Paper ID: 116639
student

IAF/IAA SPACE LIFE SCIENCES SYMPOSIUM (A1)
Radiation Fields, Effects and Risks in Human Space Missions (5)

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A FALSIFIABLE SYNERGY MODEL FOR NK CELL IMMUNOSUPPRESSION UNDER COMBINED MICROGRAVITY AND RADIATION EXPOSURE: MATHEMATICAL FRAMEWORK AND PROPOSED VALIDATION PROTOCOL

Abstract

Long-duration spaceflight beyond Low Earth Orbit (LEO) presents a unique set of physiological challenges. During deep-space missions, astronauts are simultaneously exposed to sustained microgravity and high-energy Galactic Cosmic Radiation (GCR), including high-charge, high-energy (HZE) particles. While the isolated effects of these stressors on the human immune system have been extensively documented, their synergistic biological impact remains insufficiently characterized. Natural Killer (NK) cells constitute a critical component of innate immunity against viral infections and tumorigenesis, making the preservation of their functionality essential for mission success. Currently, there is a critical lack of predictive computational frameworks capable of estimating immunosuppression under combined flight stressors, representing a significant gap in space biomedical risk assessment. To address this gap, this study proposes a bipartite framework integrating machine learning with in vitro experimental validation. First, a Random Forest classification model is developed using publicly available transcriptomic datasets from the NASA Open Science Data Repository (OSDR/GeneLab). The analysis focuses on datasets evaluating the overlapping molecular effects of ionizing radiation and mechanical unloading on immune-related tissues. By tracking dysregulation in immune-regulatory genes—particularly the NKG2D receptor pathways and perforin/granzyme effector cascades—the model generates a dynamic Immune Risk Index (IRI). This index is designed to predict the degradation of NK cell cytotoxicity prior to the onset of clinical symptoms.

Concurrently, in vitro experiments are conducted to validate the computational predictions. NK cell cultures are exposed to simulated microgravity using a 3D clinostat, followed by standard cytotoxicity assays utilizing the K562 target cell line. The resulting cytotoxicity data serves as a biological ground-truth, enabling the cross-validation of the algorithm against empirical biological responses.

We hypothesize a synergistic, non-linear immunosuppressive profile wherein the combined deleterious effects exceed the additive impact of each individual stressor. The ultimate deliverable of this research is the deployable IRI algorithm. For future missions within the Artemis Program and Lunar Gateway operations, this tool may function as an onboard early-warning indicator, facilitating timely targeted nutritional or pharmacological countermeasures before critical immune dysfunction occurs.