Osteoclast-Mediated Bone Disease

Subjects: Others

Contributor: John Kelly Smith

Astronauts are at risk of losing 1.0% to 1.5% of their bone mass for every month they spend in space despite their adherence to diets and exercise regimens designed to protect their skeletal systems. This loss is the result of microgravity-related impairment of osteocyte and osteoblast function and the consequent upregulation of osteoclast-mediated bone resorption. This entry describes the ontogeny of osteoclast hematopoietic stem cells and the contributions macrophage colony stimulating factor (M-CSF), receptor activator of nuclear factor kappa-B ligand (RANKL), and the calcineurin pathways make in osteoclast differentiation and provides details of bone formation, the osteoclast cytoskeleton, the immune regulation of osteoclasts, and osteoclast mechanotransduction on Earth, in space, and under conditions of simulated microgravity. The entry discusses the need to better understand how osteoclasts are able to function in zero gravity and reviews current and prospective therapies that may be used to treat osteoclast-mediated bone disease.

osteoclasts spaceflight osteoblasts osteocytes M-CSF RANKL bone microgravity cytokines

1. Introduction

The skeletal system of vertebrates has had millions of years to adapt to the force of gravity on Earth (9.8 m/s^2) and to allow osteocytes and the immune system to balance the activities of osteoblasts and osteoclasts. This osteoimmunological system is complex and involves commonly shared osteoclastogenic factors such as receptor activator of the nuclear factor-kappa B (NF-κB) ligand and macrophage colony stimulating factor as well as cytokines and immune cells that inhibit or enhance osteoclast ontogeny [1]. This adaptation has involved the construction of cytoskeletons supported by actin and intermediate filaments and microtubules [2][3], intracellular adhesion molecules including integrins and cell extension kinases [4][5], plasma membrane and nuclear mechanosensors [6], and thermal convection currents which renew nutrients and remove waste [7].

Man's venture into the vacuum of space where the force of gravity is one millionth of that on Earth has resulted in adverse effects on the osteoimmunological system, particularly bone homeostasis [8]. Astronauts are not only at risk of progressive bone and cartilage loss while in space but must also face the reality that space-related bone and joint changes may persist for years after their return to Earth despite efforts made to protect their skeletal systems [8][9][10][11][12][13].

2. Treatment of Osteoclast-Mediated Bone Disease

Unloading of bone on Earth and in the microgravity of space is associated with decreased bone formation and increased bone resorption. The reasons are complex but include the reduction of bone-loading signals normally transduced by shear stresses and hydraulic pressures exerted on osteocytes residing in the lacunar–canalicular network of bone, the increased secretion of sclerostin by pre-apoptotic osteocytes, and microgravity-induced disruption of osteoblast nuclei, cytoskeleton, and intracellular adhesins.

Experiments have been consistent in showing that conditions of microgravity and simulated microgravity decrease the mineral content and cortical and trabecular microstructures of bone, increase osteoclast secretion of sclerostin, decrease osteoblastogenesis and osteoblast secretion of OPG, and increase osteoclast differentiation, fusion, and expression of regulatory and osteoclast-specific genes [14][15][16][17][18][19][20][21][22][23][24][25][26]. However, why, in contrast, to osteocytes and osteoblasts, do osteoclasts with their complex cytoskeletons, remain functional under conditions of bone unloading—both on Earth and in space? How is the integrity of the sealing zone, so essential for bone resorption, maintained under such adverse conditions? What happens to the complex associations of actin and intermediate filaments, septins, and microtubules in osteoclasts subjected to microgravity? Why are M-CSF, RANKL, and calcineurin transcriptional pathways upregulated in osteoclast hematopoietic stems cells but downregulated in osteoblast mesenchymal stem cell precursors in zero gravity? Moreover, is there any relation between osteoclast survival and space-related changes in osteoclast regulation by immune cells and their cytokines? These intriguing questions should provide an ample basis for future research into the amazingly resilient osteoclast, including the development of agents capable of disabling key elements in its cytoskeleton.

In addition to bone unloading, a number of physiopathological conditions are characterized by excessive osteoclast activity. These include but are not limited to menopause, juvenile Paget’s disease of bone, inflammatory joint diseases, bone cancers such as multiple myeloma, and glucocorticoid therapy [1][2]. Thus, it is not surprising that many of the studies on bone homeostasis have been motivated by the need to find treatments capable of modifying osteoclast activity without inducing osteopetrosis [8]. I have listed below several potential treatments designed for this purpose.

2.1. Biphosphonates

Bisphosphonates have long been used with success to control osteoclast-mediated bone disease; these agents are incorporated into the bone matrix and are ingested by bone-resorbing osteoclasts, causing their apoptosis. However, biphosphonates inhibit the stimulatory activity of osteoclasts on osteoblast differentiation and, as a consequence, patients on these drugs suffer from a blockade of de novo bone formation [12][27].

2.2. Anti-RANKL Antibody

A recently developed human monoclonal antibody against RANKL, denosumab, has been shown to have undesirable side effects and, similar to biphosphonates, adversely affects osteoblastogenesis [28].

2.3. Cathepsin K Inhibitor

An inhibitor of cathepsin K, odanacatib, was shown to prevent pathological bone loss while preserving bone formation but failed in clinical phase III trials due to increased risk of stroke [29].

2.4. Anti-Sclerostin Antibody

Scientists have developed a humanized monoclonal antibody directed against sclerostin (romosozumab), which is approved for the treatment of osteoporosis. Clinical trials have shown that monthly subcutaneous injections of romosozumab are effective in increasing bone formation and density and decreasing bone resorption—results in keeping with the known effects of sclerostin on bone homeostasis [30]. However, there is some concern about the potential cardiotoxicity of romosozumab, prompting the need for further observations [31]. In addition, there is evidence in experimental animals that sclerostin generated in response to TNF-α and IL-1β improves post-traumatic osteoarthritis by inhibiting the activity of proteolytic enzymes involved in cartilage degradation [32]. Because astronauts experience an increased incidence of post-traumatic osteoarthritis involving their knees, ankles, hips, and shoulders, their use of anti-sclerostin antibody during spaceflight may prove to be a double-edge sword. It is important to note that both TNF-α and IL-1β play an important role in the pathophysiology of osteoarthritis [33].

2.5. Osteoprotegerin

Osteoprotegerin-Fc given subcutaneously to mice flown for 12 days in space produced a sustained suppression of bone resorption and, thus, deserves further study [34].

2.6. Melatonin

Ikegame and associates reported that melatonin, a well-tolerated and widely available compound, stimulated calcitonin mRNA expression and decreased RANKL mRNA expression in cultured fish scales (a surrogate for bone cultures) during an 11-day space flight aboard the International Space Shuttle. Calcitonin is an osteoclast-inhibiting hormone, and, as previously noted, RANKL binding to RANK is required for osteoclastogenesis. The authors posited that melatonin might prove useful in preventing space-related bone loss and, thus, deserves further evaluation [35].

2.7. Insulin-Like Growth Factor-1

Insulin-like growth factor (IGF)-1, which plays a major role in all phases of bone and cartilage growth, has been shown to increase rodent humerus periosteal bone formation by 37% during a 10 day Space Shuttle flight [8]. The potential of IGF-1 and other growth factors such as TGF-β and BMP to regulate bone homeostasis in situations of bone unloading merits further investigation.

2.8. Anti-IL-6 neutralizing antibody (IL-6nAb)

IL-6nAb treatment has been shown by He and associates to enhance bone formation in the tibias and femurs of adult mice subjected to simulated microgravity (hindlimb suspension for 4 weeks). They further demonstrated that mIL-6Ab treatment increased osteoprotegerin production and mRNA expression of alkaline phosphatase, osteopontin, and Runx2, and decreased RANKL production in murine pre-osteoblasts cultured under conditions of simulated microgravity. In cultures of murine pre-osteoclasts, simulated microgravity reduced mRNA expression of *cathepsin K and TRAP* and reduced numbers of TRAP positive multinucleated osteoclasts. [36]

3. Conclusions

Astronauts are at risk of losing bone mass and damaging joint cartilages despite NASA's efforts to protect their skeletal system by initiating exercise programs and nutritious diets. Bone loss is the consequence of microgravity-related impairment of osteocyte and osteoblast function and the consequent upregulation of osteoclast-mediated bone resorption. Further research is needed to better understand how osteoclasts are able to function in zero gravity and to develop more effective interventions to prevent osteoclast-mediated bone disease.

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