IAF/IAA SPACE LIFE SCIENCES SYMPOSIUM (A1)
Biology in Space (8)

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COMPROMISED ANTIVIRAL AND IMMUNE RESPONSES IN A CELLULAR MODEL AND THEIR PREDICTED DISEASE-DRUG INTERACTIONS DURING SPACE MICROGRAVITY

Abstract

Cellular models usage at the International Space Station (ISS) provides an opportunity to study the impact of microgravity on gene expression patterns and their correlations with human health and disease. Our study investigates the impact of microgravity at ISS on mRNA abundance changes on a genome-wide scale utilizing the monocytic THP-1 cell line, stimulated with the inflammatory microbial product, LPS. We obtained numerous data that can be used to further understand the mimicked disease processes and utility in drug discovery for space illnesses. First, the k-means clustering algorithm was used to study the fold changes between untreated and LPS-treated cells during time course experiments (0, 1, 2, 4, 6, and 20 hr) in Earth (gravity, ground) conditions. It pointed to an inducible expressed mRNA cluster of 439 genes that peaks at 4 hrs. This cluster was delayed and highly suppressed under space microgravity conditions (at ISS) and demonstrated a considerable reduction in interferon, cytokine, and inflammatory responses (>30% of the cluster genes). Using computational disease-gene interactions, we show that the compromised IFN response of the Space mRNA cluster is associated with the likelihood (Odd ratio >10-fold, $p<0.001$) of respiratory viral diseases (e.g., influenza and RSV), herpes virus infections, mycobacterial infection, and other microbial diseases. The inflammatory response cluster was also compromised in Space vs. Earth in the LPS-stimulated monocytic cells. For example, TNF signaling pathway was severely suppressed (>80% reduction, $p<0.01$), which included the master transcriptional factor, NFBI. The mimicked diseases that are predicted (>15-fold odd ratio, $p<0.001$) to be affected (reduced) in association with this cluster are largely of autoimmune nature, particularly rheumatoid arthritis, multiple sclerosis, and ulcerative colitis; plus, respiratory and skin allergic diseases. It is interesting to note that from this RNAseq expression/functional clustering data, several of these predicted pathologies, e.g., herpes simplex reactivation, are the same as those experienced by the astronauts during long space flights. Using an AI approach, specifically drug-gene-disease bioinformatics modules, we identified several drugs that can counteract the compromised IFN/antiviral responses as attested by the generative prediction of IFN-α and -β. This finding can lead to the use of the monocytic cell line, THP-1, as a drug discovery platform under simulated or space microgravity and for multiple disease conditions that mimic the different pathologies encountered in long-term space travel.