A070 Semaphorin-3F Inhibits Vascular Permeability During Acute Inflammation

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Introduction: Permeability of the endothelial cell barrier lining the vasculature determines the degree of tissue microvascular fluid exchange. Vascular endothelial growth factor (VEGF) mediates vascular permeability via its tyrosine kinase receptors (VEGFR). The role of the VEGF co-receptor Neuropilin-2 (Nrp2) in vascular permeability is less understood. Semaphorin 3F (SEMA3F) competes with VEGF-A binding to Nrp2 and therefore may act to inhibit vascular leakage. We hypothesize that SEMA3F, acting through its NRP2 receptor, reduces edema by inhibiting vascular permeability thereby promoting a quickened resolution of inflammation. **Methods:** To test our hypothesis we generated delayed-type hypersensitivity (DTH) cutaneous reactions in the ear skin of wild type and SEMA3F-deficient mice and analyzed tissue thickness as well as the amount of extravasated Evans blue dye in the inflamed tissues following intravenous injection. **Results:** Our results demonstrate that depletion of SEMA3F protein, either genetically using knockout mice or pharmacologically using systemic administration of SEMA3F-neutralizing antibodies, significantly prolonged tissue swelling and increased vascular permeability compared to control mice during acute inflammation. Alternately, SEMA3F over expression in mice using adenoviral constructs to deliver SEMA3F systemically caused lower levels of inflammatory edema compared to control adenovirus-treated mice. Furthermore, Nrp2 mRNA expression was down regulated in the skin of SEMA3F-deficient mice compared to littermate controls suggesting that SEMA3F levels may regulate the expression of its receptor. **Conclusions:** Taken together, our results demonstrated that the SEMA3F-NRP2 signaling cascade mediates fluid homeostasis during inflammatory reactions. SEMA3F promotes resolution by attenuating vascular permeability leading to reduced inflammation and edema. Our research suggests that the SEMA3F-NRP2 signaling axis may be a potential therapeutic target for inflammation-mediated diseases.