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Recent studies have pointed to a role for G-protein coupled receptors (GPCR's) as markers of intestinal progenitor cells in the gastrointestinal tract, but specific receptor-ligand interactions that regulate the behavior and activity of gut stem cells have not previously been reported. Work from our group has demonstrated that the CCK-2/gastrin receptor (CCK2R), a well-characterized GPCR, is highly localized to the colonic crypts where it mediates responses to progastrin, the incompletely processed precursor of gastrin. Progastrin overexpression stimulates colonic epithelial proliferation, putative stem and progenitor cell expansion, crypt fission and colonic tumorigenesis in a manner that is CCK2R-dependent, and highly suggestive of quiescent stem cell modulation. In addition, studies from our laboratory has shown that progastrin can regulate key stem cell pathways such as BMP and Wnt, and has provided data that progastrin can bind to other GPCRs that may modulate responses to progastrin-CCK2R interactions. Thus, we hypothesize that CCK2R is expressed on a quiescent colonic stem cell and regulates activation and symmetric division of this stem cell. We propose to investigate progastrin receptors through the following three specific aims. (1). Investigate the role of CCK2R in colonic crypt progenitor cells in normal physiology and development. We will attempt to establish whether CCK2R is expressed on colon stem or progenitor cells using Cre-mediated lineage tracing. (2). Explore possible interactions between progastrin and amidated gastrin at the CCK2R. We will study signaling, cellular proliferation and histopathologic effects in the setting of one or several gastrin isoforms. (3). Study the role of other GPCRs in modulating progastrin responses, possible through interactions with the CCK2R. These interactions will be investigated using both in vitro cell line models as well as through additional knockout mice. (4). Clarify the mechanisms involved in the promotion of colonic carcinogenesis by progastrin-receptor interactions. We will investigate the role of two pathways - BMP and Wnt - that may be modulated by progastrin signaling and regulate colonic stem cell quiescence or symmetric division. CCK2R as a GPCR is an attractive therapeutic target, and since antagonism or deletion can inhibit colon carcinogenesis, these studies will not only provide insight into stem cell biology but may lead to new strategies for colon cancer prevention.
