Developing high-throughput organ-on-a-chip models to investigate the effects of ionizing radiation on the central nervous system

Sherina Malkani[1,2*], Eloise Pariset[2,3], Sylvain V. Costes[2] and Egle Cekanaviciute[2,3]
[1]Blue Marble Space Institute of Science, [2]Space Biosciences Division, NASA Ames Research Center, [3]Universities Space Research Association, [*]Contact information: Bldg N288 M/S 288-2, NASA Ames Research Center, Moffett Field, CA 94035, sherina.malkani@gmail.com

One of the main health risks in human space exploration is central nervous system (CNS) damage by ionizing radiation due to exposure to the galactic cosmic rays (GCRs). In animal models, irradiation with simulated GCRs or their components has been shown to cause neuronal damage and neuroinflammation associated with cognitive and behavioral dysfunction. In general, the extent of CNS damage is partially regulated by the blood-brain barrier (BBB), which enables immune cells to enter the CNS. The main cellular regulators of BBB permeability are astrocytes, which also modulate neuronal death, immune responses and oxidative stress, and thus could serve as a robust CNS-specific target for countermeasure development. However, studies on BBB permeability and astrocyte functions in regulating CNS responses to ionizing radiation have been limited, especially in human tissue/organ analogs. Therefore, we established a high-throughput 3D organ-on-a-chip system to study human CNS and BBB impairments in response to ionizing radiation, based on commercially available OrganoPlates (Mimetas, Inc.) seeded with primary or induced pluripotent stem cell-derived human cells. We investigated both immediate and delayed CNS responses to major GCR components: 0.15-0.5 Gy 250MeV/n ^{4}He, and 0.3-0.8 Gy 600 MeV/n ^{56}Fe; as well as to 0.5-1 Gy X-rays. We observed ionizing radiation-mediated increases in BBB permeability that was exacerbated by astrocyte presence and accompanied by morphological changes in endothelial cells and tight junctions, altered cytokine profile including TNFα upregulation, and increased oxidative stress. We also quantified irradiation-mediated changes in astrocyte activation and neuronal functions, revealing major astrocyte damage mediated by 600MeV/n ^{56}Fe particles. Thus, we demonstrate that deep space radiation may contribute to CNS damage by disrupting both astrocyte and endothelial cell components of the blood-brain barrier. Our next steps include mapping and validating the transcriptomic changes induced by simulated GCRs and their components in human CNS models. Ultimately, we aim to uncover potential novel targets for countermeasure developments to mitigate CNS damage in long duration spaceflight.