

ISCC Research Project Abstracts



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INTESTINAL STEM CELL RESPONSE TO INFECTION

The intestinal epithelium exhibits a remarkable capacity of self-renewal to maintain intestinal homeostasis; this property reflects the activity of multi-potent intestinal stem cells (ISCs) that divide and differentiate to produce the different cell types that comprise the intestinal epithelium. Thus, *Lgr5* and *HopX* are examples of molecules that represent a subset of markers of cycling and quiescent stem cells in small intestinal crypts, respectively. Previous studies have developed standardized protocols for studying these ISC populations, primarily in mice, and use of these methodologies has led to a better understanding of the ISC response to several insults. Most previous studies have focused on responses to radiation, with limited information being available about responses to surgical resection, inflammatory disease, ischemia, and fasting. In contrast, the ISC response to microbial (pathogenic viral or bacterial) infection and to beneficial bacteria remains largely unexplored. Understanding whether ISCs play a significant role in repair of the epithelium within the context of microbial exposure is important given the large number of intestinal infections experienced annually and the current interest and promise in using a variety of microbes to treat intestinal dysbiosis and diarrheal disease. The long-term goal of our research program is to understand the molecular response of human ISCs to pathogenic and commensal organisms. Identifying the molecular signals required for inducing stem cell responses is critical for translating fundamental knowledge on ISC function into therapies to treat digestive diseases. We hypothesize that common small intestinal viral and bacterial pathogens and beneficial probiotic bacterial species elicit unique signals that induce stem cell proliferative responses, which are required to replenish the damaged, or maintain the healthy, intestinal epithelium. This hypothesis is based on our preliminary findings that rotavirus, a common small intestinal virus, virulence factors from *V. cholerae* (enterotoxin) and enterohemorrhagic *E. coli* (protease EspP), common small intestinal bacterial pathogens, and *L. reuteri*, a commensal bacteria, affect ISC function in human intestinal enteroid (HIE) or mouse models. Using these infection models, we propose (1) To identify the ISC population(s) affected by pathogenic or commensal microbes in small intestine-derived human and mouse enteroid models, and (2) To define the signaling pathways induced by microorganisms within the actively dividing and quiescent ISC populations in human enteroids. Our research is expected to significantly advance our understanding of pathways regulating intestinal response to damage caused by infection and compliment and extend the ongoing studies by the Intestinal Stem Cell Consortium, which have led to a foundation of knowledge about intestinal stem cell responses to non-infectious injury.