NEUROVASCULAR EFFECTS OF SIMULATED SPACE RADIATION

A major health risk for human deep space exploration is central nervous system (CNS) damage by ionizing radiation. Simulated galactic cosmic rays or their components, especially high-linear energy transfer particles such as ^{56}Fe ions, have been shown to 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 interactions between CNS and the rest of the body. Astrocytes are major cellular regulators of BBB permeability and also modulate neuroinflammation and neurodegeneration. However, BBB and astrocyte functions in regulating CNS responses to space radiation remain little investigated, especially in human organ analogs. Therefore, we developed and utilized a high-throughput 3D human neurovascular organ-on-a-chip model, seeded with induced pluripotent stem cell-derived cells. The effects of time course, ionizing radiation dose and dose rate were mapped by exposing the model to either acute, high dose rate radiation with simulated galactic cosmic rays or 600 MeV/n ^{56}Fe particles, or protracted, low dose rate gamma radiation using a ^{57}Co sealed source setup. We investigated BBB permeability, oxidative stress, cellular damage and secreted factors over the time period between 24 hours – 2 weeks after 0.1 – 0.8 Gy irradiation. We observed that ionizing radiation exposure increased BBB permeability, caused oxidative stress, damaged endothelial cells and altered expression of inflammatory cytokines with a subset of outcomes dependent on ionizing radiation dose rate. Furthermore, our results indicated that astrocyte functions were primarily deleterious at early time points and protective later after irradiation, resembling CNS responses to injury *in vivo*. Our findings in organ models were complemented by studies on true spaceflight using mouse spatial and single cell multi-omics, which similarly indicated spaceflight-mediated changes in astrocyte functions. In summary, our study evaluates the regulation of neurovascular responses to simulated space radiation, suggesting astrocytes as targets for countermeasures to mitigate CNS damage in deep space exploration.