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REVIEW

Immunomodulation of Vascular Diseases: Atherosclerosis and Autoimmunity

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Abstract The autoimmune disease atherosclerosis contributes to several vascular complications. Besides vascular cells, inflammatory cells occur prominently in atherosclerotic lesions; lymphocytes play a detrimental role in the initiation and progression of this common vascular disease. Recent discoveries have led to the identification of several important lymphocyte types within the atherosclerotic lesions. However, peripheral lymphocytes and those in the lymphoid organs both figure critically in the regulation of atherosclerotic lesion growth. Although the concept of atherosclerosis as an autoimmune disease is well known, the ways in which autoantigens and autoantibodies contribute to atherogenesis in human or even in animal models remains largely unknown. For example, autoantigen immunisation can either promote or attenuate atherogenesis in animals, depending on the antigen types and the routes and carriers of immunisation. This article summarises recent findings regarding lesion inflammatory cell types, autoantigens and autoantibody isotypes that can affect the initiation and progression of atherosclerosis from both human and animal studies.

Atherosclerosis remains the most common cause of vascular complications, including stroke, myocardial infarction (MI) and aortic aneurysms. Data suggest that atherosclerosis also constitutes an autoimmune disease, in which autoantigens and autoantibodies affect this vasculature remodelling process. Processing and presentation of autoantigens and subsequent autoantibody production can occur in lymphoid organs as well as in non-lymphoid tissues such as aortas. In human atherosclerotic lesions, many cells participate in this process, including lymphocytes, macrophages, dendritic cells (DCs), mast cells and even vascular smooth muscle cells (SMCs) or endothelial cells (ECs) (Fig. 1). Many of the inflammatory cells are recruited from the lymphoid organs or the circulation and participate in antigen or autoantigen presentation and T-cell activation. This study discusses our current understanding of how autoantigens and autoantibodies contribute to atherosclerosis in human and animal models.

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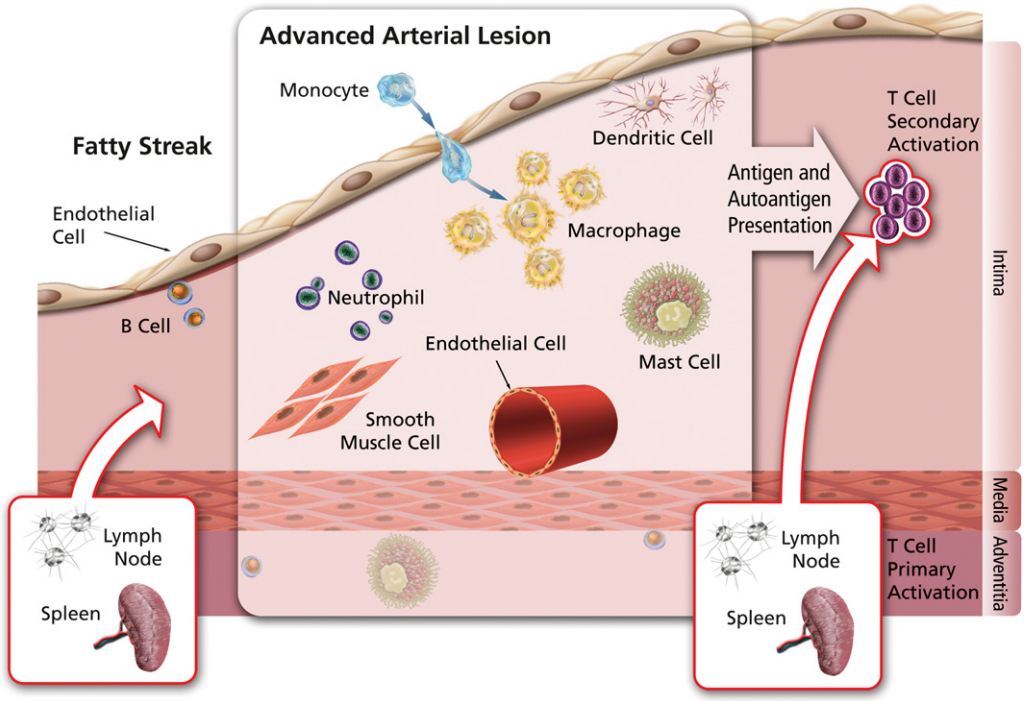

Figure 1 Atherosclerotic lesion professional and non-professional antigen presenting cells and (auto)antigen-mediated T cell activation.

Inflammatory Cells in Atherosclerotic Lesions

The best-studied inflammatory cells in atherosclerotic lesions include T cells, B cells, DCs and macrophages. Few studies focus on other 'minor' inflammatory cells such as mast cells and neutrophils. Besides T cells, all other inflammatory cells can present antigens (antigen presenting cells, APCs) to assist T-cell activation, essential for the early progression of atherosclerosis. In human or animal atherosclerotic lesions, T cells include mainly $CD4^+$ and $CD8^+$ cells, although $CD4^+$ cells dominate in number. It has been suggested that T-cell activation occurs initially in lymphoid organs such as spleen and lymph nodes and then migrates to the aorta for secondary activation by APCs that present the same antigens (Fig. 1). In turn, activated T cells can stimulate other inflammatory cells such as macrophages to secrete inflammatory cytokines, proteases and tissue factors.[1]

$CD4^+$ T cells contain two subsets: Th1 and Th2. In human atherosclerotic lesions, Th1 cells expressing the cytokines interferon-γ (IFN-γ) and interleukin 2 (IL2) prevail over IL4-, IL5- and IL10-producing Th2 cells. T cells isolated from human lesions produce a high amount of IFN-γ but a low amount of IL4.[2] B cells, which occur in much fewer numbers than T cells, appear in the fatty streak or the more external layer of the aortic wall (Fig. 1).[1] Both T and B cells play an essential role in the pathogenesis. A reduction of T and B cells can lead to decreased plaque development.[1] With $CD4^+$ T-cell transfer from immunocompetent to immunodeficient apolipoprotein E knockout *Apoe*$^{-/-}$ mice, disease increases dramatically, whereas atherosclerosis-prone but immunodeficient animals show reduced development of early lesions with the fatty streaks.[3] By contrast, low-density lipoprotein receptor-deficient *Ldlr*$^{-/-}$ mice lacking B cells had 30—40% increase in atherosclerosis, resulting in decreased serum anti-ox-LDL autoantibodies — suggesting that the B cells that make autoantibodies are anti-atherogenic. This explains why mice that go through splenectomy have enhanced atherosclerosis, a phenomenon that splenic B-cell reconstitution can reverse.[4]

In contrast to B cells, DCs occur in the sub-endothelial space with other immunocompetent cells. There, they capture autoantigens then migrate to lymphoid stations, where they present autoantigens to T cells, provoking their responses.[5] Thus, T cells isolated from human atheroma can respond to specific autoantigens while DCs and macrophages can present such autoantigens, giving rise to clonal expansion of their specific T cells and autoantibodies.

Compared with macrophages or lymphocytes, mast cells constitute minor inflammatory cells in human atherosclerotic lesions, although their low numbers do not indicate insignificance. Mast cell inactivation reduces atherosclerotic lesion development in *Apoe*$^{-/-}$mice.[6] Using mast cell-deficient *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice, we demonstrated that these minor inflammatory cells are indeed critical to diet-induced atherosclerosis in *Ldlr*$^{-/-}$ mice. *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice in the background of *Ldlr*$^{-/-}$ are protected from atherogenesis. Using mast cell reconstitution techniques, we found that mast cells release pro-inflammatory cytokines IL6 and IFN-γ to stimulate vascular cell release of matrix-degrading proteases.[7] Therefore, different inflammatory cells serve different roles in atherogenesis.

Autoantigens

Autoantigens refer to those generated by structure modification on specific moieties of endogenous molecules.