IL-10: An “Immunologic Scalpel” for Atherosclerosis?

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Mononuclear leukocyte–mediated inflammation is a central feature of atherosclerosis. Using measures that diminish lesion monocyte recruitment and macrophage-mediated inflammation, investigators have shown these specific events to be essential to the development and progression of atherosclerotic lesions. Lesion T lymphocytes have an activated phenotype and colocalize with lesion macrophages, particularly in early disease. However, the role of lesion T lymphocytes in atherogenesis is not as well understood as the role of macrophages.

A variety of inflammatory mediators, including cytokines, growth factors, and proinflammatory lipids, are present in atherosclerotic lesions. However, even in the complex milieu of a chronic inflammatory locus, a limited number of cytokines can become dominant. This concept has most recently been illustrated by the dramatic success of inhibitors of tumor necrosis factor (TNF-α) in the treatment of rheumatoid arthritis. Thus, certain inhibitors of cytokines, or anti-inflammatory cytokines, have been proposed as potential “immunologic scalpels” to diminish the activity of several chronic mononuclear leukocyte–mediated inflammatory diseases.

Interleukin (IL)-10, a prototypical anti-inflammatory cytokine, is under investigation (and in a few cases at the stage of clinical trials) for therapy of a variety of chronic diseases. These include rheumatoid arthritis, inflammatory bowel disease, psoriasis, multiple sclerosis, allergic eosinophilic inflammation, Wegener’s granulomatosis, and cardiac allograft rejection. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Pinderski Oslund et al present a novel chapter in an evolving story on the potential modulatory role of IL-10 in atherosclerosis.

A cross-regulatory role in atherosclerosis of the activated monocyte-macrophage (and Th2 immune response) product IL-10 with the Th1 response–promoting cytokine IL-12 was first proposed by Uyemura and colleagues. IL-10 downregulates IL-12 production and inhibits Th1 immune responses, which would normally be associated with IL-2 and interferon-γ (IFN-γ) expression and with T-cell and macrophage activation. IL-12 was generally expressed in atherosclerotic plaques, and highly oxidized LDL but not minimally modified LDL induced IL-12 in monocytes in vitro. But IL-10 inhibited the oxidized LDL–induced IL-12 release. Yet IL-10 was not universally expressed in a panel of atherosclerotic lesions.

In apolipoprotein (apo) E null mice, IL-12 mRNA appeared earlier than did IL-10 mRNA in atherosclerotic aortic lesions. Furthermore, daily IL-12 administration caused accelerated atherosclerosis, associated with increased serum antibodies to oxidized LDL. Thus, the expression of IL-10 may be “too little, too late” to prevent IL-12–mediated atherogenesis in apoE null mice.

In the work by Pinderski Oslund et al that appears in this issue, diet-induced atherosclerotic lesions were larger in IL-10 null mice on a C57BL/6 background than in control mice. In additional experiments, transgenic murine IL-10 expression was selectively driven in T cells by the human IL-2 promoter. Serum IL-10 does not appear to be increased, as determined in past experience with this model. Yet the transgenic IL-10 expression was associated with smaller atherosclerotic lesions than in controls. A relatively mild form of dietary atherosclerosis was studied by Pinderski Oslund et al in the C57BL/6 mice. In this regard, the atherogenic effects of T cells are believed to be greater in this model than in murine models in which more severe hyperlipidemia is induced. It is conceivable that increased IL-10 expression (at the single-cell level) in lesion T lymphocytes contributed to the atheroprotective effect. But this remains to be directly proven by study of lesions for IL-10 expression and Th1 and Th2 responses.

Systemic and intralobessional delivery of IL-10 could diminish atherogenesis by a variety of means. First, and possibly foremost, IL-10 inhibits the production of several proinflammatory cytokines (including IL-1β, TNF-α, and IL-8) by mononuclear cells, and IL-10 also induces release of the IL-1 receptor antagonist. The inhibitory cytokine activity of IL-10 includes particularly potent suppression of the expression of the CXCR2-binding chemokine KC/GROα. In this light, KC/GROα was recently implicated in intimal macrophage accumulation and the progression of complex atherosclerotic lesions in advanced disease in LDL receptor null mice in a CXCR2 null bone marrow transplant model. Less clear is the extent of the suppressive effects of IL-10 on the expression of monocyte chemoattractant protein-1 (MCP-1), the dominant mediator of monocyte recruitment to early atherosclerotic lesions.

Some of the suppressive effects of IL-10 on cytokine and inflammatory mediator production in tissues may be modulated by inhibition of interferon signaling through STAT transcription factors and by inhibition of interferon production. IL-10 also suppresses stress kinase signaling and can

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inhibit translocation of the transcription factor nuclear factor-κB. Direct inhibition of inflammatory gene expression by IL-10 also is modulated in part by AU-rich elements (ARE) present in the 3' untranslated region of sensitive genes. IL-10 effectively destabilizes the mRNA of genes with these ARE motifs, which may be clustered, as in KC/GROα.4

The ability of IL-10 to affect signal transduction is most likely mediated by a substantial presence of IL-10 on the cell surface in monocytes. Not only does surface IL-10 increase in macrophages, but also, IL-10 actively promotes differentiation of monocytes to macrophages.11 Interestingly, IL-10 inhibits antigen presentation, whereas it stimulates endocytic and phagocytic activity in macrophages.12

The ability of IL-10 to suppress certain CD40/CD40L ligand–mediated monocyte responses3,13,14 may be particularly relevant in atherosclerosis.13 Ligation of CD40 on monocytes through its interaction with CD40L, which can be presented by activated T helper cells, endothelial cells, or platelets, results in the induction of several cytokines in monocytes. These include not only the chemokines MCP-1 and IL-8 but also IL-10. CD40/CD40L interaction also rescues monocytes from apoptosis induced by serum deprivation.14 Treatment of monocytes with IL-10 attenuates CD40/CD40L-mediated activation of protein tyrosine kinase activity and ensuing inflammatory cytokine production, but not CD40/CD40L-mediated rescue from the apoptosis of serum deprivation.13,14

Suppression of the ERK1/ERK2 pathway signaling by IL-10 modulates inhibition of the CD40/CD40L-induced cytokine expression.13 In this context, broad effects of IL-10 on signaling through ERK1/ERK2 and other mitogen-activated protein kinase pathways are potentially linked in a direct way to the effects of IL-10 on mRNA stability of certain inflammatory cytokines.

The article by Pinderski Oslund et al in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology1 demonstrates for the first time that IL-10 also can inhibit MM-LDL–induced monocyte-endothelium interaction, as assessed by monocyte binding. In this regard, IL-10 can induce endothelial E-selectin, but IL-10 suppresses endothelial vascular cell adhesion molecule-1 (VCAM-1) expression, which suggests that selective effects of IL-10 on endothelial activation might contribute to the antiatherogenic effects of IL-10.

Other potential antiatherogenic activities of IL-10 include the ability to regulate monocyte-induced matrix degradation. Specifically, IL-10 inhibits lysosomal enzyme release by monocytes, suppresses the production of certain metalloproteinases, and induces tissue inhibitor of metalloproteinase-1 expression by mononuclear cells. IL-10 also inhibits tissue factor factor expression by activated human monocytes16 and thereby could help limit superimposed thrombotic complications in atherosclerosis.

Would exogenous IL-10 administration be pragmatic, effective, and safe in the treatment of established atherosclerosis? The suppressive effects of IL-10 on immune responses are generally dependent on the timing of IL-10 administration.17 Thus, modulation of murine IL-10 expression before and during the earliest atherogenic events may have been a major contributor to the substantial effects on atherosclerosis observed by Pinderski Oslund et al in IL-10 transgenic and IL-10 null mice. The timing of exogenous IL-10 administration for atherosclerosis will almost certainly determine the effects on the inflammatory response in this disease. Furthermore, cost-effective methods to optimize the systemic delivery and effects of exogenous IL-10, which are under investigation, will need to be worked out in vivo for atherosclerosis. In this context, nasal IL-10 administration has shown some systemic efficacy.18

Interference with mother nature generally brings about unexpected consequences. The costs of long-term use of IL-10 as a therapeutic would be anticipated to include the consequences of induction of antigen-specific anergy. IL-10 also can increase susceptibility to certain infections, particularly involving intracellular pathogens such as Chlamydia and Listeria monocytogenes.

Expression of the Epstein-Barr virus (EBV) IL-10 gene has been suspected to have a potential role in oncogenesis associated with long-term EBV infection. However, IL-10 can have either tumor-promoting or tumor-suppressive activities in different experimental systems. In addition, IL-10 upregulates NO synthesis by activated macrophages,19 stimulates the chemotactic migratory capacity of monocyte-derived cells, and can significantly augment platelet-activating factor receptor expression by leukocytes.20 It is recognized that IL-10 is a stimulatory factor for B cells and mast cells and that IL-10 can promote certain inflammatory responses in vivo.21 Significantly, IL-10 contributes to the early pathogenesis of diabetes in nonobese diabetic mice via a CD8+ T-cell pathway.22 The biological significance and long-term consequences of these activities in humans are unclear.

In summary, the article by Pinderski Oslund et al is a long step beyond the earliest evidence for a role of IL-10 in modulating atherogenesis. Although IL-10 can be used as an immunologic tool, IL-10 does have potential for double-edged regulatory influences on inflammation. EBV IL-10, which has broad anti-inflammatory activity but does not possess any intrinsic T-cell costimulatory activity, might be an interesting therapeutic candidate for studies of the potential for IL-10 to arrest and reverse the chronic inflammatory response in established atherosclerosis. Investigation of exogenous IL-10 as a treatment for various stages of murine atherosclerosis is strongly indicated and should provide intriguing results.

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References


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