

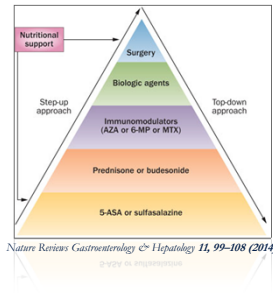
Loss of Nuclear Receptor LRH-1 Sensitizes Intestinal Epithelium to Inflammatory Injury

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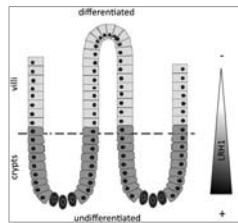
Inflammatory Bowel Disease (IBD)

- 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



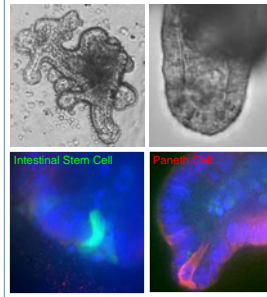
Goal:

How does loss of LRH-1 impact the intestinal epithelium and its response to inflammation?

Model System

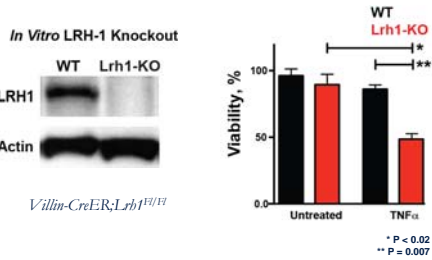
Intestinal Organoid

- *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*



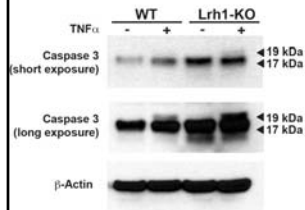
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Loss of LRH-1 Sensitizes Intestinal Epithelium to TNF α -mediated Damage



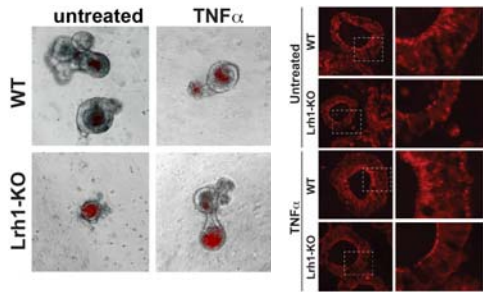
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Loss of LRH-1 Increases Crypt Apoptosis



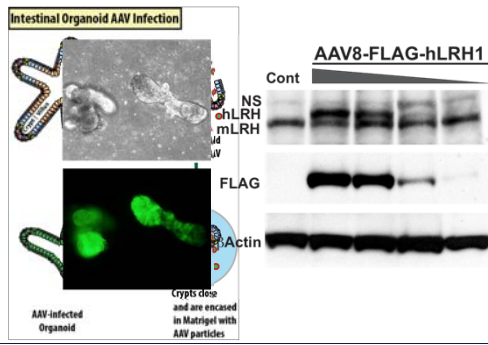
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Loss of LRH-1 Leads to Functional Impairment of the Epithelial Barrier



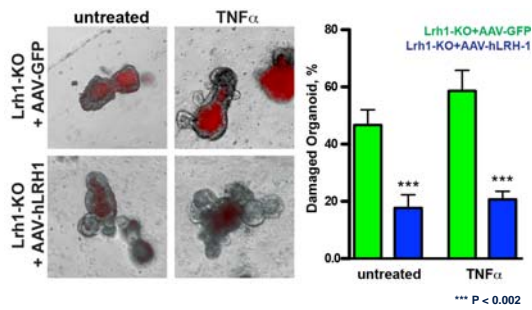
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Humanization of Intestinal Organoid LRH-1



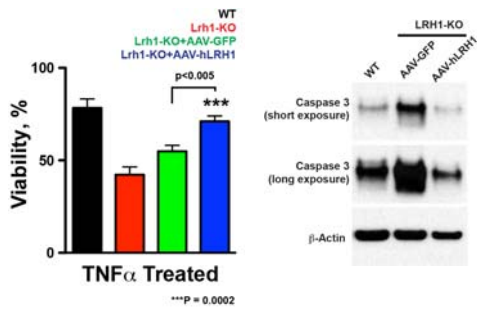
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Human LRH-1 Restores Epithelial Integrity



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Humanization Confers Inflammatory Resistance



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Summary & Future Directions

Summary

- Loss of LRH-1 increases susceptibility to TNF α -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

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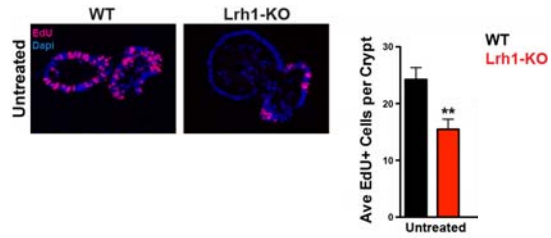
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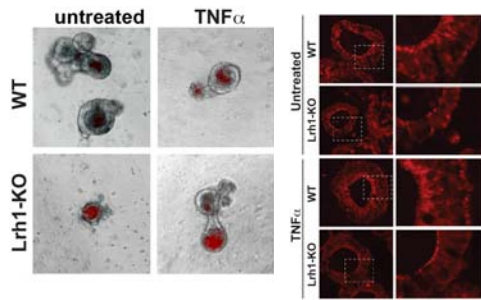
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Loss of LRH-1 Reduces Epithelial Proliferation



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



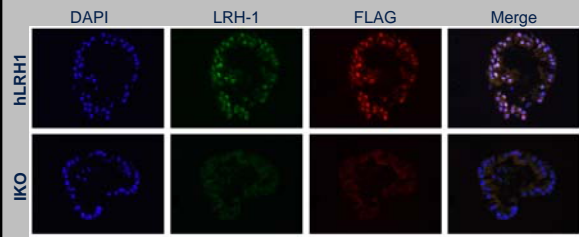
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Future Directions

- 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

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AAV-hLRH1 Expresses in Organoids and Localizes to the Nucleus



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