CXCR4 blockade induces atherosclerosis by affecting neutrophil function.

The SDF-1?/CXCR4 dyad was previously shown by us and others to be instrumental in intimal hyperplasia as well as early stage atherosclerosis. We here sought to investigate its impact on clinically relevant stages of atherosclerosis in mouse and man. Immunohistochemical analysis of CXCR4 expression in human atherosclerotic lesions revealed a progressive accumulation of CXCR4(+) cells during plaque progression. To address causal involvement of CXCR4 in advanced stages of atherosclerosis we reconstituted LDLr(-/-) mice with autologous bone marrow infected with lentivirus encoding SDF-1? antagonist or CXCR4 degrakine, which effects proteasomal degradation of CXCR4. Functional CXCR4 blockade led to progressive plaque expansion with disease progression, while also promoting intraplaque haemorrhage. Moreover, CXCR4 knockdown was seen to augment endothelial adhesion of neutrophils. Concordant with this finding, inhibition of CXCR4 function increased adhesive capacity and reduced apoptosis of neutrophils and resulted in hyperactivation of circulating neutrophils. Compatible
with a role of the neutrophil CXCR4 in end-stage atherosclerosis, CXCR4 expression by circulating neutrophils was lowered in patients with acute cardiovascular syndromes. In conclusion, CXCR4 contributes to later stages of plaque progression by perturbing neutrophil function.