Infection and Atherosclerosis
Potential Roles of Pathogen Burden and Molecular Mimicry

Stephen E. Epstein, Jianhui Zhu, Mary Susan Burnett, Yi Fu Zhou, Gregory Vercellotti, David Hajjar

Abstract—Infection has been implicated as a cause of atherosclerosis since the first half of the 19th century. Over the years, sporadic publications have appeared in the literature reflecting a persistent but relatively low level of research activity in this area. In the last decade, however, publications relating to this topic have increased markedly. And very recently, new epidemiological and mechanistic data relating infection to several different diseases, including atherosclerosis, have appeared, stimulating the emergence of important paradigm shifts in how we think about the causes of chronic disease. The following article reviews some of these newer concepts as they relate to a possible role of infection in atherosclerosis. (Arterioscler Thromb Vasc Biol. 2000;20:1417-1420.)

Key Words: infection ■ atherosclerosis ■ mechanisms

Until very recently, most investigative efforts have focused predominantly on seroepidemiological studies attempting to demonstrate an association between atherosclerosis and infection with a specific pathogen or have focused on the “proatherosclerotic” effects various pathogens exert as a result of direct infection of cells resident in the vessel wall. These latter studies have provided important mechanistic information, demonstrating a panoply of changes that infection induces in the biology of endothelial cells and smooth muscle cells that could predispose an individual to atherogenesis.

These include procoagulant effects, increased scavenger receptor expression and activity, enhanced uptake of cholesterol and of modified LDL, increased expression of adhesion molecules and of inflammatory cytokines, increased smooth muscle cell migration and proliferation, and antiapoptotic effects. Moreover, certain pathogens can exert proatherosclerotic effects in macrophages by promoting transformation of macrophages into foam cells and by stimulating macrophages to express cytokines that could lead to plaque instability and perhaps rupture.

However, it has recently been demonstrated that cytomegalovirus (CMV) infection increases the neointimal response to acute vascular injury in the rat carotid injury model in the absence of direct infection of the vessel wall (viral DNA was detectable in the vessel wall only transiently and with no evidence of replicating virus or viral gene expression). This finding necessitates exploration of a more complex paradigm as to how infection could contribute to atherogenesis. It becomes imperative to examine not only the proatherosclerotic effects of direct infection of cells of the vessel wall but also the changes that distinct infection induces in vessel wall pathology. These could be mediated through alterations caused by circulating cytokines induced by the infection of distant tissues or by the immune response to infection, in which an autoimmune mechanism(s) may be a player.

In this regard, considerable evidence derived from animal models (mainly the mouse) indicates that infection can trigger autoimmune-type responses that target self-peptides located in several tissues and that such responses can cause immunopathology. The targets of infection-induced autoantibodies include the myocardium with associated myocarditis, pancreatic islet cells with associated diabetes, herpes stromal keratitis, and the central nervous system, producing disorders similar to human neurological diseases such as multiple sclerosis, encephalitis, and Guillain-Barré syndrome.

It now seems likely that 1 of the mechanisms responsible for these infection-induced autoimmune-related diseases derives from molecular mimicry—a mechanism requiring that the infecting pathogen contain peptides homologous to those present in host proteins. The resulting immune response, although stimulated by and targeted to pathogen antigens, also attacks host tissues containing the cross-reacting peptides. This pathogen-induced mechanism of disease initiation and/or progression does not require the presence of a pathogen in the target tissue.

Given this background, a case can be made for the concept that infection-induced molecular mimicry also contributes to the development of atherosclerosis. Such a mechanism could account for a role of infection even if the candidate pathogen is not found within the atherosclerotic vessel. It is this latter assumption, ie, the need to demonstrate a resident pathogen, that commonly drives many studies attempting to add to the proof of causality.
The plausibility of the concept that autoimmune mechanisms, through molecular mimicry, contribute to atherogenic processes is further suggested by studies that have identified autoantibodies to heat shock proteins (hsp) in patients with atherosclerosis.30,31 Normally present in low concentrations, the expression of these ubiquitous intracellular proteins increases in response to stress, resulting in portions of these proteins being transported to the cell membrane, where they are accessible to the immune system. For example, heat-stressed endothelial cells carry peptides deriving from hsp on the cell surface, making the cells susceptible to complement-dependent lytic effects of anti-hsp antibodies.32,33

Although aberrant cell-surface presentation of otherwise cryptic intracellular peptides could break immune tolerance and lead to an autoimmune response, the amount of such peptides presenting on the cell-surface may be insufficient to break tolerance in an individual with low or absent levels of specific autoantibodies or autoaggressive T cells. However, if the immune response is enhanced by infection with a pathogen carrying homologous peptides, the resulting high levels of cross-reacting antibodies and/or autoaggressive T cells might then lead to autoimmune disease.

There are many possible homologous pathogen/host peptides that could cause infection-induced autoimmunity targeted to blood vessel walls and thereby contribute to atherosclerosis. Autoimmune responses to hsp could be 1 example of such a response,33–38 because all bacteria encode for hsp, and hsp are highly conserved, with high homology between prokaryotic and mammalian hsp. In addition, although viruses in general do not encode for hsp, they incorporate host hsp into their envelopes when budding from host cells.32,39

Another new issue relates to the role of multiple infections and the concept of “pathogen burden.” Studies of the role of infection in atherosclerosis have usually involved the investigation of a single pathogen. Such studies, coming from many laboratories, have independently identified several candidate pathogens that may causally relate to atherosclerosis.40–60 However, more recent studies have suggested that the impact of infection on atherosclerosis is related to the aggregate number of pathogens with which an individual is infected, a concept referred to as pathogen burden.61 Thus, one cross-sectional study61 demonstrated that whereas several individual pathogens (CMV, hepatitis A virus, HSV1, HSV2, and Chlamydia pneumoniae) are variably associated with the risk of coronary artery disease, it is the aggregate pathogen burden that most significantly relates infection to atherosclerosis. Of note, increasing infection burden was associated with increasing C-reactive protein levels. Because C-reactive protein is believed to reflect inflammation,62–68 at least part of the association between pathogen burden and coronary artery disease may be due to infection-induced inflammation, leading to the genesis of inflammatory cells and cytokines that could exacerbate atherogenic processes occurring in the vessel wall.

In a second study (J. Zhu et al, unpublished observations, 1999), which was prospective in design, increasing pathogen burden was associated with increasing risk of myocardial infarction or death. Thus, antibody status to CMV, hepatitis A virus, HSV1, HSV2, C pneumoniae, and Helicobacter pylori was determined in ≈900 patients with coronary artery disease established angiographically. Follow-up revealed that the risk of the combined end point, myocardial infarction or death, was strongly associated with pathogen burden. As the number of pathogens with which an individual was infected (determined by antibody status) increased, the event rate increased.

It is of note that pathogens selected for study in both of these investigations shared 2 common characteristics: each was an obligate intracellular pathogen, and each elicited a persistent lifelong immune response (as manifested by increased antibody levels). These criteria, which are derived from previous studies demonstrating a possible association of CMV, C pneumoniae, H pylori, HSV1, and HSV2 with coronary artery disease,40–60 led to the selection of hepatitis A virus as an additional pathogen to be studied,61 although this virus had never before been implicated in atherogenesis. The fact that hepatitis A virus was significantly associated with coronary artery disease in the cross-sectional study61 and with myocardial infarction or death in the prospective study suggests the possibility that other pathogens sharing similar characteristics may also convey atherogenic risk.

The validity of the hypothesis that infection contributes to atherosclerosis has not been definitively established, although the evidence is becoming compelling. If it is valid, atherosclerosis will be added to the list of chronic disease processes in which a role of autoimmunity, mediated through infection-related molecular mimicry, is possible. The concept is intriguing and will undoubtedly serve as the focus of many investigative studies in the first decade of the 21st century.

References


57. Key NS, Bach RR, Vercellotti GM, Moldow CF. Herpes simplex virus type I does not require productive infection to induce tissue factor in human umbilical vein endothelial cells. Lab Invest. 1993;68:645–651.


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