CONTRIBUTION OF GCR EXPOSURE TO HEMATOPOIETIC STEM CELL DYSFUNCTION AND ONCOGENESIS

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Natural sources of radiation in space include galactic cosmic rays (GCR), solar energetic particles, and trapped energetic particles in a planetary magnetic field. These sources are difficult to shield because of their high energies and dense ionization patterns, thus posing significant health risks to astronauts on long term space missions. Efforts to protect astronauts from harmful cosmic radiation require a deeper understanding of the effects of GCR on human health. In particular little is known about the effects of GCR exposure on the hematopoietic stem cell (HSC) population and whether disrupted genetic stability in HSCs could result in the development of hematopoietic malignancies in astronauts on deep space missions.

Hematopoietic stem cells (HSC) are cells isolated from the blood and bone marrow that can 1) self-renew, 2) differentiate into a multitude of cell types, 3) mobilize out of the bone marrow into circulating blood, and 4) undergo programmed cell death. HSCs are responsible for the turnover of billions of blood cells daily in order to replenish stocks of all immune cell subtypes, and for hematopoietic organ repopulation throughout the lifetime of an organism. The majority of the steady state HSC population is quiescent with very little turnover, until activation and expansion of hematopoietic cells is demanded in order to replace lost or damaged blood cells. HSCs are continuously exposed to internal and external stresses that threaten the integrity of the cell, and accumulation of damage leading to (or resulting from) genomic instability can compromise the self-renewal and repopulating capabilities of HSCs and result in a variety of blood disorders and cancers. HSCs are the origin of leukemic transformation following DNA damage. Thus maintenance of genomic stability is crucial for long term HSC function.

We and other have recently found that HSCs display diminished function and increased genomic instability with age. In particular, middle-aged individuals show frequent defects in DNA mismatch repair (MMR) in HSCs due to decreased expression of a key DNA mismatch repair protein, MLH1. Significantly, the average age of a shuttle crew has risen above 46 years. We therefore propose to study the effects of high-LET (linear energy transfer) radiation characteristic of GCR on hematopoietic stem and progenitor cells in vivo and determine changes in HSC behavior that may predispose to leukemia and lymphoma development. Importantly, we will use DNA repair deficient animals to more appropriately mimic the state of DNA repair of individuals of astronaut age. We hypothesize that high-LET radiation characteristic of the GCR that will confront astronauts on space missions will damage HSCs and the HSC niche, disrupt HSC function, and contribute to induction and progression of hematopoietic malignancies. We will test the hypothesis by: 1) characterizing the LET and dose response of colony-forming units (CFU) in wild type versus mismatch repair deficient HSCs; 2) determining whether high-LET radiation at doses relevant to astronauts on interplanetary missions affects intrinsic HSC function in vivo; and 3) characterizing the long term effects of high-LET exposure on HSCs, and the potential for disease progression.

Together the studies described here will satisfy the goal of decreasing uncertainty in the radiation risk assessment for cancer of the hematopoietic system.