Epidemiology continues to play an important role in cardiovascular research. Population-based research identified serum cholesterol and blood pressure levels as risk factors for myocardial infarction and stroke. These studies were initiated after clinical and experimental studies had pointed to a role for these factors in the pathogenesis of atherosclerosis. Together, the experimental, clinical, and epidemiological studies prompted basic research into cholesterol metabolism and blood pressure regulation, which in turn made it possible to develop lipid-lowering and antihypertensive drugs. The result of these joint efforts has been a pharmacological prevention of cardiovascular disease, which saves thousands of lives every year.

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Over the last 2 decades, inflammation has turned out to be an additional important mechanism in the pathogenesis of atherosclerosis. Analysis of human tissue identified immune cells producing proinflammatory cytokines in plaques, experiments demonstrated significant effects of immune modulation in animal models of atherosclerosis, clinical studies of acute coronary syndromes showed early elevations of inflammatory blood markers, and epidemiological investigations revealed that elevated levels of downstream markers of inflammation, particularly CRP and interleukin (IL)-6, are associated with increased risk for myocardial infarction in healthy individuals. However, most epidemiologists have been hesitant to go beyond analysis of such downstream markers, and we therefore have insufficient population data to implicate any specific pathway within the inflammatory effector response of the immune system.

A few recent studies have explored more proximal immune mechanisms in the context of cardiovascular disease. They point to important roles for adaptive immunity in atherosclerotic heart disease by showing that genetic polymorphisms for Mhc2ta, which controls expression of HLA genes, and Oxlol, a cell surface protein involved in immune cell activation, are associated with increased risk for coronary artery disease (CAD). These studies are in line with a large number of experimental investigations showing that adaptive immunity profoundly affects the extent of atherosclerosis in hyperlipidemic, gene-targeted mice. It will now be important to determine to what extent immune responses to specific antigens such as modified lipoproteins, heat shock proteins, and microbial macromolecules, account for the effects of immune genes on CAD in man.

Another line of investigations have dealt with bioactive mediators involved in the inflammatory effector responses of immunity. The 5-lipoxygenase pathway producing leukotrienes has been implicated in several genetic epidemiological studies, with allelic variants of both 5-lipoxygenase and the 5-lipoxygenase activating protein (FLAP) being associated with increased risk for myocardial infarction. Experimental and clinical studies support and extend these findings by demonstrating expression of enzymes and receptors for leukotrienes in human atherosclerotic plaques, enzyme genes as contributors to atherosclerosis in experimental animals, and by showing inhibitory effects of leukotriene B4 receptor (BLT1) blockers on vascular remodeling and atherosclerosis.

Complement may be the best characterized effector cascade of immunity. It consists of a number of specific plasma proteases that activate each other in a similar manner as the coagulation cascade (Figures). It is typically activated by antigen–antibody complexes and leads to formation of a membrane attack complex that lysed the antibody-coated cell. The complement cascade can also be triggered by certain pathogen surfaces that directly elicit activation of complement factor C3 (Figure). Finally, microbial pathogens containing mannose residues on their surface can activate complement via the mannose-binding lectin (MBL) (Figure). Activation through either of these 3 pathways leads to lysis of infected cells, opsonization of complement-coated pathogens, and release of proinflammatory chemotactic mediators (Figure). They all contribute to our innate immune defense, and genetic variants leading to reduced levels of a specific component such as MBL are associated with increased susceptibility to infections.

Complement factors were identified in atherosclerotic plaques several years ago. These findings prompted investigators to propose that complement activation accelerates atherosclerosis. This notion was supported by studies in fat-fed, C6-deficient rabbits but were not confirmed in more recent investigations using gene-targeted mice lacking C3 or C5. Remarkably, C3 deficiency increased rather than reduced atherosclerosis in Apoe mice as well as Apoe mice. Such protective effects could perhaps involve ligation of complement receptors on immune cells leading to elimination of antigen and...
Overview of the complement cascade. Complement can be activated via 3 different pathways: In the classical pathway, complement is activated by antigen–antibody complexes on the surface of cells or microbes. This leads to formation of the C1 complex, which triggers activation of the subsequent cascade. The lectin pathway is activated when mannoside residues on pathogen surfaces bind to mannoside-binding lectin (MBL), and the alternative pathway is triggered when pathogen surfaces directly activate factors C3, B, and D. All three pathways lead to formation of a C3 convertase, which cleaves factor C3 into a larger fragment, C3b, and a smaller one, C3a. The former remains on the activating surface, where it can act as an opsonin by binding complement receptors (CR) on phagocytes. C3b can also trigger the subsequent cleavage of C5 and formation of the surface-bound C5b-9 membrane attack complex (MAC) that can lyse cells. C5a and another small peptide, C5a, are proinflammatory agents that promote leakage of the venular endothelium and chemotactic recruitment of granulocytes.

Activation of protective immune responses, but the precise mechanisms remain unknown.

In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Keller et al have addressed the role of complement in atherosclerotic disease by using an epidemiological approach. A nested case–control study derived from a cohort in England was analyzed for serum levels of MBL as well as several conventional risk factors. Elevated serum MBL was associated with an increased risk of future CAD in men. It remained an independent risk factor after adjustment for other risk factors including smoking, blood pressure, LDL cholesterol, diabetes, and CRP. The odds ratio for future CAD was 1.55 for those in the quintile of highest MBL levels. Surprisingly, MBL was not a risk factor for CAD in women in this study.

The findings by Keller et al add to an already long list of studies on MBL in cardiovascular disease. Unfortunately, the results of these studies point in different directions. Most of them have analyzed MBL genotypes and concluded that alleles causing low serum MBL levels are associated either with increased or reduced risk for CAD, depending on the study. In the large Copenhagen City Heart Study, MBL genotypes were not associated with overall morbidity or mortality. In a nested case–control study based on the large Reykjavik cohort, serum MBL levels were not associated with CAD except in diabetics, where high MBL was associated with reduced risk of CAD.

These discrepancies might conceivably be attributable to different effects of MBL on atherosclerosis versus cardiac ischemia. Ultrasound analysis of patients with carotid artery stenosis suggest that the MBL genotype leading to low serum levels is associated with increased plaque growth, whereas homozygotes for alleles causing normal MBL levels develop a higher rate of restenosis. Additional studies will be needed to confirm these data.

At this stage, confusion prevails. MBL seems to be associated with CAD, but the mechanism is unknown and the epidemiological data conflicting. Therefore, it may be wise to revisit the molecular immunology literature on MBL. It has a complicated gene structure, with 2 genes in man. MBL1 is a pseudo-gene, and the functional MBL2 gene has 2 alternative transcription start sites. Importantly, its promoter structure shows that MBL is expressed in response to acute phase stimuli (although it may not be clinically useful as an acute phase reactant as CRP). Because of the MBL2 promoter, elevated MBL protein levels may reflect an inflammatory process rather than an activation of the complement system in a particular disease. The possibility that MBL is involved in complement activation in the atherosclerotic plaque and/or ischemic heart remains fascinating. It now requires experimental research to clarify any cause-effect mechanisms that may operate during the pathogenesis of CAD.

Disclosures

None.

References


