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Time course of cellular and molecular regulation in the immune system in altered gravity: Progressive damage or adaptation ?

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ABSTRACT

We summarized the current knowledge about adaptation processes of isolated immune cells, animal models and the human body to altered gravity conditions. Many studies indicate an adaptation reaction of the immune system to the new microgravity environment, at least for the T cell system. Animal and human studies indicated adaptation processes starting after two weeks and continuing until 6 month or longer, which was reflected by cytokine concentrations in blood plasma or in stimulation assays. Adaptive reactions regarding IFN-γ, TNF-α and IL-2 concentrations were detected after 12 days spaceflight in animal studies and after 2–4 months in human studies, whereas adaptive reactions regarding IL-4, IL-6, IL-8 and IL-10 were found after 6 months spaceflight. Cellular studies were performed mainly as short-term studies, and only a few studies addressed alterations longer than 3 days. However, cross validation between studies is often not possible or indicated conflicting results. Many *in vitro* studies, mostly done with T lymphocytes, demonstrated extensive cellular and molecular alterations. In contrast, long-term studies with animals and humans are completely lacking this dramatic picture of short-term cellular effects, which indicates a very efficient adaptation process, partially evidenced by new steady state of adaptive response in the human immune system after weeks until months. Therefore, we assume that the human body and its cells are equipped with a robust and efficient adaptation potential when challenged with low gravitational environments.

Contents

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1. Introduction

Gravity has been a constant factor throughout the evolution of life on Earth, and played an important role for the architecture and morphology of all biological systems. It can therefore be assumed that abrupt changes of the gravitational force have an impact on the function of living organisms. It is of great interest, if and how cellular and molecular functions adapt to gravitational changes or if they strictly depend on Earth's gravity. Many studies have been performed analyzing the effects of altered gravity on life from unicellular organisms to humans. In humans the current level of knowledge is that altered gravity, especially microgravity, leads to numerous deconditioning symptoms like bone demineralization, muscle atrophy, reduced performance of the cardiovascular system, altered neurovestibular perception as well as strong impairment of the immune system [1–4]. The dysregulation of the immune system under spaceflight conditions is described by vast number of reports [5–13]. The first observations were made already in the 1960s and 1970s where half of the Apollo astronauts developed bacterial or viral infections during spaceflight or shortly after returning to Earth [14]. Viral infections include also reactivation of latent viruses like the varicella zoster virus, cytomegalovirus and Epstein-Barr virus [15–19]. Furthermore, investigations of astronauts during and after their ISS (International Space Station) missions showed allergic hypersensitivity symptoms especially for the skin, indicating a loss of regulatory immune system function under spaceflight conditions [20,21]. At the cellular and molecular level post-flight dysregulation of the function of the human immune system has been reported frequently. Findings after landing include differences in immune cell subpopulations like e.g. in the distribution of peripheral blood leucocytes [22,23,7]. Furthermore, the reactivity of certain cell subsets is affected. Analyses of blood samples of nine astronauts after returning from the Skylab space station showed a reduced activation potential of lymphocytes upon mitogenic stimulation in comparison to the pre-flight data [24].

However, comparing the results of the numerous different missions, variable results were obtained for the different immune cell subsets [7]. Nevertheless, the collected data point out that cell populations are very sensitive to exposure to spaceflight conditions including launch and landing [7]. Monocytes, representing cells of the innate immune system, show a reduction in motility and a rearrangement of the cytoskeleton during spaceflight compared to 1 g in flight and ground controls [25]. T cells, representing the adaptive part of the immune system, are altered in their function. In Space Shuttle crewmembers, early T cell activation was elevated while in ISS crewmembers it was significant reduced after landing. In both cases, the ratio of secreted IFN-γ:IL-10 was decreased, indicating a Th2 shift in the astronauts' immune system [26]. The knowledge about the humoral immunity is sparse. A few studies described that immunoglobulin plasma levels are unaltered after short-term spaceflights [27–29]. Contradictory results are reported for long duration space missions. While one study described increased serum levels of IgA and IgG [30], another analysis showed that total serum levels of IgA, IgM and IgG were not significantly changed during long-term missions [29]. However, research in the amphibian *Pleurodeles waltl* showed no changes in the IgM heavy chain transcription but a threefold increase in the level of IgY heavy chain transcription, an analog to human IgG [31,32].

The dysfunction of lymphocytes, resulting in immune deficiencies, is thought to represent an enormous risk for long duration spaceflights [7]. Alterations in the immune response could cause a dysbalanced response to infections or cancer or lead to hypersensitivity reactions with severe clinical manifestations [33,34,6]. Hence, the underlying mechanisms of these immune dysfunctions need to be elucidated. Additionally to microgravity, the high psychological stress, as well as the high levels of radiation experienced in this extreme environment, represent environmental stressors. Nevertheless, based on numerous publications, there is strong evidence that microgravity is a factor that could be considered as major reason for an affected immune cell function during spaceflight [35–37]. During the last 40 years more and more studies came up investigating the influence of altered gravity on immune cells isolated from animal or human organisms. It could be shown that inter alia molecular mechanisms and signal transduction cascades are directly affected by microgravity or hypergravity. Hence, isolated lymphocytes are an ideal model to study direct primary effects of altered gravity at the cellular level without disturbing or interfering secondary and systemic influences of the entire organism. A combined approach of experiments performed on different microgravity platforms complemented with studies using ground based facilities [38] are important for the investigation of cellular and molecular processes influenced by altered gravity. Ground based facilities like clinostat, rotating wall vessel and random positioning machine, represent valuable tools since they often provide microgravity induced comparable results and therefore offer the possibility for relatively cost effective and fast investigations. Despite the enormous number of studies, we do not yet have a complete overview about the functions of the immune system in altered gravity including adaptation processes and reaching of new steady state levels [39].

This review provides an overview about the current status of knowledge of the effects of spaceflight on cells of the immune system with regard to adaptation in cell culture systems, animal models and human studies. We aimed to compile existing studies regarding the measured time points for potential adaptation effects.

2. Cellular studies

Many studies have been published where immune cells have been cultivated under spaceflight conditions with or without activation. The great advantage of cell culture studies is that direct and primary effects of altered gravity can be investigated on the cellular level. T cells, representing the adaptive immune system have been analyzed since long and are most likely the best investigated immune cells in cell culture.

Experiments that were performed under real as well as under simulated microgravity conditions showed that non-activated and activated T lymphocytes react sensitive to gravity with respect to cell cycle regulation [40], epigenetic [41] and chromatin regulation [42], differential gene expression [40,43] and micro RNA expression profile [44], cell motility [45,46], and regulation of apoptosis [47–49]. Furthermore, expression of cytokines such as interleukin- (IL-) 2, and interferon-gamma (IFN-γ) were changed in microgravity [50].

The effect of microgravity on the cell proliferation, maturation and function was analyzed *in vitro* by many groups. However, often only a single time point was measured and a time course monitoring the progress of the changes is missing – often due to technical and operational constraints. Table 1 summarizes the influence of microgravity and simulated microgravity on T cell proliferation after activation, a requirement for a functional immune response. The results of the different groups are listed according to the length of exposure to microgravity. *In vitro* activation of T cells under real microgravity was investigated only scarcely and is indeed described only in a few reports [43,51–53,38,54]. One describes the experiments from Cogoli and colleagues, which were performed during the Spacelab 1 mission in 1983 [51]. The reactivity