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Title: Intestinal Stem Cell Culture and Entero-Endocrine Lineage Development

Abstract Text:

DESCRIPTION (provided by applicant): Despite the recent flurry of work in the field of gut stem cells, investigators have yet to demonstrate that a single putative stem cell can be isolated, manipulated, maintained and subsequently differentiate into all specified lineages in either an in vitro or in vivo setting. This project's main goal is to demonstrate that a specific putative stem cell can give rise to long-lived clones that have multi-lineage potential. Our central hypothesis is that refinement of methods to isolate and propagate gut stem/progenitors cells will facilitate the in vitro and in vivo development along the secretory lineage as defined by unique markers. Our goals are to (A) refine the techniques and materials that will promote the growth of clusters or single cells in vitro and in vivo; (B) investigate the contribution of intestinal myofibroblasts to the intestinal stem cell niche; (C) modulate the ability of stem/progenitor cells to form fully mature enteroendocrine cells in both in vivo and in vitro models; and (D) identify and characterize other markers from uncommitted progenitors to mature enteroendocrine cells in mice. To address these goals we propose four specific aims. Specific Aim 1: To develop methods that overcome the anchorage dependency of gut epithelial cells, and promotes the survival, growth and differentiation of these cells in both in vivo and in vitro settings. Specific Aim 2: To assess the role of pericryptal myofibroblast in modulating proliferation of stem cells and the maturation of enteroendocrine cells in a novel clonogenic cell culture system. Specific Aim 3: To modulate the maturation of enteroendocrine cells from isolated uncommitted and committed endocrine progenitors in an in vivo and in vitro model. Specific Aim 4: Develop and verify further a group of unique lineage-specific markers that define distinct stages in the progression from uncommitted progenitor cells to fully mature enteroendocrine cells.