Targeting Intestinal Epithelial Cells to Promote Healing in Inflammatory Bowel Disease

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Background: Medications targeting the intestinal epithelium, including intestinal stem cells (ISCs), have the potential to enhance wound healing and reconstitution of the epithelial barrier that is compromised in IBD. Liver Receptor Homolog-1 (LRH-1, also known as NR5A2) is expressed in intestinal crypts where the ISCs reside. This nuclear receptor interacts with WNT/β-catenin, drives intestinal steroid production, and when absent exacerbates colitis. We are investigating the role of LRH-1 in intestinal renewal and epithelial barrier function with the aim of developing an intestinal organoid model system amenable to drug discovery.

Methods: To evaluate the contributions of LRH-1 to intestinal growth and epithelial integrity, we employed intestinal organoids harboring conditional LRH-1 knockout in ISCs (LrhISC) and intestinal epithelium (IKO). Lrh1 knockout was achieved by in vitro activation of an inducible Cre driven by the Lgr5 or Villin promoter (LrhISC and IKO, respectively). Organoids were evaluated for growth and resistance to TNF-α-induced inflammatory injury. The effects of LRH-1 loss on epithelial integrity were examined by tight junctions immunohistochemistry and a dextran exclusion. AAV-mediated gene delivery was used to “humanize” LRH-1 organoid expression for complementary activation studies.

Results: LRH-1 loss impairs cell growth and slows ISC-driven epithelial turnover as marked by EdU incorporation. Epithelial tight junctions are distorted with LRH-1 loss by microscopy, resulting in increased epithelial permeability to dextran. IKO organoids are more susceptible to TNF-α-mediated inflammatory epithelial damage as measured by viability assays. Overexpression of human LRH-1 in intestinal organoids induces expression of key steroidogenic enzymes.

Conclusions: Our results suggest LRH-1 is critical for anti-inflammatory and proliferative response to injury and presents a viable target for novel, epithelium-targeted IBD therapy. Additionally, the intestinal organoid system facilitates functional studies of epithelial integrity and may serve as a tool for evaluating and developing LRH-1 agonists.