Stromal Cell-Derived Factor-1 Promotes Vasculogenesis and Inflammatory Cell Invasion and Proliferation in Aneurysm Walls: A Proposed Mechanism for Aneurysm Growth and Rupture

Brian Lim Hoh MD; Koji Hosaka PhD; Daniel Downes BS; Kamil Nowicki BS; Erin N. Wilmer; Gregory James Velat MD; Edward W. Scott PhD

University of Florida, Gainesville, Florida

Introduction

Current management of unruptured cerebral aneurysms consists of clipping, coiling, or watchful waiting. If the biology of how aneurysms grow and rupture were better known, perhaps a novel drug therapy could be developed to prevent unruptured aneurysms from growing and becoming prone to rupture. Vasculogenesis and inflammatory cell infiltration have been associated with cerebral aneurysm rupture, and stromal cell-derived factor-1 (SDF-1) has been implicated in these processes, therefore, we studied these mechanisms in human aneurysm specimens, a murine elastase carotid aneurysm model, and a murine hypertensive elastase circle of Willis intracranial aneurysm model.

Methods

Human aneurysms; murine carotid aneurysms; and murine intracranial aneurysms were studied by immunohistochemistry. Flow cytometry analysis was performed on blood from mice developing carotid aneurysms or intracranial aneurysms. The effect of SDF-1 on endothelial cell and macrophages was studied by chemotaxis cell migration assay and capillary tube formation assay.

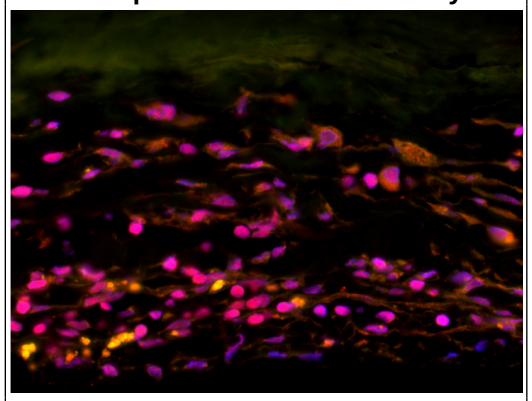
Results

Human aneurysms(n=23), murine carotid aneurysms(n=10), and murine intracranial aneurysms(n=19) all express SDF-1; and mice with developing carotid aneurysms (n=9 versus n=8 sham) or intracranial aneurysms (n=6 versus n=9 sham) have increased circulating progenitor cells expressing CXCR4, the receptor for SDF-1 ($P<0.01$ and $P<0.001$, respectively). Human aneurysms and murine carotid aneurysms have endothelial cells, macrophages, and capillaries in the walls of the aneurysms; and the presence of capillaries in the walls of human aneurysms is associated with greater macrophages ($P=0.01$). SDF-1 promotes endothelial cell and macrophage migration ($P<0.01$ for each), and promotes capillary tube formation ($P<0.001$). When mice are given anti-SDF-1 blocking antibody (n=7 versus n=7 IgG control), there is significant reduction in endothelial cells ($P<0.05$), capillaries ($P<0.05$), and inflammatory cell proliferation ($P<0.05$) in the walls of their aneurysms.

Conclusions

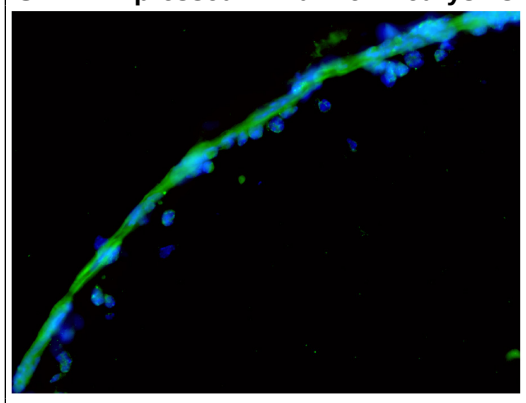
These data suggest SDF-1 has a critical role in promoting vasculogenesis and associated inflammatory cell migration and proliferation in the walls of aneurysms.

SDF-1 Expressed in Human Aneurysms



SDF-1+ expression in human aneurysms. Red: SDF-1+; Blue: DAPI

SDF-1 Expressed in Murine Aneurysms

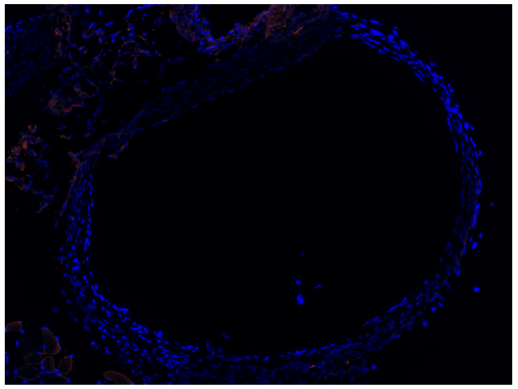


SDF-1+ expression in murine aneurysms. Green: SDF-1+; Blue: DAPI

Learning Objectives

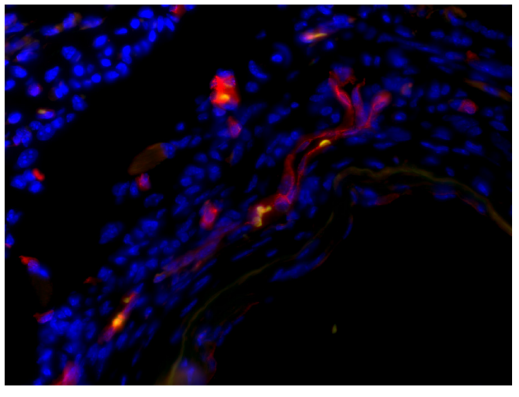
By the conclusion of this session, participants should be able to: 1) Discuss histologic findings in human and murine aneurysms; 2) Discuss vasculogenesis and inflammatory cell migration in aneurysms; 3) Discuss effects of stromal cell-derived factor-1 on vasculogensis and inflammatory cell migration.

Murine Aneurysm from Mouse Given Anti-SDF-1 Blocking Antibody



C57BL6 mice given anti-SDF-1 blocking antibody have aneurysms with no vasculogenesis in the aneurysm walls. Red: MECA-32+; Blue: DAPI

Murine Aneurysm from Mouse Given IgG Control



C57BL6 mice given IgG control have aneurysms with vasculogenesis in the aneurysm walls. Red: MECA-32+; Blue: DAPI