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Summary:
Truly quiescent and long-lived stem cells have been postulated but to date not identified in the gut. Doublecortin-like kinase 1 (Dclk1) was proposed as a stem cell marker in the intestine but was also found to be expressed in intestinal tuft cells. Recently, our group has generated Dclk1-Cre-ERT BAC transgenic mice, and we have shown unequivocally that Dclk1+ tuft cells are long-lived, quiescent stem cells that are derived from Lgr5+ stem cells but induced by nervous innervation. Our hypothesis is that Dclk1+ tuft cells play a role both as part of the intestinal stem cell niche and also as reserve intestinal stem cell, and are generated through extrinsic neural innervation. We will explore this hypothesis through three specific aims. (1) What is the role of nerves in the induction of Dclk1+ tuft cells. We will utilize both in vitro culture systems, and in vivo mouse models, to examine the role of nervous innervation, with a focus on NGF-Trk pathway in mediating the nerve-tuft cell interactions. (2) Does ablation of Dclk1+ progenitors inhibit normal intestinal epithelial homeostasis and growth, and the response to radiation injury? Dclk1-Cre-ERT mice crossed to DTR F/F mice will be treated with diptheria toxin and the regenerative response to radiation assessed using both in vitro and in vivo systems. (3). Does activation of Dclk1+ progenitors result in intestinal proliferation and increased regeneration following radiation injury? Preliminary studies suggestion that deletion of Apc in the Dclk1 lineage, and activation of Wnt signaling, is sufficien to convert Dclk1 tuft cells into active stem cells. We will explore the role of Wnt signaling using both crypt cultures and mouse models. Overall, these studies should provide new insights into the role of Dclk1 progenitors as both niche and stem cells in the intestine, and their contribution to intestinal regeneration.