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Epimorphin Regulates the Intestinal Stem Cell Niche via Wnt4 Secretion

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Short bowel syndrome results following intestinal resection as treatment for Crohn's disease or bowel ischemia and presents with malabsorption and intravenous nutrition dependence. Currently, there are few effective treatments, but stem cell therapies have been proposed. Intestinal stem cells reside at the base of the crypt-villus principal unit of the small intestine and are surrounded by a lattice network of stromal supporting cells termed intestinal subepithelial myofibroblasts (ISEMFs). Epimorphin (Epim) is a member of the family of t-SNARE vesicle docking proteins regulating growth factor secretion from ISEMFs. We previously showed that Epim deletion expands stem cell populations *in vivo* and that *in vitro*, this effect is dependent on stromal environmental effects on the stem cell niche. The aims of this project are to determine the mechanism by which Epim modulates the stem cell niche through the stromal microenvironment.

ISEMFs were isolated from WT and *Epim*$^{-/-}$ mouse small intestines by treatment with collagenase and dispase enzymes. ISEMFs were cultured in vitro and grown to confluence at which point ISEMFs were harvested for RNA. qRT-PCR was performed to analyze expression of ISEMF marker genes and target genes. Protein expression was analyzed by western blot for genes confirmed to have differential expression.

Epim$^{-/-}$ ISEMFs showed significantly increased ($p<.001$) mRNA and protein expression of Wnt4 compared to WT ISEMFs. *Epim*$^{-/-}$ISEMFs also showed a trend towards increased ($p=.080$) mRNA expression of Wnt2b, which is being investigated further.

Wnt4 primarily acts in non-canonical Wnt signaling pathways, but has been shown to function in the canonical Wnt signaling pathway depending on cellular context. Wnt4 secretion from mesenchymal cells has been shown to induce epithelial proliferation in both the large intestine and mammary tissue. Thus, we propose Epim deletion induces small intestinal stem cell proliferation through increased secretion of Wnt4 in the stromal microenvironment.