Recent Advances on the Role of Cytokines in Atherosclerosis

Hafid Ait-Oufella, Soraya Taleb, Ziad Mallat, Alain Tedgui

Abstract—Atherosclerosis is a chronic inflammatory disease of the arterial wall driven by innate and adaptive immune responses. Inflammation controls the development and the destabilization of arterial plaque. 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 have provided evidence for a dual role of cytokines: proinflammatory and T helper-1-related cytokines promote the development and progression of the disease, whereas antiinflammatory and regulatory T cell–related cytokines exert clear antiatherogenic activities. This review focuses on recent advances regarding the role of cytokines, with the exception of chemokines, in the development, progression, and complications of atherosclerosis. (Arterioscler Thromb Vasc Biol. 2011;31:969-979.)

Key Words: atherosclerosis ▪ immune system ▪ vascular biology ▪ cytokines ▪ inflammation

Human and animal studies have established that atherosclerosis is driven by a chronic inflammatory process within the arterial wall initiated mainly in response to endogenously modified structures, particularly oxidized lipoproteins that stimulate both innate and adaptive immune responses. The innate response is instigated by the activation of both vascular cells and monocytes/macrophages. Subsequently, an adaptive immune response develops against an array of potential antigens presented to effector T lymphocytes by antigen-presenting cells. Vascular cells, endothelial cells (EC), and smooth muscle cells (SMC) participate in the development of the disease by mediating leukocyte recruitment and vascular remodeling, as well as feeding back to promote perpetuation of inflammation through the release of proinflammatory cytokines and chemokines. Cytokines play a dual role in atherosclerosis. Proinflammatory and Th1-related cytokines promote the development and progression of the disease, whereas antiinflammatory and regulatory T cell–related cytokines exert clear antiatherogenic activities. This review focuses on recent advances regarding the role of cytokines in atherosclerosis (Figure 1). The role of chemokines is not covered in the review.

Biological Effects of Cytokines in Atherosclerosis

Cytokines are low-molecular-weight protein mediators that usually act at short range between neighboring cells in lymphoid organs or inflamed tissues. The cytokine group is very diverse and consists of more than 100 secreted factors, clustered into several classes, including interleukins (IL) (37 have been identified to date), tumor necrosis factors (TNF), interferons (IFN), colony-stimulating factors (CSF), transforming growth factors (TGF), and chemokines. They are involved in many physiological processes and are especially important for regulating inflammatory and immune (innate and adaptive) responses. All cells involved in atherosclerosis are capable of producing and responding to cytokines. A plethora of cytokines can be found in atherosclerotic plaques (Table).

The biological effects of proinflammatory cytokines that may account for their proatherogenic activity are multiple (Figure 2). In the early stages of atherosclerosis, cytokines can alter endothelial functions. TNF-α and IFN-γ have been shown to alter the distribution of vascular endothelial-cadherin-catenin complexes and prevent the formation of F-actin stress fibers. TNF-α increases cytosolic Ca²⁺ and activates myosin light chain kinase and RhoA, which disrupts endothelial junctions. This results in restructuring of the intercellular junctions, leading to loss of barrier function, facilitating leukocyte transmigration. Cytokines also induce the expression of chemokines and adhesion molecules on the vascular endothelium, thus favoring the recruitment, adherence, and migration of lymphocytes and monocytes into the inflamed vessel wall. Once in the intima, leukocytes can be permanently activated by locally generated cytokines, which can accelerate the transformation of macrophages into foam cells by stimulating the expression of scavenger receptors and enhancing cell-mediated oxidation. IFN-γ can induce foam cell formation through upregulation of SR-PSOX, the scavenger receptor for phosphatidylserine and oxidized low-density lipoprotein (oxLDL), which has been involved in oxLDL uptake and subsequent foam cell transformation in...
macrophages. Proatherogenic cytokines such as IFN-γ and IL-1β have been shown to inhibit the expression of the ATP-binding membrane cassette transporter A1, whereas antiatherogenic cytokines, including IL-10 and TGF-β, promote its expression. Thus, IFN-γ could serve as a molecular link between immune activity and lipid metabolism.

At a more advanced stage of the disease (Figure 2), proinflammatory cytokines destabilize atherosclerotic plaques by promoting cell apoptosis and matrix degradation. Macrophage apoptosis results in the formation of cell debris, which contributes to enlargement of the lipid core. Plaque SMC apoptosis leads to thinning in the fibrous cap, favoring its rupture. A number of proinflammatory cytokines have been shown to induce SMC and macrophage apoptosis, particularly the association of IL-1, TNF-α, and IFN-γ and promotion of Fas–Fas ligand killing. Pro- and antiinflammatory cytokines significantly affect the expression of matrix metalloproteinases (MMPs) and their inhibitors tissue inhibitor of metalloproteinases, acting synergistically with other cytokines, growth factors, or oxidized lipids to induce substantial remodeling of many components of the extracellular matrix. For example, IFN-γ inhibits collagen synthesis whereas IL-1 and TNF-α induce a broad range of MMPs in vascular cells, including MMP-1, -3, -8, and -9. The Th2-type cytokine IL-4 inhibits the production of most MMPs from macrophages but induces the elastolytic MMP-12. Finally, the antithrombotic properties of EC are deeply altered by cytokines. IL-1 and TNF-α increase the tissue procoagulant activity and suppress the anticoagulant activity mediated by the thrombomodulin-protein C system by decreasing the transcription of thrombomodulin and protein C receptor genes. Downregulation of anticoagulant mediators may in turn affect inflammation. Proinflammatory cytokines modify the fibrinolytic properties of EC, decreasing the production of tissue plasminogen activator and increasing the production of type I plasminogen activator inhibitor. As a result, proinflammatory cytokines might precipitate thrombus formation and promote the development of acute coronary syndromes.

Effect of Cytokines on Experimental Atherosclerosis

TNF-α and Structurally Related Cytokines

The demonstration that TNF-α plays a key role in atherosclerosis was obtained in experimental studies using TNF-deficient apolipoprotein E (apoE)−/− mice showing that atherosclerotic lesion size in the aortic sinus of TNF-α−/− apoE−/− mice was significantly smaller than that of apoE−/−

Table. Cytokines Expressed in Human Atherosclerotic Plaques

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<tr>
<th>Cytokines</th>
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Figure 1. Cytokines are produced by several inflammatory and vascular cells. IL-12 and IL-18, produced by macrophages (Mac), are potent inducers of IFN-γ and promote the differentiation of naïve T cells into proatherogenic Th1 cells. Macrophage-derived cytokines activate SMC and EC to produce an array of proinflammatory mediators. On the other hand, the antiinflammatory cytokines IL-10 and TGF-β, also produced by macrophages, promote antiatherogenic Treg cell differentiation. Other antiinflammatory mediators with potent antiatherogenic properties include IL-33, IL-1ra, and IL-18 binding protein (IL-18BP). In naïve CD4+ T cells from mice, Th17 cells are induced in response to a combination of IL-6 or IL-21 and TGF-β and require induction of the transcription factor RORγt. In human (h), Th17 differentiation requires TGF-β, IL-1β, and IL-6.
mice, which was associated with decreased expression of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and MCP-1. Other members of the TNF superfamily might also be implicated in atherosclerosis. TNF-related apoptosis-inducing ligand (TRAIL) has been detected in atherosclerotic plaques. TRAIL is a modulator of the immune response in vivo that maintains immune homeostasis and protects against autoimmune diseases. In particular, blocking endogenous TRAIL activity with soluble death receptor accelerates the onset of autoimmune type 1 diabetes. Although TRAIL promotes SMC proliferation and neointima formation after arterial injury, repeated injections of recombinant human TRAIL attenuated the development of atherosclerotic plaques in diabetic apoE−/− mice. Recently, CD137, a member of the TNF receptor family with costimulatory activity for activated T cells, has been shown to be proatherogenic. CD137 deficiency in apoE−/− LDLr−/− mice reduced atherosclerotic lesions, associated with decreased expression of IFN-γ, C-C motif chemokine 2, and TNF-α. IL-1 Cytokine Family

The IL-1 family comprises 11 proteins that share considerable sequence homology, including IL-1α, IL-1β, IL-1 receptor antagonist (IL-1ra), IL-18, IL-33 (the ligand of the membrane-bound ST2L receptor), and the newly discovered antiinflammatory IL-37. Like IL-1β and IL-18, IL-33 was found to have strong immunomodulatory functions. However, unlike these 2 cytokines, which mainly promote Th1-associated responses, IL-33 predominantly induces the production of Th2 cytokines (IL-5 and IL-13) and increases levels of serum immunoglobulins. The IL-33 receptor, ST2L, is preferentially expressed on Th2 cells but not Th1 cells and can profoundly suppress innate and adaptive immunity. IL-1

Expression of IL-1-family members and their receptors has been demonstrated in atherosclerotic plaques. Mouse models of atherosclerosis have confirmed the proatherogenic properties of IL-1α and IL-1β, associated with upregulation of endothelial adhesion molecules and activation of macrophages and vascular cells. Consistently, IL-1ra, a natural antagonist of IL-1, exhibits antiinflammatory properties, mainly through the endogenous inhibition of IL-1 signaling. Administration of recombinant human IL-1ra in apoE−/− mice or IL-1α overexpression in LDLr−/− mice markedly decreased the size of atherosclerotic lesions. In contrast, IL-1ra-deficient C57BL/6J mice fed a cholesterol/cholate diet had a 3-fold decrease in non–high-density lipoprotein cholesterol and a trend toward increased foam-cell lesion area compared with wild-type littermate controls. IL-1 receptor signals through MyD88, which contains a death domain, which facilitates its interaction with IL-1 receptor-associated kinase (IRAK) proteins. IRAK-2 and IRAK-4 are critical signaling mediators of the IL-1 receptor/Toll-like receptor superfamily. Genetic ablation of IRAK-4 kinase activity in apoE−/− mice was associated with diminished expression of proinflammatory genes, inhibition of macrophage infiltration, and reduction in atherosclerotic lesions. This is reminiscent of what was observed in apoE−/− mice deficient in MyD88. IL-18

IL-18 administration increased lesion size in apoE−/− mice, and overexpression of its endogenous inhibitor IL-18 binding protein reduced atherosclerosis and induced a more stable plaque phenotype. Furthermore, IL-18-deficient apoE−/− mice reproduced findings in apoE−/− mice, in which IL-18 signaling was blocked by overexpression of IL-18 binding protein, with smaller and more stable lesions compared with apoE−/− mice. 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. However, the proatherogenic effect of IL-18 can occur in the absence of T cells. Intraperitoneal injection of IL-18 in severe combined immunodeficiency/apoE−/− mice led to larger lesions and increased circulating IFN-γ compared with...
mice injected with saline solution. Natural killer cells were the most likely source of IFN-γ. Interestingly, IL-18 is implicated in the physiopathology of metabolic syndrome. Obesity and insulin resistance have been reported in mice deficient for IL-18, as well as in transgenic mice overexpressing IL-18 binding protein. Paradoxically, circulating IL-18 levels in obese subjects and in patients with type 2 diabetes are increased and predict cardiovascular events and mortality. In fact, leukocytes isolated from obese or type 2 diabetes patients respond poorly to IL-18 stimulation with IL-18 and show a 50% reduction in the expression of IL-18Rα and β chains.

**IL-33**

IL-33 was originally described as a modulator of inflammation, tipping the balance toward Th2-mediated immune responses. IL-33 may serve as a chemotactic factor for Th2 cells and induces the production of the Th2-associated IL-4, IL-5, and IL-13. In contrast with IL-1 and IL-18, IL-33 has been shown to reduce atherosclerosis development in apoE−/− mice on a high-fat diet. IL-33 treatment increased levels of IL-4, IL-5, and IL-13 but decreased those of IFNγ in serum and lymph node cells. It also enhanced serum levels of IgA, IgE, and IgG1 but decreased IgG2a, confirming the Th1-to-Th2 switch. Conversely, mice treated with soluble ST2, a decoy receptor that neutralizes IL-33, developed significantly larger atherosclerotic plaques. Furthermore, blockade of IL-5 activity with an anti-IL-5 antibody prevented IL-33-induced reduction in plaque size and reduced the amount of oxLDL antibodies induced by IL-33, suggesting that IL-33 may be atheroprotective via the induction of IL-5 and oxLDL antibodies. In agreement with these findings in experimental atherosclerosis, it has been found in patients who experienced an acute myocardial infarction that serum ST2 levels were elevated 1 day postevent and declined thereafter. ST2 levels correlated with serum creatine kinase, a standard marker of myocardial injury, and inversely correlated with left ventricular function. Moreover ST2 levels predicted mortality and clinical outcome in patients with acute myocardial infarction. Recently, in vitro and in vivo experiments provided mechanistic insights into the atheroprotective effect of IL-33. This cytokine markedly reduces macrophage foam cell formation through its receptor ST2 by decreasing oxLDL uptake, reducing intracellular total and esterified cholesterol content, and enhancing cholesterol efflux.

**IL-37**

IL-37, also known as IL-1F7, is expressed in several tissues and in inflammatory cells. In vitro, induction of IL-37 in macrophages or epithelial cells almost completely suppressed production of proinflammatory cytokines, including IL-1α, IL-1β, and TNFα. Conversely, these proinflammatory cytokines increased with silencing of endogenous IL-37 in human blood cells. Mice with transgenic expression of IL-37 were protected from lipopolysaccharide-induced shock and showed markedly improved organ functions with lower plasma levels of proinflammatory cytokines. IL-37 interacts directly in the cytoplasm with Smad3 to form IL-37/Smad3 complexes. IL-37 is a newly discovered powerful antiinflammatory cytokine, but its role in atherosclerosis has yet to be explored.

**IL-6 Family**

IL-6 signaling involves both a specific IL-6 receptor and a ubiquitous signal-transducing protein, gp130, that is also used by other members of the IL-6 family, but not by IL-31. IL-6 has been shown to enhance fatty lesion development in mice. IL-6 treatment of C57Bl/6 mice at supraphysiological concentrations resulted in an ∼5-fold increase in fatty streak size, whereas treatment of apoE−/− mice on low- or high-fat diets resulted in an ∼2-fold increase in lesion extent, suggesting that IL-6 is a proatherogenic cytokine. However, old IL-6-deficient apoE−/− mice show enhanced plaque formation with reduced collagen content, blunted synthesis, and release of IL-10 and diminished recruitment of inflammatory cells into the atherosclerotic plaque. At 1 year of age, mice showed more calcified lesions. In younger (16-week-old) IL-6-deficient apoE−/− mice, no significant difference in fatty streaks was detected compared with wild-type apoE−/− mice. Therefore, the role of IL-6 in atherosclerosis appears ambivalent. Similarly, IL-6 can be viewed as a proinflammatory cytokine, but it may also be regarded as an antiinflammatory cytokine as it induces the synthesis of IL-1ra and release of soluble TNF receptor, leading to reduced activity of proinflammatory cytokines. It also inhibits macrophage scavenger receptor-A.

IL-6 activates both signal transducers and activators of transcription (STAT) 1, and STAT3. Cytokine signaling by the janus kinase (JAK)/STAT pathway is regulated by a family of endogenous JAK kinase inhibitor proteins, suppressors of cytokine signaling (SOCS). The SOCS family consists of 8 members (SOCS-1 to SOCS-7 and cytokine-inducible SH2 proteins) all sharing a central SH2 domain and a C-terminal SOCS box. STAT3 activation by IL-6 induces preferentially proinflammatory responses, whereas STAT3 activation by IL-10 promotes antiinflammatory responses. The differential effect of SOCS3 on IL-6 and IL-10 receptor signaling is central to accounting for this apparent contradiction: the IL-6 receptor signaling is negatively regulated by SOCS3, whereas IL-10 receptor signaling is not. In agreement with this, IL-6 is able to induce an antiinflammatory response in macrophages lacking the Socs3 gene.

**IL-12 Family**

IL-12 p35/p40 is a heterodimeric cytokine that plays an important role in Th1 differentiation. Recent findings have shown that both p35 and p40 can form other cytokines with different proteins (IL-23:p19/p40; IL-35:p35/EB13). Similar to IL-12 and IL-23, IL-27 is a heterodimeric cytokine consisting of EB13 (an IL-12 p40 homologue originally described to be secreted by Epstein-Barr virus–transformed B cells) and p28, an IL-6 and p35 homologue. IL-12 production by dendritic cells and monocytes/macrophages plays a critical role in Th1 polarization. IL-12 activates the transcription factor STAT4 and a unique Th1 transcription factor (T-bet) leading to upregulation of IFN-γ and downregulation of IL-4 and IL-5 expression in T cells. T-bet deficiency clearly reduces lesion development. IL-12 has been shown...
to be proatherogenic. IL-12 appears to intervene in the atherosclerotic process during the early phase of the disease in apoE−/− mice.63 Thirty-week-old IL-12−/−apoE−/− mice showed decreased lesions, whereas 40-week-old mice had lesions of equivalent size compared with wild-type apoE−/− mice.62 Also, a selective defect of IL-12 synthesis by macrophages due to 12/15-lipoxygenase deficiency reduced plaque formation in ApoE−/−LDLr−/− and functional blockade of endogenous IL-12 by vaccination resulted in a marked reduction in atherosclerotic lesions in LDLr−/− mice.64 Conversely, injection of IL-12 in apoE−/− mice promoted lesion development.65 Interestingly, apoE stimulates the Th1-immune responses in vivo by modulating IL-12 production. ApoE selectively regulates toll-like receptor (TLR)4- and TLR3-mediated signaling of IL-12 production.66

The roles of IL-23, IL-27, and IL-35 in atherosclerosis are yet to be explored.

IL-17 and Th17 Cells

Th17 lymphocytes represent a new lineage distinct from Th1 and Th2 (see review67). TH17 cells produce, in addition to the major isofrom IL-17 (or IL-17A), other IL such as IL-17F, IL-21, and IL-22. Besides Th17, other cells are capable of producing IL-17, including γδ T cells, natural killer cells, natural killer T cells, and the newly identified lymphoid tissue inducer–like cells.68 Th17 cell differentiation requires retinoid-related orphan receptor-γt (RORγt), which cooperates with other transcription factors to induce IL-17 expression. Previous studies suggested that IL-23 is the main factor that induces Th17 differentiation.69 However, activation of RORγt induces the expression of IL-23 receptor, indicating that IL-23 acts on cells that are already committed to Th17. In vitro, the induction of Th17 subset is dependent on TGF-β and IL-6 or IL-21 (in mice) or on IL-18 or IL-23 (in humans), which activates RORγt expression and STAT3 phosphorylation. RORγt stimulates the production of IL-21 and the expression of the IL-23 receptor. IL-23 is required to expand and stabilize Th17, whereas IL-21, a member of IL-2 family, amplifies Th17 differentiation through autocrine and paracrine loops.70

Th17 cells have important roles in defense against extra- cellular bacteria and fungi.71 Besides this physiological role of Th17, these cells are involved in the development of a wide range of autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, psoriasis, and inflammatory bowel disease (see review67). IL-17A homodimers are very efficient in multiple sclerosis, psoriasis, and inflammatory bowel disease of autoimmune diseases, such as rheumatoid arthritis, confirming in vivo inhibition of IL-17 activity. Interestingly, higher IL-17 expression and STAT3 phosphorylation in human carotid plaques was associated with a more stable phenotype.72 Collectively, our data point to a protective role of IL-17 in atherosclerosis. However, others have shown that IL-17 may be proatherogenic.73–76 SOCS3 deficiency in T cells enhanced T cell–specific STAT3 phosphorylation, which promoted Th17 polarization.77 SOCS3-deficient T cells produced more IL-17 and IL-10 and a lower amount of IFN-γ. Neutralization of IL-17A using a mouse monoclonal anti-IL-17A antibody was sufficient to abrogate atheroprotection in mice transplanted with SOCS3-deficient T cells but had no effect on lesion development in control animals.78 Moreover, recombiant murine IL-17A reduced endothelial vascular cell adhesion molecule-1 expression and vascular T cell infiltration and significantly limited atherosclerotic lesion development in LDLr−/− mice. Interestingly, higher IL-17 expression and STAT3 phosphorylation in human carotid plaques was associated with a more stable phenotype. Collectively, our data point to a protective role of IL-17 in atherosclerosis. However, others have shown that IL-17 may be proatherogenic. LDLr−/− recipient mice reconstituted with IL-17R-deficient bone marrow cells exhibited decreased atherosclerosis compared with mice reconstituted with wild-type cells.79 However, this study does not provide a direct evidence for a proatherogenic role of IL-17. IL-17R signaling in reconstituted mice is not completely abrogated because this receptor has ubiquitous expression, notably in SMC and EC of recipient mice. In addition, IL-17 has been shown to inhibit the expansion of Th17 through IL-17R via a negative feedback loop.80 Therefore, it cannot be ruled out that the partial deficiency of IL-17R in reconstituted mice is responsible for increased IL-17 production and increased IL-17 signaling in the vessel wall. In vivo neutralization of IL-17 activity using antibody- or adenovirus-produced soluble IL-17 receptor significantly reduced atherosclerosis in apoE−/− mice.81–82 However, in these studies, the authors did not provide data confirming in vivo inhibition of IL-17 activity. Interestingly, it has been shown in a recent study that IL-17A neutralization by a rat anti-mouse IL-17A antibody reduced atherosclerosis in apoE−/− mice without any evidence of reduced IL-17A signaling.83 Contrariwise, treatment with a mouse anti-IL-17A antibody did not affect atherosclerosis but inhibited IL-17A signaling. A more detailed discussion about the possible reasons for the discrepancy between our study and others is presented in Taleb et al.77 In humans, increased expression of IL-17A, IL-21, and IL-23 has been reported in atherosclerotic lesions from symptomatic patients, as com-
pared with asymptomatic patients.\textsuperscript{86} Awaited results in IL-17A-deficient \textit{apoE\textsuperscript{-/-}} may provide a solution to this controversy. However, recent reports in abstract form by 2 different groups on atherosclerotic lesion formation in IL-17A\textsuperscript{-/-}
\textit{apoE\textsuperscript{-/-}} mice show opposite results. One group found that IL-17A deficiency accelerated atherosclerosis,\textsuperscript{87} whereas the other found a reduced plaque burden in IL-17A\textsuperscript{-/-}
\textit{apoE\textsuperscript{-/-}} mice.\textsuperscript{88}

**IL-19/IL-20**

Based on the structure and location of their genes, their primary and secondary protein structures, and the receptor complexes used, IL-19 and IL-20 were classified in the IL-10 family of cytokines. They act via a receptor complex that consists of the IL-20R1 and IL-20R2 chains. IL-20 is additionally able to signal via a second receptor complex (IL-22R1/IL-20R2). IL-19 and IL-20 are produced by monocytes, as well as nonimmune tissue cells under inflammatory conditions. IL-19 is associated with the development of Th2 responses. IL-19 is expressed in activated SMC and reduces intimal hyperplasia after balloon injury.\textsuperscript{89} EC also expresses IL-19, which promotes EC spreading.\textsuperscript{90} IL-20 and its receptors, IL-20R1/IL-20R2, are expressed in human and experimental atherosclerotic plaques. Moreover, systemic delivery of IL-20 accelerates atherosclerosis in \textit{apoE\textsuperscript{-/-}} mice.\textsuperscript{91} Additional studies are required to fully elucidate the role of these 2 cytokines in atherosclerosis.

**IFN-\(\gamma\) and Th1-Related Cytokines**

The majority of pathogenic T cells in atherosclerosis are of the Th1 profile, producing high levels of IFN-\(\gamma\). Th1-driven responses are detrimental to the atherosclerotic process. IFN-\(\gamma\) activates monocytes/macrophages and dendritic cells, leading to the perpetuation of the pathogenic Th1 response (reviewed in Tedgui and Mallat\textsuperscript{1}). Deficiency in IFN-\(\gamma\) receptor or IFN-\(\gamma\) significantly reduces lesion development and enhances plaque collagen content,\textsuperscript{92,93} whereas exogenous administration of IFN-\(\gamma\) enhances lesion development.\textsuperscript{93} More recently, it has been shown that postnatal blocking of IFN-\(\gamma\) function by gene transfer of a soluble mutant of IFN-\(\gamma\) receptor in adult \textit{apoE\textsuperscript{-/-}} mice prevented the progression of established plaques that remodeled toward a more stable and less inflammatory phenotype.\textsuperscript{94}

Contradictory findings have been reported regarding the role of IFN-\(\gamma\) 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.\textsuperscript{95} In contrast, others had reported a promoting effect of IFN-\(\gamma\) on SMC in culture\textsuperscript{96} and a lack of effect of T cell deficiency on injury-induced neointima formation using athymic \textit{nu/nu} rats.\textsuperscript{97} IFN-\(\gamma\) has also been shown to elicit SMC proliferation and intimal hyperplasia in a model of transplantation of pig or human arteries into the aorta of immunodeficient mice.\textsuperscript{98} Interestingly, IFN-\(\gamma\) was not found to be directly mitogenic in this study but potentiated the proliferative effect of platelet-derived growth factor-BB under low-serum conditions and upregulated platelet-derived growth factor-\(\beta\) receptors. Moreover, in a chimeric model of immunodeficient mouse recipients bearing human coronary artery grafts and intravenously inoculated with adenovirus encoding a human IFN-\(\gamma\) transgene, it was found that IFN-\(\gamma\) mediated SMC proliferation and intimal expansion in association with phosphorylation of the mTORC1 effector ribosomal protein S6 kinase.\textsuperscript{99} Another interesting aspect of the role of SMC in vascular inflammation has to do with what is known as medial immunoprivilege, which refers to the observation that atherosclerosis and graft arteriosclerosis are characterized by leukocytic infiltration of the vessel wall that spares the media. It appears that induction of indoleamine 2,3-dioxygenase in SMC by IFN-\(\gamma\) accounts for the medial immunoprivilege.\textsuperscript{100}

**IL-4/IL-5 and Th2-Related Cytokines**

Th2 cells secrete IL-4, IL-5, IL-9, and IL-13 and provide help for antibody production by B cells. Th2 cells are rarely detected within the atherosclerotic lesions. However, their induction is promoted in a severe hyperlipidemic context. 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-\(\gamma\). As a result, Th2-biased responses were proposed to antagonize proatherogenic Th1 effects and thereby confer atheroprotection. However, the role of the Th2 pathway in the development of atherosclerosis remains controversial depending on the stage and site of the lesion, as well as on the experimental model. In mouse models that are relatively resistant to atherosclerosis, a Th2 bias has been shown to protect against early fatty streak development.\textsuperscript{101} However, in more permissive models using \textit{LDLr\textsuperscript{-/-}} mice, deficiency in IL-4, the prototypical Th2-related cytokine, had no substantial effect on lesion development in 1 study\textsuperscript{102} but was associated with a decrease in atherosclerotic lesion formation in a previous work by the same group,\textsuperscript{103} suggesting a potentially proatherogenic role. Prolonged hypercholesterolemia in animal models of atherosclerosis is associated with enhanced IL-4 production, which most likely contributes to plaque progression, because IL-4 deficiency at these advanced stages greatly hampers plaque progression.\textsuperscript{62} However, other Th2-related cytokines, IL-5 and IL-33 (see above) appear to exhibit antitherogenic properties. Induction of humoral immunity by immunization of hypercholesterolemic \textit{apoE\textsuperscript{-/-}} mice with oxLDL reduces lesion size in association with the production of high levels of IgM type anti-oxLDL antibodies, likely from B1 cells (reviewed in Binder et al\textsuperscript{104}). These cells appear to be stimulated by IL-5 produced by malondialdehyde-LDL-specific Th2 cells, because antibody generation and atheroprotection were significantly reduced in mice with genetic deletion of IL-5 in bone marrow cells.\textsuperscript{105,106}

**TGF-\(\beta\)/IL-10 and Treg-Related Cytokines**

Natural regulatory T cells develop in the thymus and recognize a specific self-antigen. They are characterized by the expression of CD4, high levels of CD25, and the transcription factor Foxp3 (reviewed in Stephens and Shevach\textsuperscript{107}). They home to peripheral tissues to maintain self-tolerance and prevent autoimmunity by inhibiting pathogenic lymphocytes. Costimulation, particularly through the CD28-CD80/CD86 pathway, is required for their maintenance. Subsets of Treg
cells, induced Treg cells, are also generated in the periphery during active immune responses. Naïve CD4⁺CD25⁻ in the periphery can be converted, in the presence of TGF-β, IL-10, or low dose of antigenic peptide, into CD4⁺CD25⁺FOXP3⁺ cells (see below). The induced Treg cells induced by IL-10 are called Tr1, whereas those induced by TGF-β are called Th3. These cells mediate suppressor function through the production of IL-10 and TGF-β, respectively (see below).

**TGF-β**  
TGF-β inhibits the proliferation, activation, and differentiation of T cells toward Th1 and Th2. In addition, TGF-β1 has been shown to maintain Treg cells in the periphery by acting as a costimulatory factor for expression of Foxp3. Dendritic cells have the capacity to induce Treg cell formation depending on α(v)β8-mediated TGF-β activation. Previous studies have shown that TGF-β has anti-inflammatory and atheroprotective effects. Systemic TGF-β neutralization or genetic deficiency in TGF-β increased lesion development in apoE⁻/⁻ mice. Accelerated atherosclerosis was associated with increased infiltration of inflammatory macrophages and T cells within lesions, together with reduced collagen content. Interestingly, specific deletion of TGF-β signaling in T cells was sufficient to induce increased atherosclerosis, associated with increased differentiation of T cells toward both Th1 and Th2 phenotypes, suggesting Treg cell dysregulation. Indeed, LDLr⁻/⁻ mice transplanted with bone marrow derived cells from CD28- or CD80/CD86-deficient mice, known to display a marked reduction in peripheral Treg cell pool, showed accelerated atherosclerosis and enhanced lesion inflammation. Similarly, transfer of CD28-deficient splenocytes to immune-deficient apoE⁻/⁻/Rag2⁻/⁻ mice led to a marked acceleration of atherosclerosis compared with the transfer of wild-type splenocytes. Similar studies using inducible costimulator-deficient mice clearly showed acceleration of atherosclerosis in association with a reduction in Treg cell number and function. Furthermore, strategies using CD25 neutralizing antibodies in young apoE⁻/⁻ mice clearly demonstrated a protective role of Treg cells against atherosclerosis. Treg depletion did not influence lesion size or inflammatory phenotype in mice with specific deletion of TGF-β signaling in T cells, highlighting the role of TGF-β in the atheroprotective effect of Treg cells.

**IL-10**  
IL-10, produced by macrophages (M2) and lymphocytes, plays an important role in the control of both innate and adaptive immunity. In lymphocytes, the production of IL-10 has been associated to Th2 subset, Treg cells, and more recently to some IFN-γ-producing Th1 cells. Among the regulatory T cells, both natural Treg and induced Tr1 cells have the capacity to produce IL-10. IL-10 deficiency promotes atherosclerotic lesion formation, characterized by increased infiltration of inflammatory cells, particularly activated T cells, and by increased production of proinflammatory cytokines. Leukocyte-derived IL-10 appears to be instrumental in the prevention of atherosclerotic lesion development and in the modulation of cellular and collagen plaque composition. Consistent with a protective role of IL-10 in atherosclerosis, systemic or local overexpression of IL-10 by adenoviral gene transfer in collar-induced carotid atherosclerosis of LDLr⁻/⁻ mice was found to be highly efficient in preventing atherosclerosis. Of note, overexpression of IL-10 by activated T lymphocytes reduced atherosclerosis in LDLr⁻/⁻ mice, suggesting a protective effect for Tr1-like cells in atherosclerosis. This is consistent with a study from our group showing that transfer of clones of Tr1 cells reduces lesion development and that promotion of endogenous adaptive Tr1 cell response plays a significant role in limiting disease development.

Novel strategies to combat autoimmune diseases aim to induce Treg expansion. Such strategies are being developed in atherosclerosis. Intravenous or oral anti-CD3 therapy reduced lesion development and markedly decreased lesion progression in mice with already established atherosclerosis, associated with increased production of TGF-β and enhanced expression of Foxp3 in lymphoid organs. Others have used calcitriol, an active form of vitamin D₃, able to induce tolerogenic dendritic cells or Tregs, in apoE⁻/⁻ mice. Oral administration of calcitriol decreased atherosclerosis possibly by inducing Tregs. This is particularly interesting, given that epidemiological studies have shown an inverse relationship between low plasma levels of vitamin D₃ and predisposition to cardiovascular events.

**Type I IFN**  
Depending on the context, type I IFN (IFN-α and IFN-β) exert either pro- or anti-inflammatory immune functions, but their role in atherosclerosis has not yet been fully elucidated. In the atherosclerotic plaque, IFN-α appears to function as an inflammatory amplifier. It increases the uptake of oxLDL and enhances foam cell formation by upregulation of SR-A expression. Moreover, it upregulates TLR4 expression and intensifies TNF-α, IL-12, and MMP-9 production. IFN-β treatment accelerates atherosclerosis development in both apoE⁻/⁻ and LDLr⁻/⁻ mice, most likely because of the upregulation of specific chemokines and their receptors, including the C-C motif chemokine 5/CCR5 pathway. Furthermore, the lack of the main receptor for type I IFN, IFNAR1, in bone marrow cells transplanted in LDLr⁻/⁻ mice strongly reduces atherosclerotic lesion size and prevents necrotic core formation.

**Granulocyte/Macrophage and Monocyte CSF**  
Granulocyte/macrophage-CSF (GM-CSF) is a myeloid factor that induces dendritic cell differentiation from bone marrow and monocytes and regulates the properties of mature myeloid cells. Modified LDL induces endothelial expression of GM-CSF. The role of GM-CSF in atherosclerosis remains unclear for GM-CSF deficiency induces a decrease in lesion size in LDLr⁻/⁻ mice but an increase in apoE⁻/⁻ mice. Recently, GM-CSF has been shown to be a key factor for proliferation of CD11c⁺ dendritic cells within the atherosclerotic lesion.

Monocyte-CSF (M-CSF), a factor of differentiation and proliferation of stem cells into monocytes, can be locally produced by EC and SMC in atherosclerotic plaques. The first demonstration of the role of M-CSF in atherosclerosis was provided by osteopetrotic mice that have a gene point...
mutation that disrupts M-CSF. Osteopetrotic mice (op/op), deficient in circulating monocytes, tissue macrophages, and osteoclasts, are highly protected from atherosclerosis in the setting of hypercholesterolemia. M-CSF has emerged as 1 of the strongest risk factors for adverse outcomes in patients with stable angina. M-CSF levels were significantly elevated in patients with acute coronary syndromes 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 weeks after discharge in patients with severe unstable angina were strong predictors of cardiac events during a 2-year follow-up. In contrast, admission or discharge cytokine values were not predictive of long-term outcome.

Conclusions
Inflammation plays a major role at all stages of the atherosclerotic process, from the early events whereby leukocytes are recruited at sites of subendothelial LDL cholesterol accumulation to the late events, when plaque rupture occurs, leading to thrombus formation and adverse clinical outcomes. The chronic inflammatory disease of the arterial wall is promoted by both innate and adaptive Th1-driven immunity and is orchestrated by a complex network of proinflammatory cytokines. Murine experimental models of atherosclerosis provide clear evidence that blockade of proinflammatory cytokines results in limitation of plaque development and progression. In humans, anticytokine therapies have proven very successful against autoimmune disease. Notably, anti-TNF-α therapy has been reported to be associated with a lower incidence of cardiovascular events in patients with rheumatoid arthritis, who are at high cardiovascular risk.

However, most of the proinflammatory cytokines are central to a successful host defense against microbial pathogens. Therefore, although therapeutic targeting of these cytokines may be envisioned for a short period of time following acute coronary events, it is unlikely to be accepted for long-term treatment of atherosclerosis, given the cost/benefit ratio. As more is discovered about the complex role of adaptive immunity, especially the adaptoretective effects of Treg cells mediated by IL-10 or TGF-β, more subtle therapeutic approaches adapted to specific long-term treatment aimed at limiting lesion development and atherosclerosis-related inflammation will be developed.

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Recent Advances on the Role of Cytokines in Atherosclerosis
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죽상동맥경화증에서 여러 시토카인(Cytokines)들의 역할에 대한 최신 정보

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Summary

동맥경화증은 연령반응에 유도되는 동맥벽의 염증 질환을 지칭한다. 염증은 동맥경화의 진행과 불안정성을 조절한다. 동맥경화 과정에 관련하는 세포는 cytokine이라고 불리는 여러 가지 수용성 인자를 분비하고, 또한 이것들에 의해 활성화된다. 동맥경화 기전에 대한 최근의 중요한 발견은 이러한 cytokine의 두 가지 역할에 대해 공개를 제시한다. Proinflammatory 및 T helper-1-related cytokines는 동맥경화의 진행을 촉진하고, 반면에 antiinflammatory 및 regulatory T cell-related cytokines는 항동맥경화 작용을 나타낸다.
Commentary

Cytokine는 다양하며 100가지 이상의 종류를 가지고 있다. 이것은 다음과 같이 분류될 수 있는데, interleukin(IL)까지 37종류가 알려져 있으며, tumor necrosis factor(TNF), interferon(IFN), colony-stimulating factor(CSF), transforming growth factor(TGF), chemokine이다. 이러한 cytokines는 동맥경화반에서 증가함을 확인할 수 있다. 이러한 염증성 cytokine의 생물학적 영향은 다양하며 아래와 같이 재시할 수 있다(Figure 1).

실험적으로 유발된 동맥경화에서 cytokine의 영향

TNF-α and structurally related cytokines

동맥경화에 있어서 TNF-α의 역할은 TNF-deficient apolipoprotein-E deficient mice(아포E-)를 이용한 실험에서 확인되었다. 즉 TNF-α-/- apoE-/- mice에서 단순 apoE-/- mice보다 동맥경화의 크기가 유의하게 작을음을 확인하였다. 이것은 ICAM-1, VCAM-1, MCP-1 등의 감소와 관련이 있었다. 다른 TNF superfamily도 동맥경화와 관련이 있는데, TNF-related apoptosis-inducing ligand(TRA1)가 동맥경화반에서 발견되었다. TRAIL은 면역조절을 유지하고 자기면역질환의 발생을 예방하는 데서 면역 반응의 조절자 역할을 한다.

IL-1 cytokine family

IL-1 family에는 sequence homology를 가지고 있는 11개의 단백질이 있으며, IL-1α, IL-1β, IL-1 receptor antagonist(IL-1ra), IL-18, IL-33(ligand of the membrane-bound ST2 receptor), 그리고 새로 발견된 항염증작용을 보이는 IL-37 등이 속한다. IL-1와 같이 IL-18과 IL-33은 강력한 면역 조절작용을 하는 것으로 밝혀졌다.

IL-1

동맥경화 mice 모델에서 IL-1α와 IL-1β의 동맥경화 촉진효과가 확인되었고, 주로 endothelial adhesion molecule의 upregulation, macrophage 및 혈관세포의 활성화와 관련이 있었다. IL-1ra는 IL-1의 금형제로 항염증효과를 보이며, 주로 IL-1 signaling의 내재적 역할을 통하여 효과를 나타낸다.

IL-18

ApoE-/- mice에서 IL-18을 주입하면 동맥경화 병변이 증가한다. IL-18의 내재적 역할을 과학적시험에서 동맥경화가 감소하고 동맥경화반을 좀 더 안정적으로 만든다. IL-18의 동맥경화 촉진효과는 주로 IFN-γ에 의해 매개되는 것으로 보인다. 흩말로는 IL-18은 대사호르몬의 병태생리에도 관여한다. IL-18이 결합된 mice와 IL-18 binding protein이 과발현된 mice에서 비만과 인슐린 저항성이 보고 되었다.
IL-33

IL-33은 원래 염증 반응의 조절자로 알려져 있다. IL-1과 IL-18과의 달리, IL-33은 apoe-/-mice에서 동맥경화를 감소시키는 경향을 보였다. IL-33을 처리하면, IL-4, IL-5, IL-13은 증가하지만, IFN-γ는 감소한다. IL-33의 macrophage의 foam cell 형성을 억제하고 oxLDL uptake를 줄이며, 세포 내 cholesterol content를 감소시켜, cholesterol efflux를 향상시키는 것으로 알려졌다.

IL-6 family

IL-6은 동맥경화를 촉진시키는 것으로 잘 알려져 있다. 하지만 고주령의 IL-6 deficient apoe-/-mice에서는 동맥경화가 증가하고, 1년 된 mice에서는 calcified lesions이 많고, 16주령의 IL-6 deficient apoe-/-mice에서는 wild-type apoe-/-mice의 비교하여 fatty streak 차이가 없었다. 이처럼 동맥경화에 있어서 IL-6의 역할은 이중적인 모양이다.

IL-12 family

IL-12 p35/p40은 heterodimeric cytokine으로 Th1의 분화에 있어서 중요한 역할을 한다. Dendritic cells와 monocytes/macrophages에서 합성된 IL-12는 Th1 polarization에 있어서 중요한 역할을 하고, IL-12는 transcription factor STAT4와 unique Th1 transcription factor를 활성화한다.

IL-17 and Th17 cells

IL-17 cells는 major isomorph IL-17(0r IL-17A)과 IL-17F, IL-21, IL-22 등을 생산한다. In vitro 실험에서 Th17 subset 유형의 mice에서는 TGF-β, IL-6, IL-21에, 사람에서는 IL-1β, IL-23에 의존한다. 동맥경화 죽면에 있어서, IL-17은 동맥경화를 촉진하는 데이 다.

IL-19/IL-20

IL-19와 IL-20은 IL-10 family로 구분된다. IL-19와 IL-20은 monocytes, nonimmune tissue cells 등에서 생성되며, IL-19는 Th2 Responses와 관련이 있다. IL-19는 활성화된 SMC에서 발생되며, balloon injury 후 내막의 비후를 감소시킨다. IL-20은 apoE-/-mice에서 동맥경화를 가진다.

INF-γ and Th1-Related cytokines

INF-γ는 monocytes/macrophages 및 dendritic cells를 활성화시키고, pathogenic Th1 반응을 지속시킨다. INF-γ receptor 또는 INF-γ가 부득이한 경우 동맥경화의 진행을 억제한다. 반면, 외부에서 INF-γ를 주입할 경우 동맥경화를 촉진한다.

IL-4/IL-5 and Th2-Related Cytokines

Th2 세포는 IL-4, IL-5, IL-9, IL-13을 분비하며, B 세포의 형제생성에 도움을 드는다. Th2는 동맥경화 병변에에서는 발견되지 않지만, 심장, 고관절, 췌장에서 Th2의 활성이 촉진된다. 동맥경화가 있는 동물 모델에서 침착된 콜레스테롤은 IL-4의 생성과 연관 있으며, 이는 동맥경화반의 진행과 관련 있다. IL-5와 IL-33은 항등식경화 효과를 보인다.

TGF-β/IL-10 and Treg-Related Cytokines

Natural regulatory T cells는 thymus에서 생성되며, specific self-antigen을 인식한다. 이들은 CD4, CD25, transcription factor Foxp3 등을 발현한다. 이 세포들은 IL-10, TGF-β를 통하여 역제효과를 매개한다.

TGF-β

이전의 연구결과에 따르면, TGF-β는 항염증작용과 동맥경화 감소효과를 보였다. 전산적으로 TGF-β는 증상화하거나 유전적으로 TGF-β를 억제하면,
apoE−/−mice에서 동맥경화가 증가하였다. 이러한 동맥경화의 증가는 염증성 대식세포 및 T cells의 병변 내로의 집중과 관련이 있다.

IL-10
Macrophages(M2)와 lymphocytes에서 생성되는 IL-10은 면역억제에 있어서 중요한 조절자 역할을 한다. 근육구에서 IL-10의 생성은 Th2 subset, Treg cells, IFN-γ-producing Th1 cells와 관련이 있다. Regulatory T cells 중에서는 natural Treg와 induced Tr1 cells가 IL-10을 생성할 수 있다. IL-10의 결합은 동맥경화 병변을 촉진하고, 염증세포 침윤을 억제적으로 보이며, 염증증성 cytokine의 생성을 줄이기 때문이다.

Type I IFN
Type I IFN(IFN-α, IFN-β)는 상황에 따라 진염증성 또는 항염증성 면역작용을 보인다. 그러나 이들의 동맥경화에 있어서의 역할은 완전히 밝혀지지 않았다. IFN-α는 동맥경화세포에 있어서 염증반응을 증폭시키는 역할을 하는 것이 보인다. 이는 oxLDL의 uptake를 증가시키고, foam cell 형성을 촉진하기 때문이다.

Granulocyte/Macrophage and Monocyte CSF
Modified LDL는 혈관내피세포에서의 GM-CSF의 발현을 유도한다. GM-CSF 결합 시 LDLr−/−mice에서는 동맥경화가 감소하지만, apoE−/−mice에서는 증가한다. 이들 동맥경화에 있어서 GM-CSF의 역할은 아직 명확하지 않다.

Conclusion
염증반응은 동맥경화 진행의 모든 단계에서 중요한 역할을 한다. 동맥벽의 만성 염증은 Th1 세포에 의해 야기되는 염증반응에 의해 향상되며, 친홍성 인자의 복합적인 네트워크에 의해 조절을 이룬다. 설탕류를 대상으로 한 동맥경화 모델에서 친홍성 cytokine을 억제할 경우, 동맥경화의 발생과 진행을 저해하는 결과를 가져왔다. 또한 사람을 대상으로 한 연구에서는 anticytokine 치료가 면역억제에 효과적이었음을 보였다. 광범위한 치료는 anti-TNF-α therapy가 쥐의 실험실에서 심혈관질환의 위험성을 낮추었다는 것이다. 그러나 대부분의 친홍성 cytokine은 염증성 병변에 대한 방해 역할을 한다. 따라서, 심혈관질환의 발생 이후 일시적으로 이러한 cytokine을 target으로 한 치료가 효과적이며, 장기간 사용하는 것은 비용효과를 고려할 때 효과적이지 않다. 혈증 면역체계의 복합성 역할이 규명됨에 따라 동맥경화를 줄일 수 있으나, 정기적으로 효과적인 치료적 접근이 필요하다.

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