Neutrophil Interactions with Epithelial ICAM-1 in the Intestinal Lumen Contribute to Resolution of Inflammation by Promoting Epithelial Wound Repair

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Background: Transepithelial migration (TEM) of neutrophils (PMNs) into the intestinal mucosa is a prominent feature of Inflammatory Bowel Diseases (IBD). PMN TEM is associated with epithelial injury and disease symptoms, yet the functional significance and effects of PMN interactions with the luminal (apical) epithelial surface on intestinal epithelial cell (IEC) homeostasis are incompletely understood. ICAM-1 is a well-recognized signaling receptor and endothelial ligand for neutrophils migrating across the vascular wall. Its expression is also induced on the luminal (apical) membrane of IECs exposed to interferon γ (IFNγ), and in the colonic mucosa of individuals with active IBD. However, unlike in endothelial cells, the role of ICAM-1 in mediating functional effects of neutrophil interactions with epithelial cells in the intestine is undefined. In the current work we demonstrate that adhesion of post-migrated PMN to ICAM-1 on the apical epithelial membrane initiate Akt/β-catenin dependent signaling events to promote mucosal healing.

Methods: This work uses well established in-vitro models of PMN TEM, scratch wound and Edu incorporation assays, supplemented with molecular and protein approaches, as well as a novel, in-vivo colonoscopic biopsy-based acute colonic injury model to define the effects of PMN engagement of apical ICAM-1 on epithelial cell proliferation and wound healing.

Results: Adhesion of post-migrated PMN to ICAM-1 results in activation of Akt/β-catenin signaling pathway, leading to increased IEC proliferation and wound closure. Such responses were specific to ICAM-1, as experiments modeling neutrophil engagement of epithelial ICAM-1 by antibody-mediated crosslinking yielded similar results. Consistently, we show that ICAM-1 expression is significantly increased in-vivo in the colonic epithelium following acute mucosal wounding, and that mucosal healing required activation of epithelial Akt and β-catenin. Finally, we observed that expression of ICAM-1 in the colonic mucosa is critical for efficient wound healing, as mice lacking functional ICAM-1 failed to activate the Akt/β-catenin signaling pathways resulting in significantly impaired reepithelialization and wound closure.

Conclusions: These findings suggest that while en masse PMN transepithelial migration may cause epithelial injury, subsequent upregulation and engagement of ICAM-1 by post migrated PMN on the luminal surface may promote reparative proliferative.