Lymphocytes and plasma cells have long been detected in the plaque and adventitia of atherosclerotic human arteries,1 yet their role in regulating atherosclerosis has only recently begun to emerge.2,3 Two important studies published in 2002 provide evidence for an atheroprotective role for B cells.3,4 More recently, 2 groups broadened our understanding of B cells and atherosclerosis by providing evidence that B cells can also promote atherosclerosis. Treating atherosclerosis-prone mice with an anti-CD20 monoclonal antibody that depleted mature B2, but not B1a cells, attenuated atherosclerosis.5,6 This B2 cell depletion was associated with decreased activated splenic CD4+ T cells, T-cell proliferation, and lesional T cells, suggesting that B2 cells aggravate atherosclerosis through a T-cell–dependent mechanism. Further evidence for an atherogenic role for B2 cells was provided by studies by Kyaw et al7 who found aggravated atherosclerosis in lymphocyte-deficient apolipoprotein E−/− mice reconstituted with 80% µMT/20% C57BL/6 marrow, providing evidence that it is the loss of BAFFR on B cells mediating this effect. In agreement with their previous findings using anti-CD20 monoclonal antibody5,6 and BAFFR deletion7,9 approaches. Recent work provides evidence that splenic B cells from apolipoprotein E−/− mice home to the aorta, and provide atheroprotection.2 Yet, spleen-derived B cells are predominantly B2 cells. Might there be B2 cell–derived atheroprotective B-cell subsets in the spleen that home to the aorta? Indeed, B2 cells can give rise to regulatory B cells that produce the atheroprotective cytokine interleukin-10 (Figure). Are interleukin-10 producing Bregs atheroprotective? Is it BAFFR-dependent? Or might there be B2 cell–derived atheroprotective B-cell subsets in the spleen that constitutively home to the aorta to promote atheroprotection? Identifying the subsets of B cells in the normal aorta and throughout the progression of disease may provide important clues to the local function of B-cell subsets in regulating atherogenesis. It is also interesting to note that Sage et al7 found a significant reduction in B1b, but not B1a, cell number with BAFFR deficiency. Although the role for B1b cells in atherosclerosis remains elusive, these data suggest that subtypes within the B1 subset may also have unique functions in regulating atherosclerosis (Figure). B1a cells have been reported to be atheroprotective,11 yet recent work describes a new peritoneal B1a-derived B cell, innate response activator B cells, that produces the majority of lipopolysaccharide-stimulated granulocyte macrophage-colony stimulating factor in the spleen.12 Granulocyte macrophage-colony stimulating factor stimulates myeloid progenitors in the spleen to differentiate to Ly6C Ehi monocytes which traffic to sites of atherosclerosis,13 suggesting that specific contexts can alter B cell subset phenotypes from atheroprotective to atherogenic. Although, whether innate response activator B cells are atherogenic has not been determined.

The study by Sage et al17 adds to the accumulating evidence that depleting B2 cells in mice attenuates atherosclerosis, and
supports a role of T cells in this process. The BAFFR could be a target for reducing B2 cells as a strategy to limit atherosclerosis. Yet, a full understanding of the atherogenic and atheroprotective B-cell subsets, the impact of context on their function, and the mechanisms whereby they mediate their effects is needed in order to lead to exciting new strategies whereby immune protection against atherosclerosis could be bolstered without risk of global immune compromise.

Disclosures

None.

References


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