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PERSPECTIVE

Space health hub: Mitochondrial protection and therapeutic strategies for long-term space missions

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Prolonged space habitation poses challenges to human physiological stability, necessitating an understanding of subcellular responses to spaceflight for accurate health risk assessment and the development of protective countermeasures. Mitochondrial energy is a fundamental mechanism supporting various physiological, ecological, and evolutionary processes, while mitochondrial stress has become a fundamental characteristic of space travel. Therefore, safeguarding mitochondrial function in space is crucial for ensuring human health and performance during long-duration missions. This perspective focuses on mitochondrial changes in response to spaceflight, with an emphasis on their implications for human health. We first addressed the critical role of mitochondria in maintaining physiological stability under space conditions, highlighting the environmental factors that contribute to mitochondrial dysfunction and their associated physiological consequences. We then synthesized current research to propose a mitochondrial protection strategy that integrates personalized, long-term monitoring with pharmacological interventions. Lastly, we discussed the potential advancements in drug delivery system in space through sequential targeted delivery methods. In light of the ongoing challenges in space medicine, we underscore the importance of prioritizing research on mitochondrial protection under spaceflight conditions. Such efforts will not only advance our understanding of space-induced health risks but also pave the way for the development of effective interventions to prevent mitochondrial-related disorders, ultimately enhancing the safety and sustainability of human space exploration.

Since the first manned space mission in 1961, human space exploration has advanced rapidly, with ambitious goals now focusing on crewed missions to other planets within the solar system and the development of space resources. These long-duration space missions require astronauts to spend extended periods in space, ranging from several months to years, significantly increasing their health risks. Therefore, prioritizing the physical and mental health of astronauts is crucial to achieving these ambitious objectives.

Space presents unique survival challenges for humans, including external threats such as cosmic radiation and environmental factors like microgravity, isolation, and distance from Earth. Among these, space radiation and microgravity are the primary influences on human physiological homeostasis. The independent or combined effects of these factors contribute to well-documented spaceflight-related health issues, such as bone loss, muscle atrophy, cardiovascular adaptations, central nervous system damage, and liver and kidney injuries. While organisms have evolved biochemical and physiological response mechanisms to maintain homeostasis in high-stress environments, extreme external stimuli or overactivation of compensatory mechanisms can overwhelm these systems, leading to multi-organ dysfunction and health complications for astronauts. Investigating the common mechanisms of organ damage at the cellular or subcellular level provides critical insights into the regulation of human physiological processes and offers novel strategies for preventing and treating spaceflight-related physiological changes. Recent findings from NASA GeneLab, which conducts comprehensive omics analyses across multiple space missions and various tissue and cell lines, reveal that mitochondria, the fundamental energy units of human cells, serve as a central biological hub for the effects of spaceflight.[1] Additionally, the U.S. twin study space experiment demonstrated that astronaut Scott Kelly exhibited changes in gene expression related to oxidative stress, energy metabolism, mitochondrial DNA repair, and mitochondrial transport in his blood samples during a space mission.[2] These findings highlight the susceptibility of mitochondria to dysfunction under spaceflight conditions and their involvement in adaptive changes across multiple physiological processes.

Mitochondria are the energy centers of cells and play a crucial role in various biological processes, including signaling, cell differentiation, and apoptosis. In the space environment, space radiation and microgravity primarily affect mitochondria by disrupting energy metabolism and regulating other biological processes such as redox reactions. Space radiation, including both acute damage from solar cosmic rays and chronic harm from galactic cosmic rays, ionizes cellular molecules like DNA, proteins, and lipids, damaging their structures. It also reacts with water to generate reactive oxygen species (ROS), triggering oxidative stress. Microgravity alters mitochondrial function through three main mechanisms: (1) changing fluid dynamics, which slows the diffusion of nutrients and oxygen to mitochondria; (2) remodeling the extracellular matrix, thereby impacting cell adhesion, migration, and signaling, which in turn modifies mitochondrial behavior; and (3) impairing mechanical sensing, altering cytoskeletal structure and, consequently, mitochondrial distribution and function.

The changes in mitochondria affected by space hazards can be broadly categorized into two types: biological functional changes (redox balance, energy metabolism, and signal transduction) and physical state alterations (number, morphology, and distribution). Mitochondrial oxidative stress, acting as an early and widespread adaptive response, is closely linked to numerous issues in aerospace medicine. Cardiovascular diseases remain a significant challenge in spaceflight. Zhang et al. found that mitochondrial oxidative stress and endoplasmic reticulum stress induced by simulated microgravity (SMG) create crosstalk that promotes vascular remodeling and cardiovascular dysfunction in rats.[3] The most obvious phenomena of bone loss and muscle atrophy during space missions have also been shown to be related to mitochondrial oxidative stress. Dysfunctions of the central nervous system become more severe during long-duration space flights, particularly issues such as visual impairment and cognitive decline. Rubinstein et al. demonstrated the importance of ROS signaling in the activation of microglia in mice.[4] Due to the importance of metabolic and excretory functions and their high blood flow, the liver and kidneys face significant risks when subjected to oxidative stress. Current research indicates that oxidative stress in space plays a contributory role in the formation of kidney stones and acute kidney injury.[5] We also revealed that oxidative stress-induced mitochondrial dysfunction significantly contributes to the deactivation of hepatocytes under SMG. Disruptions in gastrointestinal function are inherently linked to the crosstalk between oxidative stress and inflammation, and these effects are intensified by the space environment. Furthermore, Capri et al. suggest that mitochondrial oxidative stress, directly or indirectly, leads to the activation of inflammatory responses in space, which acts as a driver accelerating the normal physiological aging process.[6] Admittedly, confirmation of causality through targeted perturbation studies (e.g., in situ mitochondrial modulation during orbital missions) remains a critical knowledge gap. Future validation of this paradigm would benefit from implementing mitochondrial-targeted optogenetic tools in Space Station-based experimental platforms to dissect redox

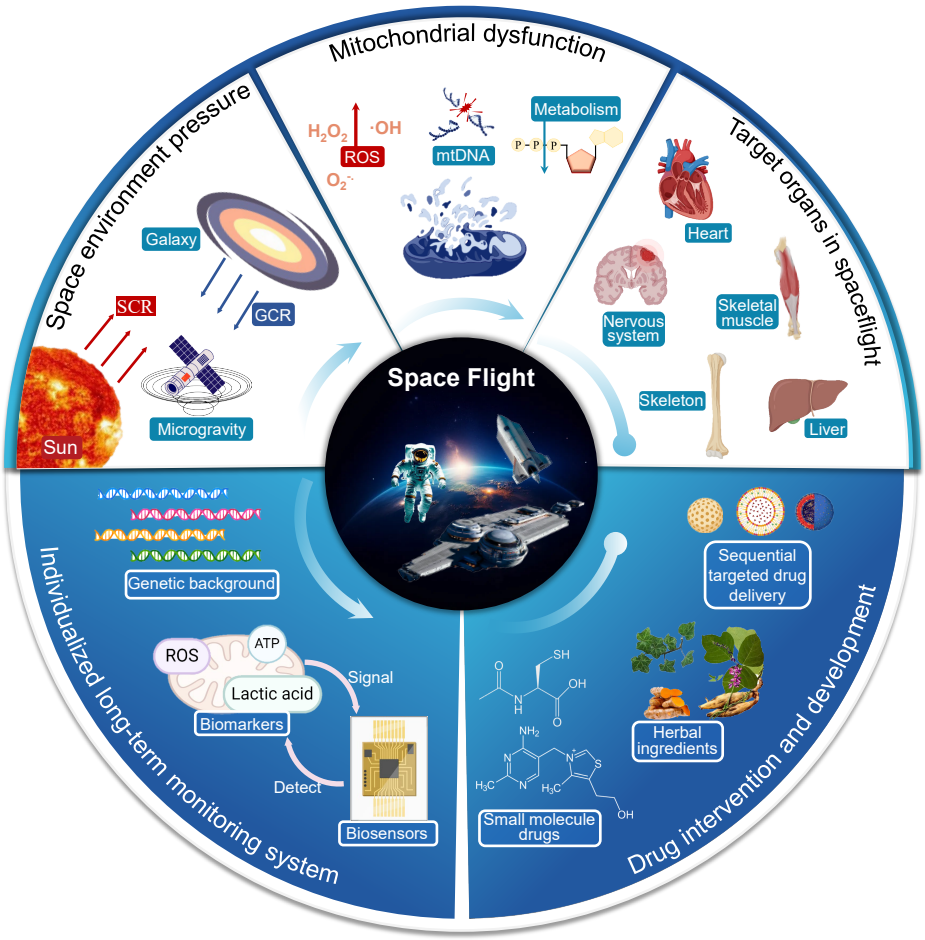

Figure 1. The role of mitochondria in the space environment and strategies to protect human mitochondrial health

dynamics.

The multifaceted roles of mitochondria create a dynamic network, where oxidative stress does not act in isolation but serves as a key factor, alongside energy metabolism and signal transduction, to regulate homeostasis. One of the most significant physiological changes in space is bone loss and muscle atrophy, which results from inadequate energy supply by mitochondria to osteoblasts, osteoclasts, and muscle cells. As a highly energy-demanding organ, the heart's contraction and relaxation are significantly influenced by mitochondrial energy metabolism. In microgravity, impaired contractile function of cardiomyocytes is linked to reduced ATP production. The crosstalk between oxidative stress and mitochondrial signaling is particularly sensitive in regulating calcium ion transmission. Fan et al. demonstrated that under SMG conditions, mitochondrial oxidative stress disrupts Ca^{2+} homeostasis by altering inositol 1,4,5-trisphosphate receptor abundance, Ca^{2+} storage, mitochondrial dynamics, and plasma membrane ion channels in brain vascular endothelial cells, leading to enhanced vasoconstriction and reduced cardiovascular function in astronauts.[7] Moreover, changes in mitochondrial physical state in space serve as adaptive adjustments that help regulate the mitochondrial network's biological functions. For instance, Mikheeva et al. observed increased mitochondria number and perimeter in the oculomotor nuclei motor neurons of mice during a 30-day spaceflight experiment, enhancing their capacity to buffer excess Ca^{2+} and maintaining cellular homeostasis.[8] In summary, mitochondria in space participate in the precise regulation of multiple processes, forming a complex regulatory network. Developing targeted interventions to modulate mitochondria function is a critical strategy for enhancing the feasibility of long-duration manned space missions.

During space missions, astronauts undergo repeated transitions between Earth and space environments, prompting mitochondria to adapt to space stressors and subsequently readapt upon return. These transitions result in dynamic and complex mitochondrial changes throughout the mission. Individual genetic variability further complicates these responses, influencing mitochondrial adaptation efficiency. Thus, personalized, long-term monitoring of mitochondrial function is essential for safeguarding astronaut health during space missions. Personalized monitoring involves analyzing epigenetic changes and individual genetic variations to identify baseline differences in mitochondrial function among astronauts, establishing personalized benchmarks for mitochondrial health. This process should begin during the ground preparation phase of space missions. For example, deep sequencing of mitochondrial DNA and nuclear genes encoding mitochondrial-related proteins can detect potential genetic variations. The data collected during the ground preparation phase should include an individual's sensitivity/tolerance to the space environment, baseline mitochondrial function, and capacity to generate endogenous antioxidants.

Long-term monitoring involves staged assessments of mitochondrial adaptability throughout the entire space mission, enabling the practical recognition of cellular energy needs. This monitoring framework includes standardized periodic sampling and analysis (e.g., blood via BD vacutainer and urine via urine transfer system to overcome microgravity) at critical mission phases (e.g., launch, microgravity adaptation, and re-entry), leveraging lab-on-chip platforms validated in NASA's Biomarker Factory Project to ensure consistency in sample processing and biomarker quantification. By integrating individual characteristics like genetic profiles, metabolic rates, and physiological responses, it allows for determining whether interventions are needed at each stage of change. Advances in biomarker research offer multiple options to assess mitochondrial function, including mitochondrial membrane protein activity (e.g., cytochrome c oxidase), ATP levels, metabolic products (lactate, ketone bodies), oxidative stress markers (ROS, 8-OHdG), and gene expression profiles (e.g., PGC-1α, TFAM). Biomarkers were identified through a dual-criterion approach requiring (1) statistical significance (adjusted P-value < 0.05) and (2) fold-change thresholds established based on pre-flight baseline variability. To address privacy concerns, genetic/epigenetic data will be de-identified with encrypted storage and strict access controls, while astronaut autonomy is ensured through informed consent protocols allowing selective opt-out of non-critical interventions. Integrating mitochondrial function monitoring into astronaut health systems during lunar base missions could enable early detection of metabolic dysfunction, ensuring timely interventions to maintain crew health. These monitoring datasets will establish dynamic thresholds for intervention, which can trigger graded therapeutic responses ranging from nutritional supplementation to pharmacological modulation.

Building upon this data-driven monitoring framework, the restoration of metabolic homeostasis becomes the next critical step. Recent mechanistic studies of space-related physiological changes are uncovering novel strategies for protecting metabolic homeostasis. For example, Han et al. found that under microgravity conditions in the Chinese Space Station, cardiomyocytes exhibit impaired thiamine utilization, which disrupts mitochondrial ATP synthesis. Supplementing thiamine in cardiomyocytes and mice effectively rescues these microgravity-induced defects.[9] This suggests that thiamine

supplementation could serve as a preventive measure for astronauts experiencing cardiac metabolic impairments during space missions. Additionally, modulating cell surface tension under microgravity may indirectly affect mitochondrial metabolism. Extracellular matrix regulators (e.g., hyaluronic acid) and phospholipid regulators (e.g., phosphatidylcholine) show potential in this context. Furthermore, advancements in the development of novel antioxidants for space-related conditions are underway. Our research group has identified melatonin as a potential inhibitor of ROS increases and mitochondrial dysfunction in hepatocytes under SMG conditions. Moreover, network pharmacology-based analyses of traditional Chinese medicine formulas reveal herbal components, such as ivy saponin, with strong antioxidant properties.

The extreme space environment necessitates the development of advanced drug delivery systems optimized for microgravity. Ideally, this system should enable stepwise, on-demand delivery of therapeutic or diagnostic agents to specific targets (e.g., organ-cell-mitochondrion) for sequential targeting, allowing precise mitochondrial intervention. For example, the E7-Lipo@Alg/Cs hydrogel microsphere system, featuring multi-layered drug encapsulation and E7 peptide modification, achieves active targeting from the intestine to bone tissue, addressing mitochondrial dysfunction to mitigate bone loss.[10] Additionally, mitochondrial targeting groups, such as triphenylphosphine, are beneficial due to their positive charge, which attracts the negative membrane potential of the mitochondrial inner membrane. However, a key limitation of current research is the scarcity of data collected in real space environments, particularly for advancing novel drug delivery systems towards space applications. Furthermore, the implementation of these advancements must carefully address ethical and safety considerations. For instance, the use of real-time biosensors raises concerns about data privacy and informed consent, as continuous health monitoring may infringe on astronauts' personal autonomy. Additionally, the potential risks of long-term pharmaceutical interventions on astronaut health, such as unforeseen side effects or drug interactions, must be thoroughly evaluated.

In a word, mitochondrial protection is essential for maintaining astronaut health during spaceflight, requiring strategies that integrate long-term monitoring and pharmacological interventions to counteract space-induced mitochondrial stress. Interdisciplinary approaches combining materials science and aerospace medicine offer promising breakthroughs for addressing mitochondrial dysfunction and advancing space health research (Figure 1).

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AUTHOR CONTRIBUTIONS

Yinghui Li and Xiaohua Lei conceived the idea. Zuoxiu Xiao prepared the manuscript with input from all authors. Pengfei Zhang, Qi Zhao, Yinghui Li and Xiaohua Lei involved in the manuscript revision. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.