Interleukin-17 and Atherosclerotic Vascular Disease

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Atherosclerotic vascular disease (ASVD) involves several overlapping pathological processes. Atherogenesis, the process by which atherosclerotic plaques develop in the arterial wall, involves inspissation of abnormal circulating lipoproteins into the vessel intima, resulting in inflammation, injury, and responses to injury. Mouse models of atherogenesis, involving impaired low-density lipoprotein clearance due to gene knockout of either apolipoprotein E (ApoE) or low-density lipoprotein receptor, are widely used to study this process. The presence of plaques in humans sets the stage for complications, such as plaque rupture or fissure that stimulate thrombosis; intraplaque hemorrhages that may rapidly cause luminal impingement; more gradual but progressive vascular stenoses due to inadequate outward remodeling that produce chronic ischemia; inflammatory aneurysms with the potential for catastrophic events, such as aortic rupture; or plaque embolization, leading to infarcts in tissues distal to the plaque site. Each of these complications arises from distinct but overlapping causes, of which inflammation is a significant component. Mouse models for the study of these complications have significant limitations.

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Inflammation in ASVD is best described as chronic active, involving acute exacerbations superimposed on a more persistent, indolent process. The initial trigger for inflammation in the vessel wall may be innate immunity, an inflammatory process that is activated by myeloid cells or some types of innate lymphocytes recognizing conserved motifs in microbe-derived molecules or of endogenous molecules that are released as a consequence of cell injury. Recognition of these conserved molecular motifs also enables certain myeloid (especially myeloid dendritic cells) or innate lymphoid cell types to effectively present antigens to T cells, triggering the adaptive immune system. Activated CD4+ T cells, a major effector cell type of adaptive immunity, function by releasing cytokines that act on myeloid cells, on other lymphocytes, and on intrinsic tissue cells in an orchestrated response to eradicate the source of antigen. Chronically activated CD4+ T effector cells may differentiate to produce a limited pattern of cytokines that trigger specific types of responses. CD4+ T cells that release interferon (IFN)-γ are designated T helper (Th)1 cells and serve as the principal mediators of host defense versus intracellular bacteria. The Th2 CD4+ T effector cell subset releases interleukin (IL)-4, IL-5, and IL-13 and mediates host defense versus helminths and other multicellular parasites. Recently, a third CD4+ T effector cell subset has been proposed, designated Th17 because these cells release the cytokines IL-17A and IL-17F, as well as IL-22; Th17 cells mediate host defense versus fungi. Each of these 3 types of Th subsets can inhibit the other 2 types. These various Th subsets also may, when inappropriately activated, lead to disease. Both Th1 and Th17 cells have been linked to autoimmunity, and Th2 cells are linked to allergy.

CD4+ T cells infiltrate atherosclerotic plaques, and certain aspects of ASVD may be a form of autoimmunity, meaning that the adaptive immune system perpetuates an inflammatory reaction by responding to self-derived rather than microbe-derived antigens. Th1 cells are the major CD4+ T cell subtype found in human atherosclerotic plaques and, in mouse models of atherogenesis, exacerbate plaque formation caused by elevated lipoproteins. More recently, IL-17-producing T cells have also been found in human plaques, but many of these cells can concomitantly produce IFN-γ, defying their neat characterization as Th17 cells. Furthermore, some human CD4+ Th cells, especially those that make IL-17, exhibit plasticity, changing the effector cytokines they release depending on environmental stimuli and sometimes even converting from effector cells to protective regulatory T cells. Although this raises questions about what kinds of T cells are present in plaques, and these may vary with disease activity or complication, the effects of the cytokines made by T cells (and other cell types) can be studied directly. What is known about the roles of specific Th cytokines in ASVD? IFN-γ is a mitogen for human smooth muscle cells within the intima or media of the vessel wall, even though it may inhibit smooth muscle cell proliferation in cell culture. It also can induce mediolugal but not intimal smooth muscle cells to express very high levels of the tryptophan-degrading enzyme indoleamine 2,3-dioxygenase, depriving infiltrating T cells of this crucial nutrient and creating a compartment of immunoprivilege. At the same time, IFN-γ may combine with other cytokines to potentiate the susceptibility of human vascular cells to killing by effector cells of the immune system. In the ApoE−/− mouse model of atherogenesis, genetic deletion of IFN-γ or its receptor inhibits plaque formation. Overall, IFN-γ is viewed as a proatherosclerotic cytokine. Much less is known about the roles of IL-17A or IL-17F in ASVD. IL-17A can collaborate with IFN-γ to increase the elaboration of inflammatory cytokines by human smooth muscle cells. It does not appear to influence cultured smooth muscle cell growth, but it has not been tested for mitogenic potential in the context of the vessel wall. Neutralizing IL-17A does not prevent intimal expansion of human vessel segments in a model of Th1-mediated transplant rejection, a process that may share some
features with atherogenesis. However, neutralizing IL-17A in ApoE−/− mice does reduce plaque size, although results in other models of atherogenesis are less clear.

In the present issue of the journal, Madhur and colleagues use a genetic approach to further address this question. Specifically, they have cross-bred IL-17A knockout mice with ApoE knockout mice, producing homozygous double-knockout animals on a CB57Bl/6 background. When fed a high-fat diet, neither the size nor the extent of plaque development in double-knockout animals differs from that of ApoE single-deficient mice on the same diet. The authors also show that in humans, IL-17A levels do not correlate with carotid intima-media ratios, a measure that correlates with coronary artery plaque burden. These findings are consistent with the conclusion that IL-17A is not important in atherogenesis, contradicting the antibody neutralization studies. However, levels of IL-17F increase, potentially compensating for the absence of IL-17A. Madhur and colleagues do find that in double-knockout animals on a high-fat diet, circulating levels of IFN-γ are decreased and inflammatory cells within the plaques of double-knockout animals show reduced numbers of myeloid cells (especially dendritic cell) and T cells accompanied by a reduction of superoxide production and an extent of plaque development in double-knockout animals differs from that of ApoE single-deficient mice on the same diet. The authors also show that in humans, IL-17A levels do not correlate with carotid intima-media ratios, a measure that correlates with coronary artery plaque burden. These findings are consistent with the conclusion that IL-17A is not important in atherogenesis, contradicting the antibody neutralization studies. However, levels of IL-17F increase, potentially compensating for the absence of IL-17A. Madhur and colleagues do find that in double-knockout animals on a high-fat diet, circulating levels of IFN-γ are decreased and inflammatory cells within the plaques of double-knockout animals show reduced numbers of myeloid cells (especially dendritic cell) and T cells accompanied by a reduction of superoxide production and an increase in NO generation. This suggests that IL-17A could play a role in some inflammatory complications of ASVD, such as plaque rupture. Interestingly, IL-17A did not affect aneurysm formation induced by angiotensin II infusion but play a role in some inflammatory complications of ASVD, where does this leave us? As noted above, ASVD is a complicated amalgam of multiple processes with different sources contributing to pathogenesis in various ways and at various times. IL-17A could well play an important role in some of these but not others. Madhur and colleagues have taken an important first step in sorting these out.

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References

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