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Innate Immune System Cells in Atherosclerosis

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Atherosclerosis is a chronic inflammatory disease of the arterial wall characterized by innate and adaptive immune system involvement. A key component of atherosclerotic plaque inflammation is the persistence of different innate immune cell types including mast cells, neutrophils, natural killer cells, monocytes, macrophages and dendritic cells. Several endogenous signals such as oxidized low-density lipoproteins, and exogenous signals such as lipopolysaccharides, trigger the activation of these cells. In particular, these signals orchestrate the early and late inflammatory responses through the secretion of pro-inflammatory cytokines and contribute to plaque evolution through the formation of foam cells, among other events. In this review we discuss how innate immune system cells affect atherosclerosis pathogenesis. © 2014 IMSS. Published by Elsevier Inc.

Key Words: Innate immune system cells, Atherosclerosis, Inflammation.

Introduction

The innate immune system functions as the first line of host defense against pathogens. This system is composed of diverse cellular components including granulocytes (basophils, eosinophils and neutrophils), mast cells (MCs), monocytes/macrophages, dendritic cells (DCs) and natural killer cells (NK cells) (1). These cells respond to noxious stimuli and conditions including infections and tissue injuries that can trigger inflammatory responses (2). In several pathologies, the inflammatory response coordinates the various mechanisms characteristic of specific diseases. In this sense, atherosclerosis is regarded as a chronic inflammatory disease as it initiates with endothelial dysfunction that permits the expression of adhesion molecules such as platelet endothelial cell adhesion molecule (PECAM)-1, intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM) (3) as well as chemokines such as monocyte chemoattractant protein-1 (MCP-1), which produce interactions among circulating monocytes and endothelial cells. Furthermore, monocytes differentiate into macrophages in the intima in response to colony-stimulating factor (M-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), an event that, along with the accumulation of lipid deposits such as oxidized low-density lipoprotein (oxLDL) as well as debris, favors the development of a necrotic core. Disease progression induces smooth muscle cells to form a fibrous layer that stabilizes the lesion. However, in advanced disease stages, a rupture of this fibrous cap may expose the necrotic core contents; therefore, platelets and fibrin form a blood clot (thrombus) that results in a partial or total ischemic arterial obstruction (4,5).

During atherosclerotic plaque development and progression, various types of innate immune cells are essential. MCs express a variety of pattern recognition receptors and Fc receptors, which are susceptible to activation by microorganisms and allergens, respectively. Classical MC activation is caused by the crosslinking of Fc receptors and IgE. However, MCs can also be activated by other mechanisms, leading to the release of various inflammatory mediators that can affect lesion development (6). Neutrophils are another cell type involved in atherosclerosis. These granulocytes are the first to respond to different antigens, and neutrophils initiate the inflammatory response

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by secreting a wide array of inflammatory mediators such as leukotrienes (7) as well as neutrophil extracellular traps (NETs) that activate the endothelium.

NK cells have been amply demonstrated to play an essential role in immune responses against viruses and tumors (8). However, the role of NK cells in atherosclerosis is not clear. Nonetheless, there is evidence to suggest NK cell involvement in lesions due to the secretion of inflammatory cytokines such as IFN-γ (9).

Monocytes are another type of leukocyte recruited during atherosclerosis; these myeloid lineage cells are of great interest in atherosclerotic disease due to their phenotypic and functional heterogeneity. In mice, two monocyte subsets, Ly-c^{high} and Lyc^{low}, have been described. Lyc^{high} monocytes have been found to participate in inflammatory responses, whereas Lyc^{low} monocytes have been associated with inflammation resolution (10). In contrast, three monocyte subsets have been identified in humans according to CD14 and CD16 expression, and evidence suggests that the three monocyte subsets function differently in immune responses (11).

Other key myeloid cells in atherosclerosis are macrophages; these cells secrete pro-inflammatory cytokines and take up oxLDL through CD36-induced foam cell formation, which is considered central to atherosclerosis (12). Macrophages can be classified as classically activated macrophages (M1) or alternatively activated macrophages (M2). M1 macrophages produce high levels of IL-12 and IL-23 and low levels of IL-10, are efficient producers of free radicals (ROI) and nitrogen intermediaries and participate in Th1 polarization. In contrast, M2 macrophages produce low levels of IL-12 and IL-23 and high levels of IL-10 and are believed to participate in Th2 polarization (13). Additionally, professional antigen-presenting cells such as DCs are found in atherosclerotic lesions and these cells play a critical role in the differentiation and activation of $CD4^+$ and $CD8^+$ T cells and NK cells (14). *In vitro* studies have established that immature DCs can mature when exposed to oxLDL and secreted inflammatory cytokines, suggesting a possible involvement of these cells in atherosclerosis (15,16). In this review, we address the involvement of innate immune cells (MCs, neutrophils, NK cells, monocytes, macrophages and DCs) in atherosclerosis pathogenesis.

Mast Cells in Atherosclerosis

MCs are innate immune cells that play a central role in allergy and asthma and are found in all vascularized tissues where they reside in close proximity to blood vessels, nerves, smooth muscle cells, mucus-producing glands and hair follicles (17,6). Interestingly, MCs are also found in the intima of healthy carotid arteries as well as in early and advanced atherosclerotic lesions and are distributed in the shoulder region, in human. The presence of MCs in an atherosclerotic lesion suggests the possibility of a role for these cells in this disease (18) and the participation of MCs was established in an *in vivo* study that showed that a specific MC deficiency significantly reduced atherogenesis in mice (19).

MC activation by allergens or microorganisms induces the release of preformed inflammatory mediators, which are localized in specialized granules and the de novo synthesis and secretion of cytokines, chemokines and eicosanoids (17). Classical MC activation occurs through crosslinking of the high-affinity FcεRI receptor, which binds to IgE (20). However, MCs are also susceptible to activation by other mechanisms such as IgG or immune complexes (21). In this context, it was recently discovered that FcεR1α deficiency resulted in a marked reduction in lipid deposition in the aortic arch intima in $ApoE^{-/-}$ mice. This reduction might be due to a lack of FcεR1α-mediated MC activation, leading to a drastic reduction in the release of pro-inflammatory mediators that could reduce the amounts of inflammatory cells such as macrophages and T cells in atherosclerotic lesions in $ApoE^{-/-}$/FcεR1$\alpha^{-/-}$ mice (22). Notably, immune complexes formed by oxLDL-IgG have been found in plaques in animal models, suggesting a role of oxLDL-IgG complexes in MC activation (23). *In vitro* data have reinforced this idea, as oxLDL-IgG immune complexes have been shown to induce the release of pro-inflammatory cytokines such as IL-8 and TNF-α from human MCs, along with other powerful mediators such as histamine and tryptase (24). Another MCs activation pathway is triggered by the Toll-like receptors (TLR). In this respect, the administration of TLR4 antagonists in mice $ApoE^{-/-}$ was shown to have no effect on the recruitment of MCs to plaques but instead to reduce the activation of lesion-derived MCs, suggesting that the MCs are susceptible to activation via TLR4. Moreover, MCs-specific activation induced apoptosis in vascular smooth muscle cells present within atherosclerotic plaques, a process that could be counteracted by a TLR4 antagonist, suggesting that TLR4-mediated MCs activation is involved in the induction of vascular smooth muscle cell apoptosis (25). Additionally, MCs in lesions could be activated through the receptor for the complement system components C3a and C5a (26,27). A study showed that $ApoE^{-/-}$ mice overexpressed the complement 3a receptor and complement 5a receptor (C5aR) in atherosclerotic plaques in response to exogenous C5a administration, suggesting that C5a acts as a potent chemoattractant for MCs as well as a ligand for C5aR, which triggers MCs activation. (26). Collectively, these studies suggest that MCs are susceptible to activation in response to soluble mediators such as C5a and receptors such as IgE, IgG and TLR, and this activation is likely to induce the release of inflammatory mediators, leading to the recruitment of leukocytes toward the lesion and promoting disease development (Figure 1).

MCs can initiate atherosclerosis through various mediators such as histamine, which augments vascular