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Submission the F2.2: Space Radiation Risk, Quality of Radiation and Countermeasures: Physical and Biophysical Mechanisms, Modeling and Simulations

Title: Potential dietary countermeasure against spaceflight-induced bone loss

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As humans venture further into space and beyond low Earth orbit, space radiation is one of the main challenges for astronauts health. Radiation-induced bone loss is a potential health problem for long duration habitation in space. We showed that a dietary countermeasure prevents bone loss in mice exposed to total body irradiation (TBI). We used a range of ionizing radiation, gamma ($^{137}$Cs), proton ($^{1}$H), iron ($^{56}$Fe), and a combination of sequential proton and iron beam ($^{1}$H/$^{56}$Fe/$^{1}$H) to evaluate skeletal responses. These TBI cover a range of linear energy transfer (LET), from low-LET such as proton, to high-LET such as $^{56}$Fe (HZE: high Z- high energy) at doses between 1-2 Gy. The countermeasure diet, composed of 25% Dried Plum (DP) was effective at preventing radiation-induced cancellous bone loss in appendicular bone (tibia). Furthermore, exposing mice to HZE radiation, such as $^{56}$Fe (1Gy), impaired *ex vivo* growth of marrow-derived, bone-forming osteoblasts, which led to reduced mineralization capacity (-77%). In contrast, mice fed the DP diet did not display these deficits, showing the diet's capacity to protect marrow-derived osteoprogenitors. Dietary DP prevented the increase of bone resorbing osteoclast cells, inflammation and oxidative stress, while protecting the osteoprogenitors and mesenchymal stem cells, which few drugs against osteoporosis may achieve. Spaceflight is a combination of multiple factors including microgravity, in addition to space radiation. Therefore, we conducted additional studies to determine if the DP diet could prevent simulated spaceflight (simulated microgravity and radiation combined) bone loss. Mice were exposed to gamma (TBI, $^{137}$Cs, 2 Gy), simulated microgravity (using the hindlimb unloading system, HU) or TBI+HU. While we observed bone loss in mice fed the control diet (CD) due to both treatments (TBI=14%, HU=20%), and a worse effect with combined treatments (TBI+HU=25%), mice fed the DP diet did not sustain significant bone loss relative to untreated controls. The DP diet prevented microarchitectural decrements in both appendicular bone (tibia) and axial bone (vertebrae). In addition, the DP diet mitigated HU-induced deficits in osteoblastogenesis. Interestingly, lower doses of DP diet (5%, 10%) did not appear to prevent cancellous bone loss, which shows the importance of identifying the active component(s) of DP. Finally, we have preliminary data showing the potential of DP to prevent radiation-induced damage at a systematic level.. In summary, this novel dietary countermeasure is a promising candidate nutritional countermeasure for spaceflight-induced bone loss and tissue damage.

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