

Project Number: U01DK85570-01

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Title: Intestinal Stem Cell Survival and Renewal Coordinately Regulated by Puma and P21

Abstract Text:

DESCRIPTION (provided by applicant): Adult tissue stem cells are believed to be responsible for maintaining tissue homeostasis and regeneration following injury in most tissues. The small intestine is one of the most sensitive organs to radiation-induced damage, which is the major complication in abdominal and pelvic radiotherapy with no effective treatment. The intestinal stem cells (ISCs) are located at or near the bottom of crypts in a unique yet poorly defined microenvironment ("niche") composed of several cell types derived from the bone marrow (BM). However, their identity remained elusive until recently. Genetic evidence demonstrated that the crypt-based columnar cells (CBCs) interspersed among Paneth cells marked by Lgr5 and some +4 cells immediately above Paneth cells marked by Bmi-1, represent perhaps distinct subsets of ISCs. Therefore, how their functions are regulated by intrinsic and extrinsic (niche-related) programs to participate in intestinal regeneration following injury is poorly understood. Work from us and others indicate that the BH3-only protein PUMA and cyclin-dependent kinase inhibitor p21 regulate the survival and regeneration of intestinal and hematopoietic systems, and the bone marrow modulates intestinal radiosensitivity. We hypothesize that both apoptosis and cell cycle arrest critically regulate the survival and regeneration of intestinal stem cells following radiation through intrinsic and extrinsic mechanisms. In this proposal, we will combine a novel ISC lineage marking and tracing mouse model with various knockout and transplantation models to 1) define the role of ISCs in crypt regeneration following radiation and develop assays for their isolation and characterization; 2) demonstrate a potential coordination of PUMA and p21 in modulating the survival and regeneration of ISCs; and 3) define the potential bone marrow contributions to intestinal regeneration. We believe that our studies can lead to a better understanding of ISC biology, and new models and strategies for isolation, characterization and manipulation of these critical cells for therapeutic purposes.

PUBLIC HEALTH RELEVANCE: The proposed studies aim to determine the underlying molecular mechanisms governing the injury, survival and regeneration of intestinal stem cells following radiation, and to develop assays for their isolation and characterization. Such studies can help devise strategies to combat intestinal damage caused by radiotherapy or accidental radiation exposure.