T Cells in Coronary Artery Disease

Different Effects of Different T-Cell Subsets*

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The simplistic view of atherosclerosis as a disorder of pathologic lipid deposition has been redefined by the more complex concept of an ongoing inflammatory response (1). Several cellular components seem to participate in this persistent inflammation, such as macrophages, vascular smooth muscle cells (VSMC), and endothelial cells. The presence of activated T cells in all stages of atherogenesis implies that these cells also are involved in the aggravation of atherosclerotic disorders (2). Indeed, T-cell–deficient severe combined immunodeficiency mice on an apolipoprotein E (apoE)-knockout background develop less atherosclerotic disease than do immunocompetent apoE-knockout mice (3). On the other hand, transfer of CD4+ T cells into these immunodeficient atherosclerotic mice accelerates the disease (3).

It has been suggested that only subsets of T cells account for their proatherogenic activity. Recently, Zhou et al. (3) showed that the absence of CD4+ cells in apoE−/− mice leads to reduced atherosclerosis, indicating that CD4+ T cells constitute a major proatherogenic cell population, and there is solid evidence from several independent groups that the T helper type 1 (TH1) subset is such a particular proatherogenic subset. First, a number of studies have colocalized CD4+ T cells and interferon (IFN)-γ within atherosclerotic lesions, suggesting predominance of TH1 cells in atherogenesis (4). More recently, high levels of interleukin (IL)-12 and IL-18 have also been detected in atherosclerotic plaques, further suggesting a TH1 profile in these lesions (5). Second, a direct role in atherogenesis has been defined in atherosclerotic-susceptible mice that are deficient in either IFN-γ receptors or the cytokine itself (6). Conversely, injection of IFN-γ or the IFN-γ–releasing factors IL-12 and −18 enhances the extent of disease in apoE−/− mice (7). These findings may be due to the fact that IFN-γ activates endothelial cells and inhibits collagen synthesis in VSMC. This cytokine may also activate macrophages to produce reactive oxygen species and matrix metalloproteinases, suggesting a role for TH1-related cytokines not only in atherogenesis, but also in plaque destabilization (8). Finally, monocytes from patients with unstable angina exhibit a molecular fingerprint of a recent IFN-γ triggering, and such patients also have raised plasma levels of IL-18 that significantly correlated with the degree of myocardial dysfunction, further implicating TH1-mediated immune responses in the pathogenesis of acute coronary syndromes (ACS) (9).

TH2 Cells: Friend or Foe?

A number of experiments suggest that TH2-driven humoral immune responses may be atheroprotective. Thus, IL-5, a typical TH2 cytokine, was recently shown to attenuate atherosclerosis, in part by stimulating the expansion of atheroprotective natural immunoglobulin M specific for oxidized low-density lipoprotein (oxLDL) (1,2). Moreover, a switch toward a TH2 cytokine profile in mouse models of atherosclerosis has been found to be associated with increased production of protective anti-oxLDL antibodies (1,2). Finally, production of high titers of immunoglobulin M-type anti-oxLDL antibodies, as in the case following immunization of LDLR−/− mice with malondialdehyde-LDL, is associated with reduced lesion size (10). Taken together, these studies suggest an attenuating effect of TH2 cells on atherogenesis, at least partly involving the induction of atheroprotective antibodies. However, TH2 cytokines may also contribute to the formation of aneurysms by inducing elastolytic enzymes, and switching the immune response of atherosclerosis from TH1 to TH2 may not necessarily attenuate vascular disease. Thus, IL-4, the prototypic TH2 cytokine, exhibits inflammatory (e.g., induction of chemokines) and oxidative (activation of NADPH oxidase) properties and has been suggested to contribute to vascular inflammation in disorders such as atherosclerosis and asthma. In fact, deficiency in IL-4 is associated with a decrease in atherosclerotic lesion formation, particularly at the advanced stages of lesion progression (11).

Regulatory T Cells: Potential Inhibitors of Atherogenesis

Several reports suggest antiatherogenic and plaque-stabilizing effects of IL-10 involving anti-inflammatory,
matrix stabilizing, antithrombotic, and antiapoptotic effects (12). Also, transforming growth factor (TGF)-β, another T-cell–derived antiinflammatory cytokine, has been shown to possess potent antiatherogenic properties. Thus, when apoE-knockout mice were crossed with transgenic mice carrying a dominant negative TGF-β receptor II in T cells, the offspring developed markedly increased atherosclerosis with larger and more unstable lesions (2). A specific component of the immune system, known as the CD4+CD25hi regulatory T cells (Treg), is specialized for the suppression of both Th1 and Th2 pathogenic immune responses against self or foreign antigens, and, interestingly, this T-cell subset seems to be a major cellular source of IL-10 and TGF-β, making it an attractive therapeutic target in preventing atherosclerosis. In fact, these T cells have been found to be powerful inhibitors of atherosclerosis in mouse models (13). Moreover, Heller et al. recently showed the expression of Treg within human atherosclerotic lesions, colocalized with both IL-10 and TGF-β1 expression (14). These findings are consistent with a critical role of these immunosuppressive cytokines (i.e., IL-10 and TGF-β) in Treg–mediated atheroprotection. Moreover, engagement of cytotoxic T-lymphocyte antigen 4 on Treg with CD80/CD86 on pathogenic cells has been identified as cell–cell contact mechanisms of suppression, at least in vitro.

**CD4^+CD28^- T Cells: Inflammatory and Proatherogenic T-Cell Subset**

The CD4^+CD28^- cells are a rare subset of long-lived directly cytotoxic CD4^+ T cells that secrete high levels of IFN-γ, and that have been implicated in the pathogenesis of various inflammatory disorders. In contrast to Treg these T cells possess proatherogenic and plaque–destabilizing properties. Thus, this T-cell subset has been found to preferentially infiltrate unstable plaque and contribute to increased endothelial cell lysis in patients with ACS (15). Moreover, CD4^+CD28^- T cells, isolated from either the plaque tissue or the blood of patients with ACS, spontaneously express IL-12 receptors (16). In animal models, CD4^+CD28^- T cells respond to any IL-12–inducing host infection with a shift in tissue trafficking and accrual in inflammatory lesions, such as an atherosclerotic lesion (16). In this issue of the Journal, Liuzzo et al. (17) present novel data underscoring the in vivo relevance of this inflammatory T-cell subset for human coronary artery disease. This group has previously reported that patients with unstable angina, but not those with stable angina, experience expansion of the CD4^+ T cells that lack the CD28 marker (18). They have also shown accumulation of this T-cell subset in unstable coronary plaques, suggesting that these cells may be involved in plaque instability (15). Here they extend these findings by showing that the frequency of this aggressive and inflammatory T-cell phenotype in peripheral blood predicts recurrent episodes of instability in patients with unstable angina.

Although they further underscore the potential pathogenic role of CD4^+CD28^- T cells in immune-mediated plaque destabilization, their novel findings also suggest that quantification of this T-cell subset could be useful in the selection of patients at risk for future and recurrent coronary events. Based on the potential pathogenic role in plaque destabilization, modulation of CD4^+CD28^- T cells in patients with unstable angina may be clinically relevant. There are some reports suggesting that statins may downregulate this T-cell subset, further supporting a role for statins in the management of unstable disease (19). Interestingly, the same team has also recently reported that the expansion of CD4^+CD28^- T cells in patients with unstable angina may be reduced by selective TNF-α blockade (i.e., infliximab) (20). Although caution should be taken when using such therapy in unstable angina, because of the potential risk for induction of apoptosis of TNF-expressing cells within the unstable lesion (e.g., foam cells, endothelial cells, and VSMC), their finding illustrates the potential for immunomodulating therapy in this disorder.

**Conclusions**

Although the pathogenic role of T cells in atherosclerosis and plaque destabilization is well established, the complex function of the various T-cell subsets in this disorder is far from clear. Although activation of Treg may be an interesting antiatherogenic target, activation of the inflammatory CD4^+CD28^- T-cell subsets may promote plaque rupture and the development of ACS. However, the dynamics of T-cell response within the plaque are still poorly understood, and both antigen-dependent (e.g., heat shock proteins, oxidized lipoproteins, different microbial antigens) and antigen-independent (e.g., IL-7 and -15) stimuli may be involved in the oligoclonal expansion of T cells in atherosclerotic plaques. Moreover, recent studies suggest that even other T-cell subsets than those that are discussed here may be involved in atherogenesis, such as the T_{H}17 subset, which produces the inflammatory cytokine IL-17, and CCR7+ T cells, potentially playing a role in the promotion of T-cell infiltration and inflammation within the atherosclerotic lesion (2,21). Nevertheless, the different nature of the various T-cell subsets as well as their complex role in atherogenesis and plaque destabilization underscores that future research in T-cell immunology not only is of interest to the basic research field but also may have relevance to clinical cardiology.

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