SPACE LIFE SCIENCES SYMPOSIUM (A1)
Fundamental Gravitational Biology (7)

Author: Prof. Oliver Ullrich
University of Zurich, Switzerland

SIGNAL TRANSDUCTION IN CELLS OF THE IMMUNE SYSTEM IN MICROGRAVITY

Abstract

BACKGROUND and PURPOSE: Since decades it is known that the activity of cells of the immune system is severely dysregulated in microgravity, but the underlying molecular aspects are not elucidated. Identification of gravity-sensitive molecular mechanism in cells of the immune system are an important and indispensable prerequisite for the development of counteractive measures to prevent or treat disturbed immune cell function of astronauts during long-term space missions to Moon or Mars. Moreover, their sensitivity to altered gravity renders immune cells an ideal model system to understand if and how gravity on Earth is required for normal mammalian cell function and signal transduction. In a set of projects we are investigating the effect of microgravity on key functions of monocytic/macrophageal cells, the antigen-presenting, phagocytosing immuno effector cells of the immune system. Such cells belong to the the innate immune system that plays a key role in defending the organism in early phases of infections and diseases and in execution of immune reactions.

METHODS: Experiments have been performed by 2D clinostat, centrifuge and parabolic flights, which addressed the influence of altered gravity on cells of the innate immune system. In our studies we investigated the influence of altered gravity on T lymphocytes, the key cell type for the specific immune response, and on monocytic cells, the antigen-presenting and effector cells of the immune system. The separate function and interaction of both cell types is indispensable for any regular immune response. In a flight experiment in the BIOLAB facility on the ISS we will investigate the effects of microgravity on the oxidative burst, the production of reactive oxygen species (ROS), in a macrophageal cell line by a chemiluminescence assay. In a flight experiment in the SHENZHOU-8 spaceship, we will investigate the effects of microgravity on macrophageal differentiation and adhesion molecule expression in a monocytic cell line.

RESULTS: In experiments with a fast rotating 2D clinostat, we detected strong and rapid initial changes of T lymphocyte signal transduction (e.g. MAPK activation) within minutes of simulated weightlessness. However, most of the initial alterations returned to "normal" levels after 15min simulated weightlessness. Only the expression of p21 protein remained constantly elevated, compared to normogravity controls. Hypergravity of 1.8g had no effects of the signal pathways investigated. In parabolic flight experiments, we found that 20s microgravity resulted in distinct changes of expression of cell-cycle regulatory genes such as p21 and p27 on the transcriptional level. Altered expression has been detected in PMA- and CD3/CD28-stimulated T lymphocytes as well as in non-stimulated lymphocytes. We found that monocytic cells responded to simulated weightlessness by tyrosine-phosphorylation of several proteins, and therefore in a similar way than after stimulation with the PKC-activator PMA. In contrast, in PMA-stimulated monocytic cells, tyrosine-phosphorylation was nearly abrogated in the presence of simulated weightlessness. In microgravity, the oxidative burst of the macrophage cell line NR8383 decreased upon stimulation and during phagocytosis, but increased distinctly in non-activated and non-phagocytosing cells. Furthermore, in parabolic flight experiments, we detected a strong downregulation of ICAM-1 (CD54) expression in non-stimulated and in PMA-stimulated macrophageal cells.

CONCLUSION: Thus we conclude that dysregulation of immune function in microgravity might be a consequence of 1.) sustained induction p21 as a cell cycle arrest signal in T lymphocytes and 2.)

downregulation of ICAM-1 in monocytes/macrophages which are then no longer capable of interact appropriate with T lymphocytes. We suppose that microgravity sets resting monocytic/macrophageal cells into a state of alert and into a state of non-specific activation, whereas activated monocytic/macrophageal cells are inhibited in microgravity. Such effect would inhibit the specific and directed action of antigen-presenting cells and phagocytes, but would stimulate large numbers of phagocytes to execute non-specific and non-directed phagocytosis, such as in bone tissue.