ABSTRACT

Atherosclerosis is a chronic inflammatory condition and the major underlying cause of heart attacks and strokes. Since the immune system is paramount in all stages of atherosclerosis, modulating the immune response is an attractive therapeutic strategy for atherosclerotic disease. Signal transducers and activators of transcription (STAT) 6 and STAT4 are essential orchestrators of the anti-inflammatory Th2 response and the pro-inflammatory Th1 response, respectively. Using bone marrow transplantation to deplete STAT6 and STAT4 expression in specific immune compartments in low density lipoprotein receptor knockout (Ldlr-/-) mice, we investigated the validity of modulating the immune response through STAT6 and STAT4 as a prospective treatment strategy for atherosclerosis. We found that myeloid-specific STAT6 depletion did not significantly impact atherosclerotic lesion area or stability in Ldlr-/- mice fed an atherogenic diet for 8 or 14 weeks. In addition, hematopoiesis in the myeloid and lymphoid lineages was not significantly affected by the absence of myeloid STAT6. In contrast, total hematopoietic system STAT4 depletion profoundly exacerbated atherosclerotic lesion area and vulnerability in Ldlr-/- mice following 8 weeks of atherogenic diet. Hematopoietic perturbations in mice transplanted with STAT4-deficient bone marrow are highly reminiscent of interferon (IFN)-γ-dependent effects on immune cell development in interleukin-12-treated mice, suggesting that IFN-γ levels may be elevated in response to hypercholesterolemia in the absence of STAT4. Myeloid-specific STAT4-deficient mice also developed larger atherosclerotic lesions in the aortic root, providing evidence that even partial STAT4 insufficiency can potentially accelerate atherosclerosis. This thesis provides novel insights into the functions of STAT6 and STAT4 in atherosclerosis.