The Effects of CDKN1a/p21 on Oxidative Stress and Mitochondrial Function During Long Duration Spaceflight

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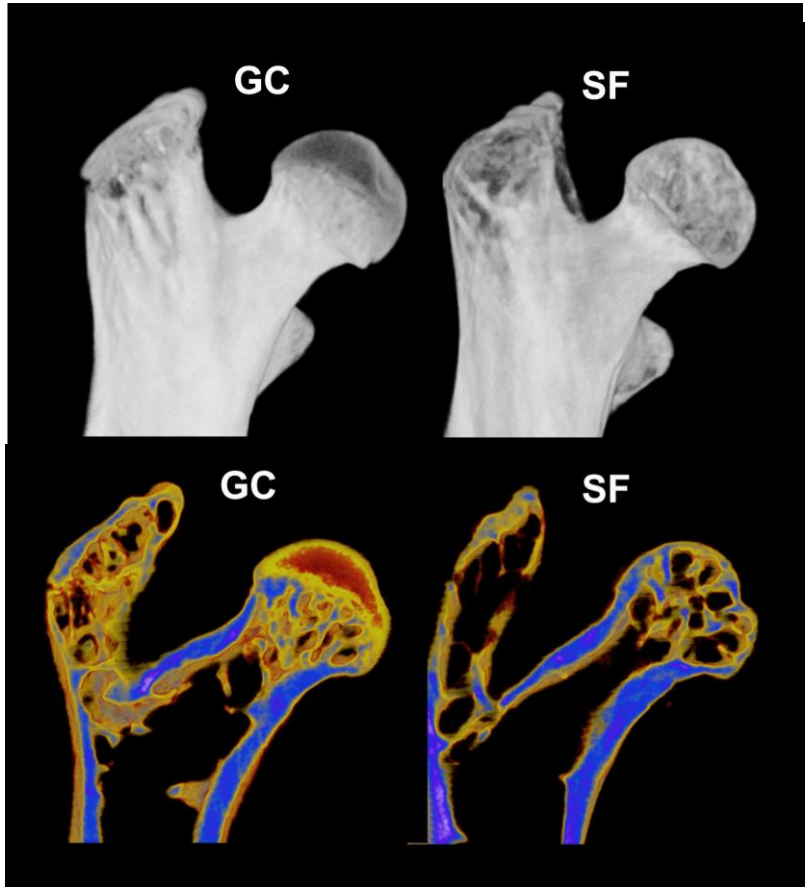
Spaceflight causes degeneration of the cardiovascular and musculoskeletal systems

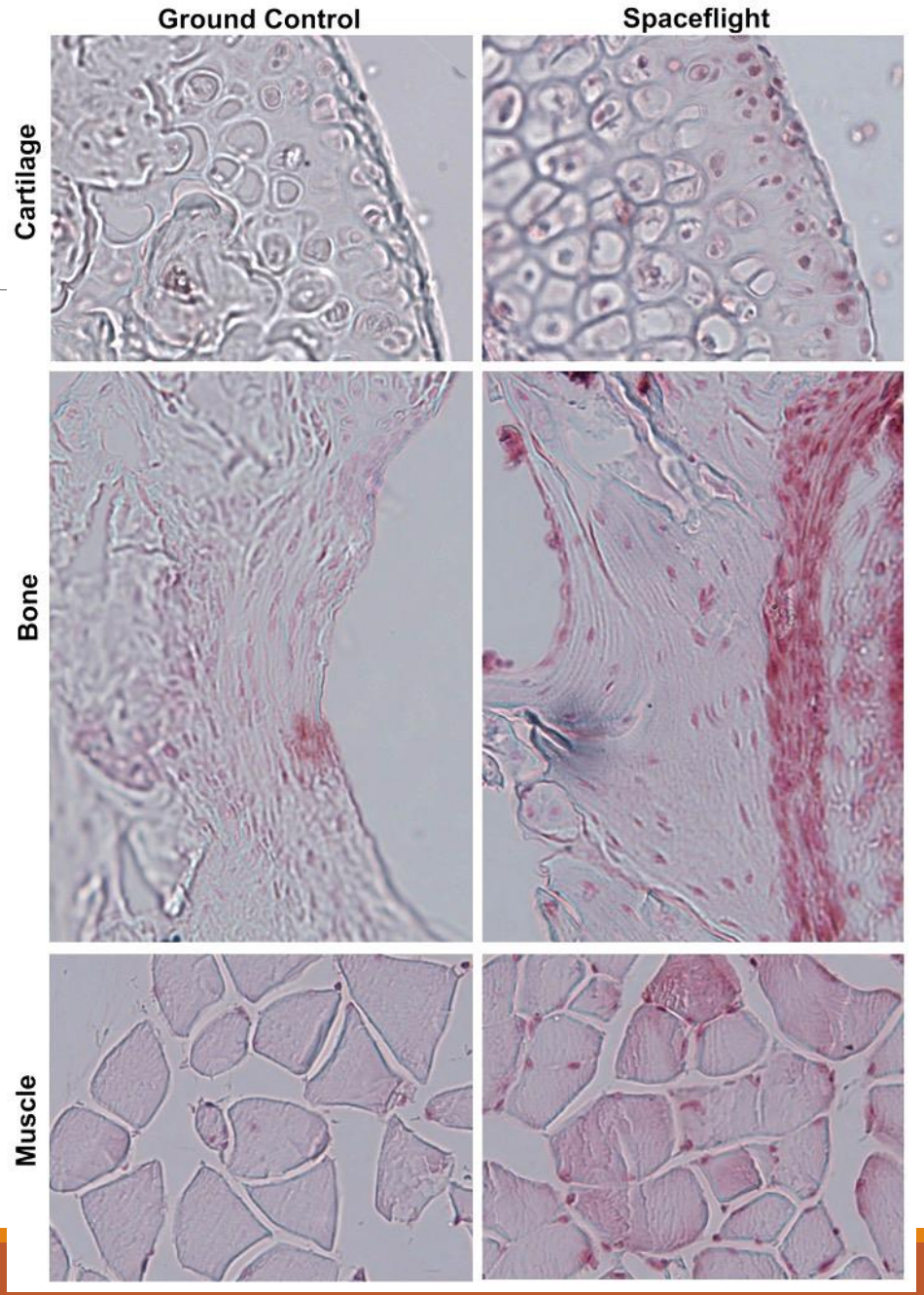
- Spaceflight factors, including microgravity and radiation exposure, are known to cause degenerative effects on mammalian physiology
  - Cardiovascular effects
  - Bone and muscle degeneration

- Radiation and unloading have been shown to cause increased levels of oxidative stress



Previous Results

- CDKN1a/p21 is a potent cell cycle arrest molecule that is activated at the G1/S transition
- Spaceflight mice exhibited increased expression of CDKN1a/p21 in osteoprogenitor cells and in other tissues (heart, skin etc.)
- CDKN1a/p21 KO mice exhibit limited regenerative capacity
- In p21 KO mice, cardiovascular alterations during HU are partially mitigated
- CDKN1a/p21 is also crucial in the cellular response to oxidative stress



Experimental Design

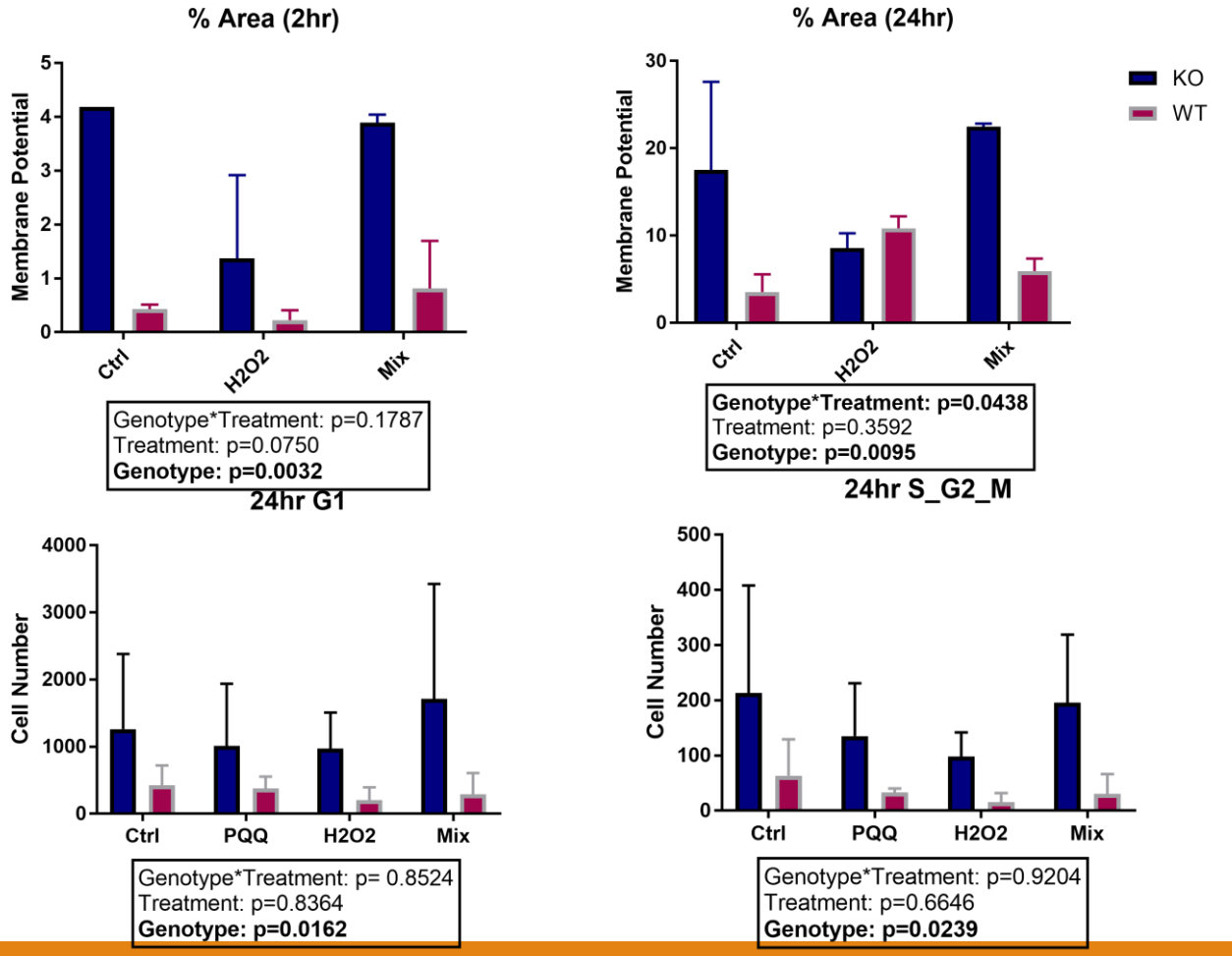
We aimed to investigate the role of p21 in oxidative stress related changes and the ability of a dietary countermeasure to mitigate these changes

Hypothesis: We hypothesize that CDKN1a/p21 status has a direct effect on the reaction of both smooth muscle cells and bone marrow stem cells to oxidative stress, through effects on quiescent versus active cell states. Furthermore, we hypothesis that PQQ (a nutritional countermeasure) may mitigate the effects of oxidative stress through attenuation of p21 expression.

Experimental Design:

- Smooth muscle cells and bone marrow stem cells isolated from CDKN1a/p21 KO and wildtype mice
- Cells exposed to oxidative stress for 1-2 h with or without a nutritional countermeasure
- Experimental parameters:
  - Mitochondrial staining
  - Cell cycle analysis
  - Gene expression

Effects of Stress on BMSCs and SMCs



- SMC results indicate that KO mice have significantly higher membrane potential than WT counterparts. Increased membrane potential was seen in WT mice 24 h after H_2O_2 treatment. This is likely a result of increased metabolic activity to reduce intracellular ROS.
- BMSC cell cycle analysis show a decrease in cells in S/G2/M compared to G1 indicating an arrest of cell cycle in WT cells but not KO.
- Our preliminary data suggest that oxidative stress has a significant effect on WT mitochondrial activity but not on KO cells.

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