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MINIREVIEWS

Atherosclerosis and the role of immune cells

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Abstract

Atherosclerosis is a chronic inflammatory disease arising from lipids, specifically low-density lipoproteins, and leukocytes. Following the activation of endothelium with the expression of adhesion molecules and monocytes, inflammatory cytokines from macrophages, and plasmacytoid dendritic cells, high levels of interferon (IFN)-α and β are generated upon the activation of toll-like receptor-9, and T-cells, especially the ones with Th1 profile, produce pro-inflammatory mediators such as IFN-γ and upregulate macrophages to adhere to the endothelium and migrate into the intima. This review presents an exhaustive account for the role of immune cells in the atherosclerosis.

Key words: Atherosclerosis; Inflammatory cytokines; Pro-inflammatory mediators; Immune cells; Adhesion molecules

Core tip: Activated endothelium to adhere to the endothelium and move into the intima with the expression of adhesion molecules appears to be an early event in atherosclerosis, which allows mononuclear leukocytes such as monocytes and T-cells. This inflammatory mechanism must be explained before determining a new therapy.

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INTRODUCTION

Atherosclerosis is one of the leading causes of morbidity and mortality arising from coronary artery disease, stroke, and peripheral vascular disease. The pathophysiology of atherosclerosis is best characterized with hyperlipidemia and inflammation[1,2].

For a long time after recognition, atherosclerosis was associated with passive lipid accumulation in the vessel wall. Nowadays we know that atherosclerosis is a chronic inflammatory disorder caused by lipids, particularly low-density lipoproteins (LDLs), and leukocytes[3]. Atherosclerosis is likely to be initiated by the activation of endothelium with the expression of adhesion molecules, and this in turn enables the adhesion of mononuclear leukocytes, such as monocytes and T-cells, to the endothelium and also their transmigration into the intima. At this point, the lesions may be present with rare cells such as dendritic cells (DCs), few neutrophils and

B-cells, and also with smooth muscle cells (SMC), which transform phenotype into synthetic SMC and move into the intima from the media[4].

Polymorphonuclears (PMNs) are recruited and adhered to the endothelium upon the subsequent expression of adhesion molecules, such as E-selectin, P-selectin and intercellular adhesion molecule 1 (ICAM-1)[5]. The endothelial cell expression of selectins and vascular cell adhesion molecule 1 (VCAM-1) is further increased by pro-inflammatory cytokines and mmLDL, and this facilitates the infiltration of the monocytes into the intima[6]. As a result of intimal lipid accumulation, disturbed blood flow, low shear stress, and other stimuli, the transition of monocytes, which are major precursors of macrophages, through the endothelium is allowed by endothelial cells[3]. Endothelial cells and SMCs are triggered by oxidized LDL (OxLDL), and this leads to the secretion of monocytic maturation factors such as monocyte-colony stimulating factor (M-CSF). Monocytes are transformed to macrophages and phagocytose modified lipoproteins, mainly due to the scavenger receptors AI and CD36[7], and then become foam cells[8]. Macrophages may be activated by PMNs following the secretion of tumor necrosis factor (TNF)-α, interleukin (IL)-8, and interferon (IFN)-γ. In addition, the release of myeloperoxidase from granules can stimulate the formation of reactive oxygen species (ROS), as well as the secretion of other pro-inflammatory cytokines, including TNF-α, IL-1, IL-6, IL-8 and granulocyte macrophage colony stimulating factor (GM-CSF) from macrophages. In response, ROS transform the extravasated LDL into OxLDL, consequently forming the foam cell development[9].

Monocyte recruitment and the size of atherosclerotic lesion are bound to decrease if a failure is experienced in adhesion molecules, such as P-selectin, ICAM-1 and VCAM-1, or their interactions with their respective ligands are constrained[10,11].

MONOCYTES AND MACROPHAGES

After the migration from the circulation into the intima of the arterial wall, monocytes are converted to macrophages and DCs. These cells then transform into foam cells by taking up modified lipoproteins[12]. There are three major monocyte subsets in humans[13,14]: the classical $CD14^{++}CD16^{-}$ subset is similar to the mouse Ly6C high inflammatory subset and also presents a high expression of CCR2, and the non-classical $CD14^{+}CD16^{++}$ monocytes are considered to match the $Ly6C^{-}$ cells in mice, which express high levels of CX3CR1 and CCR5 but low levels of CCR2[15]. The third subset, however, is known as the intermediate $CD14^{++}CD16^{+}CCR2^{+}$ subset[16]. Of these, the classical subset includes nearly 90% of the monocytes circulating in humans[17]. The patients with coronary artery disease present with increased amount of pro-inflammatory $CD14^{+}CD16^{+}$ monocytes and serum TNF-α levels[18], and this monocyte subset is in negative correlation with fibrous cap thickness[19].

After chemokinesis, monocytes adhere to and spin on endothelial cells by interacting with E- and P-selectins[20,21]. Lipoprotein-binding proteoglycans are secreted by monocytes in the intima, leading to enhanced accumulation of modified LDL, which carries on inflammation[22,23].

Tissue damage and repair are closely linked to monocytes, and a discrepancy to occur in these processes may have critical results for plaque formation and stability. Importantly, monocytes consist of dissimilar subsets along with different cell surface markers and functional features, and this diversity of components may be associated with the angiogenic processes in atherosclerosis[24].

The formation of atherosclerotic lesions is heavily dependent on the transformation of monocytes into macrophages; for instance, M-CSF-knockout mice show resistance to the development of atherosclerosis[25].

Every phase of the course of disease includes abundant amounts of monocyte-derived macrophages[12], and these cells an important role in lipid accumulation and advancement of atherosclerosis[24]. Also, their crucial role in atherogenesis has been proven by the reduction of lesion formation in monocyte-deficient apolipoprotein E (ApoE) knockout mice and LDL receptor knockout mice[26,27].

The polarization of macrophages towards a specific phenotype has been reported to be positively affected by lipids, growth factors, and cytokines; the M1 macrophages that are classified by means of classical methods may result in plaque vulnerability, whereas the M2 macrophages which are activated by alternative methods may increase plaque stability[28]. The phenotypes of M1/M2 macrophages can be exchanged depending on the conditions of their microenvironment[29].

Many macrophages and dendritic-like cells are known to have membrane-bound lipid droplets in the cytoplasm even at very early phases of atherogenesis. As they comprise lipid deposits, these cells are called "foam cells" and their course of development is initiated when apolipoprotein B-containing lipoproteins (apoB-LPs) are absorbed and processed by phagocytes[21]. While producing matrix metalloproteinases with regards to plaque rupture, macrophages can be primed by oxLDL to develop a foam cell macrophage which bears the characteristics of M1 and M2 activation[28]. Inflammatory cytokines and chemokines that promote inflammation and contribute to the regulation of monocyte/T cell infiltration are generated by macrophages/foam cells[30-33]. With the macrophages in the atherosclerotic plaque, it is possible to generate a wide range of proinflammatory cytokines such as IL-1, IL-6, IL-12, IL-15, IL-18, TNF family members, and MIF, as well as anti-inflammatory cytokines like IL-10 and transforming growth factor beta family members[34,35]. Additionally, IFNγ may trigger the macrophages to produce ROS and neopterin. It has been reported that neopterin levels increased in acute coronary syndrome and neopterin may be useful for the assessment of inflammation related to atherosclerosis[36].

Being the most abundant cell type in atherosclerotic plaques, macrophages have a strong effect on plaque

development and progression due to its overwhelming influence on intra-plaque cholesterol homeostasis, inflammation, necrotic core initiation, and extracellular matrix degradation[37].

Toll-like receptors (TLRs) represent the most comprehensively studied and described type of pattern recognition receptors. TLRs are characterized as type 1 transmembrane proteins involving an ectodomain with leucine-rich patterns that are needed to recognize pathogen associated molecular patterns, a transmembrane region, which determines the locations of the cells, and an intracellular toll interleukin 1 receptor region required for downstream signaling. Up to now, a minimum of 13 TLRs have been described, and each of them present with a degree of specificity for a number of endogenous and exogenous ligands[38]. Expression of TLRs is performed by a number of various cells, such as leukocytes, DCs, and T and B lymphocytes[39]. Atheroma development can be directly influenced by TLRs since the lipid uptake is promoted when the stimulation of macrophages is conducted with TLR2, TLR4 and TLR9 ligands[40,41]. According to recent studies on ApoE$^{-/-}$ mice, even small amounts of TLR4 and TLR2 have positive effects on the deposition of early-stage intimal foam cells in some regions in the aorta which are sensitive to lesion development[42]. The macropinocytosis of lipids in differentiated macrophages can be stimulated by TLR4[43]. Increased expression of scavenger receptors induced by TLR3, TLR4 and TLR9 can be used as a mediator for increased lipid absorption[39,44]. These receptors and their ligands may also interrupt the cholesterol efflux mechanisms, which may have a contributory role in the development of foam cells[28].

THE DENDRITIC CELLS

Dendritic cells, which are antigen-presenting cells (APCs), exhibit a variety of antigens to T cells in addition to initiating and sustaining immune responses as well as inhibiting the activation of T cells. The capacity of DCs in the activation or inhibition of T cells relies on its cytokine production profile and expression of cell surface co-stimulatory molecules. DCs are transformed by activated innate immune receptors, such as the TLR, into APCs that activate T effector cells, whereas, immunological tolerance is produced by antigen presentation which develops when TLR activation is not present. Therefore, DCs play a critical role as a connector between innate and adaptive immune responses[45].

DC has a heterogeneous population with four major categories: conventional DCs (cDCs), plasmacytoid DCs (pDCs), monocyte-derived DCs, and Langerhans cells[46]. Monocytes or DC precursors, which are present in the bone marrow, constitute the two sources of DCs.

Monocytes are completely transformed into monocyte-derived DCs in inflammation and as a reaction to growth factors like GM-CSF or TLR4 ligands. The capacity of presenting antigens along with the ability to cross-present antigens belongs to the DCs that originate from monocytes[37]. DCs are capable of generating a wide range of anti-inflammatory and proinflammatory cytokines. As an example, some proinflammatory cytokines, such as TNF, IL-6, and IL-12, which have been proven to contribute to the atherosclerosis can be generated by TLR binding[47-49]. However, TLR binding may also generate IL-10, which is known as an atheroprotective cytokine[50].

The DCs in mice are best known for their expression of CD11c and they present with healthy mouse aortas, predominantly in the adventitia[51]. In mice, the amount of mRNA expression of CD11c is higher in the sites of the aortic arch susceptible to atherosclerosis, compared to the sites that are resistant to atherosclerosis. Contrary to healthy vessels, most of the DCs in atherosclerotic aortas are localized in the intima[52].

The deposition of CD11c^{+} DCs at the vascular regions prone to atherosclerosis is associated with the increase in the expression of VCAM-1[53]. Mature DCs are more abundant in advanced lesions. High level of expression of human leukocyte antigen (HLA)-DR and interactions with T cells are mostly observed in the sites of the plaque that are predisposed to rupture[54]. The deposition process of the dendritic cells in the intima may be interrupted if the fractalkine receptor CX3CR1 in the aorta is impaired, and this may be an indication that these cells may be transformed from Ly-6Clo monocytes which are known to induce high levels of CX3CR1[55]. OxLDL, in line with the elevation in the production of T cells, functions as an antigen upregulator for the DC expression of HLA-DR and its co-stimulatory molecules[56]. DCs carry out the expression of scavenger receptors (LOX-1, CD36 and CD205) which facilitate their uptake of oxLDL activating the NFκB pathway, and evolution to DCs with a pro-inflammatory cytokine profile[57]. Once DCs are activated by oxLDL in the plaque, they move to secondary lymphoid organs and initiate the clonal proliferation of the T cells that are specific to oxLDL[28].

Following TLR9 activation, it is a common event for pDCs to produce high amounts of IFNα and β, and TLR9 has been reported to contribute to atherosclerosis by promoting macrophage recruitment[58]. The recruitment of monocytes, memory T cells, and DCs to the region of inflammation is reportedly influenced by the CCL2 secreted by DCs[59].

DCs, as prominent mediators of immune responses, may also act as the regulators of innate or adaptive immunity against the potential antigens that are engaged in atherosclerosis[60]. In brief, the roles of dendritic cells in atherosclerosis can be summarized as the induction of chemokines and cytokines, presentation of antigens, and lipid absorption that might trigger inflammation or promote tolerance[37].

T CELLS

The role of adaptive immunity in atherosclerosis was

verified by the presence of antibodies and oxLDL-specific T cells along with the accumulation of oligoclonal T cells in lesions[6,61]. T cells are targeted to the vessel wall in line with macrophages, but to a lesser extent. Activation of T cells in the arterial wall is a reaction to antigens, and after this activation, the T cells initiate the production of pro-inflammatory mediators, by which the inflammatory response is intensified and thus the disease development is worsened[62]. Moreover, most of the pathogenic T cells in atherosclerosis have the characteristics of Th1 since they generate pro-inflammatory cytokines such as IFN-γ and perform the activation of macrophages[63,64]. The reactions mediated by Th1 have harmful effects on the development of atherosclerosis. Vascular smooth muscle cells are recruited by IFN-γ to inhibit the synthesis of collagen, and this leads to harmful effects for the protective thick fibrous cap of the plaque. Also, the activation of monocytes/macrophages and dendritic cells by IFN-γ results in the continuation of the pathogenic Th1 response[30].

Previous studies report that the removal of IFNγ or its receptors leads to a reduction in atherosclerosis, whereas the injection of recombinant IFNγ results in a growth in the size of the lesions[65-67]. The detection of Th2 cells in the atherosclerotic lesions is a rare occurrence. The cytokines produced by Th2 cells include IL-4, IL-5, IL-9, and IL-13. Th2 cells also have contributory effects on the production of antibodies by B cells. As the production of IFN-γ is decreased by these cells, the responses caused by Th2 were thought to be the antagonists of proatherogenic Th1 effects, hence rendering atheroprotection. Nevertheless, how atherosclerotic progress is affected by Th2 pathway has yet to be proven and the role Th2 pathway relies not only on the phase and location of the lesion but also on the method of experimentation to be used[62]. According to some studies on animals, both Th1 and Th2 responses are involved in the progression of atherosclerosis, and lesion formation is started primarily by Th1 activation through a switch towards a proatherogenic response by Th2 in the chronic stage of plaque formation[68]. The expansion and cytokine induction of highly activated effector T cells can also be inhibited by another T cell called TCRγδ$^+$ CD4$^-$ CD8$^-$, and this cell may need to be further analyzed since it is likely to have antiatherogenic characteristics[69,70]. The regulatory T cells (Tregs) have critical roles in the inhibition and suppression of inflammation and also in the regulation of adaptive immune responses. Moreover, these cells can induce tolerance by inhibiting the effector CD4$^+$ and CD8$^+$ T cells[71,72].

IL-10 has been reported to inhibit atherosclerosis, and thus the athero-protective effects of regulatory T cells may be improved when they generate IL-10[73,74]. Studies also report that IL-10 has a protective function in the development and stability of atherosclerotic lesions[72,73].

Th17 lymphocytes represent another T helper subset associated with inflammation, and this subset does not share the same lineage with Th1 and Th2[75]. IL-17 has been demonstrated to have protective and pathogenic effects in a number of autoimmune diseases[76,77].

The main cytokines expressed by Th17 cells include IL-17A and IL-17F along with IL-21 and IL-22. The role of Th17 is still debatable despite the detection of Th17 cells in the atherosclerotic lesions in mice and humans, because both atherogenic and atheroprotective effects have been attributed to these cells[78-80]. IL-17 is also considered to enhance plaque stability since elevated IL-17 induction in human lesions results in a decrease in the number of macrophages, an increase in SMC deposit, and a phenotype with a more fibrotic profile[81].

Proatherogenic profile of IL-17 has been shown previously by many studies[82-85]. In these studies, the evidence for the proatherogenic effect of IL-17 is attributed to the fact that both IL-17 and IFN-γ are expressed by the CD4$^+$ T cells that are separated from atherosclerotic coronary vessels[86].

CD8+ T cells are detected in both murine and human plaques[87,88]. The number of CD8$^+$ T cells is low in the early stages of lesions; however, these cells seem to be the dominant T cell type in the advanced stages of human lesions[88]. CD8$^+$ T cells may have a proatherogenic function since the lesion size was increased and also the recruitment of these cells to the lesion site was promoted when the responses of these cells were stimulated with a CD137 agonist[89].

B CELLS

The responses produced by the Th2 cell have important roles in the activation of B cells, the differentiation of plasma cells, and the production of antibodies that are unique to antigens. B cells are evident in atherosclerotic lesions, but their population is smaller than that of T cells[90]. However, the role of B cells in atherosclerosis remains controversial as two recent studies have reported that the atherosclerotic progression in mice is inhibited when B cells are blocked by the use of an antibody against CD20[91,92]. The evidence that some types of IgM and IgG have atheroprotective effects may suggest that B cells have the ability to protect against atherosclerosis. Moreover, plaques have been detected with both IgM and IgG at all phases of lesion progression[93]. Anti-oxLDL IgM antibodies have been proven to provide protection against atherosclerosis, probably because they achieve oxLDL binding and thus suppress oxLDL absorption by using macrophages and avoid the development of foam cells[94,95]. On the other hand, to what extent the oxLDL-specific IgG is effective remains a controversial issue because both beneficial and inverse effects have been reported in epidemiological studies[96]. OxLDL-specific antibody IgG titers are associated with atherosclerosis[94,97,98], whereas oxLDL-specific IgM titers are related to atheroprotection[99,100]. Nonetheless, the B cell subsets and their roles in atherosclerosis need to be further

analyzed[37].

CONCLUSION

Atherosclerosis is a multiphase process which is characterized with the activation of endothelial cells with the expression of adhesion molecules and monocytes/macrophages, and the transmigration of DCs, T cells and some B-cells into the intima, and also the transfer of modulated types of LDL to matrix components. Monocytes/macrophages are highly abundant and differentiate into foam cells which are rich in modulated LDL.

According to clinical and experimental data, the atherogenic process involves the cells of both the innate and the adaptive immune system, and these cells generate diverse cytokines that may have both pro and anti-inflammatory functions[101-103]. To immunomodulate the atherosclerosis is the primary aim of some clinical studies. Among these, the experimental studies with anti-LDL antibodies and vaccination studies with LDLs are under way[1,104]. Oral administration of oxidized LDLs is reported to be effective on the inhibition of atherosclerosis and production of Tregs in peripheral lymphoid tissues[105]. The functions of immune and inflammatory modulators in the formation and development of atherosclerosis have been better analyzed in recent years and thus provided a deeper insight into these mechanisms. Accordingly, more and more advanced techniques in the diagnosis and prognosis of atherosclerosis, along with new treatment procedures for inflammatory and immune factors, have been developed[106]. However, there is still much to learn about immune cells and their mechanisms affecting atherosclerosis. We believe that further studies investigating immune cells and their mechanisms will help to shed light on atherosclerosis.

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