OXIDATIVE STRESS RESPONSES TO SIMULATED SPACEFLIGHT IN MINERALIZED AND MARROW COMPARTMENTS OF BONE AND ASSOCIATED VASCULATURE

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Long-term spaceflight causes profound changes to the musculoskeletal system attributable to unloading and fluid shifts in microgravity. Future space explorations beyond the earth's magnetosphere will expose astronauts to space radiation, which may cause additional skeletal deficits that are not yet fully understood. Our long-term goals are twofold: to define the mechanisms and risk of bone loss in the spaceflight environment and to facilitate the development of effective countermeasures if necessary.

Our central hypothesis is that oxidative stress plays a key role in progressive bone loss and vascular dysfunction caused by spaceflight. In animal's models, overproduction of free radicals is associated with increased bone resorption, lower bone formation, and decrements in bone mineral density and structure which can ultimately lead to skeletal fragility. Evidence in support of a possible causative role for oxidative stress in spaceflight-induced bone loss derive from knockout and transgenic mouse studies and the use of pharmacological interventions with known anti-oxidant properties. In our studies to simulate spaceflight, 16-wk old, male C56Bl/6J mice were assigned to one of four groups: hindlimb unloading to simulate weightlessness (HU), normally loaded Controls ('NL') (sham irradiated, no hindlimb unloading), irradiated at NASA Space Radiation Laboratory 'IR' with 1-2Gy of (600MeV/n) alone, or in combination with protons (0.5Gy Protons/0.5Gy ^{56}Fe), (IR) or both hindlimb unloaded and irradiated, 'HU+IR'. Mice were exposed to radiation 3 days after initiating HU and tissues harvested were 1-14 days after initiating treatments for analyses.

Results from our laboratories, which employ various biochemical, gene expression, functional, and transgenic animal model methods, implicate dynamic regulation of redox-related pathways by spaceflight-related environmental factors. As one example, we found that combined HU and radiation exposure caused oxidative damage in skeletal tissues (lipid peroxidation) of wildtype mice, whereas bone from transgenic mice that overexpress human catalase in mitochondria were protected. Interestingly, marrow cells grown under culture conditions that select for endothelial progenitor cells (EPC), showed that HU but not IR reduced EPC cell migration; in contrast HU and IR each inhibited growth of marrow-derived osteoblast progenitors.

Taken together, these results indicate that unloading and ionizing elicit distinct effects on progenitor and mature cells of vascular and skeletal tissue, and that oxidative damage may contribute to skeletal and vascular deficits that may emerge during extended space travel.

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