Review Article

Atherosclerosis as autoimmune disease

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Abstract: No attention is usually focused on the possible involvement of immune mechanisms, particularly of autoimmunity, on the development and progress of atherosclerosis. The pioneering work occurring almost 50 years ago was overlooked, and the idea of atherosclerosis as an autoimmune disease only started gaining traction about 10 years ago. Our review discusses the recent findings and offers insights into the possibility that alterations of the immune system play a significant role in the development of atherosclerosis.

Keywords: Atherosclerosis; cholesterol; immunity; inflammation

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Introduction

Atherosclerosis represents a multiphase pathological process characterized by activation of endothelial cells with subsequent expression of adhesion molecules. Old dogma focused on a multifactorial genesis of atherosclerosis, involving both external (high calories input, too much fat and saccharides, smoking, lack of physical activity) and internal (genetically determined problems with lipid metabolism) factors. The mainstream treatment consisted of a combination of cholesterol-lowering medication (various forms of statins) and low fat diets.

However, the first interesting studies suggesting the role of immune mechanisms in development of atherosclerosis appeared as early as the 1970s, unfortunately without gaining any significant interest. It might be worth of mentioning that the hypothesis of atherogenesis being accompanied with inflammatory processes originated in studies of Virchow (1,2).

Within the last 20 years, new approaches in the study of atherosclerosis causes and interpretation of their effects began appearing. Particularly important was the European Society meeting for atherosclerosis, which took place in 2001 in Geneva. Over 200 participants focused on new data strongly suggesting that atherosclerotic processes are mostly caused by immune mechanisms; downplaying the role of traditional risk factors such as smoking or diabetes type II. Data showed that approximately 40% of people with either infarct or stroke were never exposed to these risk factors. On the other hand, it was shown that atherogenesis is accelerated by immunopathological problems such as systemic lupus erythematosus, antiphospholipid syndrome, rheumatoid arthritis, and vasculitis. The meeting concluded that immune mechanisms and inflammatory processes are directly involved in the formation of atherosclerotic plaques, and that it is "*high time to start thinking about new immunomodulatory properties in prevention and treatment of atherosclerosis*" (3). It is not surprising, therefore, that we have seen a strong increase in the understanding of the mechanisms regulating the recruitment and activation of various immunocytes in atherosclerosis (4). On the other hand, it was shown that atherogenesis is accelerated by immunopathological problems such as systemic lupus erythematosus, antiphospholipid syndrome, rheumatoid arthritis, and vasculitis (5).

Atherosclerosis is accompanied by development of tertiary lymphatic tissue

Atherosclerosis is one of the main causes of cardiovascular

diseases. It represents a multifactorial disease which is by general consent caused by long-term high level of blood cholesterol. The particular problematic is the LDL form of cholesterol, which is stored in the walls of veins, where is forms atherosclerotic plaques (atheromas). However, the current opinions believe that arteries represent tertiary lymphatic organs (ATLO, artery tertiary lymphoid organs) with variable cellular complexity, producing several immunocompetent factors. In these functions, ATLO are similar to secondary lymphoid tissues (6). Contrary to primary and secondary lymphoid organs and tissues which develop during embryogenesis as primary anlage, ATLO develop *de novo* postembryonally during chronic noninfectious inflammations. ATLO development has three distinct phases. First, ATLO arise in parallel with formation of atheroma without structured T and B zones, despite the fact that T and B chemoattractants are already produced. Next, a differentiation of T and B zones appears, accompanied by neogenesis of lymphatic venules associating with arterial wall. A final phase of ATLO development is characterized by highly differentiated T and B cell follicles with active germinal centers, including dendrocytes and plasmacytes, and neogenesis of blood vessels. Analyses of ATLO immune cells suggested antigen-specific T and B cell immune responses within the atherosclerotic arterial wall adventitia (6). Experiments using apolipoprotein E^+ mice demonstrated that ATLO control multilayered territorialized atherosclerosis B cell response (7). ATLO emerge during non-resolving peripheral inflammation, but their impact on disease progression is still not fully known. Animal experiments have shown that ATLO control aorta immunity and protect against atherosclerosis via vascular smooth muscle cell lymphotoxin β receptors (8).

Atherosclerosis as infectious disease

In 1988, it was discovered that patients with cardiovascular problems often have high titers of antibacterial antibodies, particularly anti-*Chlamydia pneumoniae* antibodies (9). Deposition of atherosclerotic plaques might be caused by several bacteria or viruses. Among major pathogens are Epstein-Barr virus, herpes simplex virus, cytomegaloviruses and *Helicobacter pylori*. Some studies have suggested a direct relationship between infection with *C. pneumoniae* and elevated titers of IgM and IgG antibodies in patients after stroke or infarct. In addition, a high T cell reactivity against chlamydial antigens in atherosclerotic plaques was found (10). For more information on myocardial problems and infection, see the article written by Hansson (4). In addition, some chronic diseases, such as chronic bronchitis or periodontitis, were also suggested as possible accelerant factors of the atherosclerotic processes. Heat shock protein HSP65 *C. pneumoniae* has been intensively studied for almost three decades. This protein activates autoreactive T lymphocytes recognizing human HSP60, resulting in diminished immunological tolerance. Elevated titers of HSP60/65 antibodies found in atherosclerotic patients suggest that these antigens are responsible for the development of both T and B cell response (11,12).

Existence of pathogens and their DNA in atherosclerotic plaques (demonstrated both by electron microscopy and immunofluorescence), circulating bacterial toxins, antiviral and antibacterial antibodies, various macrophage-derived cytokines, and high levels of C-reactive protein are considered to be primary risk factors for etiopathogenesis of atherosclerosis (13) and a direct prediction of cardiovascular disease. The role of infections in this disease is also supported by the fact that many patients with acute cardiovascular problems were treated a few weeks earlier for bacterial or viral infections.

Atherosclerosis as autoimmune process

Our views on mechanisms of natural immunity as nonspecific branch of the defense reactions preceding adaptive immunity were completely changed in last decade. These mechanisms are not only non-coordinated autonomous reactions of inflammatory factors causing or accompanying inflammation and phagocytosis, but hierarchical and reciprocal sequence of steps, which at the beginning recognize pathogen-associated molecular patterns (PAMP) and later changing into highly specific adaptive cellular and humoral immune response.

At the beginning of inflammatory response is the recognition of damaging noxis by intracellular sensors of natural immunity, which are now generally referred to as inflammasomes (14). Inflammasomes are complexes of cytoplasmic proteins able to recognize not only PAMP, but other harmful substances as well. Four different inflammasomes have been described to be involved in the development of gout (uric acid), Alzheimer disease (amyloid), asbestosis and silicosis (asbestos fibers and silicon crystals), and malaria (hem molecule).

PAMP or other potentially harmful structures are recognized by Toll-like receptors (surface) or endoplasmic Toll-like receptors and cytoplasmic NOD-like receptors

(intracellular). A recognized signal is transferred to proteins, which subsequently activate cytoplasmic enzyme caspase-1, representing the majority of the inflammasome, as it directly starts inflammatory cascade; i.e., formation of endogenic factors (fever) and cytokines (most of all IL-1β, IL-18, and macrophage-activating IFN-γ). These cytokines are produced and immediately secreted into the intracellular milieu by both free immunocytes (NK cells, macrophages and T lymphocytes) and venous epithelial cells. Local adaptive immune response closely follows these promotors of inflammation.

Chronic activation of inflammatory apparatus occurring during atherogenesis is based on recognition of damaging noxy, probably by another type of inflammasome. An important step towards our understanding of these processes was the recognition of cholesterol and modified lipids as endogenous PAMP (15,16). Formation of lipid bands during the first stages of atherosclerotic plague development is accompanied by expression of vascular cellular adhesive molecule 1 (VCAM-1) on endothelium. It occurs in damaged areas (17) or as a response to bioactive lipids (such as oxidized LDL) captured on the vascular wall. Healthy vascular endothelium is not permeable for LDL. However, when changes caused by any of the possible processes, such as chemical or mechanical damage, the endothelium starts to be permeable. Accumulation of LDL in the intima starts induction of the atherosclerotic process, as LDL binds to proteoglycans of vascular wall extracellular matrix via apolipoprotein B. Oxidized LDL also increases expression of adhesive molecules on endothelial cell and leukocyte membranes, further increasing the adhesion of these cells to the endothelium. Adhering leukocytes under the influence of chemokines migrate into the subendothelial layer. This movement is regulated via chemokines, particularly MCP-1. Production of this chemokine is also stimulated by oxidized LDL.

Nitric oxide, which is formed by macrophages, has also strong inflammatory effects. Final products of advanced non-enzymatical glycolizations, lipoxidation and protein oxidation (AGE, ALE, AOPP) are also involved in atherosclerotic inflammation (18,19). Locally induced cytokines and chemokines attract mononuclear cells and T lymphocytes which bind VCAM-1. As monocytes transform into fully mature macrophages, they increase expression of other receptors, particularly Toll-like and scavenger receptors (20). Lesions contain large numbers of macrophages and, with the discovery of the scavenger receptor pathway, we now understand that they engulf and accumulate cholesterol and transform into foam cells. Activation of T lymphocytes occurs simultaneously, leading to production of inflammatory mediators. This accelerates formation of atherosclerotic plaques and further potentiates development of the disease. Further progression is dependent on the balance of inflammatory and anti-inflammatory factors, mediators, and cytokines. These bioactive molecules regulate apoptosis, collagen formation, and reaction of smooth muscles, which subsequently influence stability of plaque and thus the susceptibility to formation of thrombus (21,22).

A highly heterogenous population of macrophages represents the central cellular component involved in the primary atherogenic process. Phenotypical heterogeneity of macrophages is a result of a different exogenous and endogenous impulses (23), which subsequently determines their functional specialization in responding to basically any signal molecule. Similar to Th1 and Th2 lymphocytes, macrophages are also categorized into M1 and M2 subpopulations (24). M1 are proinflammatory classically activated macrophages playing a role in immune reactions (25). M2 subpopulation is mainly involved in wound healing and regulation of inflammation (26). In the plaque, macrophages with various phenotypes are localized to specific regions. Polarization of macrophages is imperative for atherosclerotic plaque development (27). Polymorphonuclear neutrophils are adhered to the endothelium upon expression of adhesion molecules such as P-selectin, E-selectin, and ICAM-1. Polymorphonuclear neutrophils can subsequently activate macrophages via secretion of IL-8, TNF-α, and IFN-γ. Release of myeloperoxidase can result in formation of reactive oxygen species and other proinflammatory cytokines (28).

Adaptive immunity

Mechanisms of adaptive immunity represent a second line of defense based on specific mechanisms of antigenic recognition via T cell receptors and on processes resulting in formation of specific antibodies. Although we know that various immunocytes are present in atherosclerotic lesions, there is no generally accepted concept of which immune cells trigger the disease or at which step individual subsets influence the disease. Numerous hypotheses have been suggested (29).

The presence of T cells in atherosclerotic plaques was reported in 1985 (30). Approximately 10% of these T lymphocytes recognized chemically-modified LDL via

MHC II antigens, T cell-derived cytokines, and anti-LDL antibodies (31-34).

Mouse models showed that atherosclerotic plaque contains both CD4 and CD8 cells. CD4 cells, which occur at the start of the process, probably have pro-atherogenic effects. It is assumed that the role of CD8 cells is less important, but some findings suggest that they might be activated by the infection and that in the final stages they stimulate atherogenesis (21,35).

T cell response starts by antigen presentation by dendritic cells. These cells phagocytose atherogenic antigens present in arterial intima and transport them into lymph nodes (36). Antigen presentation occurs not only there, but also in lesion, where several cell types, including macrophages, endotheliocytes, and muscle cells, can be involved (37). This local antigen presentation increases T cell response.

Experimental research has identified numerous candidate antigens. Atherogenic antigens are not only part of pathogenic microorganisms, but also self-molecules which were modified by lipid peroxidation (38). Oxidation-modified LDL is an autoantigen, found in T cells isolated from human atherosclerotic lesions (34). In addition, circulating specific IgG antibodies were found both in human models and in experimental animals (39,40), which further stresses involvement of B cell immunity. B cells not only produce anti-atherogenic antibodies, but also secrete further factors modulating additional parts of immune reactions.

Another autoantigen involved in atherosclerosis is β2-glycoprotein I (apolipoprotein H) which is a phospholipids-binding protein found in human atherosclerotic plaques. Autoantibodies against this protein were found not only in patients with atherosclerosis, but also in those with other inflammatory diseases (lupus erythematosus and antiphospholipid syndrome).

Conclusions

Cardiovascular disease ending in heart attack or stroke and based on atherothrombotic vascular disease is lately one of the most common causes of death worldwide. Today, atherosclerosis is considered to be a chronic inflammatory disease. In last decade, both experimental and clinical investigations have shown significant improvements in our understanding of molecular pathogenesis of atherosclerosis. Atherogenesis is induced by a series of autoimmune processes, in which the humoral factors and immunocompetent cells take part. This new approach to this important and often fatal disease opens new windows for treatment. The possibility of using anti-inflammatory drugs or specific vaccines for prevention of atherosclerosis seems to be genuine. Encouraging data suggesting that immune modulation or immunization can reduce or even block the progression of the disease are available. Treatment with immunomodulators, like beta-glucans (41), and immunosuppressing agents might offer additional possibilities. However, there is still much to learn about the role of immune cells in atherosclerosis.

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Footnote

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