Annexin A1 counteracts chemokine-induced arterial myeloid cell recruitment.

Abstract:
Chemokine-controlled arterial leukocyte recruitment is a crucial process in atherosclerosis. Formyl peptide receptor 2 (FPR2) is a chemoattractant receptor that recognizes proinflammatory and proresolving ligands. The contribution of FPR2 and its proresolving ligand annexin A1 to atherosclerotic lesion formation is largely undefined. Because of the ambivalence of FPR2 ligands, we here investigate the role of FPR2 and its resolving ligand annexin A1 in atherogenesis. Deletion of FPR2 or its ligand annexin A1 enhances atherosclerotic lesion formation, arterial myeloid cell adhesion, and recruitment. Mechanistically, we identify annexin A1 as an endogenous inhibitor of integrin activation evoked by the chemokines CCL5, CCL2, and CXCL1. Specifically, the annexin A1 fragment Ac2-26 counteracts conformational activation and clustering of integrins on myeloid cells evoked by CCL5, CCL2, and CXCL1 through inhibiting activation of the small GTPase Rap1. In vivo administration of Ac2-26 largely diminishes arterial recruitment of myeloid cells in a FPR2-dependent fashion. This effect is also observed in the presence of selective antagonists to CCR5, CCR2, or CXCR2, whereas Ac2-26 was without effect when all 3
chemokine receptors were antagonized simultaneously. Finally, repeated treatment with Ac2-26 reduces atherosclerotic lesion sizes and lesional macrophage accumulation. Instructing the annexin A1-FPR2 axis harbors a novel approach to target arterial leukocyte recruitment. With the ability of Ac2-26 to counteract integrin activation exerted by various chemokines, delivery of Ac2-26 may be superior in inhibition of arterial leukocyte recruitment when compared with blocking individual chemokine receptors.