Mitigating HZE radiation-induced deficits in marrow-derived mesenchymal progenitor cells and skeletal structure

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PROBLEM
Future long-duration space exploration beyond the earth’s magnetosphere will increase human exposure to space radiation and associated risks to skeletal health.

We showed previously that a diet supplemented with Dried Plum (DP) prevents short term bone loss caused by total body irradiation (Schreurs et al. Scientific Reports, 2016 Feb 11;6:21343).

HYPOTHESIS
DP diet mitigates persistent, damaging effects of HZE radiation on bone structure and marrow-derived osteoprogenitors and stem cells.

BACKGROUND
Bone remodeling: a balance between bone resorption by osteoclasts and bone formation by osteoblasts.

Ionizing radiation & bone loss: clinical and space relevance
• Radiation Therapy Sequelae
  • Osteoradionecrosis (rare)
  • Contributes to weakening: post-menopausal and age-related osteoporosis
  • Secondary tumor induction outside magnetosphere and long durations

Prior evidence shows that total body irradiation stimulates osteoclastogenesis and impairs both osteoblastogenesis and bone formation by mature osteoblasts.

METHODS
Animals: Male C57Bl/6J mice, 16 wk old at time of total body irradiation (TBI)
Study design: 2X2 study design. Control diet X Dried Plum (25%) and (50%)-sham vs IR:
- Radiation: Total Body Irradiation (TBI); single exposure, ± 50 Gy
- ¹³³Cs: 0.86 Gy/min
- Dual (1Gy total dose) Sequential: proton (0.25 Gy) ± Fe(0.5 Gy) ± proton (0.25 Gy)
  56Fe: E = 600 MeV/n
  Proton E = 150 MeV/n
  ± ¹³³Cs: E = 600 MeV/n
Timeframe: - pretreat 14-21 days with control diet (CD) or Dried Plum diet (DP)
  samples recovered 1d, 11d or 30d post-TBI
Gene expression: qPCR
Statistics: data shown are Mean ± S.D., 1-factor or 2-factor ANOVA, Tukey-Kramer post hoc

RESULTS
DP reduced expression of pro-osteoclastogenic cytokines 1d after TBI (¹³³Cs)

DP gene expression 11 days after TBI (¹³⁷Cs):
- No changes in mRNA levels of the following:
  • Bone Marrow Cells
    • Bone-related: Rankl, Opg, BMP2, IGF1, Runx2, BMP4, Nfatc1
    • Oxidative stress/DNA damage-related: SOD1, Foxo3, Nfe2l2, Gadd45a, Cdkn1a

DP prevented damage to marrow-derived osteoprogenitors 30d after TBI (⁵⁶Fe)

SUMMARY/CONCLUSIONS
• DP diet fully protected radiation-induced bone loss from low LET or high LET radiation
  - relevance for spaceflight and radiotherapy

• Possible mechanisms for DP radioprotective effects:
  - mitigate early increase in pro-osteoclast cytokines
  - reduce oxidative damage, in bone and systemically
  - prevent damage to osteoprogenitors and mesenchymal stem cells

ACKNOWLEDGEMENTS
Research was supported by National Space Biomedical Research Institute grant #MA02501 (RKG, CL, JSA) under NASA cooperative agreement NCC 9–58, a DOE-NASA Interagency Award #DE-SC0001507, supported by the Office of Science (BER), U.S. Department of Energy (RKG), and a NASA Postdoctoral Program fellowship (AS, JSA)