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

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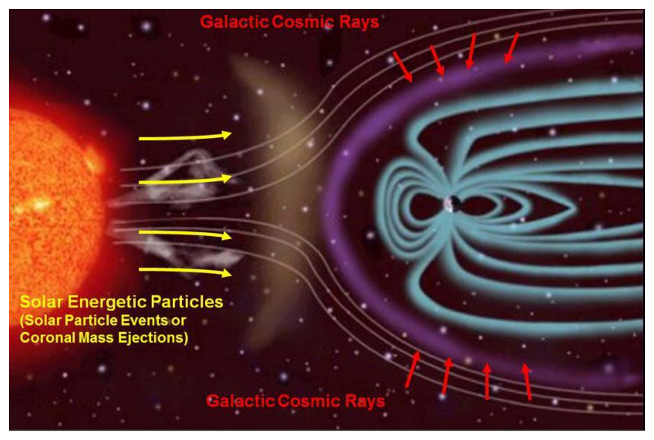
PROBLEM

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



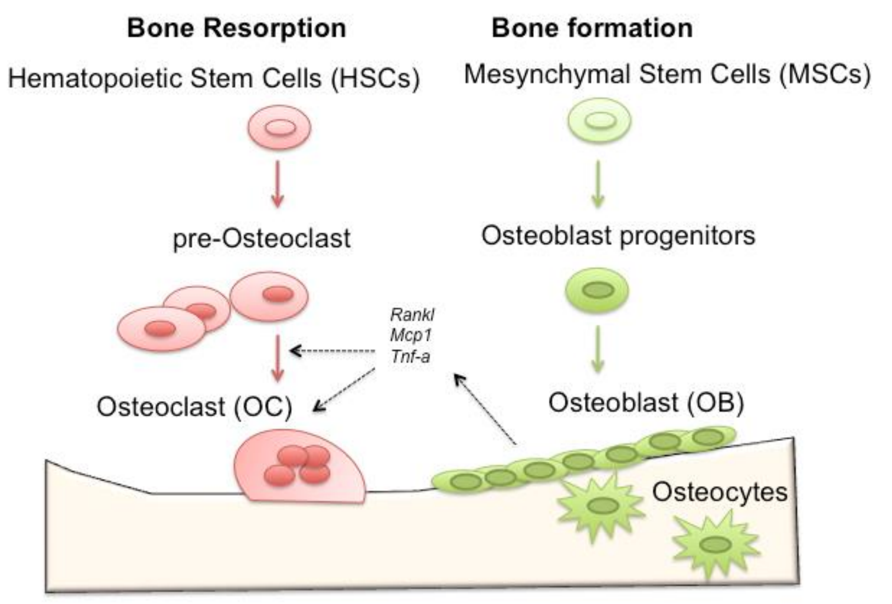
We showed previously that a diet supplemented with Dried Plum (DP) prevents short term bone loss caused by total body irradiation
(Schreurs et al. Scientific Reports, 2016 Feb 11;6:21343).

HYPOTHESIS

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

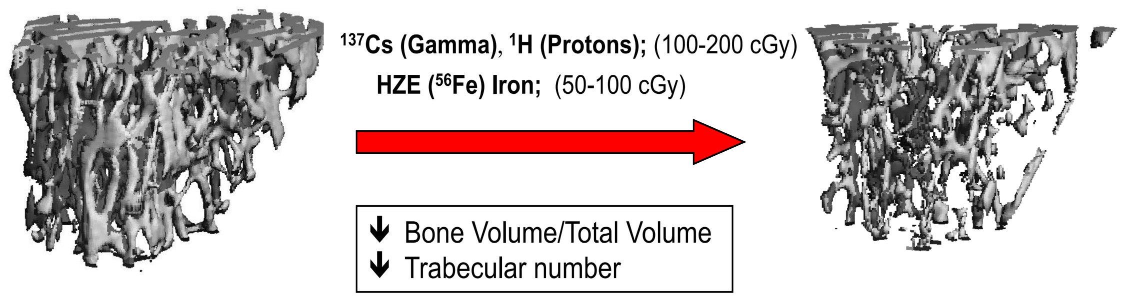
BACKGROUND

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

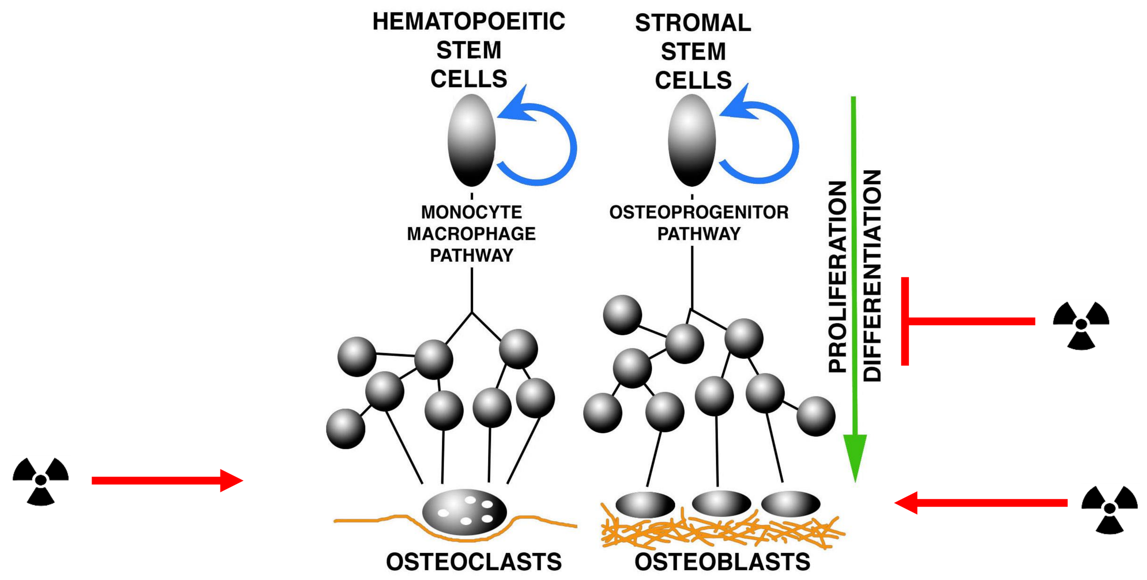


Ionizing radiation & bone loss: clinical and space relevance
• Radiation Therapy Sequelae
- Osteoradionecrosis (rare)
- Contributes to weakening: post-menopausal and age-related osteoporosis
- Secondary tumor induction

ɔutside 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 C57Bl6/J mice, 16 wk old at time of total body irradiation (TBI)
Study design: 2X2 study design: Control diet X Dried Plum (25%) and (0Gy-sham vs IR);
Radiation: Total Body Irradiation (TBI), single exposure, ≤ 2Gy

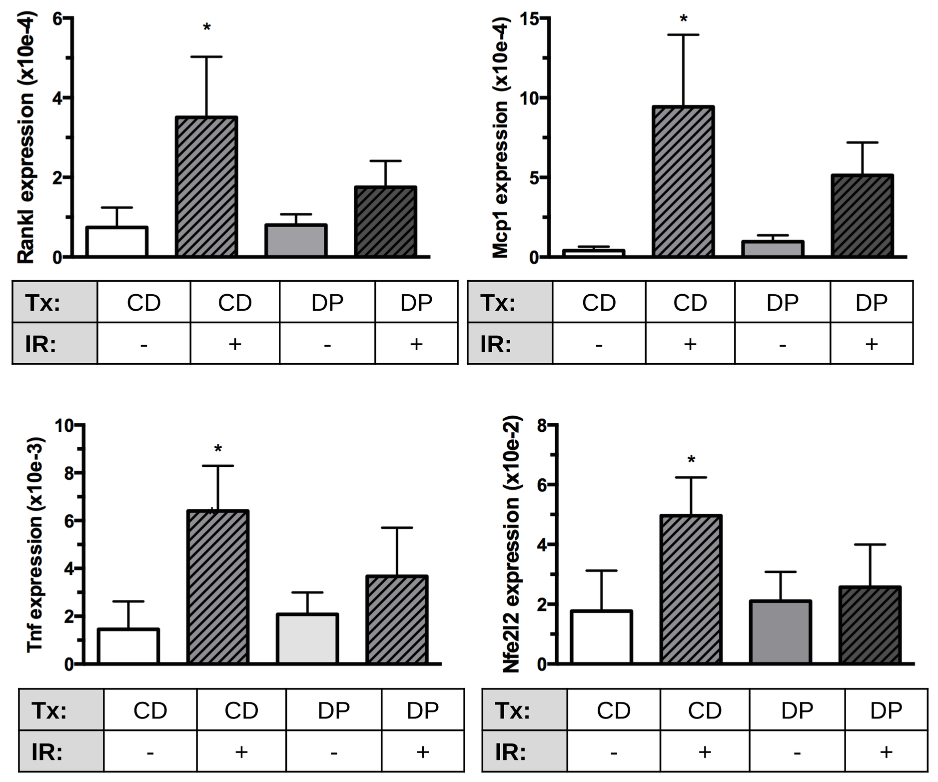
-^{137}Cs	0.86 Gy/min
-Dual (1Gy total dose)	Sequential: proton (0.25Gy)- ^{56}Fe(0.5Gy)-proton(0.25Gy) 56Fe: E = 600 MeV/n Proton: E = 150 MeV/n
-HZE: ^{56}Fe (1Gy)	E = 600 MeV/n

Timeline:
- prefeed 14-21 days with control diet (CD) or Dried Plum diet (DP)
- samples recovered 1d, 11d or 30d post-TBI

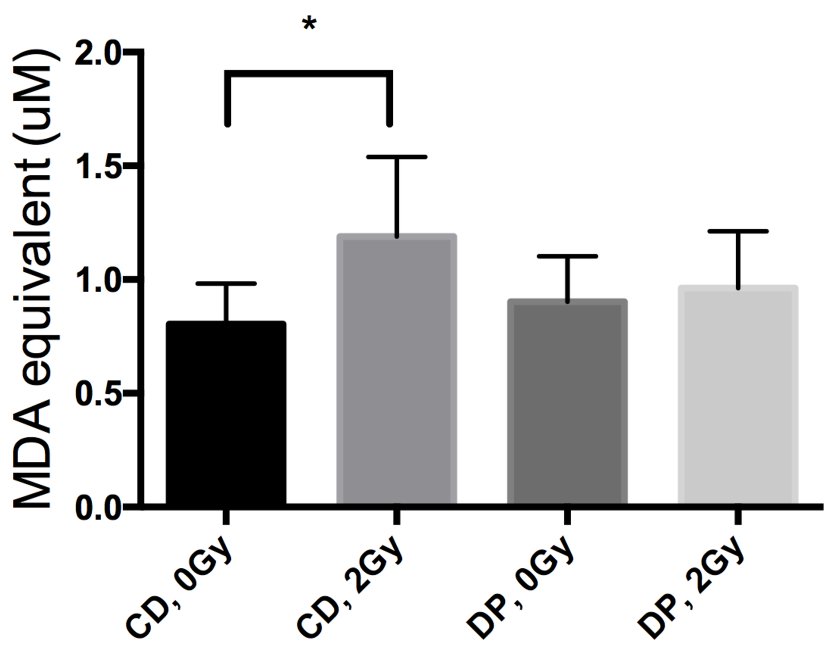
Gene expression: qPCR
Statistics: data shown are Mean ± S.D., 1-factor or 2-factor ANOVA, Tukey-Kramer post hoc

RESULTS

DP reduced expression of pro-osteoclastogenic cytokines 1d after TBI (^{137}Cs)

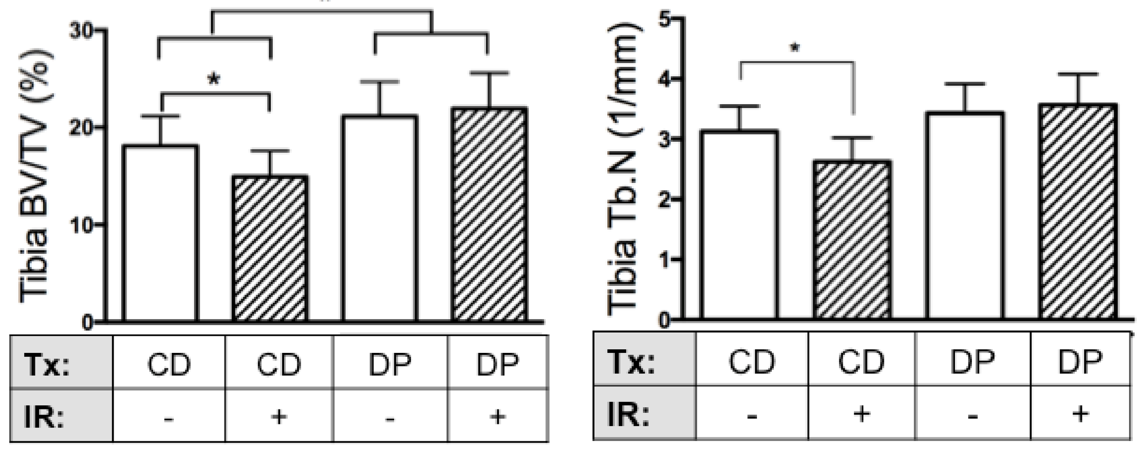


DP reduced serum oxidative stress marker (serum TBARS) 11d days after TBI (^{137}Cs)



CD= control diet (AIN93M), DP=25% Dried Plum in AIN93M, MDA= malondialdehyde equivalent (Tbars assay).

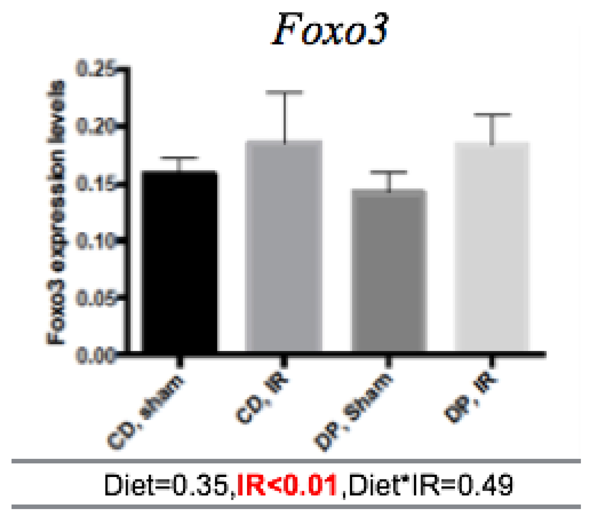
DP prevented decrements in cancellous bone structure 30d after TBI (^{56}Fe)



Tx= treatment; CD= control diet (AIN93M), DP=25% Dried Plum in AIN93M, BV/TV%= cancellous Bone Volume/Total Volume, Tb.N= Trabecular number

DP gene expression 11 days after TBI (^{137}Cs): few changes

Mineralized tissue



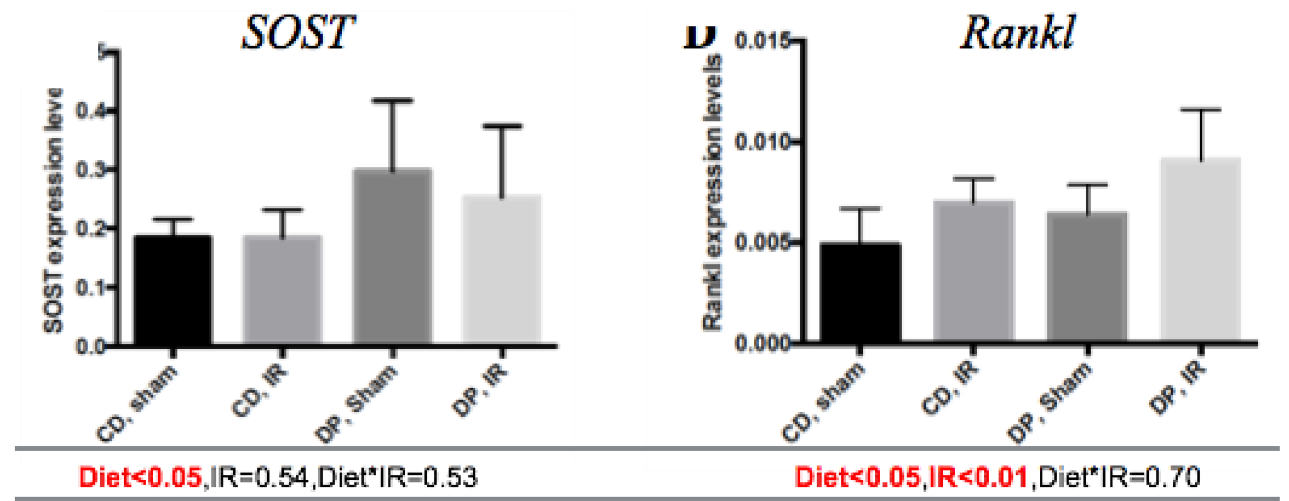
2-factor ANOVA

No changes in mRNA levels of the following:

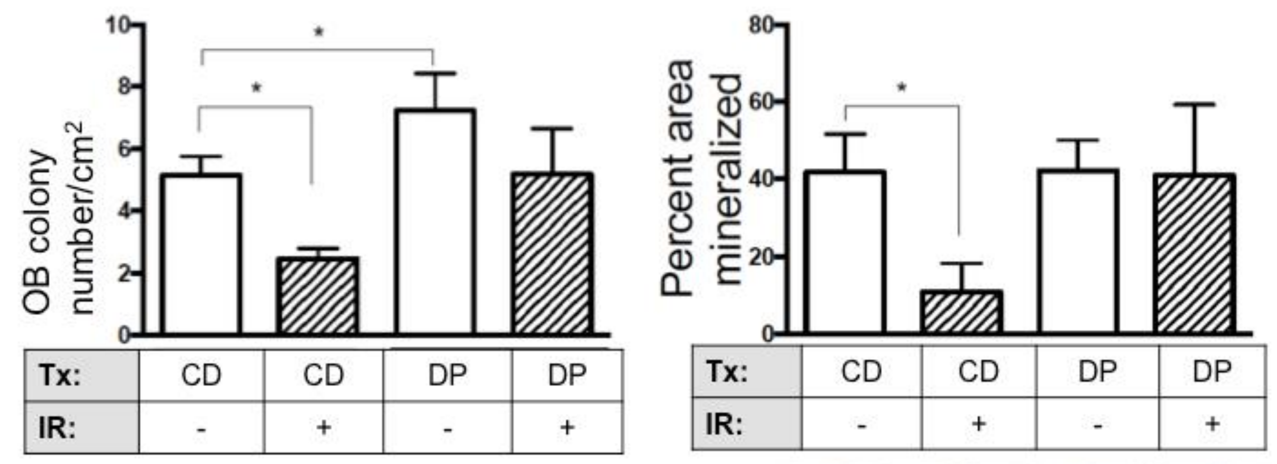
Bone Marrow Cells
• Bone-related: Rankl, Opg, BMP2, IGF1, Runx2, BMP4, Nfatc1
• Oxidative stress/DNA damage-related: SOD1, Foxo3, Nfe2l2, p53, Gadd45a, Cdkn1a

Mineralized tissue (shaft):
• Bone-related: Postn, Bglap
• Oxidative stress/DNA damage-related: mTOR, Nfe2l2, p53, Gadd45a, Cdkn1a

Mineralized tissue | Mineralized tissue



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



mineralized nodules:

Tx= treatment; CD= control diet (AIN93M), DP=25% Dried Plum in AIN93M,marrow cells flushed post-TBI and grown in osteogenic medium. Ob colony number (day 7 in culture) and mineralized nodules stained by von Kossa (21d in culture)

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

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