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ACCELERATED HEMATOPOIETIC STEM CELL AGING IN SPACE

Abstract

Hematopopietic stem cell (HSC) fitness declines in response to macroenvironmental and microenvironmental stressors, including aging and inflammation. While the NASA Twins study revealed inflammatory cytokine upregulation, chromosomal alterations, and telomere changes indicative of hematopoietic defects, the direct impact of spaceflight on reduced HSC fitness and accelerated aging were not studied. To investigate the effects of spaceflight on human HSC fitness and aging, our NASA-supported Integrated Space Stem Cell Orbital Research (ISSCOR) team developed human HSC fitness-detecting bone marrow niche nanobioreactors with lentiviral FUCCI2BL fluorescent cell cycle reporters in automated CubeLabs, each equipped with a confocal fluorescence microscope and AI algorithms for real-time clonal tracking. These space nanobioreactors were flown in four separate 30 to 45-day missions to the International Space Station (ISS) (NASA SpX-24, 25, 26, 27) and compared with ground controls followed by functional colony survival, replating and stromal co-culture recovery assays combined with whole genome sequencing and whole transcriptome sequencing analyses to detect mutations and transcriptomic alterations. After a month in space, we observed reduced clonal dormancy, decreased telomere length, reduced ADAR1p150 self-renewal gene expression and decreased replating (self-renewal) capacity as well as mitochondrial DNA amplification, APOBEC3-induced C-to-T mutagenesis, and repetitive element alterations typical of accelerated aging and pre-leukemic disorders. Space-induced HSC fitness deficits were partly reversible on HS27 stromal co-cultures. Space-associated accelerated and pre-malignant HSC aging may be predictable and preventable with appropriate countermeasure implementation.