Refining the Role of B Cells in Atherosclerosis

Heather M. Perry, Coleen A. McNamara

Lympocytes and plasma cells have long been detected in the plaque and adventitia of atherosclerotic human arteries, yet their role in regulating atherosclerosis has only recently begun to emerge. Two important studies published in 2002 provide evidence for an atheroprotective role for B cells. 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. 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 al who found aggravated atherosclerosis in lymphocyte-deficient apolipoprotein E-/- recombination activating gene 2+/- common cytokine receptor γ chain-deficient or to B-cell–deficient atherogenic mice after adoptive transfer of 5×10^6 B2, but not B1, B cells. Sagd et al present another important study on the impact of loss of B2 cells on atherosclerosis by using a genetic strategy of B cell-activating factor receptor (BAFFR) deficiency to deplete B2 cells. BAFFR is a tumor necrosis factor receptor family member that is critical for maintaining mature B2 B cells. The authors reconstituted lethally irradiated low-density lipoprotein recepotor+/- mice with bone marrow from BAFFR-deficient mice leading to a markedly diminished ability to replenish B2 cells in peripheral lymphoid tissue or blood. This was associated with reduced atherosclerosis, measured by Oil Red O staining of the aortic root, after 6 and 8 weeks of high-fat diet. Low-density lipoprotein receptor+/- mice reconstituted with 80% µMT/20% Baffr+/- also had reduced atherosclerosis compared with those reconstituted with control 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 antibody depletion of B2 cells, they also found that B2 B cell depletion due to BAFFR deficiency reduces the proportion of spleen-derived activated CD4+ T cells and CD4+ T-cell proliferation. Additionally, they found reduced numbers of T cells in aortic roots from Baffr+/+ reconstituted mice at 6 (but not 8) weeks of high-fat diet, and at 8 weeks of diet in lesions from µMT/Baffr+/- mice compared with controls, underscoring that in the context of atherosclerosis B2 cells are necessary for activation and proliferation of CD4 T cells. Consistent with the findings of Sage et al, Kyaw et al also recently published that Baffr+/- apolipoprotein E-/- mice had depletion of mature B2 cells, reduced lesional inflammation, and attenuated atherosclerosis. Taken together, these studies clearly demonstrate that significantly reducing B2 B cell number attenuates atherosclerosis.

Yet several important questions about B cell subsets, the context in which they reside, and their role in atherosclerosis, remain unanswered. Reduced T-dependent circulating antibodies to modified lipids may be one mechanism of atherosclerosis by which B2 cell depletion attenuated reduced circulating IgG to malondialdehyde-modified low-density lipoprotein was seen with both anti-CD20 monoclonal antibody and BAFFR deletion approaches. Recent work provides evidence that splenic B cells from apolipoprotein E-/- mice home to the aorta, and provide atheroprotection. 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 important atheroprotective B1 cells 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 al 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 B1a cells may be atheroprotective, yet recent work describes a new peritoneal B1a-derived B1 cell, innate response activator B cells, that produces the majority of lipopolysaccharide-stimulated granulocyte macrophage-colony stimulating factor in the spleen. Granulocyte macrophage-colony stimulating factor stimulates myeloid progenitors in the spleen to differentiate to Ly6C<sup>high</sup> monocytes which traffic to sites of atherosclerosis, 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 al 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**


**KEY WORDS**: atherosclerosis ◼ B cell-activating factor receptor ◼ B cells ◼ B-cell subtypes within the B1 and B2 lineages. Conventional B2 B cells promote atherosclerosis. Functions linked to atherogenesis include CD4 T-cell activation and proliferation. The role of Bregs in atherosclerosis is not yet determined. They may attenuate or promote atherosclerosis by secretion of interleukin-10 (IL-10) or IL-12 respectively. Peritoneal B1a cells are atheroprotective. Mechanisms linked to atheroprotection include production of IgM and IL-10. The role of innate response activator B cells (IRA; derived from peritoneal B1a cells) is unknown. Function linked to atherogenesis includes production of granulocyte macrophage-colony stimulating factor (GM-CSF). The role of B1b cells in atherosclerosis is unknown. *Role in atherosclerosis, not yet determined.***

Figure. B-cell subtypes within the B1 and B2 lineages. Conventional B2 B cells promote atherosclerosis. Functions linked to atherogenesis include CD4 T-cell activation and proliferation. The role of Bregs in atherosclerosis is not yet determined. They may attenuate or promote atherosclerosis by secretion of interleukin-10 (IL-10) or IL-12 respectively. Peritoneal B1a cells are atheroprotective. Mechanisms linked to atheroprotection include production of IgM and IL-10. The role of innate response activator B cells (IRA; derived from peritoneal B1a cells) is unknown. Function linked to atherogenesis includes production of granulocyte macrophage-colony stimulating factor (GM-CSF). The role of B1b cells in atherosclerosis is unknown.

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References

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