MPS Final Review Paper - Space Biology
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Abstract

Microphysiological systems (MPS) are emerging as powerful tools for studying biological systems in space. This review explores the types of MPS used in space biology, including organ-on-a-chip systems, 3D cell cultures, and microfluidic devices. MPS offer advantages over traditional methods for modeling the rapid physiological changes in astronauts that often replicate disease states and aging pathologies on Earth. These systems enable high-throughput studies of space radiation effects on DNA damage, the cardiac system, and the nervous system, as well as the long-term impacts of microgravity on human physiology, such as cardiovascular deconditioning, muscle atrophy, and fluid shifts. Challenges and limitations of MPS in space biology are addressed, including technical issues, reproducibility, and validation within *in vivo* studies. Future directions and opportunities are highlighted, emphasizing multi-organ system integration, advanced technologies, and collaboration between space agencies and research institutions. MPS-based regenerative medicine studies can accelerate the translation of therapies to the clinic, advancing our understanding of the effects of space travel on human health and developing countermeasures for long-duration space exploration while informing treatments for patients on Earth.

Introduction

Microphysiological systems, also known as “body-on-a-chip” or “organ-on-a-chip” systems, are a promising and innovative technology that could have major impacts on space biology and enhance the medical capabilities of the International Space Station (ISS). These miniaturized microfluidic cell culture systems enable the growth and study of human cells, tissues, and even organs in a precisely engineered microenvironment that can simulate some aspects of the human body. They provide unique capabilities that make them highly applicable to certain areas of space research and have the potential to be integrated into the ISS as improved platforms for biological and medical research in the spaceflight environment. Microphysiological systems offer key benefits that address current limits in space biology fields such as studies of altered gravity, the effects of space radiation, and the testing of medical countermeasures. First, they allow for unprecedented control over experimental conditions. This is essential for parsing out the effects of microgravity versus radiation or other variables in space. They also permit high-throughput, repeatable experimentation with human cells that is not possible with traditional cell cultures or animal models. Additionally, microphysiological systems enable organ-level human biology research with small cell quantities in confined spaces – an important capability given the space and resource constraints for experiments onboard the ISS. As such, this technology transforms what biological investigations can be conducted in space, significantly strengthening the experimental power of ISS medical missions. In this paper, we review major areas of promise for microphysiological systems on the ISS, highlighting their potential advantages for space biology and human health in orbit. Key opportunities include microgravity studies on the immune system, bone loss, and radiation effects as well as the testing and development of medical interventions or countermeasures. We also examine technical and integration considerations for implementing these systems aboard the ISS. Cumulatively, microphysiological systems can accelerate fundamental research critical to longer human space missions while also contributing key physiological data to enable better

prediction and prevention of medical risks during spaceflight. The continued incorporation of this technology is vital for fully realizing benefits from the ISS platform and expanding fundamental knowledge needed for long-duration space exploration. Figure 1 is a comparison showcasing the benefits of MPS in space biology rather than 2D or animal culture models.

Space Biology Fields	Traditional Methods	MPS
Physiological relevance	Limited, often uses 2D cell cultures or animal models	High, can mimic 3D tissue structure and function
Modeling disease states and aging	Slow, difficult to replicate spaceflight-induced changes	Rapid, can model accelerated pathologies similar to those seen in astronauts
Study of space radiation effects	Limited, often relies on in vivo animal studies	High-throughput, can study effects on DNA damage, cardiac system, and nervous system
Investigation of microgravity impacts	Clunky, incomplete, or impractical (e.g., bedrest, water immersion)	Practical, allows for studying long-term effects on cardiovascular system, muscles, and fluid shifts
Cost and resource requirements	High, requires large quantities of cells and reagents	Reduced, miniaturized systems use fewer resources
Reproducibility	Variable, dependent on animal models or 2D cell culture conditions	Improved, can standardize conditions across experiments
High-throughput capabilities	Limited, time-consuming and labor-intensive	Enhanced, allows for rapid testing of multiple conditions and treatments
Translation to clinical therapies	Slow, often requires extensive animal testing before human trials	Accelerated, can bridge gap between in vitro and in vivo studies
Potential for multi-organ systems	Challenging, requires complex in vivo models	Promising, can connect multiple organ-on-a-chip devices
Collaboration and standardization	Limited, often siloed within individual research groups	Encouraged, can promote data sharing and standardization across institutions on a global stage

Figure 1: Table highlighting the benefits MPS provides over traditional methods in space biology research

Disease Modelling

The physiological changes observed in astronauts during spaceflight often mimic disease states and aging processes that occur more gradually on Earth. Microgravity exposure leads to rapid alterations in genes, cells, and whole organisms, resembling the changes associated with the development and progression of various diseases. By modeling these accelerated changes and their reversals using microphysiological systems (MPS) in vitro, researchers can gain valuable insights into the underlying molecular mechanisms of numerous common human disorders. This approach has the potential to expedite the discovery of novel therapeutic targets and interventions for patients on Earth.

Cardiac Disease:

In a space environment, microgravity and radiation affect the cardiovascular system and cause symptoms similar to patients on earth with heart conditions like ischemic cardiomyopathy. The changes the body undergoes in space can be rapid, like the immediate relocation of fluids towards the upper body due to a microgravity environment, while other changes are long term like the atrophy of muscles from a weakened workload. In space, there is a 10% decrease in cardiac mass, along with a 11% blood volume decrease (Gallo, 2020). In addition, post-flight arterial stiffness is observed in astronauts, similar to arterial stiffness in older people on Earth due to diet, age, or other diseases. Thus, cardiac tissues sent to space can provide a good model for disease progression and drug testing for cardiac disease, as shown by the experiment protocol in Figure 2. Recently, a team from Stanford University have been working with their previously developed, well characterized, engineered heart tissue (EHTs) platforms to match molecular and electrophysiological disease patterns in ischemic cardiomyopathy to the EHTs that were exposed to microgravity. Ischemic cardiomyopathy is when damage from lack of blood supply enlarges and weakens the left ventricle of the heart, leading to decreased ability to pump oxygenated blood to the rest of the body. The goal is to then develop high-throughput, heart tissue assays for drug candidate screening for ischemic cardiomyopathy (Wu, 3UH3TR002588).

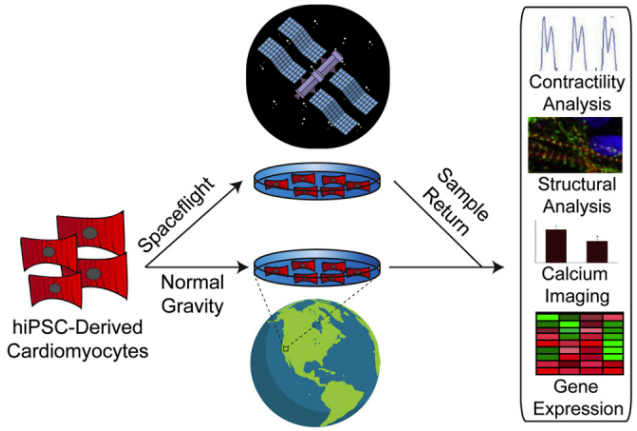

Figure 2: Experimental process for hiPSC-derived cardiomyocytes exposed to microgravity on the ISS showed altered calcium handling, differential gene expression, and enriched mitochondrial pathways compared to ground controls. (Wnorowski et al., 2019)

There is also an initiative from Johns Hopkins to create more mature EHTs from hiPSC-CMs in order to create disease models for chronic heart disease which new therapeutic strategies can be tested on (Kim, 3UH3TR003519).

Muscle:

In a microgravity environment, astronauts experience a 1-1.5% bone density loss per month, which is more pressing as longer exploration space flights are on the horizon in the future (Stavnichuk et al.,, 2020). In addition, there is a rapid onset of up to 20% loss of skeletal muscle mass in the first month in space (Juhl et al., 2021). On Earth, patients face issues like osteoporosis (loss in bone density), along with sarcopenia (age related muscle wasting), especially since humans are living longer and become more vulnerable to the effects of aging. A team from University of Florida aims to leverage this musculoskeletal atrophy in space by sending human myocytes isolated from a diverse set of individuals to validate this as a model for sarcopenia. This “lab on a chip”, will be compact, remotely controlled, fully automated, and complete with microfluidic chambers designed for space considerations. Differing from the large laboratories on Earth where media changes can be done with relative ease, tissue chips in space are designed to maximize space efficiency, along with the constraints of limited manipulation ease in a microgravity environment. Once validated, the team plans to test a battery of different anti-atrophy products in order to study disease progression of atrophy along with increasing efficacy and toxicological testing for muscle wasting drugs (Malany, 4UG3TR002598).

Kidney:

In space and on Earth, humans experience kidney dysfunction that can lead to dangerous, uncomfortable, and unpleasant conditions like proteinuria, osteoporosis, and kidney stones. Bone loss in space causes calcium to leak into the kidneys, causing an elevated risk of kidney stones, and progression of kidney related conditions progress faster and happen more often in space. A team from University of Washington will send polarized proximal and distal tubule epithelial cells, which are key parts of the kidney filtration system, to the ISS in order to investigate the impact of microgravity on the tissues (Himmelfarb, 5UH3TR002178). Disease state models will be generated to model proteinuria from these cultures, along with growing oxalate microcrystals on distal tubule kidney cultures to simulate kidney stones. The aim is to gain insight into the disease pathways of these kidney conditions and discover new potential therapeutic targets that can help alleviate, prevent, or reverse proteinuria, osteoporosis, and kidney stones for both astronauts in space and patients on Earth.

Organ/Tissue	Disease	Benefits of OOO Space Modeling	Goal
Heart	- Ischemic cardiomyopathy - Chronic heart disease	- Damage from microgravity is similar to effects of ischemic cardiomyopathy - Accelerated aging → more mature cardiomyocytes	- High throughput drug screening for ischemic cardiomyopathy
Skeletal Muscle	Sarcopenia	- Compact, remotely controlled, and fully automated - Aging is accelerated in space	- Study disease progression for sarcopenia - Test several different anti-atrophy products
Kidney	- Proteinuria - Kidney stones	- Gain insight into kidney damage mechanism from space radiation and microgravity	- Discover disease pathways - Discover new therapeutic pathways to alleviate, prevent, or reverse disease

Figure 3: Table highlighting 3 examples of organ chips being sent to space, along with the specific benefits of the space environment for these chips and the goals of these studies.

Regenerative Medicine:

Microphysiological systems (MPS) have emerged as a powerful tool for advancing regenerative medicine research and its applications for patients on Earth. These systems can be used to model various disease states and injury conditions, enabling the development and testing of targeted regenerative medicine therapies. By mimicking the complex microenvironment of native tissues, MPS allows for more accurate and physiologically relevant studies compared to traditional in vitro methods.

MPS technology offers unique opportunities to study stem cells and stem cell-derived products, which are promising tools and therapeutic agents in regenerative medicine. Space-based research using MPS can provide insights into controlling stem cell potency, expansion, and differentiation, as microgravity has been shown to influence these properties. For example, recent studies have found that cardiac progenitor cells cultured on the International Space Station (ISS) exhibited increased proliferative and migratory potential due to changes in mechanotransduction pathways and cytoskeletal organization. Similarly, mesenchymal stem cells (MSCs) cultured in microgravity demonstrated enhanced therapeutic potential in a traumatic brain injury model (Sharma et al., 2022). These findings highlight the potential of space-based MPS research to advance stem cell-based regenerative medicine therapies on Earth.

One of the key advantages of MPS in regenerative medicine is the ability to conduct high-throughput screening of potential therapies. This allows for the rapid identification of promising treatments and the optimization of treatment protocols, accelerating the translation of regenerative medicine approaches from bench to bedside. MPS-based regenerative medicine

studies can also help bridge the gap between in vitro and in vivo studies, reducing the need for animal testing and providing a more streamlined path to clinical trials.

Additionally, the ISS provides a unique platform for biofabrication research, which has significant implications for regenerative medicine. Microgravity conditions may enable the generation of complex, 3D tissue constructs using techniques such as bioprinting, which could be used for tissue engineering and regenerative medicine applications on Earth. The ISS also allows for the testing and maturation of biofabricated materials in a microgravity environment, potentially leading to the development of novel biomaterials with enhanced properties for regenerative medicine. However, there are challenges that need to be addressed in the application of MPS for regenerative medicine, including the need for standardization, validation, and scalability of these systems to ensure reproducibility and reliability of results across different laboratories and institutions. Efforts are being made to establish common protocols and benchmarks for MPS-based regenerative medicine research to facilitate collaboration and comparison of findings.

Future directions in MPS-based regenerative medicine research are focused on the development of more complex and integrated systems, such as multi-organ platforms that can capture the interactions between different tissues and organs. Additionally, the incorporation of patient-derived cells, such as induced pluripotent stem cells (iPSCs), into MPS models holds great promise for personalized medicine applications. By using patient-specific cells, researchers can study disease mechanisms and test targeted therapies tailored to an individual's genetic background and medical history.

In conclusion, microphysiological systems offer a powerful platform for advancing regenerative medicine research and its applications for patients on Earth. By leveraging the unique environment of microgravity and the ISS, researchers can gain valuable insights into stem cell biology, biofabrication, and disease modeling, accelerating the development of effective regenerative medicine therapies. As the field continues to evolve, the integration of MPS technology with advancements in automation, artificial intelligence, and machine learning will further enhance the impact of space-based regenerative medicine research on improving patient outcomes and quality of life on Earth.

Space Radiation

Microphysiological systems are a promising tool for understanding the biological effects of spaceflight environments. Space radiation is one important aspect of the spaceflight environment and a conundrum in space medicine. Space radiation has been associated with DNA damage, cancer, and other diseases, which may affect the welfare of astronauts during deep-space travels. Recent research has provided many discoveries as to the effects of space radiation in different organ systems as well as potential treatments to these effects.

Contents of Space Radiation

The environment in space at low orbit missions (altitude of 2,000 km or less) is subject to some radiation, yet it is mostly shielded by Earth's magnetic field (Mu et al., 2022). As space missions approach distances beyond this altitude the environment is subject to high levels of ionizing radiation, primarily from the so-called 'solar wind' and galactic cosmic radiation,

originating from the outwards expansion of plasma from the sun and other galactic events (Chancellor et al., 2014). These radiations contain energetic protons, alpha particles, and high-energy, all of which can cause various biological effects that researchers are currently investigating, some of which are highlighted in Figure 4. The risks of space radiation become greater as astronauts begin to perform more extended missions into space, such as spaceflight missions to Mars, which is why there is a need to properly investigate the effects of space radiation and devise countermeasures to protect astronauts. Due to space restrictions in vessels such as the International Space Station (ISS), there is a need to test the effect of space radiation in a high throughput, low space manner. This is the benefit that microphysiological systems provide, due to their relatively small size requirements, recapitulation of tissue-level physiology, and possible automated operations (Mu et al., 2022).

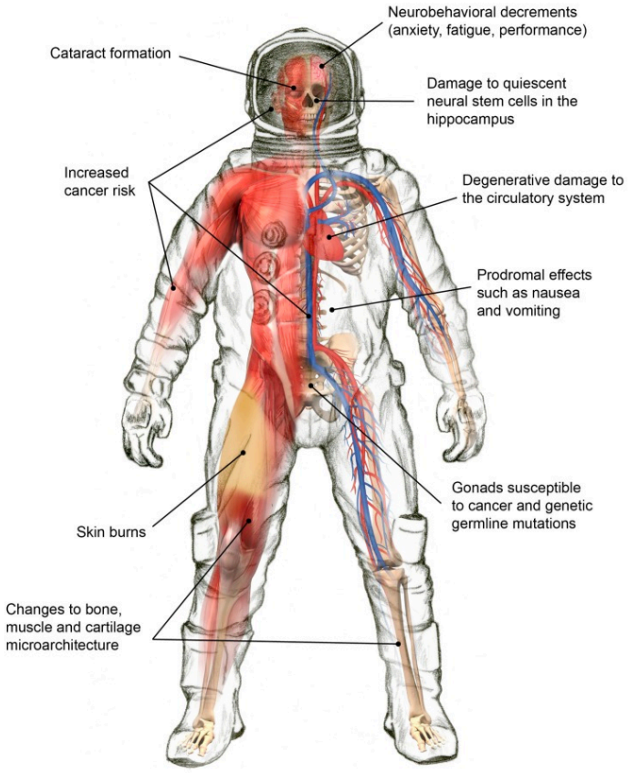

Figure 4: Select health effects due to space radiation exposures (Chancellor et al.)

Radiation-Induced DNA Damage

The most commonly studied effect of radiation is the associated damage to DNA caused by free radicals. This is a critical concern as long-term exposure to radiation can compound the effect of DNA damage leading to cancer in astronauts. In recent years, microfluidic chips have been used to investigate this as the pose as the basic operation of cell culture can be integrated into the chip making them much easier to study in spaceflight. A recent study highlighted the design of a microfluidic chip used to culture bacteria with a fused SOS-related *recA* promoter and green fluorescent protein reporter gene to evaluate the DNA damage caused by radiation (Wang et al., 2022). The study proved the capability of the chip to successfully culture bacteria. In addition, the chip was tested with chemically induced DNA damage, which provided the

expected changes in fluorescence. The next steps of this and similar studies is to move their constructs into actual spaceflight, to enable high-throughput analysis of DNA damage.

Radiation Effect on Cardiac System

The research on the effect of radiation on the cardiovascular tissues is one of the most dependent on microphysiological systems. Initial studies cultured hiPSC-CMs on Earth, and then sent a portion of the plated cells onto the ISS while managing a control population on Earth in parallel. The studies observed an upregulation of Sarcomeric and Myocyte enhancing genes, but little difference in the functional readout of the tissues (Wnorowski et al., 2019). This may be potentially attributed to the fact that these were 2D cultures and not very representative of actual cardiac tissue.

In order to test the isolated effect of space radiation on cardiac tissue, researchers at Columbia University designed a microphysiological system that can then be exposed to a level of acute radiation similar to that in space. In the study they took a standard approach to culturing muscle tissue for space radiation research. They created an MPS platform where human iPSC-derived cardiomyocytes and primary fibroblasts are seeded into a fibrin gel between two flexible pillars. They were allowed to mature for 4 weeks in conjunction with regular electrical stimulation as seen in Figure 5. The researchers then exposed the matured tissue to acute levels of radiation representative of space radiation, and then evaluated the tissues for structural, functional, and molecular changes after 3 weeks. The primary discovery was an impairment of conduction and excitability but greater force generation in the irradiated tissues. This was corroborated by an observed upregulation of genes related to sarcomere organization and genes associated with cardiac hypertrophy (Tavakol et al., 2023).

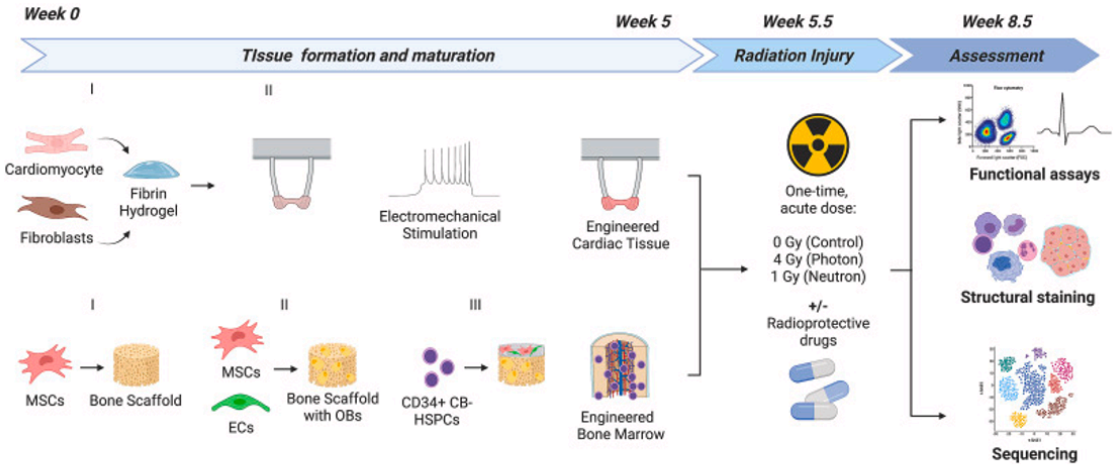

Figure 5: Experimental design for engineered human tissue models for assessing the effects of galactic cosmic rays (Tavakol et al.)

After analysis of the irradiated cardiac tissue, the study went further to try and test Radioprotective drugs to mitigate the effects of the radiation. They discovered that pre-radiation treatment with the drug Amifostine has the potential to restore the cardiomyocyte function to its original levels. The study was also similarly conducted on bone marrow tissues and it was discovered that the addition of cytokine granulocyte-colony stimulating factor was able to restore function to the bone marrow tissues. Overall the study shows promising results for dealing with

the cardiac effects of space radiation. In addition, it has the potential to be individualized using iPSCs from a single individual. However, there is a need to study the effect over a longer period and investigate the genetic and epigenetic changes as actual space flight can occur over the course of years. Additionally, increased throughput and evaluation of other approved drugs is needed to broaden the study. Finally, as with many other studies, investigation into multi-organ systems are needed to investigate cross-talk between organs, as this could play a major role in the results

Radiation Effect on Nervous System

In addition to cardiac tissue, one of the known effects of space radiation is damage to the Central Nervous System (CNS). This inspired research investigating the effect on space radiation on CNS cells using a commercially available organ-on a chip system known as OrganoPlate™. The system was seeded with astrocytes and brain endothelial cells to study the role of astrocytes in mediating radiation responses (Verma et al., 2022). Similar to the cardiomyocyte studies, the system was exposed to acute radiation representative of space radiation. The initial observations of the study were increased vascular permeability, damages to tight junctions, oxidative stress, and inflammatory cytokine production discovered using respective assays. More interestingly, however, was the fact that post-radiation the astrocytes exhibited an anti-inflammatory regulatory phenotype, suggesting that astrocytes could be a target for radiation countermeasures to mediate the endothelial damage. Overall, the activation of the astrocytes in this study were corroborated by observations from in vivo rodent models. The designed system provides a high throughput method of quantifying the effects of radiation of the blood brain barrier. However, further research is required to investigate the exact pathways affecting the astrocytes as well as the addition of other cells in the CNS such as neurons or perivascular pericytes.

Microgravity - Human Physiology Impacts

The long-term effects of microgravity on the human body have been well known for decades: bone loss, muscle atrophy, cardiovascular deconditioning, decreased plasma volume, and the collection of fluids towards the upper body (Wolfe & Rummel, 1992). However, previous models for studying the effect of below full 1-g load on the human body long term have been clunky, incomplete, or impractical, including bedrest, water immersion, dry immersion, and immobilization techniques. While studies have been done for over half a century to investigate the change the human body undergoes in space during manned space flights, these studies are still limited in scope as they do not look closely at organs or tissues due to constraints of a space flight (Yeung et al., 2020). Furthermore, animal models are studied in space, but the magnitude of human translation from these animal results are unknown. Microphysiological systems offer a compact, replicable, and practical way to study the interactions of microgravity with human physiology, which will provide a more in depth and accurate understanding of the changes caused by long term exposure to microgravity along with what can be done to counteract these effects for astronauts.

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Cardiac Deconditioning

In space, microgravity decreases stroke volume and cardiac output of the heart, along with an overall decrease in blood volume. In addition, the lack of orthostatic pressure from gravity decreases arterial pressure which leads to an overall reduction in workload on the heart. Over time, the cardiovascular system deconditions to the environment on Earth and changes in response to the microgravity in space. The effects become more prominent and longer lasting with increased spaceflight length. Within the first 24-48 hours, the left ventricle experiences a 20% size increase in microgravity. Inherently, medical research is more constrained in space due to size limits for equipment and small sample sizes. Furthermore, in space it is easier to collect samples like blood or urine, but acquiring samples from organs and tissues is not practical. Thus, MPS is an exciting frontier for studying biology in space by allowing for an accurate model of the microenvironments of the cardiomyocytes that can be replicable and high throughput. An exciting first step towards these models was Wnorowski et al. when they were able to demonstrate that hiPSC-CMs can model the effects of microgravity, as those cells respond like the whole heart to microgravity effects through gene expression changes (2019). From this foundation, these hIPSC-CMs can be seeded on MPS platforms in order to produce replicable and reliable results by investigating the effects of microgravity on cardiac cells directly.

Muscle Atrophy

Microgravity also reduces the strain on the musculoskeletal system, and despite the extensive exercise that astronauts do everyday to combat atrophy from decreased use, muscles experience a loss of integrity, especially with the myofibrillar proteins which constitute its structure. Muscle tissue chips, seeded with myoblasts collected from a diverse population of young and active individuals along with older, sedentary individuals, were sent into space, while equivalent chips remained on Earth as a control. After a transcriptome RNA-Seq analysis, the muscle chips that were sent into a microgravity environment were found to have a downregulation of key genes that encode structural proteins (MYH1, MYH2, MYH6, MYL10, ACTN3) along with a modulation of the Pi3K/Akt pathway which is critical for regulating the cell cycle (Parafati et al., 2023). In the myobundles, an upregulation of CSF3R was observed, and since CSF3R helps control the production of granulocytes, the regulation of which could be part of the reason why the immune system is also affected in space.

Cerebral Changes:

Gravity helps regulate fluids in the body by providing a downward that is ever present for life on Earth. In a microgravity environment, the body experiences a variety of shifts in blood, plasma, cerebrospinal, lymph, and interstitial fluids. Fluid migration upward can also contribute to potential brain damage from long term spaceflight, as gray matter in the brain was observed to decrease in astronauts after spaceflight (Ly et al., 2022). Another side effect of a headward fluid shift is visual impairment. Researchers are proposing that the weakening of the blood brain barrier (BBB) is a possible cause for changes in gray to white matter ratio and volume in the brain (Amselem et al., 2022). Emulate conducted a brain-on-chip study on ISS to assess effectiveness of anti-inflammatory drugs for maintaining BBB integrity (Levner, 5UH3TR002188).

They also aim to reveal new effects that microgravity has on the BBB for normal and disease states, which could lead to further discoveries on the cause and the actual effects of microgravity on the BBB and the brain.

Human Physiology Impacts from Microgravity	**Effects**	**Why it is Difficult to Study**	**MPS Benefits/ Discoveries/Goals**
Cardiac Deconditioning	- Left ventricle grows 20% in size in first 24-48 hours - 11% loss in blood volume - Orthostatic intolerance	Confines of ISS means that there are limited samples and data cannot be recorded at a cellular or molecular level easily	hiPSC-CMs can model the effects of microgravity on a cellular level
Muscle Atrophy	- 20% loss of muscle mass in the first month - Loss of structural myofibrillar proteins	Limited samples of individuals in space (astronauts are not representative of average persons)	- MPS revealed downregulation of genes for structural proteins for skeletal muscle tissue in microgravity - MPS also revealed modulation of pf the Pi3k/Akt pathway
Cerebral Changes	- Decrease in gray matter after spaceflight - Headward fluid shifts affect the environment of the brain	Molecular and cellular level observation of the brain is difficult from the measurements and characteristics that are available in space	- Aim to understand correlation of inflammation and BBB integrity - Understand microgravity effects on normal and disease states

Figure 6: Table highlighting 3 human physiological changes in space along with what benefit or discoveries MPS can provide.

Conclusion

Microphysiological systems (MPS) have emerged as a powerful and innovative tool for advancing space biology research and understanding the complex effects of the space environment on human physiology. This comprehensive review has explored the various types of MPS, including organ-on-a-chip systems, 3D cell cultures, and microfluidic devices, and their wide-ranging applications in studying the impact of microgravity, space radiation, and other spaceflight-related factors on the human body for both patients on Earth and for astronauts in space. By providing a detailed analysis of the current state of MPS technology and its potential for future development, this review serves as a valuable resource for researchers, space

agencies, and policymakers working at the intersection of space science, biomedical engineering, and human health.

One of the key advantages of MPS over traditional research methods is their ability to provide improved physiological relevance, high-throughput capabilities, and the capacity to model the rapid changes observed in astronauts, which often mimic disease states and aging pathologies on Earth. These advanced systems have enabled researchers to investigate the effects of space radiation on DNA damage, the cardiac system, and the nervous system, as well as the long-term impacts of microgravity on cardiovascular deconditioning, muscle atrophy, and fluid shifts. By recapitulating the complex microenvironment and functionality of human organs and tissues in a miniaturized, controllable setting, MPS offer unprecedented insights into the mechanisms underlying the physiological adaptations and health risks associated with spaceflight.

The potential of MPS to improve astronaut health and performance during long-duration space missions cannot be overstated. By developing personalized countermeasures, optimizing drug therapies, and creating artificial organ systems, MPS can help mitigate the adverse effects of microgravity on the musculoskeletal, cardiovascular, and immune systems. These advancements are crucial for ensuring the safety and well-being of astronauts as they embark on increasingly ambitious missions to the Moon, Mars, and beyond. Moreover, the translational benefits of MPS research in space extend far beyond the realm of space exploration, as the knowledge gained from these studies can directly inform the development of novel therapies and regenerative medicine approaches for age-related disorders and degenerative diseases that affect millions of patients on Earth.

However, it is important to acknowledge the challenges and limitations that must be addressed to fully realize the potential of MPS in space biology research. Technical issues related to device fabrication, operation, and standardization, as well as concerns regarding reproducibility and the need for validation with in vivo studies, are among the key hurdles that need to be overcome. Furthermore, the development of multi-organ systems that can capture the complex interactions between different tissues and organs, the incorporation of patient-derived cells for personalized medicine applications, and the integration of advanced sensing and monitoring technologies are essential for expanding the capabilities and translational impact of MPS in space biology research.

To address these challenges and accelerate progress in this field, future research efforts should focus on several key areas. Continued investment in the development and optimization of MPS technology specifically tailored for space applications is essential. This includes the miniaturization and automation of MPS platforms to ensure their compatibility with the limited space and resources available in spaceflight missions, as well as the development of robust and reliable systems that can withstand the harsh conditions of the space environment. Moreover, the establishment of standardized protocols and validation methods for MPS studies is crucial for ensuring the reproducibility and comparability of results across different research groups and institutions. This will require close collaboration between space agencies, academic researchers, and industry partners to develop common guidelines and best practices for the design, fabrication, and operation of MPS in space biology research. The incorporation of advanced technologies, such as artificial intelligence (AI) and machine learning, into MPS platforms holds immense promise for enhancing the predictive power and automation of these

systems. By leveraging the vast amounts of data generated by MPS experiments, AI algorithms can help identify novel biomarkers, drug targets, and therapeutic strategies for mitigating the health risks associated with spaceflight (Niazi et al., 2023). Moreover, the integration of AI-driven monitoring and control systems can enable real-time adjustments and optimization of MPS experiments, thereby improving the efficiency and effectiveness of space biology research. Globally, exploring the potential for on-orbit MPS research facilities and long-term space missions is a critical step towards advancing our understanding of the effects of prolonged spaceflight on human health. The establishment of dedicated MPS research modules on the International Space Station (ISS) or future space habitats would provide unprecedented opportunities for conducting extended studies on the physiological adaptations and health risks associated with long-duration space travel. Such facilities would also serve as valuable testbeds for the development and validation of countermeasures and therapies designed to protect astronaut health during extended missions.

In conclusion, microphysiological systems represent a transformative technology with the potential to revolutionize space biology research and contribute to the development of effective countermeasures and therapies for both astronauts and patients on Earth. By providing a more physiologically relevant and controllable platform for studying the complex effects of the space environment on human health, MPS can help unlock new frontiers in our understanding of the fundamental mechanisms underlying spaceflight-induced physiological changes and disease processes. However, realizing the full potential of MPS in space biology research will require a concerted effort from the scientific community, space agencies, and policymakers. The integration of expertise from various fields, including biology, engineering, and computer science, as well as international cooperation and knowledge sharing, will be essential for accelerating progress and overcoming the challenges associated with the development and application of MPS technology in space.

As we stand at the threshold of a new era of human space exploration, with ambitious plans for long-duration missions to the Moon, Mars, and beyond, the importance of advancing our understanding of the effects of spaceflight on human health has never been greater. Microphysiological systems offer a powerful tool for addressing this challenge, and their continued development and application in space biology research will undoubtedly play a critical role in ensuring the safety, well-being, and success of future space explorers while also driving breakthrough discoveries that can transform healthcare on Earth.

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