Chapter 10
The Immune System in Space: Are We Prepared? Conclusions, Outlook, and Recommendations

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Humans have been traveling to space for more than half a century and have adapted remarkably well to the altered gravity environment. However, several limiting factors for human health and performance in microgravity have been clearly identified (Comet 2001) and substantial research and development activities are required in order to provide the basic information for appropriate integrated risk management, including efficient countermeasures and tailored life support systems (Horneck and Comet 2006). In particular, serious concerns arose whether spaceflight-associated immune system weakening ultimately precludes the expansion of human presence beyond Earth's orbit (Guéguinou et al. 2009).

The Apollo missions were the first to show significant changes in multiple biological systems: vestibular disturbances, in-flight cardiac arrhythmia, reduced postflight orthostatic tolerance, postflight dehydration, and weight loss. Furthermore, a significant decrease in red blood cell mass and negative in-flight balance for nitrogen and a significant loss of calcium and bone were discovered (Hughes-Fulford 2011). During the Skylab missions, osteoporosis was found to occur on the longer Skylab missions (Vogel 1975) and the lymphocytes of astronauts were shown to be heavily compromised (Kimsey 1977). In the years and decades to follow, studies have shown that microgravity strongly compromises immune cell function, which is currently considered the main reason for dysregulation of immune cell function during spaceflight. The results of space-related clinical and fundamental studies indicate that

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A. Choukèr, O. Ullrich, *The Immune System in Space: Are we prepared?*, SpringerBriefs in Space Life Sciences, DOI 10.1007/978-3-319-41466-9_10

both short- and long-duration spaceflight could largely trigger immune dysfunction, which may exacerbate immunopathology during the course of inflammation and result in altered resistance to infection or cancer or to altered hypersensitivity reactions, yielding severe clinical manifestations that could endanger the host.

Numerous studies carried out with T lymphocytes, cells of the monocyte-macrophage system and endothelial cells in microgravity have clearly shown that individual cells are sensitive to gravity. These experiments, conducted under real and simulated microgravity conditions, have contributed greatly to our current knowledge of how gravitational forces affect basic cellular mechanisms. However, it has not been possible so far to identify a generally accepted primary mechanism from these various effects that underlies the effects of altered gravity on immune cells.

The multitude of cellular and molecular responses to the new gravitational environments have been obviously less ordered than the responses to other environmental changes. This came not as a surprise, since life evolved on Earth in constant gravitational force for 4.8 billion years and, therefore, little or no genetic memory of life responding to gravitational force changes can be expected. Therefore, studying the adaptive processes in cells to altered gravity will clearly increase our understanding of the role of gravity in evolution on Earth. Whereas immune system alterations seem to persist during long-duration spaceflight (Crucian et al. 2015), rapid adaption mechanism could be observed at the cellular level.

To understand these adaptation processes, we tried to summarize individual cellular and molecular effects on a timescale. But we quickly realized that this effort was a “mission impossible”: Experimental conditions varied widely from study to study, from types and concentrations of stimuli to cell culture conditions, using different media and supplements. Finally, nearly all studies used chemically undefined medium supplements, often in different concentrations. In the future, research in gravitational biology of the immune system should benefit from the latest technology for the standardization of cell and tissue cultures and the development of defined conditions at all levels, including stimuli and media.

The health risks pose serious obstacles when planning long-term space exploration missions. Therefore, after a thorough estimation of the indirect stress-related (through neural and hormonal changes) and direct (microgravity, radiation) effects of spaceflight – and the holistic approach to understand the intrinsic and extrinsic loops (see Chap. 2) – reliable treatments have to be identified and further developed to overcome the limiting nature of the human body.

The venues for the identification of the causes will build up on several pillars: investigations in human and with ex vivo onboard analyses of cell responses, using single cell analyses and genetic and protein analyses within an integrated Omics approach. Here, harmonizing of the technical tools and arrays between the agencies and researchers involved needs to be assured and together with sharing such data within the ISS partners, an increase of the number of subjects investigated and scientific impact will be assured. Moreover, these functional and molecular data have to be brought into the context of the duration of the mission and the changes of the other organ systems´ functions and microbial composition, for example, by the analysis of microbiota composition in the gut before, during, and after flight in and

correlation to immune activity and environmental conditions, including the degree of oxygenation or the content of carbon dioxide.

Preconditioning and metabolic control can be two general and efficient tools to adapt to new environmental challenges and to reduce metabolic activities. By definition, preconditioning presents a stressful but nondamaging stimulus to cells, tissues, or organisms to promote a (transient or even permanent) adaptive response so that stress response resulting from subsequent exposure to a harmful stimulus (stressor) is reduced. These benefits aim to target the preservation of energy in the cell, and hence the cell homeostasis, and to increase resistance to a following/secondary damaging impact. Since several types of preconditioning such as pharmacological, thermal ischemic, and especially hypoxic preconditioning have been shown their efficacy, they can be applied to humans as to other biological systems to counteract the unwanted effects of spaceflight on the immune system and other organ systems and to thereby increase resistance and mission success. To which degree the understanding of preconditioning effects and modulation of mitochondrial functions can be used with other tools and conditions to induce even permanent status of hypometabolism (torpor/hibernation) needs to be identified.

The adoption of *cell-based therapies* is promising with respect to effectiveness, safety, range of application, and ease of use. The majority of the health issues in space were already addressed by research and clinical trials in the field of cell-based therapies. In combination with lyophilization, to guarantee low cost and reliable storage of cell products, therapeutical cells could amount to comprehensive treatment and prophylaxis in the future – not only in space, but also on Earth.

The knowledge of the effects of gravitational changes on immune cell regulation and the identification of gravity-sensitive cell responses will help to understand the molecular mechanisms of inhibited immune cell function in altered gravity and provide new targets for therapeutic or preventive interventions with respect to the immune system of astronauts during long-term space missions (Ullrich and Thiel 2012). Those studies may clarify whether and to which extent gravity is involved in normal cell function, how cell function is impaired by altered gravity, and how cells adapt to the new situation. Finally, *knowing the cellular and molecular mechanisms* is an invaluable requirement for a better risk assessment and development of in vitro tests for medical monitoring. For these endeavors, *standard protocols of cell and tissue cultures* should enable cross-study analysis, especially at the timescale of adaptation.

The rearrangement/reorganization of *cytoskeletal structures* was found in lymphocytes and in dendritic cells (DCs) and throughout different microgravity platforms. Supposing that the cytoskeleton is the central gravisensitive element, it possible that the observed alterations have indirect effects on all kinds of cellular functions via intracellular signal transduction and transcriptional pathways. Thus, these cytoskeletal changes can contribute to all kinds of pathological conditions observed during altered gravity conditions.

Testing and validation of such new approaches will require onboard immune function tests, and on-ground spaceflight analogue studies might be able to provide more information to understand the underlying mechanisms and to produce corresponding mitigation strategies to prepare for the coming interplanetary space explorations (Pagel and Choukèr 2016). Complementary to the “golden standard” of the

real exposition to spaceflight (ISS, or sounding rocket, Bion capsules), the important elements of such understanding will be based on the use of high-fidelity ground-based facilities for estimation of either indirect stress-related effects, as investigated in bed rest facilities and in isolation/confinement studies, as well as in scenarios to evaluate the gravitational or radiation-depending damaging effects, for instance by using hypergravity centrifuges for cells, animals, as well as microgravity simulators such as Clinostats, random positioning machines, and rotating wall vessels with and without concomitant radiation effects. Since research in the area of gravitational science is extremely expensive and elaborate, resources should be spent wisely. Thus, in order to achieve the highest level of reliability and comparability of the results, gravitational-related immunobiological research should benefit to a large extent from the latest technology for the standardization of cell and tissue cultures and the development of chemically defined media. In addition, and as a bridging element, the use of experimental animal facilities (e.g., of rodents, as well as amphibians) in space should be used more extensively and in an internationally coordinated fashion.

As interplanetary space exploration and a mission to Mars are contemplated, it is critical to improve our understanding on how immune dysfunctional states occur and to which pathology they can lead. This will be the prerequisite to target new preventive and therapeutic countermeasures to mitigate such risks.

New and innovative approaches have been initiated and will be applied in the future and in space and will, more than before, be based on the strong interaction between the clinical understanding of stress-related maladaptations and a cell-based state-of-the-art molecular approach. This more holistic strategy using new technologies and experimental tools in challenging environments will help us better understand the complexity of immune interactions on the organ and cellular level, for Earth as in space. This knowledge will help enable the ultimate goal of sending man to outer space, and to bring him back safely.

Especially since exploration-class deep space missions are characterized by high radiation exposure, confinement, limited clinical care, and the impossibility of an evacuation to Earth in case of emergency, such missions will be always missions into the unknown. Even if we should have unlimited research resources and endless time to prepare, it is impossible to assess and monitor all possible medical aspects, to elucidate all scientific aspects, and to exclude all risks. Perhaps, our current knowledge will turn out to be incomplete or wrong someday. Maybe, despite all efforts and despite all "modern" science, we could have overlooked something relevant. For preparing exploration-class missions, we should focus, trust, and rely on the crew: highly skilled and professional astronauts with solid scientific and technological backgrounds. Exploration-class missions should be equipped with all scientific, technological, and medical devices and tools to analyze and to solve problems that might occur during the mission: from high-end point-of-care-testing systems (POCT), highly flexible analysis and monitoring systems up to the possibility of efficient cell-based therapies on board. But finally, no one can guarantee 100 % that our knowledge is sufficient to foresee and counteract all facets of the biological reality, and no one can guarantee that we are prepared for everything. Someday, everything will depend on the few astronauts who will commence on the greatest journey of mankind, prepared for the worst and hoping for the best.

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