Recent Advances in the Role of Immunity in Atherosclerosis

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The immune system serves to protect the host from a diverse array of pathogens that evolve rapidly in an effort to breach immune security checkpoints. These defense mechanisms operate continuously to keep exogenous pathogens from propagating their own species, although this heightened security has unintended and detrimental consequences to the host. Although this maladaptive immune response is classically associated with noninfectious diseases, such as arthritis, gout, and lupus, uncontrolled inflammation is emerging as a causative factor in the development of cardiovascular disease as well.

Atherosclerosis is a widely known condition in which the immune system causes harm to the host. Classically defined as a disease that is initiated by alterations in cholesterol metabolism and the subendothelial retention of low-density lipoproteins (LDL), we now know that activation of both innate and adaptive immunity participate in atherogenesis. Advanced atherosclerotic plaques are characterized by highly inflammatory lesions that can both impede blood flow and precipitate thrombosis because of plaque rupture, leading ultimately to the clinical manifestations of atherosclerosis: myocardial infarction, and stroke. The progression of atherosclerosis in humans is associated with increased circulating levels of proinflammatory C-reactive protein, as well as increased white blood cell count.

A considerable amount of evidence implicates the innate immune system in the progression of atherosclerosis. Recent studies suggest that polymorphonuclear neutrophils (PMNs) drive the accumulation of monocytes in atherosclerotic lesions in a manner dependent on PMN granule proteins, such as the cathelicidins (ie, cathelicidin-related antimicrobial peptide). Other comorbidities, such as hyperglycemia, also contribute to the mobilization of PMNs from the bone marrow during atherosclerosis progression. Interestingly, the PMN/lymphocyte ratio may have value in predicting future cardiovascular events over the white blood cell count alone. Although the role of PMNs in atherogenesis is emerging, the roles of monocytes and macrophages continue to be clarified further. Monocytes are recruited to sites of arterial inflammation because of subendothelial retention of LDL and the production of monocyte chemoattractants, such as chemokine (C-C-motif) ligand-2, sphingosine-1-phosphate, and CCL20. Hypercholesterolemia is associated with increased peripheral blood monocytes (ie, monocytes), which arise from the bone marrow and splenic reservoirs. In mice, hypercholesterolemia promotes selective expansion of monocytes that express high levels of surface glycoprotein, Ly6C, which may arise, in part, because of granulocyte-macrophage colony-stimulating factor and interleukin (IL)-3–dependent extramedullary hematopoiesis. In humans with atherosclerosis, CD14\(^+\)CD16\(^-\) monocytes analogously increase and are of predictive value in the context of cardiovascular disease. Acute myocardial infarction also increases monocytes and atherosclerosis burden, which may relate to the fact that humans with a prior myocardial infarction have an increased risk for future cardiovascular events. Arterial inflammation at sites of disturbed blood flow and LDL retention facilitates monocyte adhesion via increases in inflammatory signaling pathways (ie, nuclear factor-κB, c-Jun N-terminal kinase-1) and subsequent surface expression of endothelial adhesion molecules.

Interestingly, microparticles shed from activated or apoptotic cells can perpetuate this process by transferring adhesion molecules to endothelial cells. Recent evidence indicates that loss of endogenous counter-regulatory signaling pathways, such as inhibitor of differentiation 3 and Kruppel-like factor 2, also contributes to enhanced vascular inflammation and increased endothelial adhesion of both monocytes and PMNs.

On infiltrating the vessel wall, monocytes differentiate into macrophages and rapidly take-up oxidatively modified LDL, a process that transforms macrophages into foam cells. In the absence of cholesterol efflux to high-density lipoprotein, which...
is mediated, in part, by ATP-binding cassette transporters A1 (ABCA1) and ABCG1, foam cell formation propagates. It has been shown recently that myeloid-specific deficiency of both ABCA1 and ABCG1 increases atherosclerosis, monocytecytosis, and neutrophilia in mice and ABCA1-mediated cholesterol efflux is perturbed by hypoxia in macrophages.26-27 In addition, cholesterol efflux by these transporters also regulates chemotaxis of macrophages by redistributing membrane cholesterol from the inner leaflet of the cell membrane to the outer leaflet.28 Interestingly, it has been reported recently that ABCA1 deficiency increases macrophage clearance of Listeria monocytogenes, highlighting that perhaps the host response to bacterial infection evolved in a manner that increases risk for the development of sterile inflammatory diseases, such as atherosclerosis.29

Foam cells are abundant in atherosclerotic lesions and assume an M1 phenotype that perpetuates inflammation. Recent studies indicate that in addition to positive regulators of M1 activation (eg, interferon-γ), loss of endogenous counter-regulatory pathways, such as the nuclear receptor Nur77, may allow for M1 conversion and enhanced atherosclerosis.30 Moreover, macrophage populations in atherosclerotic lesions are heterogeneous because alternatively activated (M2) macrophages (mammosphere receptor; MR+) are also present and localize to stable areas of the plaque.31 These MR+ macrophages, which are generated in response to Th2 cytokines IL-4 and IL-13, contain smaller lipid droplets than MR− macrophages, have lower cholesterol handling, and have a higher phagocytosis capability, which may be related to high levels of prominent M2 gene, 15-lipoxygenase.32 Moreover, M2 macrophage gene ar- ginase-1 is upregulated by liver X receptor-α and may be a feature of macrophages in regressing plaques.32 This phenotype is characteristic of macrophages during the late phases of wound repair and actively resolving acute inflammation. Complete resolution of inflammation requires blunting of inflammatory gene transcription and the clearance of apoptotic cells (ie, efferocytosis).33 Interestingly, altered clearance of apoptotic macrophages is thought to give rise to necrotic cores characteristic of advanced atherosclerosis and, in support of this view, it has been demonstrated recently that deficiency of receptors that mediate apoptotic cell uptake (eg, MerTk) increases apoptotic cell accumulation in both atherosclerotic lesions and in the heart during myocardial infarction.25,34,35 Other emerging protective roles of macrophages in atherosclerosis include the autophagic processes that quiesce excessive lesional oxidative damage, decrease necrotic core formation, and regulate the inflammasome.6,36 In contrast, decreasing endoplasmic reticulum stress-mediated apoptosis through CCAAT/enhancer binding protein homologous protein deficiency seems to reduce necrotic core formation and plaque growth.38

Plaque development encompasses several processes, including monocyte infiltration, macrophage phenotype, and the dynamics of the clearance of apoptotic cells. The importance of monocyte recruitment as a driver of lesion development is underscored by a large body of literature demonstrating that genetic deficiency of monocyte chemokines (ie, CCL2) or their receptors blunts atherosclerosis progression.39 Adding to this body of evidence, using a novel mouse model of apo- lipoprotein E complementation, it was reported recently that suppression of monocyte recruitment is sufficient to promote plaque regression.40 In addition to recruitment, other studies indicate that macrophages can proliferate locally in atherosclerotic lesions, which is a previously unrecognized mechanism for macrophage expansion first characterized in the context of a Th2 immune response during parasitic infection.41-42 There is also evidence that macrophages can leave atherosclerotic plaques, which has been demonstrated largely in animal models of atherosclerosis regression using aortic transplants. In these studies, macrophage removal from plaques was mediated by chemokine receptor, CCR7.43 Interestingly, CCR7-dependent macrophage efflux from lesions may also underlie theatheroprotective effects of statins beyond lowering cholesterol.44 This view also suggests that a failure of macrophages to leave plaques may contribute to lesion progression, which is supported by a recent study demonstrating that neuroimmune guidance cue, netrin-1, retains macrophages in plaques by inhibiting their migration.45 Pro-inflammatory processes driven by lesional macrophages propagate atherosclerosis and emerging evidence points to new atherogenic roles for IL-1β and IL-1α.46,47

In addition to innate immunity, accumulating evidence suggests that extensive cross-talk between the innate and adaptive arms of the immune system contributes to atherogenesis.9 Dendritic cells (DCs), which classically link innate and adaptive immune responses as the key antigen-presenting cells, have emerged as mediators of atherosclerosis. Although both positive and negative contributions of plasmacytoid DCs in atherosclerosis progression have been described,47,48 recent studies indicate that CCL17- (thymus and activation-regulated chemokine) DCs accumulate in both human and mouse plaques and that they promote atherosclerosis by suppressing regulatory T cells (Tregs).49 These studies are in line with others supporting a proatherogenic role of DCs, in which these antigen-presenting cells stimulate CD4+ T cells to secrete inflammatory mediators in the vessel wall that, in turn, drive plaque progression. In contrast, MyD88 signaling in CD11c+ DCs was found to be important in stimulating Treg.50 Furthermore, recent studies demonstrated that depletion of protective Foxp3+ Treg promotes lesion development and that IL-2 therapy reduces atherosclerosis by stimulating CD4+CD25+Foxp3+ Treg proliferation.51-53 Unlike Treg, other T-cell populations, such as CD4+ T (Th1) cells and Th17 cells, contribute to atherosclerosis progression by producing inflammatory cytokines that recruit and polarize macrophages to an inflammatory phenotype.54 The role of Th17 cells in atherosclerosis is evidenced by decreased lesion formation and macrophage recruitment to atherosclerotic lesions in mice with genetic deficiency in IL-17 or its receptor, IL-17-receptor A.55 Interestingly, the anti-inflammatory cytokine, IL-27, was found to restrain IL-17A production during atherosclerosis, because mice deficient in the IL-27 receptor develop more atherosclerosis and have increased IL-17A production.56 However, the role of Th17 cells in atherosclerosis remains controversial because a separate study suggests that IL-17A deficiency does not affect lesion burden.57 Advanced atherosclerotic lesions are characterized by necrotic cores, which arise from postapoptotic secondary necrosis of macrophages and other cells within the plaque.25 Along these lines, cytotoxic CD8+ T cells directly promote the
accumulation of apoptotic cells in atherosclerotic lesions. Importantly, adoptive transfer of CD8+ cells deficient in granulocyte-macrophage colony-stimulating factor (GM-CSF) or perforin have been found not to enhance lesion development and apoptotic cell accumulation, implicating these cells as important drivers of plaque necrosis. Finally, an important contribution of humoral immunity to atherosclerosis has been gaining attention. Building on observations that depletion of B cells by anti-CD20 antibodies confers protection in atherosclerosis, along these lines, emerging strategies may be more successful. Along these lines, emerging evidence indicates that actively resolving inflammation is mediated by agonists that not only dampen inflammation but also promote apoptotic cell removal and bacterial containment by phagocytes. Whether more precise inflammation-resolving strategies such as these can be beneficial in the context of atherosclerosis remains to be determined.

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