functional class and higher TNF- α concentrations (440, 485). IL-18 appears likely to participate in the pathophysiology of congestive heart failure.

G. sCD40L

In light of the experimental data showing an important role of CD40/CD40L in atherosclerosis, clinical studies were carried out to evaluate the value of sCD40L as a biomarker of cardiovascular risk. It has been reported that apparently healthy women with elevated levels of CD40L have an increased risk of MI, stroke, or cardiovascular death, a finding that remained after adjustment for traditional cardiovascular risk factors (608). Furthermore, among patients with carotid atheroma, sCD40L levels may predict the presence of lipid pool on high-resolution carotid magnetic resonance imaging (56).

Platelet stimulation is the major source of circulating sCD40L, suggesting that the sCD40L levels may be of greatest predictive value among those with ACS. Consistent with this hypothesis, sCD40L levels identify patients at risk of having recurrent ischemic events (277, 693). The c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) study demonstrated that elevated levels of sCD40L identified the subgroup of patients with ACS who are at highest risk of death or nonfatal MI over 6-mo follow-up (277). Moreover, the risk associated with elevated sCD40 ligand levels was markedly attenuated by randomization to treatment with the glycoprotein IIb/IIIa receptor antagonist abciximab.

H. IL-10

We have seen that IL-10 is a potent antiatherogenic cytokine. Measurement of IL-10 levels has thus been sought in several clinical studies in an attempt to evaluate its value as a predictor of adverse cardiac events. Patients with UA who had cardiac events during a 3-mo follow-up period showed lower levels of IL-10 on admission when compared with patients with a noncomplicated evolution (20). In the CAPTURE trial, elevated IL-10 serum levels were associated consistently with a significantly improved outcome of patients with ACS (276). The predictive value of IL-10 serum levels was independent of elevated troponin levels. Thus a reduced IL-10 serum level is not only a marker of plaque instability favoring the development of ACS but, more importantly, is indicative of a poor prognosis even after the occurrence of an acute ischemic event caused by plaque instability. In addition, the beneficial effect of elevated serum levels of IL-10 was restricted to patients with elevated CRP serum levels indicative of an enhanced systemic inflammatory response. These data support the concept established from experimental data that the balance between pro- and anti-inflammatory cytokines is a major determinant of plaque instability and of patient outcome in ACS. In addition, increased IL-10 serum levels are associated with improved systemic endothelial vasoreactivity in patients with elevated CRP serum levels, demonstrating that the pro- and anti-inflammatory balance is a major determinant of the endothelial function (203).

I. M-CSF

M-CSF has emerged as one of the strongest risk factors for adverse outcomes in patients with stable angina (590). Significantly elevated M-CSF is a harbinger of ACS in these patients. M-CSF levels were significantly elevated in patients with ACS compared with patients with stable angina, the pathophysiology of which may be the aforementioned SMC loss caused by the activation of

MMPs in the plaque. Serum M-CSF levels determined 6 wk after discharge in patients with severe unstable angina were strong predictors of cardiac events during a 2-yr follow-up (558). In contrast, admission or discharge cytokine values were not predictive of long-term outcome.

VIII. THERAPEUTIC POTENTIAL

The inflammatory nature of atherosclerosis has prompted efforts to prevent development and/or progression of disease by targeting inflammatory mediators, including cytokines, chemokines, and MMPs. However, given the long-life evolution of the disease, the benefit of such approaches is likely to be lost after the withdrawal of treatment, implying a need for the indefinite drug administration, with the attendant risks of chronic adverse side-effects, including immunosuppression. Based on our current knowledge of the role of cytokines in the disease, we would like, in conclusion, to propose some novel therapeutic strategies to combat atherosclerosis.

A. Use of Anticytokines

Several natural endogenous inhibitors of IL-1, IL-18, and TNF- α have been identified; these include IL-1ra, soluble IL-1 receptors, IL-18BP, and soluble TNF- α receptors. Although increased levels of these natural inhibitors usually occur in sera and at sites of inflammation in patients with inflammatory diseases, there might be locally an excess of these cytokines compared with their respective natural inhibitors that favors their proinflammatory action. Therefore, a potential therapeutic maneuver for treating atherosclerosis is to neutralize these implicated cytokines. Biologic agents aimed at inhibiting the proinflammatory activities of these cytokines thus far have included cytokine receptor antagonists, anticytokine monoclonal antibodies, and fusion molecules consisting of soluble cytokine receptors combined with human fusion protein constructs or polyethylene glycol. A successful example of this approach is Etanercept, a soluble TNFR fusion protein, the use of which has been shown to be effective and safe in rheumatoid arthritis (reviewed in Ref. 518). Nevertheless, blocking the bioactivity of proinflammatory cytokines, crucial activators of host defense, has proven to be accompanied by an increased susceptibility to infections. Caution is therefore warranted when these treatments are given to patients.

B. Targetting Downstream Inflammasome

The molecular characterization of the molecular complex, inflammasome, that activates the inflammatory caspase-1 and caspase-5, opens the door to new therapeutic

tic approaches for the treatment of autoinflammatory disorders, characterized by recurrent inflammatory episodes not mediated by autoantibodies or antigen-specific T cells (297), by reducing IL-1 β and IL-18 production, because of the key roles of these two cytokines in many inflammatory diseases, including atherosclerosis. Orally active inhibitors of caspase-1, including pralnacasan, are in clinical trials in patients with rheumatoid arthritis, and decreased disease activity has been observed, particularly in patients with elevated CRP levels (559). Treating inflammation with an orally active, highly specific anticytokine agent holds considerable promise in inflammatory diseases like atherosclerosis.

C. Targetting the JAK/STAT Pathway

A selective JAK3 antagonist, designated CP-690 550, has recently been developed (115). As predicted by studies in humans with mutations of JAK3 and its associated receptor subunits, the drug is a potent immunosuppressant. An important feature of this drug is that it has selectivity for JAK3 and does not induce unacceptable anemia, leukopenia, or thrombocytopenia, which would be indicative of substantial JAK2 inhibition. Because JAK3 has limited tissue expression, and its only meaningful biological function is restricted to immune cells, a JAK3 antagonist is not associated with widespread effects in other organs; in this way, the selective JAK3 antagonist distinguishes itself from other immunosuppressants. The drug is effective in a preclinical model of renal allotransplantation in nonhuman primates (73). As the drug moves towards clinical trials in humans, it will be important to determine its value in atherosclerosis.

D. Activation of the Natural Anti-inflammatory Intracellular Pathway (SOCS)

SOCS1, when overexpressed, can inhibit signals from most hematopoietic and inflammatory cytokines that utilize the JAK/STAT pathway. Thus, although the main physiological role of SOCS1 appears to be to control IFN- γ , this promiscuous activity implies that SOCS1 agonists or mimetics might also prove beneficial in the control of inflammation mediated by multiple cytokines as occurred in atherosclerosis. In a murine model of inflammatory arthritis, overexpression of SOCS3 by periarticular injection of a SOCS3 adenovirus reduced the severity of inflammation and joint damage (635). SOCS3 is also highly expressed in inflamed intestinal mucosa of patients with ulcerative colitis and Crohn's disease (415, 657). Such diseases are driven by excessive STAT3 activation. It is postulated that SOCS3 is a negative regulator of inflammation in these diseases and that SOCS3 agonists will reduce bowel inflammation. This suggests that small

molecule effectors of SOCS3 activity might be of great interest in the treatment of atherosclerosis.

E. Stimulation of Treg Cells

An existing approach for the treatment of atherosclerosis results from the identification of circulating autoantibodies against oxidized LDL in humans (526) and from the observation that an immunization with oxidized LDL significantly reduces atherosclerosis. The atheroprotective effect of this approach is mediated through the induction of antibodies against oxidized epitopes of oxLDL. Specific immunoreactive antigenic epitopes in the apolipoprotein B-100 component of LDL have been recently identified (210), and experimental observations have provided a proof of concept that active vaccination using these antigenic epitopes may represent a novel therapeutic approach for the prevention and treatment of atherosclerosis (599, 624).

In light of our recent findings on the role of Treg cells in atherosclerosis (8, 437), treatments aimed at promoting Treg cell generation such as Tr1 cells, CD4⁺CD25⁺ cells, or Th3 cells can represent an attractive tool for treating and/or preventing atherosclerosis. This might be accomplished by promoting a regulatory immune response distinct from the humoral response that generates anti-oxLDL antibodies, which would limit the risk of inflammatory complications associated with the induction of autoantibodies.

Of note, studies in nonobese (NOD) diabetic mice indicate that short-term treatment with monoclonal antibodies against CD3 induces long-term remission of established diabetes (118, 119) through the induction of CD4⁺CD25⁺ Treg cells (44). The CD3-specific monoclonal antibodies used in these studies recognize the ϵ -chain of the CD3 complex, which is associated with the TCR for antigen recognition (117). The precise mechanisms involved in the CD3-specific antibody-induced CD4⁺CD25⁺ Treg cells are unknown, but Treg cells from mice treated with CD3-specific antibodies produce high levels of TGF- β , and in vivo neutralization of TGF- β prevents the remission of autoimmune diabetes in NOD mice (44). Interestingly, use of a humanized anti-CD3 antibody in patients with recent-onset type 1 diabetes shows that short-term treatment preserves residual β -cell function for at least 18 mo (333). Induction of TGF- β -dependent Treg cells by using anti-CD3 antibodies may limit the development and progression of atherosclerosis in patients with high cardiovascular risk factors.

An alternative way to induce and maintain immune tolerance in atherosclerosis would be to use peptide-based therapeutic vaccines (371). Prolonged subcutaneous infusion of low doses of peptides can transform mature T cells into CD4⁺CD25⁺ Treg cells, persisting for

long periods of time, even in the absence of antigen, and capable of stimulating specific immunological tolerance upon encounter with antigen (24). Such strategy of delivering low doses of specific peptides for a long period of time has been successfully used in experimental models of allergy (84, 290). Also, peptide derived from HSPs for the treatment of diabetes and rheumatoid arthritis has provided encouraging results (550, 561). This prompted us to evaluate the value of therapeutic vaccination using specific atherosclerotic plaque peptides in murine models of atherosclerosis.

F. Stimulation of Macrophage Emigration From Atherosclerotic Lesions

It had been proposed by the beginning of the 1980s that lipid-laden foam cells can migrate back from the intima into the bloodstream by crossing the arterial endothelium (229). Yet the molecular mechanisms responsible for macrophage emigration from the atherosclerotic plaque were totally unknown. Of note, recent *in vitro* and *in vivo* studies exploring the mechanisms of monocyte egress from the vessel wall revealed that PAF and lysophosphatidic acid (LPA) inhibit monocyte transmigration (410). Moreover, cells that emigrate from atherosclerotic lesions to lymphoid organs, after transplantation of an atherosclerotic aortic segment from an apoE^{-/-} donor to a C57BL/6 recipient, express high levels of the major histocompatibility complex class II molecules I-Ab, CD11b, and the M-CSF receptor CD115. Clearance of monocytes from the atherosclerotic plaque by conversion into migratory cells using a specific set of cytokines may bolster plaque regression.

IX. CONCLUSION

Much has been learned about the role of cytokines in atherosclerosis since their presence in the human atherosclerotic plaque was first discovered over 25 years ago. Proinflammatory cytokines stimulate chemokines and adhesion molecules, leading to early recruitment of monocytes and lymphocytes in the intima. Furthermore, cytokines exert potential noxious effects in late atherosclerosis when they activate MMPs in macrophages and vascular cells and promote cell apoptosis, resulting in weakened plaques that are more prone to rupture or erosion. The balance between pro- and anti-inflammatory cytokines has emerged as a major determinant of plaque stability. Nonetheless, many aspects of plaque formation and evolution remain unresolved. For one, most if not all of our understanding of the molecular mechanisms of atherogenesis are based on experiments in murine models of atherosclerosis. To what extent can the findings obtained in apoE^{-/-} or LDLr^{-/-} mice be translated to

human atherosclerosis? Inasmuch as no model can reproduce plaque rupture or plaque erosion in humans, how can the importance of cytokines be evaluated in these settings? Atherosclerosis definitely proceeds from a local inflammatory process. Yet, in atherosclerosis increased expression of cytokines in the plaque usually parallels that in spleen cells (541, 572, 791). Is atherosclerosis then really a local or a systemic inflammatory disease (422)?

The upsurge in our understanding of the role played by inflammation in atherosclerosis has significant implications for current and future therapeutic approaches for primary and secondary prevention of atherothrombotic events. The development of new treatments will focus on strategies that decrease the inflammatory response and tip the balance in favor of anti-inflammatory mediators and, therefore, plaque stability. However, crucial questions still arise: Are there cytokines that are more specific of atherosclerosis? Do they have site specificity: coronary versus carotid versus peripheral arteries? Do cytokines play a similar role in early and late atherosclerosis? We have seen that future therapeutic approaches may include agents that block proinflammatory cytokine signaling, agents that augment the anti-inflammatory activity of other cytokines, and agents that either block the transcription of inflammatory mediating molecules or upregulate anti-inflammatory molecules. Yet, when and how long to treat patients with CAD with such agents that trigger the cytokine network remains to be resolved.

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GRANTS

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