Loss of Nuclear Receptor LRH-1 Sensitizes Intestinal Epithelium to Inflammatory Injury

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Inflammatory Bowel Disease (IBD)

- Chronic medical condition affecting 4 million worldwide
- Aberrant host inflammatory response to commensal luminal bacteria coupled with impaired mucosal healing
- Need to understand the factors contributing to epithelial health and healing

Liver Receptor Homolog-1 (LRH-1) in Gut

- Nuclear hormone receptor
  - Co-regulated by phospholipid ligands
  - LRH-1 expression is highest in the intestinal crypts
  - Loss exacerbates experimental colitis

**Goal:**
How does loss of LRH-1 impact the intestinal epithelium and its response to inflammation?
Model System

Intestinal Organoid
- Ex Vivo culture of intestinal crypt/villus
- Contain self-renewing intestinal stem cells
- Normal differentiation into absorptive and secretory subtypes
- Non-transformed cells
- Organoids derived from genetic models allow extension of studies in vitro

Loss of LRH-1 Sensitizes Intestinal Epithelium to TNFα-mediated Damage

Loss of LRH-1 Increases Crypt Apoptosis
Loss of LRH-1 Leads to Functional Impairment of the Epithelial Barrier

**Zo-1**
*P* < 0.05; ***P* < 0.0001

Humanization of Intestinal Organoid LRH-1

Human LRH-1 Restores Epithelial Integrity

**AAV8-FLAG-hLRH1**

**Cont**

**NS**

**mLRH1**

**LRH1**

**ΔLRH1**

**Actin**

**FLAG**

***P* < 0.002**
Summary & Future Directions

Summary
- Loss of LRH-1 increases susceptibility to TNFα-mediated epithelial injury through up-regulation of apoptosis
- Loss of LRH-1 impairs epithelial barrier function
- Expression of human LRH-1 in mouse organoids restores resistance to inflammatory injury and barrier function

Future Directions
- Introduce LRH-1 mutants into organoids to probe importance of ligand binding and receptor modification to function
- Generate animals with inducible intestinal expression of hLRH-1 for use in IBD models
Loss of LRH-1 Reduces Epithelial Proliferation

Loss of LRH-1 Leads to Functional Impairment of the Epithelial Barrier

Future Directions

- LRH-1 and Inflammation
  - Mechanistic studies to further investigate loss of viability
  - Extend hLRH-1 rescue experiments
  - Introduce LRH-1 mutants into organoids to delineate importance of ligand binding and receptor modification to function
- LRH-1 in IBD
  - Generating animals with inducible intestinal expression of hLRH-1 for use in animal IBD models
AAV-hLRH1 Expresses in Organoids and Localizes to the Nucleus