Title:
Deep Space Radiation Affects Neurovascular Functions in Human Organ-on-a-Chip Models

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Abstract:
A major health risk for human deep space exploration is central nervous system (CNS) damage by galactic cosmic ray radiation. Simulated galactic cosmic rays or their components, especially the highlinear energy transfer (LET) particles such as 56 Fe ions, cause CNS damage, neuroinflammation and cognitive dysfunction in rodent models, but their effects on human CNS remain to be investigated. CNS damage from any insult, including ionizing radiation, is partially mediated by the blood-brain barrier (BBB), which regulates the interactions between CNS and the rest of the body. The main cellular regulators of BBB permeability are astrocytes, which also modulate neuronal health and neuroinflammation. However, there have been few studies on BBB and astrocyte functions in regulating CNS responses, especially in human tissue/organ analogs. Therefore, we utilized a high-throughput human 3D organ-on-a-chip system, seeded with induced pluripotent stem cell-derived endothelial cells, astrocytes and neurons, to study human neurovascular responses to simulated deep space radiation. We investigated BBB permeability, oxidative stress, cellular and tissue damage, and secreted factors over the time period of 24 hours-1 week after irradiation with 0.25-0.5 Gy 5-ion simplified simulated galactic cosmic rays and 0.3-0.8 Gy high-LET 600MeV/n 56 Fe particles, and compared the outcomes to low-LET irradiation with 0.1-1 Gy doses of X-rays and gamma rays. Both high and low-LET radiation increased neurovascular permeability, caused oxidative stress, damaged endothelial cells and tight junctions, and altered expression of inflammatory cytokines. Ionizing radiationinduced neurovascular permeability and oxidative stress peaked at 3 days after irradiation and were further exacerbated by the presence of astrocytes. Furthermore, in response to particle irradiation, astrocytes stimulated interleukin-1 signaling by inhibiting the expression of interleukin-1 receptor antagonist. Thus, we also evaluated interleukin-1 receptor antagonist as a potential countermeasure against particle radiation. Ultimately, our results may help develop countermeasures to mitigate human CNS damage in deep space exploration.

Bio:
Sonali started work in the Radiation Biology Lab in October 2020 as a Research Associate affiliated with Blue Marble Space's Young Scientist Program. She also worked as part of NASA's Aerobiology Lab starting in July 2019 as well as NASA's GeneLab project. Before this, she was an undergraduate student at the University of San Francisco, where she completed a B.S. in Molecular Biology with minors in Astronomy and Biochemistry. As an undergraduate, she worked at the University of California, San Francisco in a number of labs, including the Rock Lab, the Perera Lab, and the Willenbring Lab, where she had the opportunity to study gut peristalsis, subtype switching in pancreatic ductal adenocarcinoma, and liver stem cell differentiation. At the University of San Francisco, Sonali worked on cultural astronomy research focused on the cultural and scientific contributions of indigenous peoples that led to mathematical and cosmological discoveries. In her free time, Sonali enjoys spending time with her friends, sharing funny photos, and imagining all the dogs she wants to own in the future.