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Mechanisms of Bone Loss in Space

Kendal Flowerdew OMS-2
Marian University - Indianapolis

Fei Wei

Melanie Coathup

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Introduction

The unique conditions of microgravity and radiation exposure in space have a substantial impact on human tissue function, resulting in extreme bone loss. The goal of this project is to synthesize the current knowledge on bone loss in space for use in future research. There is clear evidence, based on past research, that microgravity, cosmic radiation, fluid flow, and mechanotransduction influence bone function during space travel and result in significant loss. However, there is a need for future research on how these factors relate to each other and their collective influence on mechanisms of bone regeneration and repair. In addition, there is a need for more research on potential solutions to prevent the bone loss seen during space travel.

Normal Mechanisms of Bone Regeneration and Repair

- Achieved through the actions of osteoblasts, osteoclasts, osteocytes, and bone lining cells
- Osteocytes detect bone damage to bone and signal this to bone lining cells via factors, such as PGE2, PGI2, NO, and IGF-1
- Bone lining cells recognize and respond by recruiting osteoclast precursors to the site of damage
- Osteoclast precursors maturation mediated by RANK-L
- Osteoclasts digest bone through excretion of acid that degrades hydroxyapatite
  - Undergo apoptosis – initiated by osteoprotegrin (OPG)
- Osteoblasts recruited to area of newly digested bone by growth factors: IGF-I, IGF-II, TGFβl, and TGFβ2
- Osteoblasts deposit osteoid in cavity → mineralized to form new bone

Potential Solutions

Combating Fluid Flow Effects
- Bisphosphonate: inhibits osteoclast activity
- Intermittent Compression: improves blood flow to affected limb
- miR-33-5p Supplementation: promotes osteoblast differentiation
- mLIPUS: promotes osteoblast proliferation

Combating Radiation Effects
- Amifostine: protects cells from DNA damage caused by radiation
- Antioxidant Supplementation: protects against reactive oxygen species

Effects of Fluid Flow and Mechanotransduction

Mechanotransduction and Fluid Flow
- Mechanotransduction: process of taking mechanical energy and converting it into electrical energy and biochemical signals
- When bone is bent or compressed, a pressure gradient forces fluid out of the area of strain
- Fluid and charge movement creates a streaming potential that alters the electrical environment of the surrounding bone cells and activates several secondary events, leading to the resorption and formation of new bone in the damaged area
- Velocity of the interstitial fluid movement is thought to play a key role in activating surrounding cells when bone is under stress

Cytoskeleton's Role in Mechanotransduction
- Cytoskeleton: network of actin, microtubules, and intermediate filaments, which provide shape and stability to cells
- Actin filaments within cells sense mechanical force and generate contractile and protrusive forces
- Intermediate filaments serve as sensors of mechanical force direction and strength
- Cytoskeleton reacts to changes in fluid shear stress and has been linked to bone cells response to loading

Fluid Flow and Bone Loss in Space
- Microgravity reduces fluid flow within bone by two means: cephalad fluid shifts and loss of mechanical loading
  - Loss of the gravitational pressure gradient increases pressure in the upper body and decreases pressure in the lower body
  - Bone experiences unloading during space travel because it no longer bears the weight of the astronaut
- Decrease in fluid velocity and loss of loading-induced flow of interstitial fluid through the lacuna-canalicular network decreases the mechanosensitivity of the bone cells
- Osteocytes undergo apoptosis due to the lack of fluid shear force stimulation, resulting in a reduction in bone mass
- Unloading decreases proliferation of osteoblast precursor cells and causes resistance to parathyroid hormone (PTH) and Insulin-like growth factor type 1 (IGF-1) in osteoprogenitor cells
- L-type calcium channels in osteoblasts are inhibited under microgravity, blocking their major means of initiating bone formation
- Unloading caused osteocytic disuse leading to resorption
- Under microgravity conditions, this assembly of the cytoskeleton is altered because they do not have the gravity vector as a guide for growth
- Under microgravity conditions, cell growth is blocked either the G1 phase or G2/M checkpoint due to cytoskeletal changes

Effects of Cosmic Radiation

Cosmic Radiation
- Radiation environment in space is a mix of galactic cosmic radiation, solar particles, and geomagnetically trapped particles
- Galactic cosmic radiation (GCR) is "background" radiation originating from outside the solar system, but mostly from within the Milky Way galaxy
- Solar particles (SPE) come from solar flares and coronal mass ejections, when large masses are randomly ejected from the sun
- Geomagnetically trapped particles are protons and electrons within the geomagnetic field layer, which is the magnetic field surrounding the Earth
- As astronauts move further away from the Earth, the radiation exposure shifts from mostly geomagnetically trapped particles to GCR and SPE
- When GCR and SPE particles interact with spacecraft shielding, they can create secondary radiation and increase the potency of heavy ion irradiation

Cellular Response to Radiation
- The body responded to radiation through inflammation, DNA damage repair, and release of ROS scavengers
- Inflammation is initiated by activation of stress-sensitive kinases, proinflammatory transcription factors, and upregulation of proinflammatory cytokine production.
- DNA repair mechanisms: base excision repair, nucleotide excision repair, mismatch repair, homologous recombination, and non-homologous end joining

Radiation-Induced Bone Loss in Space
- Radiation causes osteoblast deficiency, osteocyte destruction, fibrosis of bone marrow, decreased BMSCs, and transient increases in osteoclasts
- Reduction of osteoblasts occurs almost immediately after exposure to radiation
- Osteoclasts increase in number and activity when exposed to radiation
- Solar particles and galactic cosmic radiation negatively affect hematopoietic stem cells (HSC), both directly and indirectly
  - Direct: genetic changes and alterations in cytokine expression, resulting in decreased cell output from these progenitor cells
  - Indirect: "Biological Bystander Effect"
- Mesenchymal stem cells preferentially differentiate into adipocytes instead of myocytes, osteoblasts, neurons, and chondrocytes
- Cosmic radiation is believed to sensitize bone to the effects of microgravity and their combined effects are what lead to injury and bone loss experienced in space

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