Paper ID: 47762
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IAF/IAA SPACE LIFE SCIENCES SYMPOSIUM (A1)
Biology in Space (8)

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RAPID ADAPTATION TO MICROGRAVITY IN CELLS OF THE IMMUNE SYSTEM

Abstract

The hostile environment of microgravity during human spaceflight bears a multitude of limiting factors for human health and performance, in particular as a result of immune system weakening. Therefore, to understand the biology and homeostasis of immune modulation under spaceflight conditions is mandatory for appropriate integrated risk assessment for human spaceflight and the development and validation of prevention, countermeasures, monitoring and intervention strategies. We therefore investigated signal transduction, molecules of cell-cell-interaction, metabolism, functional parameters and gene expression responses in human lymphocytes and macrophages in different gravity environments through a multi-platform approach (parabolic flights, suborbital ballistic rockets, International Space Station and 2D clinostat and centrifuge experiments), including rigorous control experiments. A multi-platform approach not only allows for cross-validation of findings in independent experiment platforms, but also for understanding the time-course of mechanisms. In primary T lymphocytes, membrane proximal, cytosolic and nuclear signaling in primary human T lymphocytes were not severely altered. Primary human macrophages exhibited neither quantitative nor structural changes of the cytoskeleton after 11 days in microgravity during the CELLBOX ISS experiment, and only minor alterations in the metabolite spectrum. The ISS experiment TRIPLE LUX A provided direct evidence of cellular sensitivity within seconds and a subsequent ultra-fast adaptation in only 42s to microgravity, through real-time on orbit measurements. We next addressed the question, if gene expression homeostasis is constantly shaped by the gravitational force on Earth and determined the time frame of initial gravitational force-transduction to the transcriptome and assessed the role of cation channels. We detected profound alterations in the transcriptome after 20s of microgravity or hypergravity. We found that nearly all initially altered transcripts adapted after 5min. Only 2.4% of all microgravity-regulated transcripts were sensitive to the cation channel inhibitor SKF-96365. We identified three gravity-regulated genes, ATP6V1A/D, IGHD3-3/IGHD3-10 and LINC00837. We revealed an overall high stability of gene expression in microgravity and identified olfactory gene expression in the chromosomal region 11p15.4 as particularly robust to altered gravity. Neither sensitivity nor stability of gene expression in altered gravity was randomly distributed in the chromatin, suggesting that the spatial chromatin organization may play an important role in transduction of the non-specific gravitational force into a specific gene expression and transcriptome response. We also conclude that microgravity alters gene expression homeostasis not stronger than other environmental factors in the investigated cell types and probably does not impose an unacceptable risk during long-term space missions at the cellular level.