Atherosclerosis is associated with immune activation and with systemic immune responses and signs of inflammation.1–3 Atherosclerotic plaques contain a large number of immune cells, particularly macrophages and T cells.4,5 Histopathological and clinical investigations point to immune activation of plaques as a cause of plaque rupture and acute coronary syndromes. Seroepidemiological studies suggest links between atherosclerosis and microbial infections.6,7 Animal studies have identified specific immune cells that play a role in atherogenesis. For example, congenital deficiency of macrophages, lymphocytes, and the Th1, effector pathway, generated by cross-breeding apolipoprotein (apo) E knockout (KO) mice with op/op mutant mice,8 recombinase activating gene-1 KO mice,9 and interferon-γ receptor KO mice,10 respectively, have resulted in the reduction of atherosclerotic lesions. Furthermore, the blockade of c-fms, a receptor for macrophage colony stimulating factor, also caused marked suppression of atherogenesis in apo E-deficient mice, where macrophage differentiation was impaired. These and other studies suggest that immunomodulation may be used to treat or prevent atherosclerosis.

Therapy with immunoglobulin has been used in the treatment of immune-mediated disorders for more than 25 years.11–13 The mode of action of immunoglobulin is still unclear and may involve both Fc and V region-dependent mechanisms: blockade of Fc receptors on macrophages and effector cells, antinflammatory effects by attenuation of complement-mediated damage, regulation of the production of cytokines, or inhibition of lymphocyte proliferation. Several of these mechanisms might be beneficial in atherosclerosis.14 Indeed, we have found that immunoglobulin therapy markedly suppressed atherosclerosis because of Fc receptor-mediated immunomodulatory actions in apoE-deficient mice.15

In the present issue of Circulation Research, Hernández-Vargas et al report that Fcγ receptor deficiency protects against the development of atherosclerosis in apo E KO mice.16 Using double knock out (DKO) mice by crossing apo E KO mice with IgG Fc receptors (FcγRs) deficient mice, they demonstrated that DKO mice exhibited a reduction in the atherosclerotic lesion size compared with apoE KO, control mice without alterations in serum lipid profiles. FcγR deficiency in DKO mice significantly diminished the macrophage and T cell count, the expression of monocyte chemoattractant protein-1, regulated on activated normal T-cell expressed and secreted (RANTES), and adhesion molecule-1 in the lesions. In addition, cultured vascular smooth muscle cells from both FcγR deficient and DKO mice failed to respond to immune complexes, shown by impaired chemokine expression and NF-κB activation. Furthermore, DKO mice exhibited lack expression of FcγRI and FcγRIIIA (both activating receptors), while FcγRIIB (inhibiting receptor) was potentiated. The authors concluded that FcγR deficiency limits development and progression of atherosclerosis, and pointed out the critical role of FcγRs in atherogenesis.

Fc receptors act as trigger molecules for inflammation, allergic, endocytotic, and inhibitory activities of immune effector cells.17 Recently, specific classes or FcγRs have been well characterized.18 Two general classes of FcγRs are known, the activating and the inhibitory receptors, which transmit their signals via immunoreceptor tyrosine-based activation (ITAM) or inhibitory motifs (ITIM). In activating receptors, the ITAM motif can be intrinsic to the receptor, as in FcγRIIA (a receptor not found in the mouse), and in FcγRI, FcγRIIIA, and FcγRIV (receptors conserved between mouse and human). The inhibitory receptor (FcγRIIB) contains the ITIM sequence, and binds IgG and immune complexes with low affinity. Recently, it has been postulated that FcγR activation is involved in a wide range of inflammatory and immune diseases.18–21 Accordingly, a novel therapeutic target in atherosclerosis is the FcγR.

In previous studies, FcγRIIB mediated not only an inhibitory effect on experimental autoimmune myocarditis in rats13 but also an antiatherosclerotic effect in apo E deficient mice,15 using the entire immunoglobulin molecule. Specifically, an intact immunoglobulin, but not F(ab’), fragments of immunoglobulin, inhibited myocarditis or atherosclerosis through the Fc portion. Gill et al demonstrated the targeting effect of immunoglobulin on adhesion molecules using ischemia/reperfusion model in cats, suggesting the downregulation of adhesion molecules via Fc receptors. Recently, it has been shown that Fc receptors play a pivotal role in experimental neointimal vascular hyperplasia via ITIM.23 Furthermore, Mineo et al demonstrated FcγRIIB-mediated C-reactive protein (CRP) inhibition of endothelial nitric oxide (NO) synthase.24 They found that in control mice, CRP blunts acetylcholine-induced increases in carotid artery vascular conductance, and that, in contrast, CRP enhances a cetycholine responses in FcγRIIB KO mice.24
It is known that FcRIIB is expressed in human endothelial cells and in mouse endothelium,\textsuperscript{24} and that CRP levels are strongly correlated with increased risk for myocardial and vascular inflammatory diseases.\textsuperscript{25,26} Based on the current study and also on previously published data, FcγRIIB blockade may be a novel therapy for inflammatory cardiovascular diseases.

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None.

References


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