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MICROGRAVITY ALTERS MATRIX-INTEGRIN–KINASE SIGNALING CASCADES RESULTING IN ARREST OF THE CELL CYCLE IN BONE OSTEOPROGENITOR CELLS

Abstract

Mechanical unloading of human tissues during spaceflight significantly alters their physiology, including during growth and regeneration. We hypothesize that somatic stem cells may require mechanical stimulation of the matrix-integrin-kinase pathway to proliferate and differentiate at normal rates, and that in microgravity; mechanical unloading may impair these functions. Additionally, the subsequent loss of mechano-stimulated signaling in stem cell derived tissue progenitors results in loss of regenerative capabilities. We tested these hypotheses by conducting experiments in altered gravity above and below 1g. We found that in hypergravity primary osteoprogenitor cells have increased focal adhesion formation, pFAK recruitment and proliferation in a matrix-dependent manner, strongly suggesting that signaling downstream from matrix-integrin-kinase mechano-stimulation may be relevant to microgravity effects. To test this idea, we investigated alterations in expression of key cell growth and survival genes regulated by integrin pathways including, Pi3K/Akt, MAPK, p21/p53, and NF-κB. To study the effects of decreased mechanical loads on these pathways we exposed 16-week-old female mice to 15 days spaceflight on the STS-131 shuttle mission. Quantitative-PCR and gene array results show altered expression of key components within the signaling cascades activated by integrin/FAK signaling. Specifically, flight samples showed down-regulation of MAPK signaling molecules and subsequent loss of AP-1 transcription factor complex formation, and down-regulation of NF-κB subunits and up-regulation of NF-κB inhibitors resulting in cytoplasmic trapping of NF-κB. These gene expression alterations observed in microgravity may explain the inhibition of cell cycle progression, via the inactivation of AP-1 proliferative signaling and

activation of p21 cell cycle inhibitor, independent of p53-induced apoptosis. Furthermore, the 1g reloading of bone marrow osteoprogenitors isolated post-spaceflight resulted in a 7-fold increase in bone nodule formation and 53% increase in mature osteoclast formation, suggesting a proliferative arrest and accumulation of osteoprogenitors in microgravity. Gene expression analysis in post-flight osteoprogenitors showed down-regulation of stem cell markers and failure to express terminal markers supporting the hypothesis that microgravity arrests somatic stem cell progenitors in a pre-differentiation stage. These results suggest that normal gravity mechano-stimulation and signal transduction through matrix-integrin-kinase interactions may be an important component to tissue growth and regenerative health. Microgravity effects on these signaling pathways and subsequent alteration of proliferation and differentiation may explain the observed tissue degenerative effects of spaceflight.