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MICROGRAVITY AFFECTS GENE EXPRESSION ON HUMAN IPSC-DERIVED 3D BRAIN MODELS OF PARKINSON'S DISEASE AND MULTIPLE SCLEROSIS

Abstract

Microgravity in low-Earth orbit (LEO) is known to impact cardiac, musculoskeletal, and immune system significantly; however, there is still scant information on the effects of microgravity on the central nervous systems (CNS). Our team has been investigating the role of microglia – the resident immune cells of the central nervous system – in primary progressive multiple sclerosis (PPMS) and Parkinson's disease (PD) by developing in vitro iPSC-derived 3D models of human brain cells. In addition, we have adapted these model systems to investigate the effects of microgravity on microglia and neurons to improve our understanding of pathogenic mechanisms of neuroinflammation underlying neurodegeneration. Leveraging differentiation protocols previously developed, we integrated human iPSC-derived microglia into 3D cultures of dopaminergic and cortical neurons and established the first long-term cultures of patient-specific neural cells in LEO onboard the International Space Station (ISS). Our experiment involved four human iPSC lines, derived from one person with primary progressive multiple sclerosis (PPMS) and one with idiopathic Parkinson's disease (PD) and their age/sex-matched healthy controls. At the ISS U.S. National Laboratory, the brain organoids were transferred to CubeLab flight hardware – designed by Space Tango – and launched onboard a SpaceX Falcon 9 rocket as part of the 18th, 19th, and 24th SpaceX Commercial Resupply Services mission for NASA (SpX CRS-18, SpX CRS-19, and SpX CRS-24). Upon returning to Earth, cortical and dopaminergic organoids show significant differences in gene expression and protein secretion when cultured for 30 days in microgravity compared to the ground control samples. In addition, gene set enrichment analysis (GSEA) of spaceflight samples suggests dysregulation of cell division, DNA repair and packaging, and post-translational modifications of proteins. This unique study is the first long-term 3D cell culture using patient-derived dopaminergic and cortical organoids with microglia to study Parkinson's disease and multiple sclerosis in microgravity. Overall, the results of these experiments are laying the groundwork for further studies to dissect the fundamental neurodegenerative mechanisms and understand the impact of microgravity on these disease-relevant processes to develop potential treatments for patients on Earth and countermeasures for astronauts.