HUMAN IMMUNE SYSTEM AND AEROSPACE ENVIRONMENT

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Human immune system and aerospace environment

O sistema imune humano e o ambiente aeroespacial

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Abstract

Introduction: The exposure to the extraterrestrial environment induces complex physiological changes in the human body, with the immune system (IS) being particularly affected. **Objective**: Describe changes in human immunity related to space missions. **Methods**: An integrative review of the literature was conducted using keywords selected in DeCS (https://decs.bvsalud.org/) and MeSH (http://www.ncbi.nlm.nih.gov/mesh), which were combined into search strategies used for bibliographic research in PubMed/MEDLINE (https://pubmed.ncbi.nlm.nih.gov/). **Results and Discussion**: Twenty-six articles were selected, whose information was organized in terms of changes in innate and adaptive immunity. The effects of microgravity and cosmic radiation were highlighted, with emphasis on the reduction in the activity of certain sectors of immunity and the possibility of infection by genetically modified and alien pathogens. **Conclusion**: Understanding the immunological impacts of staying in the extraterrestrial environment is critical for the continuity – of a safe – human activity in space. New studies are needed to address gaps in knowledge on the subject.

Key words*: Adaptive Immunity; Innate Immunity; Extraterrestrial Environment; Space Flight.*

Resumo

Introdução: A exposição ao ambiente extraterrestre produz alterações fisiológicas complexas no organismo humano, dentre as quais se destacam as modificações do sistema imune (SI). **Objetivo:** Descrever as alterações da imunidade humana relacionadas às missões espaciais. **Método:** Procedeu-se revisão integrativa da literatura a partir de unitermos selecionados no DeCS (https://decs.bvsalud.org/) e no MeSH (http://www.ncbi.nlm.nih.gov/mesh), os quais foram combinados em estratégias de busca utilizadas para a pesquisa bibliográfica no PubMed/MEDLINE (https://pubmed.ncbi.nlm.nih.gov/). **Resultados e Discussão:** Selecionaram-se 26 artigos, cujas informações foram organizadas em termos das alterações do SI inato e do SI adaptativo. Os efeitos da microgavidade e da radiação cósmica foram destacados, com destaque para redução da atividade de determinados setores da imunidade e a possibilidade de infecção por patógenos geneticamente modificados e alienígenas. **Conclusão**: A compreensão dos impactos imunológicos da permanência no ambiente extraterrestre é crítico para a continuidade – em segurança – da atividade humana no espaço. Novos estudos são necessários para a abordagem das lacunas científicas sobre o assunto.

Palavras-chave: *Ambiente Extraterrestre; Imunidade Adaptativa; Imunidade Inata; Voo Espacial*.

INTRODUCTION

The launch of Sputnik 1, the first artificial satellite in history, in 1957, Yuri Alekseyevich Gagarin's groundbreaking space flight in 1961, and the salutary Apollo 11 mission in 1969, which took *Homo sapiens* to the Moon – also an unprecedented feat – represented significant milestones in human activity in the extraterrestrial environment (Russomano, 2013; Pessoa Filho, 2021; Carvalho-e-Silva et al., 2023). These events paved the way for advances in aerospace, with particular emphasis on collaboration between different nations, the crowning achievement of which was the creation of the *International Space Station* (ISS) (Figure 1) by space agencies such as the *National Aeronautics and Space Administration* (NASA), the *European Space Agency* (ESA) and the *State Space Corporation ROSCOSMOS* (NASA, 2020; ESA, 2024; ROSCOSMOS, 2024).

The continued presence of astronauts on the ISS offers important opportunities to conduct multidisciplinary research and test technologies that may be critical for future interplanetary missions, such as the journey to Mars (NASA, 2023). Such endeavors are not without risks, among which are the impacts of the extraterrestrial environment on the human body, including the effects of isolation, exposure to cosmic radiation and microgravity (Castro-Costa et al., 2024; Strigari et al., 2021). Therefore, continuous research and innovation are needed to ensure the safety and success of space missions (Pessoa Filho, 2021).

Figure 1. The International Space Station photographed by Expedition 56 crew members from a Soyuz spacecraft after undocking. NASA astronauts Andrew Feustel and Ricky Arnold and Roscosmos cosmonaut Oleg Artemyev flew around the orbiting laboratory to take pictures of the station before returning home after spending 197 days in space. The station celebrated the 20th anniversary of the launch of the first Zarya element in November 2018. Credit: NASA/Roscosmos (October 4, 2018). Creative Commons license. Available at: https://www.flickr.com/photos/nasa2explore/44911446704/in/photostream/).

The exposure an alien environment triggers complex physiological changes in the human body (Carvalho-e-Silva et al., 2023). Microgravity contributes to a rapid loss of muscle mass and a reduction in bone density, increasing the risk of sarcopenia and osteoporosis (Russomano et al., 2022). Changes in cardiovascular function can lead to orthostatic hypotension and circulatory disorders, such as increased arterial stiffness and a change in the somatic distribution of blood flow (Krittanawong et al., 2023; Shibata et al., 2023). Air pressure and quality on the space station affect respiratory function, while sensory deprivation disrupts circadian rhythm and causes sleep dysfunction (Serrão; Rocha, 2018). Isolation and psychological stress can affect astronauts' mental health, resulting in anxiety and depression. Changes in eating habits and gastrointestinal function promote abdominal discomfort. In addition, exposure to cosmic radiation is associated with an increased risk of cancer (Serrão; Rocha, 2018; Carvalho-e-Silva et al., 2023).

In particular, the astronaut's immune system (IS) is usually affected by the aforementioned challenging conditions of the aerospace environment (NASA, 2020). In fact, the suppression of the immune response (IR) by extraterrestrial radiation and the effects of reduced gravity make astronauts more susceptible to infectious conditions (Castro-Costa et al., 2024), in the context of innate and adaptive immunity (Crucian et al., 2020). In addition, the physical and psychological stress associated with extraterrestrial life further impairs IR (Córdova Martínez; Alvarez-Mon, 1999), due to the actions of catecholamines and cortisol on Th1 cellular immune response pattern (Siqueira-Batista et al., 2024). Staying indoors – such as space stations – is associated with an increased risk of spreading pathogens (Cruvinel et al., 2010). To protect the health of astronauts, space agencies have proposed various measures, including the provision of immunobiologicals – e.g. vaccination against herpes zoster (Crucian et al., 2018), an etiological agent whose infection can be reactivated during extraterrestrial missions – and the application of strict biosafety protocols (NASA, 2020).

Modifications to astronaut' IR are capable of impacting their interactions with infectious agents, since the IS's ability to recognize, control and eliminate pathogens can become compromised, resulting in greater susceptibility to infections (NASA, 2019; Huang; Shao, 2023). Based on these considerations, understanding the changes in astronauts' immunity during space missions – the focus of this article – is extremely important for mitigating disparate health risks, and joint research efforts are needed to clarify the persistent gaps

METHODS

Search strategy

The first step was to select the keywords – on the DeCS (Health Science Descriptors: https://decs.bvsalud.org/) and MeSH (Medical Subject Headings: http://www.ncbi.nlm.nih.gov/mesh) websites – which are listed below: (1) "*Adaptive Immunity*", (2) "*Immune System*"; (3) "*Immune System Diseases*"; (4) "*Immunity*"; (5) "*Immunity, Innate*"; (6) "*Extraterrestrial Environment*"; and (7) "*Space Flight*". The descriptors were combined into ten search strategies, which were used for the bibliographic search in PubMed/MEDLINE (https://pubmed.ncbi.nlm.nih.gov/). The numbers of citations obtained are shown in Table 1

Table 1. Search strategy used in the literature review and respective results.

Search strategy	PubMed/MEDLINE
(*Adaptive Immunity*) AND (*Extraterrestrial Environment*)	02
(*Adaptive Immunity*) AND (*Space Flight*)	149
(*Immune System*) AND (*Extraterrestrial Environment*)	36
(*Immune System*) AND (*Space Flight*)	729
(*Immune System Diseases*) AND (*Extraterrestrial Environment*)	04
(*Immune System Diseases*) AND (*Space Flight*)	137
(*Immunity*) AND (*Extraterrestrial Environment*)	35
(*Immunity*) AND (*Space Flight*)	647
(*Immunity, Innate*) AND (*Extraterrestrial Environment*)	05
(*Immunity, Innate*) AND (*Space Flight*)	52
TOTAL	**1796**

Search end date: 30/06/2024.
Source: prepared by the authors.

Characteristics of the study, selection of articles and criteria

After reading the titles and abstracts, the articles were pre-selected according to the aforementioned objective. Next, the full texts were read in order to select those that contemplated the alterations of the human immune system (IS) to the extraterrestrial environment, with an emphasis on spaceflight; articles published in Spanish, English and Portuguese and published up to June 30, 2024 were selected. This step-by-step process is detailed below.

The flow diagram (Figure 2) illustrates the process followed for collecting and selecting the studies included in the review. Initially, a total of 1,796 citations were identified, of which only 215 were directly related to the research topic (based on a preliminary title analysis).

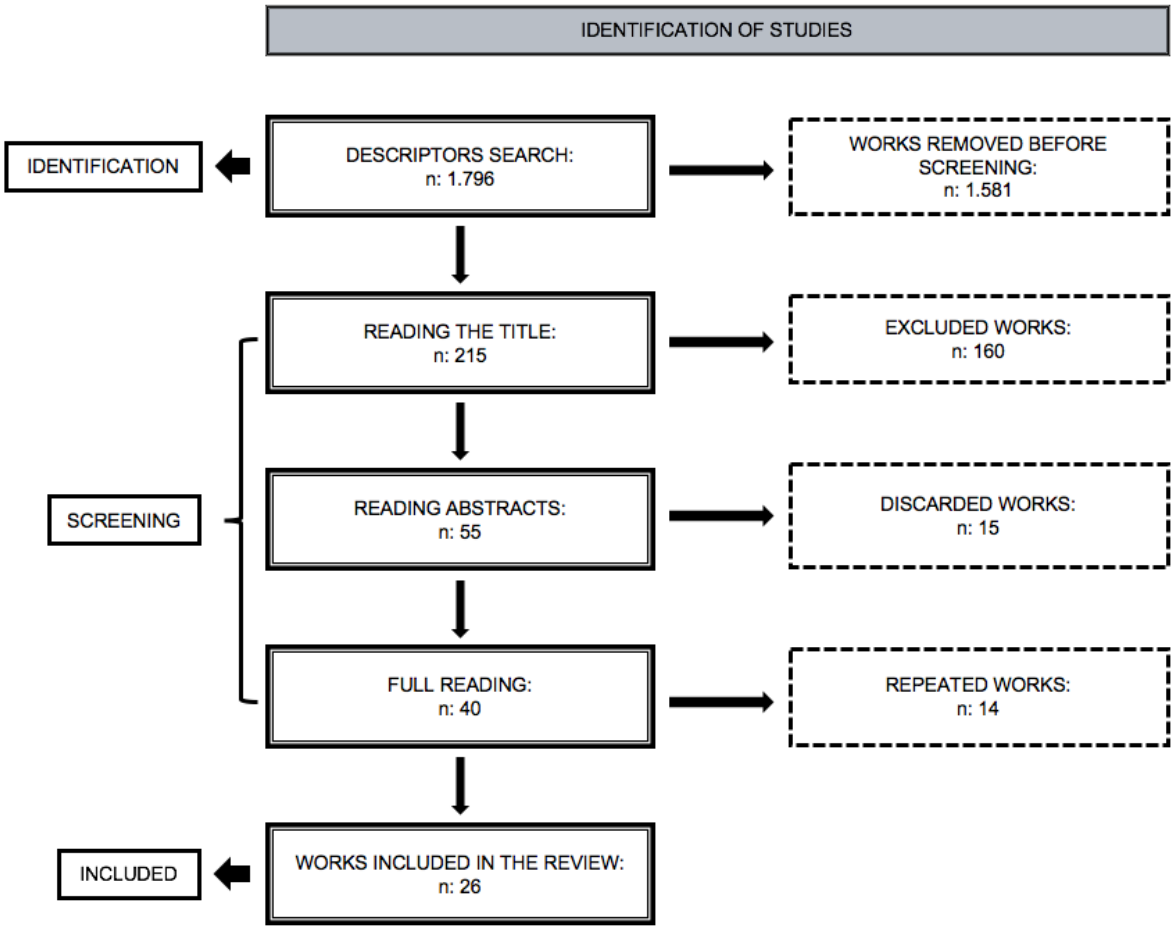

Figure 2. Flow diagram used for the integrative review.

Source: Prepared by the authors.

After a detailed appraisal of the titles, 160 texts were excluded. After reading the abstracts, 15 studies were discarded and 40 were selected for reading in full, as 14 were repeated studies. Finally, after examining the full texts, 26 manuscripts (Table 2) were selected for this study, preferably original research (literature reviews – articles and book chapters – were included when they contained new *insights* into the problem at hand).

RESULTS AND DISCUSSION

Table 2 summarizes the data obtained from the articles chosen from the search and selection strategy.

Table 2. Articles used in the integrative literature review.

AUTHORS	YEAR	OBJECTIVE	CONCLUSIONS
Burke et al.	2024	To evaluate the multisystemic immunological and endocrine responses to simulated cosmic radiation in mice of different sexes.	Females have a faster and more specific immune response and more effective regulation of the inflammatory process up to the 14th day after exposure to simulated radiation, when compared to males. These results suggest an immunological dimorphism between the sexes in cosmic radiation conditions.
Garcia-Medina et al.	2024	Investigate immunological adaptations, telomere length dynamics, cell-free DNA release, genomic stability, single-cell transcriptomic analysis and biochemical adaptations of I4 crew members to determine the effects of short-duration space flight on these parameters.	The telomeres lengthened, but after returning to Earth, they soon shortened. Analysis of free DNA indicated an increase in the immune signatures of the cells after the mission. There was no clonal hematopoiesis with undetermined potential (CHIP) or genome instability. Cellular adaptations remained active for months after the mission.
Kim et al.	2024	To characterize the immune responses induced by space flight in members of the SpaceX Inspiration4 mission.	Eighteen cytokines/chemokines – related to inflammatory processes, ageing and the maintenance of muscle homeostasis – underwent changes after the space flight. A unique genetic signature associated with the mission was obtained, with the development of oxidative phosphorylation, immunity and TCF21. T cells increased their expression of FOXP3, while MHC class I genes were durably inhibited.
Jacob et al.	2023	To review the literature on the current effects of microgravity and radiation on the immune system.	Microgravity, ionizing radiation and psychological stress caused suppression of the immune system, hyperinflammation, allergies (microorganisms promoted biofilms and space dust caused skin and eye irritations), increased propensity to cancer (radiation and immunosuppression are important conditions for the appearance of neoplasms), autoimmune events and reactivation of latent viruses
Moser et al.	2023	To investigate whether hypergravity can neutralize the immunological alterations induced by microgravity.	Hypergravity, when used as preconditioning, minimized the alterations in T cells; however, it was unable to neutralize the high pro-inflammatory potential of monocytes.

Stratis et al.	2023	To examine the molecular response by capturing the leukocyte transcriptomes of astronauts during long-duration space missions.	When the astronaut enters space, there is a transcriptomic reduction related to the immune system and an increase in basic cellular functions, while when the astronaut returns to Earth, the opposite occurs.
Kuzichkin et al.	2022	To study the levels of von Willebrand factor (vWF), thrombomodulin (TM) and highly sensitive C-reactive protein (hs-CRP) in the blood plasma of cosmonauts after long-term orbital expeditions on the ISS, and to compare the results with parameters that characterize the state of the immune system, which may be involved in endothelial dysfunction.	There was an increase in plasma levels of vWF and hs-CRP and a decrease in TM concentration after the space flights. Variations were observed in parameters that show changes in the state of the immune system. These changes can lead to an increase in procoagulant activity in the blood, a reduction in protein C activation, inhibition of thrombin and amplification of the adhesive potential of platelets, especially in changes in blood flow during readaptation to Earth. It is possible that IS plays a role in vascular damage during prolonged space missions.
Ponomarev et al.	2022	To investigate the effects of short-term confinement on human innate immunity.	Short-term confinement can have a negative impact on human innate immunity by altering the levels of immune cells and cytokines. The effects of confinement on the immune system may have implications for individuals exposed to similar conditions, such as astronauts or people in quarantine.
Dhar et al.	2021	To review the changes in human adaptive immunity due to microgravity, with a focus on T cell signaling pathways.	Microgravity causes immune dysfunction in T cells due to impacts on gene expression, oxidative stress, inappropriate activation and/or changes in cell signaling, influencing the adaptive immune response of astronauts in space.
Green et al.	2021	Review how bacteria manage to adapt to microgravity and the behavior of the immune system in response to these microorganisms.	Bacteria proliferate more easily, form biofilms and express virulence genes. The immune system has difficulty recognizing pathogens. In addition, there is a change in the formation and expression of cytokines, which impairs the adaptive immune response.
Spatz et al.	2021	Characterize the effects of simulated microgravity (sμG) on surface activation markers and intracellular signaling responses of immune cells cultured in the Rotating Wall Vessel.	The study indicates that specific parameters such as leukocyte distribution, T-cell function and cytokine production profiles are altered by sμG. These findings distinguish sμG dysregulation from the stress-related changes observed immediately after landing. The study provides a reading, at the cellular level, of the immune dysfunctions induced by sμG.

Buchheim et al.	2020	Explore innate immunity during spaceflight and the effects of the space environment on the immune system.	Maintaining a healthy immune system during space travel is essential, especially in terms of nutrition. Further research is needed to deepen our understanding of this subject.
Crucian et al.	2020	Investigate improvements in immune dysfunction, stress and reactivation of latent herpesviruses in ISS astronauts and identify the possible causes of these improvements.	Immune dysfunction associated with spaceflight was positively influenced by operational improvements and biomedical countermeasures on board the ISS. It is suggested that, although an operational challenge, agencies should incorporate, within vehicle *design* limitations, dietary, operational and stress relief countermeasures into deep space mission planning. In addition, the specific countermeasures that have benefited astronauts could also serve as a therapeutic complement for terrestrial patients with acquired immunodeficiency.
Wang et al.	2020	Analyze how microgravity affects innate immunity.	Microgravity suppresses the production of inflammatory cytokines and innate immune signaling pathways, as well as causing changes in the intestinal microbiota (dysbiosis).
Bigley et al.	2019	To determine whether the function of *natural killer* cells (NK) is affected during a six month mission on the ISS.	The cytotoxic capacity of NK cells is compromised during and after space flight, especially in astronauts who are carrying out their first mission in space.
Garrett-Bakelman et al.	2019	To describe, in an integrated and multidimensional longitudinal way, the effects of a 340-day mission on board the ISS.	During space flight, there were changes in the expression of genes related to the immune system. After returning to Earth, most of these changes reverted to their original state, but approximately 7% of the genes remained modified. Microgravity induced a small inflammatory state and increased immune activity, causing an attempt to adapt to the hostile environment. Also during the mission, telomeres lengthened, but then shortened on their return, reaching levels lower than the initial ones. The intestinal microbiota also underwent changes, but returned to normal after the flight.
Bradley et al.	2017	Investigate whether the simulated microgravity environment can impact the T cell activation process.	Microgravity can compromise T-cell activation by decreasing IL-2 production and leading to cell exhaustion.

Fernandez-Gonzalo et al.	2017	To review the local and systemic immunological changes caused by particle irradiation.	Particle irradiation can increase the effectiveness of the anti-tumor immune response. Cosmic radiation does not act positively on the immune system.
Van Walleghem et al.	2017	To evaluate immunological changes in simulated microgravity through a cytokine release assay *in vitro*.	IL-2 and IFN-y responses were inhibited when stimulated by recall antigens and mitogens. Microgravity had an impact on the levels of all cytokines that were stimulated by recall antigens. There was an increase in the secretion of tumor necrosis factor alpha (TNF-a) when induced by heat-killed *Listeria monocytogenes* (HKLM). There was also a variation in immune responses between individuals.
Benjamin et al.	2016	Measure recent thymic emigrants (RTE) within peripheral blood mononuclear cells (PBMC) of astronauts returning from flights aboard the ISS and evaluate stress-associated glucocorticoids in parallel.	A significant reduction in TEN levels, indicating a drop in the number of T cells. This change lasted for three months after returning to the terrestrial environment, indicating a slow thymic recovery. At the same time, there were significant increases in endogenous glucocorticoids in plasma and urine.
Sanzari et al.	2015	To compare the effects on leukocyte counts after exposure to simulated radiation from solar particles, composed of protons and electrons.	Electron radiation led to a faster restructuring of the leukocyte counts in the animals. Proton radiation was more efficient at reducing peripheral leukocyte counts and caused greater difficulty in restoring neutrophils.
Verhaar et al.	2014	To elucidate the mechanisms by which microgravity interacts with human immunity, which may provide clues for developing rational ways of dealing with exaggerated immune responses, such as in autoimmune diseases.	The results identify the Jun-N-terminal kinase as a relevant target in microgravity immunity and support the use of specific Jun-N-terminal kinase inhibitors for the treatment of autoimmune conditions.
Crucian et al.	2013	Investigating the effects of space flight on adaptive immunity.	Changes in the distribution of leukocytes, T cells and cytokine production persist during long-duration space flight and could have significant implications for the health of astronauts on future long-duration missions in space.

Kinra et al.	2012	To examine immunological parameters in healthy adults before and after exposure to simulated microgravity.	The experiment showed a slight reduction in cell-mediated immunity and in the cytokines involved in innate immunity.
Crucian and Choukèr	2011	Introduce the immune system and innate *versus* adaptive immunity, and discuss how stress and space flight influence the immune system.	Most of the data on immunological changes related to the space environment relate to post-flight assessments, which do not necessarily illustrate the condition of immunity during the trip. There is consistent data, however, on changes in the distribution of leukocytes in the peripheral blood and a reduction in the function of specific subpopulations of lymphocytes (e.g. T lymphocytes and *natural killer* cells), as well as an increase in stress hormone levels.
Martinelli et al.	2009	To investigate the proliferation and viability of lymphocytes upon exposure to rotation in a three-dimensional (3-D) clinostat.	After 48 hours of rotation in the clinostat, there was a decrease in cell proliferation and viability, which was not seen after 24 hours. Immune depression may also be related to microgravity.

Source: prepared by the authors.

The information from the bibliographical references listed in Table 2 consulted for the preparation of the text – plus data obtained from additional texts known to the authors – was organized into two subtopics – (1) the innate immune response and (2) the adaptive immune response – which will be presented below.

Innate immune response

The proper functioning of innate immunity – the human body's first line of response to pathogens – requires the coordination of different organic systems, with emphasis on (1) epithelial barriers (skin and mucous membranes), (2) complement system proteins and (3) cellular components [*natural killer* (NK) cells, neutrophils, macrophages and their cytokines] (Siqueira-Batista et al., 2015; Siqueira-Batista et al., 2024). The most striking features of innate immune response (IR) include (i) rapid action in the presence of a foreign agent (e.g. a microorganism), with (ii) maintenance of the same pattern in the presence of new contacts with the same stimulus, (iii) without, however, constituting memory (Vaillant et al., 2022).

Recent studies have evaluated how microgravity affects this fundamental IR. Research has been carried out with human biological samples, obtained from astronauts (Figure 3), and non-human samples – e.g. animal models – and cell culture systems. In fact, volunteers

subjected to environments simulating reduced gravity expressed a slight decrease in cell-mediated immunity and cytokines, indicating a possible influence of the space environment on this response modality (Kinra et al., 2012). In addition, a significant decrease in the number of NK cells and neutrophils was observed after a period of confinement in simulated microgravity conditions, highlighting the complexity of SI behavior in this context (Verhaar et al., 2014; Ponomarev et al., 2022). Notably the differences between sexes with regard to the regulation of the inflammatory process under experimental context of simulated cosmic radiation (Burke et al., 2024).

Figure 2. NASA astronaut Peggy Whitson takes a blood sample in the European Space Agency's "Columbus" module on board the International Space Station (ISS). The blood sample was used to study the astronauts' immune systems. The blood samples were transported to Earth for terrestrial analysis at room temperature to preserve cell viability. The individual pictured provided written consent for the publication of this image. To maintain viability, samples were collected during space flights in anticoagulated tubes. The average time from collection on board the ISS, through landing, to analysis in Houston, Texas, was approximately 37 hours.
Credit: CRUCIAN, B. E. et al. Frontiers in Immunology, v. 9, p. 1437, 2018. Creative Commons license. Authorization for publication also obtained from *Frontiers in Immunology*. Available at: https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2018.01437/full.

The importance of innate IR during space travel has been highlighted in research carried out with astronauts. During long-duration space flights, such as missions on the ISS,

dysfunction of the human immune system (IS) has been observed—particularly involving NK cells—which likely persists throughout the entire mission (Crucian; Choukèr, 2011; Bigley et al. 2019; Crucian et al., 2020). Some studies have demonstrated the maintenance of IS cellular adaptations for months after the mission (Benjamin et al., 2016; Garcia-Medina et al., 2024). These findings highlight the need to maintain the proper functioning of the IS during space travel to ensure the health of astronauts (Buchheim et al., 2020).

In addition, more recent research, such as that conducted by Stratis et al. (2023), has explored the molecular response involved in the loss of conditioning of multiple body systems, including the immune system, during long-duration space flights. This study revealed rapid adaptations in the leukocyte transcriptome in response to entry into space, followed by opposite changes upon return to Earth. During space travel, there was immune suppression, increased cell maintenance functions and reduced cell proliferation, while return to Earth was associated with immune reactivation (Stratis et al., 2023). Changes in humoral components (cytokines/chemokines) which are involved in different organic processes – inflammation, senescence and maintenance of muscle homeostasis – have also been shown to change after space flight (Garrett-Bakelman et al., 2019; Kim et al., 2024).

Another relevant study, conducted by Kuzichkin et al. (2022), investigated markers of endothelial activation and damage in cosmonauts after an extended stay in an extraterrestrial environment. The results revealed a significant increase in plasma levels of certain markers – such as von Willebrand factor (vWF) and highly sensitive C-reactive protein (hs-CRP) – indicating a potential link between changes in SI, coagulation alterations and vascular damage during prolonged missions in space.

The influence of simulated microgravity on innate immunity and gut microbiota in mice infected with *Escherichia coli* has also been investigated (Wang et al., 2020). The results showed that simulated microgravity not only reduces innate immunity, but also increases the risk of bacterial infection, causing dysbiosis in the gut microbiota and altering the metabolism of short-chain fatty acids, highlighting the complex effects of microgravity on the body's immune system and gut health (Castro-Costa et al., 2024; Wang et al., 2020).

Adaptive immune response

Adaptive or acquired immunity – generated from the clonal selection of B and T lymphocytes – has (1) specificity and diversity of interactions and (2) the development of immunological memory – which allows for a more effective response in the event of new exposure to the same agent – as its main characteristics (Cruvinel et al., 2010). Lymphocyte receptors specifically recognize different non-self components (e.g. pathogen proteins) in the host organism. Two basic patterns of adaptive IR have been described: humoral immunity, directed at extracellular microorganisms and whose action depends on the production of antibodies; and cellular immunity, directed especially at intracellular pathogens and whose effectors are IS cells (Siqueira-Batista et al., 2024).

Adaptive IR can be affected by a variety of environmental factors, including microgravity – a condition often found in space that can negatively impact on immunity – including the production of immune dysfunctions characterized by an increase in pro-inflammatory states of monocytes and a reduction in the activation capacity of T cells (Crucian et al., 2013; Bradley et al., 2017; Moser et al., 2023), and changes in the cytokine release profile *in vitro* (Van Walleghem et al., 2017). As a consequence, it should be noted that exposure to environments with reduced severity is associated with the reactivation of latent pathogens, such as the herpes virus (Simon et al., 2021)

In this sense, a study by Green et al. (2021) made it possible to observe the effects of microgravity on the adaptations of prokaryotes and aspects of human immunity in space. The results show that microgravity can cause immune dysfunction in astronauts, increasing the risk of opportunistic infections by bacteria and viruses. Furthermore, species of prokaryotes have been described on board space missions – or grown in an analog of microgravity – which exhibit greater virulence, biofilm formation and antibiotic resistance (Green et al., 2021). Understanding the effects of microgravity on prokaryotes and the immune system could have implications for astronaut health, the development of new therapies and vaccines, and long-term space exploration.

The verification carried out by Martinelli et al. (2009) – in which the effect of microgravity on the human IS is not only related to physical and psychological stress, but also to intrinsic aspects immunity, especially the action of lymphocytes – shed light on the subject. The results indicated a significant decrease in cell proliferation and viability after 48 hours of

rotation in the 3-D clinostat, suggesting that microgravity itself negatively affects these processes. The research also pointed out that exposure to a reduced gravitational field can result in a decrease in the proliferative response of immune cells, which has the potential to compromise the immune system. These findings suggest that microgravity, even if simulated, can be a significant factor in reducing cellular immunity. The molecular and cellular mechanisms involved in these changes include alterations in gene expression, cell signaling, cytokine production, and immune cell differentiation.

Studies such as the one carried out by Crucian & Choukér (2011) have explored how microgravity can affect adaptive IR. It was highlighted that space flight results in dysfunction of the human immune system that persists for the entire duration of a six-month orbital flight. Similarly, it was observed that changes in adaptive immunity persist during long-duration space flight. Still on the subject of microgravity, a recent investigation used a 41-parameter mass cytometry approach to assess the functional responses of specific cells in peripheral blood mononuclear cells (PBMCs) from eight healthy adult donors exposed to 1G or sμG for 24 hours. It was observed that most leukocyte subsets were not altered by sμG, but were altered after landing (Spatz et al., 2021).

The expression and function of various receptors and signaling molecules on T cells – such as the TCR/CD3 complex, CD28, CD95, NF-KB, MAPK, PI3K/Akt and calcineurin/NFAT – has been studied in terms of adaptive IR. It was noted that microgravity influences the morphology and cytoskeleton of T cells, affecting their adhesion, migration, polarization and cytokine secretion (Dhar et al., 2021).

The deleterious effects on the IS in the context of space travel, more related to cosmic radiation, have also been investigated. Chronically exposing astronauts to the different components of rays and particles – without the protection of the Earth's atmosphere and magnetosphere – represents a significant obstacle to longer-term extraterrestrial activities, such as the mission to Mars and a long-term stay on the Moon. The potential immunological impacts of simulated cosmic radiation were analyzed by Fernandez-Gonzalo et al. (2017), with emphasis on the appearance of functional changes in white cells and a reduction in the populations of T lymphocytes (CD8+ more sensitive than CD4+) and B lymphocytes, the latter more pronounced. Data from Sanzari et al. (2015) already pointed to a reduction in circulating leukocyte counts – particularly lymphocytes – an observation documented as early as four hours

after exposure. Finally, it remains to clarify, in a more definite manner, the possible role of microgravity as a potentiator of the deleterious effects of radiation on the IR of *Homo sapiens* (Russomano; Rehnberg, 2018).

A significant point that needs to be taken into account in the context of immune changes in the space environment concerns the possible consequences of infectious processes triggered by genetically modified pathogens (e.g. due to microgravity and/or radiation) and, more than that, the possibility of human contact with alien life forms – for example, microbes (Warmflash et l., 2007; Netea et al., 2020). The outcomes of this situation are unpredictable for the time being, so that serious reflection on the subject – seeking to size up the scientific and ethical issues involved (Siqueira-Batista; Gómez, 2025) – will need to be considered for future technological developments.

To meet these challenges, the ESA Astronaut 2.0 concept aims to prepare a new generation of space travelers for future space exploration missions in low Earth orbit, on the Moon and on Mars. This concept involves the study of immunity in space, as well as the development of new therapies and vaccines to protect astronauts. The study by Jacob et al. (2023) discusses this perspective and reviews current studies investigating the molecular and cellular mechanisms involved in IR in space and in microgravity analogues, such as the downward sloping resting bed, parabolic flight and the random rotation model. It also addresses the opportunities and challenges for the study of immunity in space, such as the use of artificial intelligence, three-dimensional cell culture systems and nanotechnology.

FINAL CONSIDERATIONS

The changes that occur within immunity in extraterrestrial environments directly influence how the human organism performs different aspects of homeostasis, including mounting an effective response to pathogens and the consequent ability to control different infectious conditions.

The studies listed in this article highlight the main immune alterations described in the space context and emphasize the need for more detailed investigations in order to gain a broader understanding of the complex modifications to the IS induced by living in extraterrestrial

environments, particularly when considering the possibility of infection by genetically modified germs (e.g. as a result of altered gravitational conditions and radioactive exposure) and even by non-terrestrial life forms

Another essential point of research concerns the genetic evaluation of astronauts, since genetic material is unique to each human being and replication behavior can differ from individual to individual. These scientific frontiers are all the more relevant given the need to understand the effects of microgravity and radiation, respectively, in the field of immunogenetics and/or sexual differences in immune responses in space.

Scientific advances in this field could provide essential *insights into* the health and well-being of astronauts on future missions, with emphasis on research into countermeasures to the deleterious effects of the extraterrestrial environment – such as the systematic adoption of physical activity, improving blood circulation and increasing the supply of nutrients essential to the proper functioning of the immune response – which could have a direct impact on maintaining adequate homeostasis, especially in the context of long-duration missions, as in the fictional Star Trek, heading for "*space, the final frontier*".

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