The notion that inflammation plays a role in atherosclerosis dates to separate observations by Virchow and von Rokitansky in the middle of the 19th century that atherosclerotic blood vessels contained evidence of cellular inflammation. This concept remained stagnant until the 1970s, when Russell Ross demonstrated that monocyte adhesion to the endothelial surface was an early and essential feature of atherosclerosis. These observations, coupled with knowledge that modified low-density lipoprotein (LDL) supports foam cell formation and promotes atherosclerosis disease activity, focused early investigative efforts on monocytes and macrophages, the foam cell precursors. Indeed, it is clear that neutrophils and monocytes enter lesion-prone arterial sites, the latter differentiate into macrophages, and then take up accumulated LDL-cholesterol to form foam cells and early atherosclerotic lesions. Innate immune responses, such as recognition of modified LDL-derived epitopes via macrophage Toll-like receptors, prompts cytokine-mediated recruitment of other inflammatory cells to the lesion that, in turn, promote the adaptive immune responses responsible for the chronic inflammation of atherosclerosis. Emerging evidence has helped to refine this paradigm and identify critical events in adaptive immunity that could represent therapeutic opportunities for immune modulation of atherosclerosis.

Activated endothelium is characterized by adhesion molecule expression and reduced barrier function that mediate the recruitment of both monocytes and T-cells into lesion-prone sites in the arterial wall. With regard to T-cells, histological examination of atherosclerotic lesions demonstrates the presence of both CD4+ T helper (Th) cells, CD8+ cytotoxic T (Tc) cells, and regulatory T cells (Treg) in lesions, although Th cells generally predominate. Lesional T-cells represent a cellular minority (compared to monocyteid cells), but are known to profoundly impact atherosclerosis with Th cells generally promoting the disease and Tregs exhibiting inhibition. Reconstitution of CD4+ Th cells into Scid mice accelerates atherosclerosis as does expansion of lesional Th cell numbers due to limiting Treg activity. With regard to Tregs, their population in the arterial wall is enhanced by CXCL10 deficiency, leading to reduced atherosclerosis. In this regard, it is interesting to note that diet-induced hypercholesterolemia profoundly limits the population and function of Treg cells in atherosclerotic lesions. Reversal of hypercholesterolemia, however, prevents the loss of lesional Tregs and preserves their function. These data suggest that cholesterol lowering may impact atherosclerosis, at least in part, by changing the distribution and activity of T-cell populations within the arterial wall.

The profound impact of T-cells on atherosclerosis fits with their known function(s) in immune modulation. Histology of atherosclerotic lesions often demonstrate colocalization of T-cells, with antigen presenting cells such as dendritic cells and MHC class II expressing macrophages. These findings fit with models of adaptive immunity whereby T-cells become activated through interaction with antigen presenting cells. The latter are typically mature dendritic cells that have a high surface density of MHC-antigen complexes that are required for conversion of naïve T-cells to effector/memory cells that propagate adaptive immunity. Thus, relatively few Th cells and dendritic cells have the capacity to promote expansion of adaptive immunity.

Classical models for the transition from innate (immediate) to adaptive (long-term) immunity involves migration of T-cells and mature dendritic cells to secondary lymphoid organs, where dendritic cell antigen presentation affords T-cell differentiation and activation. One key component of this process is the chemokine receptor type 7 (CCR7) that is required for lymphoid organ colocalization and the interaction of dendritic and T-cells. Accordingly, deficiency of CCR7 results in defects in the transition from innate to adaptive immune responses, and this paradigm extends to atherosclerosis. Mice lacking CCR7 exhibiting a 50% reduction in lesion formation on the LDL receptor-null background, with no impact on cholesterol levels by CCR7 status. In lesions, the lack of CCR7 was associated with reduced macrophage content and, surprisingly, increased numbers of dendritic cells and T-cells. These latter 2 cell types were notably absent from lymph nodes of CCR7-null mice, suggesting that atherosclerosis is dependent on cycling of T-cells and dendritic cells between the vessel wall and secondary lymphoid organs. These observations indicate that our focus on the arterial wall as the major site of atherosclerosis-associated inflammation needs to be revisited to include secondary lymphoid organs. Moreover, the possibility exists that manipulation of lymphoid tissue could represent an attractive and accessible target for therapeutic intervention of atherosclerosis.

Dendritic cells (as well as classes of B-cells and macrophages) promote inflammation primarily through antigen presentation, a process that involves endocytosis of extracellular antigens followed by their loading onto MHC class II molecules in late endosomes and subsequent cell surface expression of the stable MHC class II antigen complexes. MHC class II maturation depends on CD74, and mice lacking this so-called invariant chain have defective antigen presen-
tation. When bred onto the LDL receptor-null background, CD74-null mice were protected against atherosclerosis and exhibited impaired adaptive immune responses to modified LDL epitopes as manifest as reduced Th cell cytokine release and production of Th-dependent IgG antibodies. Conversely, CD74-null animals exhibited an increase in peripheral B-1 cells and increased titers of B cell-dependent antibodies (IgM, IgG3) against modified LDL. These data suggest that antigen presentation has a role in the relative activities of T-cell versus B-cell mediated responses, with the latter having an atheroprotective role. Consistent with this notion, serum IgM deficiency promotes both the extent and complexity of atherosclerosis in LDL receptor-null mice. These data highlight the notion that some inflammatory responses in atherosclerosis are protective and may restrain more aggressive disease.

Dendritic cells are not only important for T-cell activation, but they are also critical for self-tolerance, because dendritic cell apoptosis is thought to be an important mechanism for limiting antigen presentation and, as a consequence, adaptive immunity. The role of dendritic cell apoptosis in atherosclerosis has recently been investigated using animals expressing an apoptosis inhibitor (bcl-2) under the control of a dendritic cell-specific promoter (CD11c). This model achieved expansion of dendritic cells and enhanced T-cell activation in vivo with a relative shift toward Th1 cells and increases in anti ox-LDL antibodies of the IgG2c type, indicative of Th1 activation. Despite the fact that Th1 activity is thought to promote atherosclerosis, this model of dendritic cell expansion showed no increased atherosclerosis when transplanted into either LDL receptor-null or ApoE-null mice. This seemingly paradoxical result was due to an ~25% reduction in cholesterol with dendritic cell expansion in either model of hypercholesterolemia. Conversely, acute depletion of dendritic cells in either model resulted in a significant increase in total cholesterol. Thus, dendritic cells appear to have a previously unrecognized role in the clearance of cholesterol. The key role of dendritic cells in self tolerance has been exploited as a means to impact disease. Dendritic cells exposed to IL-10, an immunosuppressive cytokine, adopt a tolerogenic phenotype characterized by reduced generation of proinflammatory cytokines, Treg generation, and antigen-specific T-cell anergy. These observations have been exploited in experimental atherosclerosis by incubating IL-10-treated dendritic cells with apolipoprotein B-100 to generate tolerance to the protein moiety of LDL. In so doing, Hermansson and colleagues found that injection of these cells into atherosclerosis-prone mice produced a 70% reduction in the development of atherosclerosis with predictable defects in cellular immunity to Apo B-100. These data add to the body of literature that strategies exist for manipulation of immunity in a manner that could attenuate atherosclerosis.

As our knowledge of adaptive immunity has advanced, it has become clear that atherosclerosis involves activation of both cellular and humoral immunity that balance the response to LDL deposition in the arterial wall. We now have the tools, at least in experimental models, to alter the course of atherosclerosis through immune modulation. Despite these exciting advances, the best strategies for the treatment of established atherosclerosis remain a challenge that must be addressed in order to bring immune modulation of atherosclerosis into the clinical realm.

**Sources of Funding**

Dr Keaney’s research efforts are supported by National Institutes of Health Grants HL092122 and HL098407.

**Disclosures**

None.

**References**


**Key Words:** atherosclerosis
Immune Modulation of Atherosclerosis
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Circulation. 2011;124:e559-e560
doi: 10.1161/CIRCULATIONAHA.111.074096
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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