Atherosclerosis can be considered a chronic inflammatory condition of the vessel wall. Fatty streaks, the earliest morphological lesions of atherosclerosis, are caused by lipids (primarily of cholesteryl esters) accumulated within the macrophages (foam cells) and smooth muscle cells in the intimal layer. These lesions progress into atherosclerotic plaques containing extracellular matrix components, smooth muscle cells, macrophages, connective tissues, lymphocytes, and a fibrous cap over a pool of extracellular lipid. The primary pathogenic event in atherosclerosis is not clear. The “response to injury hypothesis” postulates that long-term endothelial cell injury, from a variety of mechanisms, alters endothelial permeability and induces leukocyte and platelet adhesion. The release of mitogenic factors from platelets and leukocytes was proposed to induce the migration and proliferation of smooth muscle cells from the media. The “lipid hypothesis” proposes that the retention and oxidation of LDL in the subendothelium play a central role in the atherosclerotic process. The uptake of oxidatively modified LDL by the macrophage via the scavenger receptor induces foam cell formation, but unmodified native LDL has no effect. Products of LDL oxidation, such as oxidized cholesterol, phospholipids, and isoprostanes have been detected in atherosclerotic plaques. Oxidized LDL has a number of pro-atherogenic effects, such as being chemotactic to monocytes and T cells, promoting inflammatory gene expression in vascular cells, and inducing the expression of the macrophage scavenger receptor.

Many genetic, environmental, inflammatory, and hemodynamic factors seem to modify the progression of the fatty streak to an advanced atherosclerotic plaque. In recent years, the importance of immunological mechanisms in the progression of these lesions has been recognized. The oxidation of LDL renders it antigenic. Neoepitopes, formed either by the oxidized lipids or by the adducts between oxidation products and associated proteins, elicit an autoimmune response. Autoantibodies reacting with oxidized LDL have been cloned and characterized from animal models and in humans and have been localized to the atherosclerotic plaque.

In murine models of atherosclerosis, the titer of these autoantibodies to oxidized LDL correlates with the progression of atherosclerosis. The presence of autoantibodies to an epitope of oxidized LDL is an independent risk factor for the progression of carotid atherosclerosis. In addition to oxidized LDL, immune responses to a number of other autoantigens in atherosclerotic lesions, such as heat-shock protein 60/65, β2-glycoprotein I, and cardiolipin, have been postulated to have a role in the progression of the atherosclerotic lesions. Furthermore, immune responses to a number of infectious agents have also been proposed. Chlamydia pneumoniae has been retrieved from atherosclerotic tissues, and the level of raised plasma titers of antibodies to C pneumoniae correlates with the severity of symptomatic atherosclerotic disease. C pneumoniae-responsive T cells have been identified in atherosclerotic plaques. The atherosclerotic plaque also contains T cells expressing interleukin-2 receptor and interferon γ, which is a clear indication of antigen-induced stimulation. Aberrant immune responses within the atherosclerotic lesions may underlie the accelerated growth of the plaques in certain inflammatory conditions.

Systemic lupus erythematosus is associated with increased morbidity and mortality due to cardiovascular disease. In the current issue, Svenungsson et al investigated the relevance of traditional and nontraditional risk factors for cardiovascular disease in systemic lupus erythematosus. They studied these risk factors in women with systemic lupus erythematosus, with and without cardiovascular disease, and matched controls (26 women in each group). In addition to traditional risk factors (carotid intimal-media thickness, dyslipidemia, raised lipoprotein(a), low HDL cholesterol, and high homocysteine level), women with systemic lupus erythematosus and cardiovascular disease had a striking association with autoantibodies to oxidized LDL (P<0.001) and lupus anticoagulant (P<0.007). Lupus anticoagulants are immunoglobulin antibodies that interfere with phospholipid-dependent coagulation tests. Lupus anticoagulants, along with anticardiolipin antibodies, are a heterogeneous group of antibodies with specificities toward anionic phospholipids, anionic phospholipid-binding proteins, and a complex epitope formed by the combination of both. Despite a large amount of work, the mechanism of the hypercoagulable state associated with antiphospholipid antibodies has been frustratingly difficult to elucidate. Of interest is the reported cross-reactivity between many antiphospholipid antibodies and oxidized LDL. In this study by Svenungsson et al, the elevated levels of oxidized LDL were measured by the monoclonal antibody E06. The E06 antibody binds to oxidation-specific epitopes in LDL, cardiolipin and, possibly, many other molecules. This antibody, which was initially developed...
because of its reactivity toward oxidized LDL, is identical to the V genes in the germ-line–coded natural antibody T15 with phosphorylcholine specificity. These natural antibodies, which are synthesized by CD5+ B1-cells, contain germ line or minimally mutated V regions and can bind structurally different antigens with relatively low affinity. These antibodies are also involved in innate immunity against certain bacterial and virus infections. The pathophysiological significance of the cross-reactivity of these natural antibodies with oxidized LDL is not clear.

In systemic lupus erythematosus, the germ-line–coded antibodies are increased in the circulation. Furthermore, these innate antibodies are also induced in infections. The reactivity toward oxidized LDL may provide a mechanism for the progression of atherosclerosis and, possibly, other inflammatory conditions such as lupus. The immune responses to the oxidized LDL can accelerate the progression of the atherosclerotic lesions in a number of ways. The immune complexes formed at the plaques can further stimulate the macrophages to release proinflammatory cytokines and growth factors via the macrophage Fc receptors. In addition, the uptake of immune complexes consisting of oxidized LDL bound to anti-LDL antibodies by the macrophages via their Fcγ receptors can lead to foam cell formation in a manner similar to the scavenger receptor–mediated uptake of oxidized LDL. However, it should also be noted that under certain conditions, immunization of LDL receptor–deficient mice with oxidized LDL reduces atherosclerosis and that this mechanism does not seem to involve the induction of high titers of antibodies.

The appreciation of immunological mechanisms in atherosclerosis has renewed interest in the role of infections in atherosclerosis. Epidemiological studies have shown raised antibody titers against several microorganisms in atherosclerosis. Epidemiological studies have shown raised antibody titers against several microorganisms in atherosclerosis. The delineation of autoimmune mechanisms in the progression of atherosclerotic plaque formation allows additional opportunities for therapeutic interventions on the basis of immunomodulation. Intravenous immunoglobulins have been used to treat a number of autoimmune disorders because they down-regulate the production of autoantibodies. In fact, in a mouse model of atherosclerosis, intravenous immunoglobulins have been shown to ameliorate atherosclerotic lesions. The identification of the precise epitopes responsible for pathogenic antibodies will provide strategies to inhibit autoantibody formation selectively by antigen-specific immunosuppression, to immunize against infections that induce antibodies that cross-react with oxidation-specific neoepitopes and, possibly, to attenuate the lesions by inducing the formation of neutralizing antibodies.

References

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