

Atherosclerosis and Autoimmunity

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Atherosclerosis is a chronic pathological condition in which arteries undergo gradual thickness of the intima causing decreased elasticity, narrowing, and reduced blood supply to target organs. The blood vessels most commonly affected and of clinically relevance include the aorta, coronary, carotid, and cerebral arteries, collectively classified under cardiovascular disease. Several inherited and environmental risk factors have been identified as contributors to the initiation and progression of atherosclerosis. These risk factors are thought to disrupt a number of lipid regulatory and inflammatory mechanisms within the arterial wall. The appearance of lipid-laden foam cells in the arterial intima is a characteristic histological finding of early atherosclerosis. High plasma levels of low-density lipoprotein (LDL) in combination with arterial shear stress may contribute to vascular inflammation that promotes the oxidative modification of LDL. The causal relationship between oxidized LDL (oxLDL) and atherosclerosis is almost universally accepted. OxLDL transported into the subendothelial space is ingested by macrophages in the arterial intima via scavenger receptors, resulting in excessive intracellular accumulation of oxLDL and foam cell (plaque) formation.

OxLDL is the principal plasma lipoprotein found in atherosclerotic lesions and it colocalizes with β 2-glycoprotein I (β 2GPI), the major antigenic target for antiphospholipid antibodies. Furthermore, there is wide consensus that anti- β 2GPI antibodies play a central role in the development of the clinical complications that characterize the antiphospholipid syndrome (APS). It has been recently demonstrated that oxLDL forms complexes with β 2GPI in atherosclerotic lesions and that such oxLDL/ β 2GPI complexes are present in the bloodstream of patients with various rheumatic diseases, such as systemic lupus erythematosus (SLE) and APS as well as in chronic renal disease, diabetes mellitus, and acute coronary syndrome (i.e., myocardial infarction and unstable angina). Furthermore, recent in vitro studies have shown that oxLDL/ β 2GPI complexes are more rapidly internalized by macrophages as IgG immune complexes. These macrophages will then express β 2GPI antigenic peptides (on MHC class II) to specific T cells. In this issue, the metabolic pathways of LDL under oxidative conditions and the biological and immunological implications of its metabolites are explored.

The accelerated or premature development of atherosclerotic cardiovascular disease in patients with rheumatic diseases has been recently reported, and the possible autoimmune proatherogenic mechanisms involved are also discussed in this issue. Pentraxins, C-reactive protein (CRP), amyloid protein P, and long pentraxin 3 are members of a highly conserved family of proteins that belong to innate immunity. These proteins and their autoantibodies are somehow involved in the induction, progression, and/or regulation of atherosclerosis in autoimmune disease. Furthermore, several epidemiological studies have revealed that host immune reactions against persistent infectious pathogens such as *Helicobacter pylori* may

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promote the development of atherosclerosis. Notably, immune responses against pathogen-derived heat shock protein 60 (HSP60) contribute to atherogenesis.

The issue also addresses the novel concept that oxidation “unmasks” antibodies in healthy individuals revealing autoantibodies that are associated with autoimmune disorders. Conversely, oxidation of autoantibodies from individuals with autoimmune diseases also can cause remasking of their autoantibodies that then become undetectable. These conversions depend upon oxidation–reduction reactions and define a new family of autoantibodies that has been designated “redox-reactive autoantibodies” that may be associated with atherosclerosis. We should note that there have been extensive reviews on this subject, including the related area of oxidation and autoimmunity, many of which are discussed within these papers, including the following literature [1–34]. One theme which is omitted from this issue is the concept of etiology; etiology is the most difficult issue to understand in autoimmunity and, for completeness, we cite the following recent symposia [35–44].

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