OXFORD JOURNAL
OF STUDENT
SCHOLARSHIP

The Human Immune System in Space

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ABSTRACT

The immune system is subjected to a unique mix of environmental and physiological stresses that are not experienced on Earth during human spaceflight. Various aspects of microgravity interactions with confining conditions, altered nutrition, ionizing radiation, sleep disruption, and changes in the host microbiome can lead to alterations in immune-cell development and function. Experimental models and astronaut studies indicate that spaceflight may cause immune dysregulation, rather than a blanket immunosuppression, with some immune functions being suppressed while others are altered in their inflammatory signalling and regulation. The ability of T cells to become activated and proliferate may be affected, natural killer (NK) cell cytotoxicity may be reduced, the innate inflammatory pathways may become dysregulated, and latent herpesviruses may be reactivated or shed more often. In addition, space radiation contributes to oxidative stress and DNA damage and is likely to be more of an issue when operating outside of low Earth orbit. In the last few years, there have been a number of multi-omic studies, such as the NASA Twins Study and the Inspiration4 crew, that have offered high-resolution evidence of shifts in immune-related gene expression, cytokine levels, cell composition, and host–microbiome interactions. These findings are relevant as they can affect a person's ability to recover from infection, develop inflammatory diseases, and other health problems in long-duration missions. Existing countermeasures include exercise, proper nutrition, stress and sleep management, radiation shielding, vaccination, pharmacological measures and serial immune monitoring. The combined stressors need to be understood, and future research should incorporate multi-omics, AI, personalized spaceflight analogues and biomarkers, and organoid models. Understanding these changes is crucial to designing strategies to keep regulated immune function during future deep space and Martian and lunar missions.

Keywords: *Spaceflight; immune system; microgravity; astronauts; space radiation; immunosuppression; inflammation; space medicine; long-duration missions*

1. INTRODUCTION

The human immune system is a complex and highly integrated system of cells, tissues, molecules, and signalling mechanisms that defend against infectious microorganisms and abnormal cells and preserve tissue homeostasis. It is composed of adaptive and innate components in general. Innate immunity provides immediate (relatively non-specific) protection by cells like neutrophils, monocytes, macrophages, dendritic cells, and natural killer (NK) cells. Adaptive immunity has antigen-specific responses (B and T lymphocytes) and has immunological memory. The regulation of these responses is crucial for normal health, as their overactivity or inability to be appropriately controlled can result in damage to host tissues.

The spaceflight environment is a unique one in which multiple stressors are present. The microgravity environment, radiation, launch and landing acceleration, alteration in the distribution of fluids, confinement, psychological stress, alteration in sleep and circadian rhythm, and limited access to normal terrestrial environments are all experienced by astronauts. These can affect the homing of cells, cell signalling, endocrine control, metabolism, and the microbial ecosystem. For some immune parameters, changes have been reported to persist throughout the mission and, in some cases, after return to Earth (Winer et al. 2025; Akiyama et al. 2020), suggesting that this might happen on a mission.

The significance of microgravity lies in the important roles played by the immune system in migration, receptor signalling, cell-cell interaction, and activation, processes that are all affected by mechanical forces and cytoskeletal organization. Experimental studies in spaceflight have demonstrated changes in immune-cell activation, changes in inflammatory responses and changes in expression of multiple genes under simulated and actual spaceflight conditions (Wu et al. 2024; Spatz et al. 2021). Another important stress factor is space radiation: high-energy cosmic rays consist of high-energy protons and heavier ions, which can cause damage to DNA, oxidative stress, mitochondrial damage, and cellular senescence. Under the influence of the Earth's magnetic field, radiation is not a major concern, but it is more of a concern for lunar and Martian exploration (Winer et al. 2025; Dobney et al. 2023).

These can be enhanced by other factors. Stress and reduced sleep can shift neuroendocrine pathways, which can impact immunity. Limited nutrients and dietary modifications may affect antioxidant defence, metabolism of immune cells, and inflammatory signalling. This could include nutritional limitations affecting antioxidant functions, immune cell metabolism, as well as altered immune cell metabolism and function with changes in the microbiome. Astronauts' immune systems are altered, which has led to viral reactivation, including that of the Epstein–Barr virus (EBV), cytomegalovirus (CMV), and varicella-zoster virus (VZV) (Rooney et al. 2019).

With the advent of long-duration space missions, space immunology has become more and more relevant. The 6-month International Space Station (ISS) missions are informative; however, the radiation environment in the Moon and Mars missions will be different, the durations will be longer, and there will be partial gravity. Recent research has started to identify conserved molecular signatures of the immune changes induced by spaceflight via single-cell and multi-omic methods (Kim et al. 2024; Tierney et al. 2024). It is therefore important to know the interactions of the various space stressors to understand the interactions that can be used to create effective countermeasures.

This overview outlines existing understanding of the human immune system in space, which includes a discussion on the effects of microgravity, radiation, stressors associated with spaceflight, findings from astronaut studies, effects of immune dysfunction, protective measures, and future research needs.

2. REVIEW METHODOLOGY

The present study was a narrative review that explored the impact of spaceflight stressors on the human immune system with a focus on immune-cell function, inflammatory signalling, viral reactivation, and

measures that could be used to counter these effects. Literature published from January 2016 to September 2026 was included as key foundational evidence.

The literature search was done in PubMed, Scopus, Web of Science, and Google Scholar. The keywords also encompassed the topics of spaceflight, microgravity, simulated microgravity, astronaut immunity, immune dysregulation, T cell function, natural killer cells, cytokines, space radiation, herpesvirus reactivation, sleep disruption, psychological stress, microbiome, and immune countermeasures. Boolean terms (AND/OR) were used to merge these terms.

Any study investigating any of the following aspects was deemed relevant: (i) immune-cell composition or function during or after human spaceflight; (ii) astronaut analogue environments (e.g., head down bed rest, isolation and confinement studies); (iii) animal models exposed to stressors associated with spaceflight or simulated spaceflight stressors; and (iv) in vitro studies examining the effects of microgravity, radiation or combined stressors on immune cells. Studies from the literature (i.e., review articles and original research studies) that directly supported the goals of the review were included.

Studies were excluded if they did not address immune-related outcomes or had limited relevance to human spaceflight. The evidence was sorted by the experimental model (direct human spaceflight studies versus astronaut analogue, animal, and in vitro studies). Special emphasis was placed on study design, sample size, length of mission, experimental conditions, measures of immunity studied, and limitations reported.

This was a narrative review and therefore statistical pooling was not used. Evidence from laboratory and analogue models was used to give mechanistic context, with more focus on evidence gathered firsthand by astronauts. Restrictions of using analogue, animal and in vitro studies to extrapolate to long-duration lunar and Martian missions were also evaluated.

3. THE HUMAN IMMUNE SYSTEM

3.1 Innate Immunity

Immediate defence of the body is innate immunity. It involves cellular and molecular mechanisms which recognize common features of pathogens or tissue damage, in addition to physical barriers. Neutrophils and monocytes quickly migrate to areas of inflammation, and macrophages are involved in phagocytosis, repair, and production of cytokines. Dendritic cells are involved in both innate and adaptive immunity, and they have the ability to capture antigens. But NK cells kill infected or transformed cells without prior antigen-specific sensitisation. These responses are further orchestrated by proteins of the complement system, interferons, chemokines and inflammatory cytokines (Winer et al. 2025; Jacob et al. 2023).

3.2 Adaptive Immunity

B and T lymphocytes play a major role in adaptive immunity. B cells are the cells that mature into plasma cells that secrete antibodies, and T cells are the cells that have a cellular immune function. The CD4+ T

cells regulate immune responses by producing cytokines and differentiation to functional subsets, and CD8+ T cells kill infected or malignant cells. In subsequent exposures to the same antigen, memory B/T cells will respond more quickly. It is speculated that this adaptive arm is especially vulnerable to the effects of changed gravity, stress hormones, and radiation (Jacob et al. 2023; Akiyama et al. 2020).

3.3 Immune Cells and Their Functions

Most immune cells are derived from the bone marrow, from hematopoietic stem cells. They grow and spread in special types of tissues: bone marrow and thymus. These environments might change in space, which could influence the development of lymphocytes and immune-cell homeostasis. Changes have been reported in a variety of immune-cell subsets, including lymphocytes, monocytes, and NK cells, in astronauts. The direction and size of these differences are different among people and missions (Kim et al. 2024).

3.4 Cytokines, Inflammation, and Immune Regulation

The cytokines and chemokines facilitate information exchange between immune and non-immune cells. Interleukins, tumour necrosis factor, interferons, and chemokines are responsible for inflammation, antiviral response, recruitment of cells, and repair of tissue. Spaceflight may create an imbalance between the inflammatory and regulatory pathways. A series of astronaut multi-omics studies have recently revealed changes in various cytokines and chemokines related to inflammation, ageing, and tissue homeostasis (Kim et al. 2024). So, spaceflight should be thought of as a condition of immune remodelling, a decrease in protective immune function and an inappropriate increase in inflammatory activity.

Immune suppression is a decrease in one or more of the immune protection functions, including the activation of lymphocytes, proliferation of immune cells, antibody production or cytotoxicity. Immune dysregulation, on the other hand, occurs when there is a failure in immune regulation, such that some immune protection is lost but other immune mechanisms, such as inflammatory signalling, are inappropriately activated or poorly regulated. These conditions co-exist and can co-occur (Goldmann et al. 2024). The decrease in T cell activation, the decrease in the activity of natural killer cells, and the disruption of antiviral surveillance are some of the immune suppression effects that are observed in spaceflight; whereas the changes in cytokine production, inflammatory signalling, and immune-cell regulation are some of the immune dysregulation effects observed in spaceflight (Marchal et al. 2024). Thus, spaceflight-associated immune alterations should be viewed as a state of immune dysregulation rather than as a complete immunosuppression.

4. EFFECTS OF MICROGRAVITY ON IMMUNE SYSTEM

4.1 Microgravity and Immune Cell Function

Cells are placed in a different mechanical environment in space. The mechanical environment of cells changes in space. Immune cells usually receive gravitational and mechanical signals which regulate

cytoskeletal dynamics, adhesion, distribution of receptors on the cell surface and intracellular signalling pathways. In microgravity, these cues are changed, which may have an impact on cell shape and signal transduction. Changes in immune-cell gene expression, cytoskeletal pathways, metabolism, and inflammatory signalling have been demonstrated during the simulated microgravity experiment and spaceflight investigations that were performed on the ground (Spatz et al. 2021).

The effects are not consistent between cell types. Some of the innate pathways can be made more inflammatory, and specific defensive functions may be lessened. A single-cell study in 2024 identified changes in the following pathways: interferon signalling, pyroptosis, IL-6-associated inflammation, cytoskeletal regulation, and sirtuin pathways. This same study reported decreased function of T cells and NK cells, reinforcing the concept that there is a more complex immune phenotype in microgravity depending on the type of cell (Wu et al. 2024).

4.2 Changes in T Cells and B Cells

One of the most commonly studied immune cell populations during spaceflight studies is T lymphocytes. Antigenic stimulation can decrease the activation of T cells, and changes in transcription factors and signalling pathways necessary for proliferation. Hypoactivation can be detrimental for cell-mediated responses and can play a role in suboptimal responses to new pathogens.

There may also be some effects on B cells, but there is less evidence than for T cells. The changes in lymphopoiesis, antibody production, and distribution of immune cells have been observed in spaceflight and simulated-microgravity experiments. These changes in the bone marrow and thymic microenvironment may be involved in these effects (Akiyama et al. 2020).

4.3 Altered Cytokine Production

The inflammatory and immune-cell communication balance can be disrupted by spaceflight. Changes in interleukins and chemokines, including those consistent with altered inflammatory activity, have been reported. These changes can be affected in astronauts by factors such as exercise, stress, radiation, sleep, diet, and individual biologic factors. Thus, the use of a single cytokine cannot be regarded as a marker of immune status.

4.4 Effects on Innate Immune Responses

There is the possibility of activation of innate immunity and impairment of innate immunity during spaceflight. Certain parts of the inflammatory response that involve monocytes become more active, and other functions like antigen presentation or phagocytosis can be decreased. The early line of defence against virus-infected and transformed cells is facilitated by highly important NK cells. Experimental studies have indicated that the human cytotoxicity of natural killer cells (NK cells) has been found to decrease in simulated microgravity (Kuhlman et al. 2024). This could impact viral control and tumour immune surveillance.

4.5 Microgravity-Induced Immune Dysregulation

The immune system can be dysregulated in microgravity by changes in the cytoskeleton, oxidative stress, mitochondrial function, and epigenetic regulation. Activated adaptive immunity may be decreased, while other inflammatory pathways may be activated or dysregulated. Conserved molecular changes are seen across simulated and actual spaceflight conditions at the single-cell level (Kim et al. 2024).

5. SPACE RADIATION AND HUMAN HEALTH

5.1 Types of Space Radiation

Spaceflight radiation exposure consists of trapped radiation, which occurs in certain orbits, solar particle events (SPEs), and galactic cosmic radiation (GCR). GCR consists of high-energy protons, alpha particles, and heavier, high-charge, high-energy ions. Particularly important in deep space missions are these particles, which are protected by the Earth's atmosphere and magnetic field and are not present or are reduced beyond LEO (Dobney et al. 2023).

5.2 Radiation-Induced Cellular Damage

Ionising radiation may damage the DNA directly or indirectly as a result of the production of ROS. Cellular stress responses are triggered by DNA strand breaks, oxidative damage, mitochondrial dysfunction, and/or changes in gene regulation. Some types of lymphocytes may be especially susceptible, as they can only be more tolerant to DNA damage. There may be a difference between biological effects of chronic exposure at low dose and the biological effects of an acute exposure at high dose.

5.3 Effects on Immune Cells

Radiation has the potential to affect the survival, proliferation, differentiation and signalling of immune cells. Three experimental models have demonstrated the occurrence of lymphocyte depletion, failure of immune-cell function, oxidative stress and changes in inflammatory pathways. The damage inflicted on DNA by heavy ions can be complex and difficult for cells to repair. Radiation can, therefore, affect the dysfunction caused by microgravity, instead of being a stress factor by itself (Winer et al. 2025).

5.4 Radiation, Inflammation, and Long-Term Health Risks

Cell damage due to radiation may cause inflammation in the cells and may lead to cancer, heart disease, brain degeneration, or premature ageing. Chronic radiation exposure can cause a decline in immune surveillance, as well as elevate inflammatory stress from an immune point of view. Radiation protection is therefore a key element of mission planning for long-duration missions. To date, spacecraft shielding and the study of new materials (such as water, poly material, regolith, and advanced composites) have been used (Spatz et al. 2021).

6. OTHER FACTORS AFFECTING

6.1 Psychological Stress and Isolation

Space missions demand that astronauts live in enclosed spaces where they have to share space with other astronauts, have limited privacy, face operational requirements, and have to perform continuously for the duration of the mission. The neuroendocrine pathways are not only activated by psychological stress, but may also affect the trafficking and inflammatory responses of the immune cells. The effects of microgravity and sleep disruption can thus be exacerbated by stress (Mane 2025).

6.2 Sleep and Circadian Rhythm Disruption

The astronauts have to adjust to a different light-dark cycle, irregular work hours, and noise and confinement. Short or interrupted sleep may affect the production of cytokines, the activities of immune cells, metabolism, and response to vaccines. It is possible that circadian disruption will be indirectly involved in immune dysregulation. One of the non-pharmacological countermeasures is to keep a regular sleep schedule and proper light exposure (Zong et al. 2025).

6.3 Nutrition and Metabolic Changes

Spaceflight diets may differ from normal diets regarding energy density, how food is processed, nutrient availability, and freshness of the foods. Protein, micronutrients, essential fatty acids, and antioxidant activity have been shown to play an important role in maintaining the metabolic functions of immune cells and tissue repair. Spaceflight is also found to cause metabolic changes, which can modulate immune function (Tang et al. 2021). Thus, nutritional strategies need to be tailored to individuals instead of relying on a common nutritional supplement.

6.4 Altered Microbiome

The human microbiome is constantly in touch with the immune system. Spaceflight may alter the abundance, community structure, gene expression, and host–microbe interactions of microbes. A longitudinal study of the Inspiration4 crew in 2024 revealed transient variations in multiple body locations and more persistent variations in the oral microbiome, which aligned with gene expression of immune cells (Tierney et al. 2024). The findings indicate that the management of the microbiomes may be a part of the future health program for astronauts.

6.5 Confinement and Environmental Conditions

There are several differences between closed spacecraft and terrestrial environments in the areas of ventilation, humidity, microbial exposure, and storage of foods and surface ecology. Confinement can not only change the exposure to microorganisms, but can also limit the opportunities for environmental variation. Environmental microbiology and infection control strategies will be necessary for future spacecraft and habitats, especially if they will not be able to be evacuated.

6.6 Combined Effects And Interactions Of Spaceflight Stressors

Spaceflight can only be understood as a whole when the immune effects of each of the environmental stressors are considered. Immune response may be a complex response due to interactions of all these factors through overlapping cellular and physiological mechanisms in microgravity, radiation, psychological stress, sleep disruption, nutritional changes, and confinement. The role of these interactions in humans, however, is not fully understood.

In microgravity, the cytoskeleton can change, as well as the adhesion of cells, internal signaling in cells, and the metabolism of immune cells. Meanwhile, exposure to ionizing radiation can also result in increased oxidative stress, DNA damage, and impairment of mitochondrial function. Such processes could intersect with inflammatory pathways and cell stress-response mechanisms, and impact lymphocyte activation, innate immune mechanisms, and immune-cell survival.

These responses can be further modified by the effects of psychological stress and circadian disruption via neuroendocrine pathways. Changes in both the glucocorticoid and catecholamine signaling might regulate immune-cell trafficking, cytokine production, and inflammatory control. Immune-cell activity and metabolic homeostasis could also be disrupted during sleep, which may make it more difficult to manage immune changes arising from microgravity and radiation.

Nutritional restrictions and metabolic changes can affect the availability of the substrates needed for immune-cell growth, antioxidant defense and repair of damaged tissues. Meanwhile, shifts in the microbiome of the gut and other body sites can impact host-microbe interactions and immune signalling. These could all be some of the reasons for the differences in reacting to spaceflight.

Overall, these mechanisms imply that spaceflight-associated immune dysfunction could be the result of multiple interacting stressors collectively, and not any one of them alone (Winer et al. 2025). For instance, oxidative stress, dysregulated metabolic regulation, and neuroendocrine signalling may interact to regulate immune-cell function and inflammatory balance. Such interactions may lead to impaired antiviral surveillance and/or elevated or dysregulated inflammatory responses.

However, there is little direct evidence for synergistic interactions between the different stressors in spaceflight in humans. Numerous studies are available that investigate a single stressor in conditions of simulated microgravity, cell culture, and/or animal models. The interactions proposed should thus be regarded as mechanistic hypotheses supported, to a greater or less extent, by experimental evidence. Combined-stressor experiments, longitudinal astronaut monitoring, and integrated multi-omics experiments are necessary to quantify and understand the magnitude and clinical relevance of these interactions in future research.

Overall, the available data indicate that the spaceflight-associated immune alterations are not to be viewed as the result of a single exposure to spaceflight. Poor sleep, psychological stress, microbiome shifts, oxidative stress, and changes in mitochondrial function may affect related pathways, including nutrition, neuroendocrine signalling, inflammatory regulation, and cellular metabolism, which may be affected by

microgravity and radiation. But evidence varies in the strength of each of these interactions. Changes in astronaut immunity observed during spaceflight are most commonly derived from direct studies in astronauts, while evidence for specific synergistic mechanisms comes more often from analogue, animal, and in vitro studies more often. It should be noted that interactions between stressors can be biologically plausible mechanisms and need to be validated, but may not be consistently observed as clinical effects.

7. EVIDENCE FROM SPACE MISSIONS AND ASTRONAUT STUDIES

7.1 Findings from Short-Duration Space Missions

Evidence for changes in the immune system in short-duration missions has been provided. Within days of going into space, astronauts can exhibit changes in their immune-cell distribution, cytokine profiles, and shedding of viruses. Short missions show that immune responses do not necessarily develop over months of exposure, but can change rapidly as well (Rooney et al. 2019).

7.2 Immune Changes During Long-Duration Missions

Immune changes are more likely to be long-lasting during long-duration ISS missions. Multiple months-long missions have been shown to be associated with alterations in T cell function, inflammatory signalling, and herpesvirus reactivation. Importantly, there is considerable individual variability; not all astronauts exhibit the same magnitude or pattern of immune response during spaceflight (Rooney et al. 2019).

7.3 Evidence from International Space Station Studies

ISS research has yielded the widest human evidence available, as astronauts are subject to repeated monitoring before, during, and after flight. Results show changes in the number and function of immune cells, regulation of cytokines, and viral control. There are also biological experiments that can be conducted under certain conditions on the ISS to complement the astronauts' observations.

Table 1. Overview of major human spaceflight studies investigating immune-related changes

Study	Population and sample size	Mission duration	Main parameters	Major findings
NASA Twins Study, Garrett-Bakelman et al. (2019)	One astronaut in space and one Earth-based twin	Approximately 340 days	Multi-omics, gene expression, immune-related markers, physiological changes	Identified extensive molecular and physiological changes during and after long-duration spaceflight
Inspiration4, Kim et al. (2024)	Four civilian crew members	Approximately 3 days	Single-cell multi-omics, immune-cell profiles, gene expression and chromatin	Identified cell-type-specific and sex-associated molecular responses to short-duration spaceflight
Inspiration4, Tierney et al. (2024)	Four civilian crew members	Approximately 3 days	Host–microbiome interactions, multi-omics and immune responses	Identified longitudinal changes in microbiome composition and host–microbiome interactions
Astronaut herpesvirus studies, Rooney et al. (2019)	Multiple astronaut cohorts across included studies	Short- and long-duration missions	Herpesvirus shedding, viral reactivation and immune-related parameters	Reported spaceflight-associated herpesvirus reactivation and shedding

ISS immune studies discussed by Crucian et al. (2018)	Astronaut cohorts from multiple studies	Varying mission durations	T cell function, cytokines, immune-cell distribution and antiviral responses	Reported alterations in several immune functions and potential countermeasures

Major human spaceflight research studies offer complementary evidence on immune-cell function, molecular response, viral surveillance and host–microbiome interactions. Table 1 summarizes representative astronaut studies and points to the differences in mission duration, population studied, outcomes, and limitations.

7.4 Changes in Immune Cells and Cytokines

Immune responses have become more easily studied in recent years, due to the ability to perform single-cell profiling. A spaceflight-associated molecular signature and cytokine and chemokine changes were identified in the Inspiration4 study. It has also been reported to cause gene-related repression of MHC class I gene-related molecules and T cell regulatory characteristics (Kim et al. 2024). These investigations reveal that there is a multi-level change in immune system cells, at the transcriptional and chromatin level.

7.5 Evidence from Astronaut Analogue Studies

Astronaut analogue studies are complementary since there are limitations with direct human spaceflight studies due to the small number of studies and/or mission-specific conditions. Selected physiological effects of reduced mechanical loading can be achieved by performing a head-down bed-rest study, while psychological stress, sleep disruption, altered circadian rhythms, and changes in environmental exposures can be achieved by performing a study of isolation and confinement (Ong et al. 2021). There are also additional mechanistic data at the cellular level, gained from experiments under the simulated condition of microgravity. These models do not simulate the entire spaceflight environment, though. In particular, bed rest does not provide microgravity, isolation studies do not provide orbital radiation exposure, and simulated microgravity studies do not necessarily provide combined physiological and operational conditions that are experienced during the flight of astronauts (Bajaj et al. 2026). Thus, data obtained from analogue research must be taken as supplementary, not as alternative, to astronaut data.

7.6 Viral Reactivation and Infection Risk in Astronauts

Latent herpesviruses can be used as an indicator of decreased immune surveillance. Studies have been conducted in astronauts showing that astronauts shed more EBV, CMV, VZV, and Herpes Simplex Virus-1 (HSV-1) in or following spaceflight. Viral shedding has been correlated with immune changes and could be a clinically relevant consequence of the immune alterations observed in T cells and NK cells (Rooney

et al. 2019). Viral reactivation is more of a concern in missions with limited treatment options, although not always resulting in clinical disease.

7.7 Post-Flight Recovery of Immune Function

There are several immune and molecular alterations that seem to return to their normal state following re-entry to Earth. The NASA Twins Study showed that there were significant physiological differences, but a majority of them recovered following the one-year mission (Garrett-Bakelman et al. 2019). Some biological indicators that registered inflammation, immune system activity, gene expression, etc., however, continued to be different over a longer time. It is, therefore, not always a straightforward or full recovery.

7.8 Limitations of Current Astronaut Studies

The major restrictions are the small number of samples, variations in the duration of the mission, differences in age and sex, various spacecraft environments, and the difficulty in distinguishing microgravity effects from the effects of radiation, stress, sleep, diet, etc. Also, the astronauts are very healthy and thoroughly screened, reducing the generalizability. Standardised sampling, more subjects, longer follow-up, and combining human, animal, cellular, and computational data would be useful in future studies.

8. CONSEQUENCES OF IMMUNE DYSFUNCTION IN SPACE

8.1 Increased Susceptibility to Infections

Impaired activation of T cells, impaired function of NK cells, and impaired innate responses may lead to a decreased ability of the host to resist infectious microorganisms. This is especially worrisome in closed areas where members of the crew might be able to transmit it very quickly. Several crew members infected at the same time could result in an operationally important infection even from a normal infection.

8.2 Reactivation of Latent Viruses

The reactivation or enhanced shedding of latent herpesviruses could be related to changes in antiviral immune surveillance in spaceflight. Monitoring viral biomarkers may give a good indication of changes in immune status (Rooney et al. 2019), although shedding of the virus does not mean the animal is necessarily clinically affected.

8.3 Chronic Inflammation and Immune Dysregulation

Spaceflight can cause a decrease in protective immunity and an increase in inflammatory signalling. Low-grade inflammation can be a contributing factor to tissue injury and could play a role in cardiovascular, metabolic, neurological, and musculoskeletal changes. This double exposure renders the immune dysfunction even more complicated than simply suppressing immune function (Kim et al. 2024).

8.4 Delayed Wound Healing and Recovery

Wound healing takes place through a well-coordinated inflammatory, proliferative, and remodelling phase. If injuries are sustained and the immune cells do not get recruited or the inflammatory process is not regulated, then healing may take longer. This is of critical importance from an operational point of view because there will be fewer medical facilities during deep space missions (Babocs et al. 2025).

8.5 Effects on Overall Astronaut Health and Performance

Immune dysfunction can have an indirect effect on performance, via infection, inflammation, fatigue, delayed recovery, and interactions with other physiological systems. The overall health of astronauts is an important aspect of mission safety; this is because they have to make complex decisions and undertake demanding tasks (Crucian et al. 2018).

8.6 Implications for Long-Duration Missions to the Moon and Mars

More extended missions will result in greater total exposure to microgravity, radiation, confinement and stress. Limited emergency support and communication delays will be a part of a mission to Mars. Thus, even mild immune impairment may prove to be clinically significant. The combination of these factors could add to the complexity of medical risk for long duration missions, especially if emergency treatment and evacuation are limited. (Winer et al. 2025; Akiyama et al. 2020).

9. STRATEGIES TO PROTECT ASTRONAUT IMMUNE FUNCTION

The countermeasures that are described in this section can vary in terms of evidence and maturity. Some measures such as exercise, nutrition management, sleep/circadian management and radiation protection are already being used in astronaut health and mission planning. Other methods such as individualized immune biomarker monitoring and pharmacological immune modulation need further testing for spaceflight applications. New technologies, like the AI-supported multi-omics monitoring and individual immune-risk modelling, are still being studied.

9.1 Exercise and Physical Activity

Physical activity is already a primary preventive measure against bone and muscle loss, and may offer indirect immune protection via effects on metabolic health, inflammatory regulation, sleep and psychological wellbeing, but has not been fully investigated for its role in the prevention of spaceflight-associated immune dysfunction. Regular physical activity (exercise) has a potential effect on metabolism, inflammatory signalling, sleep and psychological wellbeing. Exercise prescriptions shall be customised for specific missions and individual astronauts' condition (Amirhossein Ahmadi Hekmatikar and Suzuki 2025).

9.2 Nutritional and Dietary Strategies

The nutritional strategies should ensure sufficient energy, protein, vitamins, minerals and essential fatty acids, as well as account for antioxidant activity, food stability, health of the microbial community, and individual metabolic needs. Unless there is evidence to suggest otherwise, high doses of supplements are unnecessary, as they can also be involved in normal cellular signalling (Tang et al. 2021).

9.3 Sleep and Stress Management

Sleep and circadian stability may help to decrease neuroendocrine stress and help regulate immune function. Mission-related stress can be mitigated through scheduled sleep periods, appropriate lighting, workload management, psychological support, communication with family, and behavioral interventions (Zong et al. 2025).

9.4 Radiation Protection

Protection continues to be a key radiation-mitigating measure. Basic materials like water, polyethene, and locally available materials like lunar regolith are being considered in advanced composites. Passive shielding, mission design, radiation monitoring, and shelter strategies for solar particle events should be incorporated into spacecraft design (Dobney et al. 2023).

9.5 Pharmacological and Medical Interventions

Immune modulation in spaceflight is not recommended routinely; however, pharmacological modulation is recommended in certain clinical situations such as the treatment of infection or specific inflammatory disorders. Pharmacokinetics, adverse effects, storage requirements, drug stability, and altered physiology during spaceflight (Crucian et al. 2018) should all be taken into account when considering potential interventions. Additional mission-specific research is thus needed before general recommendation for immune-modulatory medications is made for their use as prophylaxes.

9.6 Monitoring Immune Biomarkers

The use of serial immune monitoring for early detection of change before clinical disease occurs is a new approach. Immune-cell subsets, cytokine profiles, antibody responses, viral shedding, gene-expression signatures and microbiome characteristics are candidate measures. Multi-omics and artificial intelligence (AI) integration of these data is on the horizon and still investigational, and needs to be validated in larger longitudinal astronaut cohorts (Winer et al. 2025; Kim et al. 2024).

10. FUTURE PERSPECTIVES AND RESEARCH GAPS

10.1 Need for Long-Term Human Studies

Little is known, because there are only a few astronauts and, for a relatively short time period, most astronaut studies have been of short duration. Systematic immune sampling prior to, during, and after flight should be planned for future missions to the Moon and Mars. To separate the effects of "transient adaptation" from "clinically significant persistent dysfunction," longitudinal studies will be needed.

10.2 Personalised Monitoring of Astronaut Immune Function

Astronauts are genetically different, old, female, infected with previous diseases, hand ave varying microbiomes, stress responses, and immune statuses. Immune baselines may be better personalised for the identification of abnormal changes. Instead of having a single threshold for each astronaut, future astronaut systems could use a pre-flight trajectory for each astronaut as a baseline for comparison.

10.3 Development of Advanced Countermeasures

To prevent countermeasures from being ineffective, they should be implemented through multiple avenues. Treatment may require the use of more than one of the above treatment options. It may be different for different missions, depending on the player.

10.4 Role of Artificial Intelligence (AI) and Biomarker Monitoring

Longitudinal astronaut monitoring data involves the collection of high-dimensional immune, molecular, and microbiome data, which may be incorporated with the aid of AI-based strategies. Machine-learning models have been investigated for the identification of immune signatures linked to simulated microgravity (Wu et al. 2024), but the clinical value of such models in predicting immune dysfunction during spaceflight is yet to be determined.

10.5 Advanced Radiation Protection Technologies

GCRs are highly penetrating, and block efficiently is challenging for deep space missions; therefore, improved shielding strategies are needed. Advanced composites, hydrogen-rich materials, and regolith-based shielding and active shielding research will minimise radiation exposure. Materials, however, need to be assessed for their mass, structural characteristics, their ability to produce secondary radiation, and how they can be utilized in spacecraft and habitats (Gohel et al. 2022).

10.6 Use of Organoids and Laboratory-Based Space Models

Complementary studies by human organoids, immune-cell cultures, tissue chips, and sophisticated three-dimensional models can help fill in the gaps in astronaut studies. These models provide scientists with an environment to study one stressor at a time and combinations of microgravity and radiation. But simulated microgravity can't completely mimic actual spaceflight, so the data from astronauts is still needed to validate the experiments (Mozneb et al. 2025).

10.7 Challenges of Immune Health During Mars and Deep-Space Missions

Immune health strategies will be needed in future Mars missions, which will include long exposure, partial gravity, radiation, isolation, communication delay, and limited medical support. The research efforts should thus be directed toward the development of autonomous monitoring, early detection of clinically important immune changes, and countermeasures that can be taken without immediate medical assistance on land.

10.8 Future Directions in Space Immunology

Astroimmunology is a new field that should strive to develop models that integrate immune, metabolic, neurological, endocrine, and microbiome standards. All missions will be standardized and have interoperable datasets for comparison. What is to come in the next generation of high-resolution is the possibility of single-cell resolution multi-omics, single-cell personalised, AI-assisted analysis, personalized medicine, and improved radiation and gravity analogues (Winer et al. 2025). The ultimate aim is not just to avoid immune suppression but to keep the immune system at a level that would be stable and regulated for the entire mission.

11. CONCLUSION

Spaceflight is linked to intricate changes in immune-cell function, inflammatory signalling and antiviral surveillance. So far, the available evidence is consistent with a model of immune dysregulation, where some immune functions may be weakened, but others are modified. The magnitude and duration of these changes are different for different persons, missions and experimental conditions.

Advances in the last few years, especially in the fields of single-cell and multi-omic technologies, have significantly helped to elucidate these changes. NASA Twins Study and Inspiration4 crew studies reveal that there are many molecular responses that are reversible, while others may remain following flight. The challenge is then to identify normal adaptation from changes that may pose a risk to the health of astronauts.

More effective and individual strategies will be needed for future lunar and Martian exploration missions. Incorporate aspects of exercise, nutrition, sleep management, radiation shielding, vaccination, monitoring of infection, pharmacological interventions, and the use of biomarkers into mission planning. Targeting intervention through the use of personalized multi-omics analysis and personalized medicine may enable the early detection of immune dysfunction and targeted intervention. Research on an ongoing basis and the use of state-of-the-art laboratory models will be necessary. A cornerstone of safe and sustainable human space exploration is the protection of immune function.

Acknowledgements: I would like to thank my parents and school teachers for their constant support and motivation.

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