

ISCC Research Project Abstracts



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REGULATION OF DISTINCT POOLS OF INTESTINAL STEM CELLS

The small intestine epithelium renews every 2 to 5 days, making it one of the most regenerative mammalian tissues. Understanding the intestinal stem cells (ISCs) that fuel this renewal is both an important basic science question and an essential starting point for translational approaches in regenerative medicine. Genetic inducible fate mapping (GIFM) studies have identified two principal epithelial stem cell pools in the intestine. One pool consists of columnar Lgr5-expressing cells that cycle rapidly and are present predominantly at the crypt base, and the other consists of cells expressing Bmi1 or other markers that largely reside above the crypt base. We have recently demonstrated (Tian et al, Nature, 2011) that Bmi1-expressing ISCs give rise to Lgr5-expressing ISCs under normal physiological conditions. Importantly, when we specifically ablated Lgr5-expressing ISCs, Bmi1-expressing ISCs were able to maintain epithelial homeostasis in the proximal small intestine. These results, which have been confirmed by several other groups, indicated that Lgr5- and Bmi1-expressing ISCs constitute two distinct, although possibly partially overlapping, populations. An important question is which signaling pathways regulate these different stem cell populations, and a growing body of evidence indicates that Wnt and Notch signaling guide both Lgr5- and Bmi1-expressing stem cell self-renewal. In this application, we propose to employ pathway-specific blocking antibodies to understand the differential and combinatorial effects of Wnt and Notch signaling on self-renewal and lineage fate decisions in ISCs. This unique approach - combining antibody blockade and genetic fate mapping - opens up interesting new avenues beyond the traditional purely genetic approaches. The results of these studies will shed important light on the mechanisms by which ISCs self-renew and differentiate, which will help to understand the roles of these ISCs in homeostasis and disease and will help to lay the groundwork for future attempts at organ regeneration.