

Project Number: U01DK85551-01

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Title: The Intestinal Stem Cell Niche

Abstract Text:

DESCRIPTION (provided by applicant): Stem cells are defined by the capacity for long-term self-renewal and multilineage specification. Until recently, our understanding of stem cells, as well as their role in human diseases has been rather limited. Moreover, interest in harnessing the stem cell's capacity for self-renewal to promote organ and tissue regeneration traverses many medical disciplines. It is now recognized as imperative that we better understand the complex genetics and processes that support and define the stem cell. This proposal is a multidisciplinary approach to this problem, combining the scientific strengths of four investigators, as well as institutional core facilities and support into a cohesive approach to study the intestinal stem cell. Recently, genetic studies have identified robust markers for stem cell populations in the intestine. These advances now make it possible to isolate stem cell populations for more advanced molecular investigations. They also provide us an opportunity to study how disease environments impact upon stem cell viability and specification. Stem cells are highly reliant upon mechanisms to counter the numerous stresses associated with cellular replication. Defects in maintaining genome stability in the face of such challenges cause stem cell losses. If this process is unchecked, it can lead to the premature onset of age-related degenerative pathologies. Another challenge encountered by stem cells is to correctly determine their tissue identity based upon environmental cues. Errors in stem cell identity are encountered in intestinal metaplasia of the esophagus and stomach, as well as many gastrointestinal cancers. With these observations in mind, we propose to test the following hypothesis: Intestinal stem cell identity and viability can be modulated by cell-autonomous and non-cell autonomous processes. This hypothesis will be pursued by the following interrelated Specific Aims: (1) Functional characterization of the contribution by bone-marrow derived cells to the intestinal stem cell (ISC) niche in vivo. (2) The homeodomain transcription factor Cdx2 specifies the stem cell's "intestinal" identity. (3) Develop novel strategies to identify new intestinal stem cell markers and assay stem cell functions. This proposal seeks to exploit our combined expertise in order to better understand the molecular events that support and specify intestinal stem cells. Understanding these molecular processes will greatly improve our ability to develop novel therapeutic strategies to exploit the regenerative potential of stem cells, as well as correct stem cell deficiencies that contribute to many GI diseases.

PUBLIC HEALTH RELEVANCE: Stem cells are critical for the renewal of the intestinal epithelium. Many human diseases can affect stem cell viability and capacity for self-renewal and differentiation. This proposal explores contributions to intestinal stem cell biology and survival by bone-marrow and stromal elements, as well as cell-autonomous mechanisms. Knowledge gained here will have applications for regenerative medicine, aging, and carcinogenesis.