Perivascular Macrophages Prime Vascular Endothelial Cells to Promote Neutrophil Adhesion and Transendothelial Migration

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Abstract

Neutrophil (PMN) transendothelial migration (TEM) in post-capillary venules is a key event in inflammatory responses against pathogens and the ensuing tissue damage. Perivascular macrophages (PVMs) have been previously suggested to promote PMN recruitment during bacterial skin infection via chemokine release, however, in the current study we identified a new mechanism where PVMs prime endothelial cell (ECs) to regulate PMN TEM. We used intravital microscopy on lipopolysaccharides (LPS)-inflamed intestines to demonstrate that PVMs were critical for PMN migration and accumulation in the intestinal mucosa. Anti CSFR-1 antibody-based macrophage depletion significantly reduced PMN adhesion and TEM in inflamed intestines *in vivo*. Removal of macrophages also resulted in significantly lowered expression levels of EC ICAM-1, a major PMN adhesive receptor. Mechanistically, using murine and human ECs and macrophages (bone marrow-derived and human THP-1 macrophages) we determined that TNFα secreted by activated macrophages led to a robust EC ICAM-1 induction and increased PMN retention and migration. Antibody-mediated neutralization of TNFα in macrophage supernatants inhibited ICAM-1 upregulation and decreased PMN TEM. As such, our findings identify an important and clinically relevant new mechanism by which macrophages promote PMN recruitment in inflamed mucosa.