Abstract:
Inflammation has been closely linked to auto-immunogenic processes in atherosclerosis. Plasmacytoid dendritic cells (pDCs) are specialized to produce type-I interferons in response to pathogenic single-stranded nucleic acids, but can also sense self-DNA released from dying cells or in neutrophil extracellular traps complexed to the antimicrobial peptide Cramp/LL37 in autoimmune disease. However, the exact role of pDCs in atherosclerosis remains elusive. Here we demonstrate that pDCs can be detected in murine and human atherosclerotic lesions. Exposure to oxidatively modified low-density lipoprotein enhanced the capacity of pDCs to phagocytose and prime antigen-specific T cell responses. Plasmacytoid DCs can be stimulated to produce interferon-β by Cramp/DNA complexes, and we further identified increased expression of Cramp and formation of neutrophil extracellular traps in atherosclerotic arteries. Whereas Cramp/DNA complexes aggravated atherosclerotic lesion formation in apolipoprotein E-deficient mice, pDC depletion and Cramp-deficiency in bone marrow reduced atherosclerosis and anti-double-stranded DNA antibody titers. Moreover, the specific activation of pDCs and interferon-β treatment promoted plaque growth, associated
with enhanced anti-double-stranded-DNA antibody titers. Accordingly, anti-double-stranded DNA antibodies were elevated in patients with symptomatic versus asymptomatic carotid artery stenosis. Self-DNA (e.g., released from dying cells or in neutrophil extracellular traps) and an increased expression of the antimicrobial peptide Cramp/LL37 in atherosclerotic lesions may thus stimulate a pDC-driven pathway of autoimmune activation and the generation of anti-double-stranded-DNA antibodies, critically aggravating atherosclerosis lesion formation. These key factors may thus represent novel therapeutic targets.