Atherosclerosis has long been recognized as a disease characterized by chronic arterial inflammation. More recent studies have indicated that this inflammation is driven by adaptive immune responses against modified self antigens (such as oxidized LDL) that have been trapped in the artery wall. Does this mean that atherosclerosis should be seen as an autoimmune disease? In a traditional sense, that is probably not the case, but there is considerable support for the notion that autoimmune responses against oxidized LDL and other modified vascular self antigens play an important role in modulating disease activity and hence represent interesting targets for the development of novel interventions to prevent cardiovascular disease. The picture emerging from studies that have used hypercholesterolemic mouse strains deficient in various components of the adaptive immune system suggests that activation of immune responses of T helper 1 (Th1) cells toward vascular antigens are strongly proatherogenic, whereas activation of immune responses involving regulatory T cells and B lymphocytes are protective. The balance between these pathogenic and protective immune responses would then determine if lesions progress or regress (1).

The concept of the atheroprotective B cell is now being challenged, however, by a recent study from Ait-Oufella and coworkers published in the Journal of Experimental Medicine (2). In this provocative and interesting study, the authors used injections of a CD20-specific monoclonal antibody (mAb) to deplete apolipoprotein E–deficient and LDL receptor–deficient mice of B cells. CD20 mAb treatment reduced the number of B cells in the blood, spleen, and bone marrow by >90%, did not affect plasma cholesterol concentrations, and reduced the growth of atherosclerotic lesions by between 20% and 50%, depending on diet, length of the treatment period, and mouse model. The most pronounced reductions were observed in mice with lower plasma cholesterol (chow diet) and a longer treatment period (12 weeks). It is apparent that the results came as a surprise to the authors, because previous studies had indicated an atheroprotective role for B cells in mice. Transplantation of B cell–deficient bone marrow (obtained from μMT mice) into irradiated LDL receptor–deficient mice had been shown to enhance the progression of atherosclerosis by 30% to 40%, compared with transplantation of wild-type bone marrow, a result clearly indicating an atheroprotective role for B cells. Also reported was that the more aggressive development of atherosclerosis that occurs in splenectomized mice can be reversed by B-cell transfer. The reasons for this apparent discrepancy remain to be fully understood, but it is clear that the role of B cells in atherosclerosis is complex and that they may have both protective and pathogenic effects. This consideration may also explain why the results of epidemiologic studies of the association between autoantibodies against atherosclerosis-relevant antigens (such as oxidized LDL) and cardiovascular disease have been inconsistent. High concentrations of IgM against oxidized LDL have generally been associated with less severe atherosclerosis and lower cardiovascular risk (3). These antibodies primarily target oxidized phospholipids on the surface of oxidized LDL particles and are identical to the natural B1 cell–derived antibodies that recognize and help to remove apoptotic cells. They likely function as unspecific waste removers that help to limit organ damage and the risk for the development of autoimmunity. Collectively, the available experimental and clinical evidence provide strong support for a protective role for IgM in recognizing oxidized LDL, suggesting that at least B1 cells are atheroprotective. The role of IgG against oxidized LDL remains more controversial, however, and high antibody concentrations have been reported to be associated with both higher and lower cardiovascular risk and disease severity. Interestingly, some studies have suggested that high concentrations of IgG against oxidized LDL with only minor modifications [antibodies recognizing native apolipoprotein B (apo B) peptides] are associated with lower cardiovascular risk, whereas high concentrations of IgG against more severely oxidized LDL (malondialdehyde-modified apo B sequences) are associated with higher...
risk. Although these epidemiologic studies provide support for an involvement of B-cell responses against oxidized LDL antigens in cardiovascular disease, they do not help to explain whether they play a pathogenic or protective role. Findings from animal studies, however, support the notion that these antibodies also have a protective role in atherosclerosis. Mice lacking Fcγ receptor IIb, an inhibitory receptor that is activated by immune complexes containing IgG, are characterized by a more aggressive development of atherosclerosis. Injection of oxidized LDL–specific human recombinant IgG (generated against a malondialdehyde-modified apo B sequence) inhibits atherosclerotic plaque formation in hypercholesterolemic mice and can also induce plaque regression when combined with lowering of plasma cholesterol concentrations (4). This antibody (BI–204) is presently in early clinical studies for possible use in the prevention and treatment of cardiovascular disease. Against this background, it appears less likely that Ait-Oufella and coworkers’ finding of decreased atherosclerosis in B cell–depleted mice is explained by an effect on antibody generation.

Looking for alternative explanations, the authors examined how CD20 mAb treatment affected T-cell activation. As discussed above, there is convincing data from other animal studies that T-cell responses against plaque antigens play a critical role in modulating the disease process. It is also clear that proinflammatory Th1 responses are proatherogenic, whereas activation of regulatory T cells has a protective effect. In their study, Ait-Oufella et al. found that the depletion of B cells was associated with a marked reduction in T-cell accumulation in atherosclerotic lesions, as well as with signs of decreased activation of effector T cells in the spleen. A particularly interesting observation was that although CD20 mAb treatment decreased interferon-γ production in spleen T cells, it also enhanced interleukin-17 (IL-17) production. Because recent studies from the same laboratory had identified an unexpected protective role for IL-17 in atherosclerosis, the authors blocked IL-17 in CD20 mAb–treated animals by coadministering an IL-17–neutralizing antibody. This treatment completely neutralized the atheroprotective effect of CD20 mAb.

It is becoming clear that the role of B cells in atherosclerosis is much more complex than previously anticipated. Although there is strong evidence that B cells may inhibit disease progression via the secretion of protective antibodies, the studies by Ait-Oufella and coworkers imply that they may also contribute to the progression of disease through activation of T cells. Much work remains to clarify the pathophysiological relevance of the latter finding, as well as to understand the mechanisms involved. As the authors suggest, one possibility is that B cells could promote plaque development by suppressing the potentially atheroprotective cytokine IL-17. That B cells may contribute to the inhibition of IL-17 production is not unexpected, because Th17 cells have been implicated in several autoimmune diseases. That the price to pay for this suppression would be an increased susceptibility to the development of atherosclerosis clearly represents a more unexpected consequence. One should keep in mind, however, that the role of IL-17 in atherosclerosis remains controversial, and several groups have reported findings suggesting that it promotes rather than inhibits disease development. Another possibility is that B cells could promote atherosclerosis through presentation of disease-relevant antigens to T cells and that this effect leads to the generation proinflammatory Th1 cells that become activated when they encounter their antigen in atherosclerotic lesions. If this supposition is correct, the findings by Ait-Oufella et al. could imply that B cells carry out much of the antigen presentation that drives atherosclerosis. Finally, whether B cells have the adverse effects of the regulatory T cells proposed to suppress the atherosclerosis activity of Th1 cells needs to be explored.

Understanding the complexities of B-cell behavior in atherosclerosis may appear to be something primarily of academic interest. Seen in the larger context of the emerging importance of the immune response in modulating the progression of cardiovascular disease, however, B-cell behavior certainly appears to have considerable importance. The therapies available today for preventing and treating ischemic heart disease and stroke rely almost exclusively on risk factor intervention, whereas therapies directly targeting the actual disease process in the vascular wall are lacking. Experience from randomized clinical trials suggesting that a risk reduction of greater than 30% to 40% is difficult to achieve through current intervention strategies emphasizes the need for the development of alternative therapies directly targeting the disease process in the atherosclerotic lesions. The primary aim of such therapies should be to down-regulate inflammation locally in atherosclerotic plaques, thereby allowing repair processes to stabilize lesions. Systemic antiinflammatory therapy does not appear to be a feasible approach, because nonsteroidal antiinflammatory drugs have been associated with, if anything, increased cardiovascular mortality. Against this background, considerable interest has focused on the possibility of selectively inhibiting plaque inflammation by down-regulating proinflammatory autoimmune responses against plaque-specific modified self antigens such as oxidized LDL. The first generation of such therapies is now approaching clinical testing (5). One example is a vaccine based on an apo B–derived antigen believed to
act through enhancing immunologic tolerance to oxidized LDL. Successfully applying such new therapies, however, critically requires a better understanding of the complex role of the immune system. This knowledge also will be required for developing the diagnostic tools needed to identify individuals at “immunological risk” for cardiovascular disease and to monitor the effect of immunomodulatory therapies.

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References