npj | microgravity

Review

Published in cooperation with the Biodesign Institute at Arizona State University, with the support of NASA

https://doi.org/10.1038/s41526-025-00547-z

Stem cells in space: microgravity effects on stem cell fate and implications for regenerative medicine

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Microgravity offers a unique platform for understanding how physical forces influence the fate and function of stem cells. This review integrates recent findings on genomic, epigenetic, and mechanotransductive responses of diverse stem cell types under actual and simulated microgravity conditions. It uniquely relates these biological insights with space-based biomanufacturing, translational applications, and ethical frameworks, highlighting how space-enabled stem cell research advances regenerative medicine both in orbit and on Earth.

Stem cells possess two defining features: the ability to divide through mitosis while maintaining their population, and the ability to transform into specialized cell types. These unique properties have established their fundamental importance in regenerative medicine, disease modeling, and drug discovery[1]. Mesenchymal stem cells (MSCs), pluripotent stem cells (ESCs/iPSCs), neural stem cells (NSCs), and hematopoietic stem cells (HSCs) are important stem cell types owing to their clinical and industrial benefits, which stem from their accessibility and versatile therapeutic applications[2–6]. However, inconsistent differentiation effectiveness, aging during cell expansion, and challenges in preserving stable cell phenotypes throughout in vitro culture restrict the extensive use of stem cell technologies[7,8].

Spaceflight exposes stem cells to physical and biochemical challenges absent in standard laboratory environments. Unique outer space conditions expose stem cells to reduced gravitational forces, altered shear stress, fluid redistribution, increased radiation levels, and the absence of convection currents. These conditions impact essential cellular functions, including cytoskeletal organization, mechanotransduction, gene expression, and intercellular communication[9,10]. Thus, the distinctive characteristics of outer space, such as microgravity, have emerged as promising platforms for innovative stem cell culture and manipulation methods. These unique conditions profoundly alter cell biology. Under microgravity, stem cells adopt three-dimensional (3D) growth and aggregation behaviors rather than the flattened two-dimensional (2D) morphology typically observed on Earth, thereby reshaping cell–cell and cell–matrix interactions. Additionally, exposure to high-energy particles—such as galactic cosmic rays (GCRs) and solar particle events (SPEs)—contributes to the radiation-induced genomic instability and stress responses observed in biological systems[11,12].

Studies conducted under actual microgravity conditions—such as those on the International Space Station (ISS) and Earth-based simulation devices such as clinostats—have revealed that stem cells exhibit distinct proliferation patterns, enhanced spheroid formation, modified differentiation pathways, and changes in cytokine secretion[13]. For example, MSCs maintain their multipotency over extended periods while undergoing modified osteogenic and adipogenic differentiation under microgravity conditions[14]. However, a spaceflight study conducted on the ISS demonstrated that MSCs retained osteogenic and adipogenic differentiation capacities comparable to those of on-ground controls[15]. These contrasting findings highlight that differentiation outcomes may vary depending on the type of microgravity exposure (simulated vs. spaceflight) and the specific experimental context. Space-based experiments have demonstrated that iPSCs exhibit increased expression of pluripotency markers, accompanied by modifications in epigenetic regulation[16]. These effects are mediated by alterations in the cytoskeletal tension, extracellular matrix interactions, and nuclear architecture, which serve as mechanosensitive elements[17].

Furthermore, space-based platforms for large-scale stem-cell biomanufacturing have become increasingly popular. Larger and more resilient 3D aggregates, including spheroids and organoids, form under microgravity conditions. These cultures exhibit greater physiological relevance than 2D cultures and are preferred for regenerative medicine applications. NASA's *Tissue Chips in Space* initiative includes deploying organ-on-chip systems on the ISS for disease modeling in microgravity[18]. One functional demonstration used a muscle tissue chip payload aboard the ISS to study muscle cell biology under spaceflight conditions[19]. The European Space Agency (ESA) also supports the Microgravity for Personalized Medicine (M4PM) program, which aims to develop tumor/organoid/spheroid models in microgravity for personalized medicine applications[20].

NASA's *Tissue Chips in Space*, Space Tango, and the ESA's bioreactor experiments represent commercial and governmental initiatives for evaluating biological production capabilities in low Earth orbit (LEO)[19,21,22].

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This review integrates existing knowledge at the intersection of space biology research and stem cell studies. It outlines the fundamental characteristics of the space environment and its impact on cellular systems. The effects of microgravity on various stem cells are investigated by observing their proliferation rates, differentiation pathways, genomic stability, and paracrine signaling mechanisms. Subsequently, the potential of space-based stem cell mass production and functional improvements is examined. Finally, the technological challenges and ethical dilemmas associated with space-based stem cell research, as well as their future implications, both in the orbital environment and on Earth, are discussed.

The space environment and its biological impacts

The Earth's gravitational force has shaped biological evolution and is a vital force controlling cell shape, development, and function, including cell growth and signal conversion. Altering the Earth's gravitational constant through spaceflight microgravity conditions or Earth-based simulations produces unique biological environments that reveal previously hidden regulatory mechanisms and stress responses in simple to complex organisms[23]. The space environment presents a near-weightless environment, along with increased ionizing radiation, low shear fluid dynamics, temperature fluctuations, and atmospheric variations. Cellular physiology experiences multidimensional perturbations owing to these factors in outer space.

The space environment: a unique regulator of cell biology

Microgravity is an environment where gravitational acceleration drops to nearly zero levels (approximately less than 10^{-4} g), which occurs during orbital free fall inside a spacecraft, such as the ISS[24]. Organelle sedimentation, cell culture stratification, and fluid convection driven by buoyancy forces are substantially reduced under these conditions. The absence of gravitational force affects both nutrient diffusion and intracellular and extracellular interactions[25,26]. In stem cells, this results in cytoskeletal remodeling and redistribution of focal adhesion complexes, along with impaired actomyosin contractility, which substantially affects mechanosensitive gene regulatory pathways[27].

Microgravity also disrupts the mechanical homeostasis governing stem cell fate by interfering with core mechanotransduction pathways such as integrin-focal adhesion kinase (FAK) signaling, Rho-associated coiled-coil–containing protein kinase (RhoA–ROCK)-actomyosin contractility, Yes-associated protein/WW domain–containing transcription regulator 1, and transcriptional co-activator with PDZ-binding motif (YAP/TAZ) nuclear localization[28]. The absence of gravitational forces destabilizes these key systems, impairing the ability of stem cells to sense substrate stiffness and mechanical strain. These alterations modulate downstream gene expression and influence cell differentiation trajectories, including a notable shift in the balance between osteogenic and adipogenic fates of MSCs[29]. Studies under actual and simulated microgravity (SMG) have demonstrated that disruptions to integrin signaling, YAP/TAZ localization, and the RhoA–ROCK pathway significantly affect stem cell mechanobiology by altering cytoskeletal tension and mechanotransduction signaling, thereby regulating pluripotency, multipotency, and stemness depending on the stem cell type[16,17,27,30].

Space radiation effects

The space radiation environment is complex, mixed, and temporally variable, presenting distinct challenges beyond microgravity for living systems. In addition to GCRs, which include high-energy protons and heavy ions, biological samples in LEO are intermittently exposed to SPEs and trapped charged particles within the Van Allen belts, generating a mixed-field radiation spectrum that is challenging to reproduce on Earth[31,32]. High-energy heavy (HZE) ions produce dense ionization tracks, resulting in clustered DNA damage and formation of reactive oxygen species (ROS), which disrupt chromatin organization and compromise genomic integrity[33]. These complex physical and chemical interactions influence DNA repair, telomere maintenance, and cell cycle control, which are crucial for highly proliferative cell types, such as stem cells[34].

Outside the Earth's magnetosphere, cells encounter increased ionizing radiation from GCRs and SPEs beyond the microgravity environment. The ISS experiences radiation levels between 80 and 160 mSv during its 6-month missions, surpassing the Earth's average background radiation by a factor of nearly 100. Elevated radiation exposure poses the risk of DNA double-strand breaks and chromosomal instability, leading to telomere shortening and cancer transformation in proliferative cells, including stem cells[35].

Although radiation typically poses a threat to genomic stability, unexpected results have been observed in stem cells, including short-term telomere extension in astronauts[36]. Depending on cell type and context, interactions between microgravity and radiation produce either synergistic or antagonistic effects, highlighting the need for comprehensive models in space biology. Recent studies have demonstrated the additive effects of microgravity and ionizing radiation on the production of ROS, apoptosis, and DNA damage, implicating RAC2-mediated oxidative stress pathways[37]. Additionally, radiation exposure modulates telomere structure and telomerase activity, which may contribute to instability and potential stem cell reprogramming[38].

Within LEO, such as aboard the ISS, partial protection by Earth's magnetosphere reduces radiation exposure compared to that in deep space, although it still results in radiation levels of approximately 80–160 mSv over 6 months—nearly 100 times higher than that on Earth. Beyond the magnetosphere, such as during transit to Mars or the lunar surface—cells and tissues are directly exposed to high fluxes of GCRs and sporadic SPEs—resulting in cumulative doses exceeding 1 Sv during extended missions. This deep-space radiation environment is dominated by HZE ions that penetrate shielding and generate dense ionization tracks, posing severe challenges to genomic stability, DNA repair, and regenerative processes in stem cells[33,34]. These distinctions are critical when extrapolating ISS-based experimental findings to future lunar and Martian missions.

Additionally, the lunar surface presents a distinct deep-space radiation environment, relevant to upcoming Artemis missions. Unlike the ISS, the Moon lacks a global magnetic field or dense atmosphere, exposing biological systems directly to GCRs and SPEs. Measurements from the Apollo missions indicated average surface doses of approximately 1–1.4 mSv per day, consistent with current modeling of the predicted exposure range of the Artemis program[39,40]. These lunar data provide critical context for understanding radiation-driven biological effects and guide future stem cell experiments planned for the Moon's surface.

Simulation platforms and models

The fluid dynamics shift toward surface tension dominance rather than gravity control under microgravity conditions. As convective mixing and sedimentation do not occur, cell cultures develop under diffusion-limited conditions. Microgravity-induced changes in fluid dynamics affect oxygen, nutrient, and metabolic waste movement through culture media, directly influencing stem cell metabolic functions and survival rates[41,42].

When suspension cultures operate under microgravity conditions, mechanical load distribution becomes more uniform, whereas shear forces diminish. Under these specific conditions, cells naturally assemble into 3D spheroids, which better replicate in vivo tissue architecture and paracrine communication than traditional 2D monolayer cultures[43]. Spheroids produced from stem cells demonstrate increased stemness characteristics and distinct differentiation behaviors compared to 2D cultures on Earth[44]. Reduction in mechanical shear was confirmed through numerical fluid modeling in random positioning machines (RPMs), which revealed localized shear on the order of tens of mPa, a condition different from that of standard Earth-based culture systems[45].

The scarcity of orbital platform access has triggered the development of multiple ground-based technologies that can mimic microgravity conditions. Ground-based technologies developed to simulate microgravity include clinostats (2D and 3D varieties), RPMs, and rotating-wall vessel bioreactors. These platforms create time-averaged weightlessness by randomizing the direction of the gravitational vector. Several studies have used SMG platforms to explore stem cell behavior under mechanical unloading

conditions. For example, mouse embryonic stem cells cultured in clinostat-based SMG exhibit reduced proliferation and altered differentiation potential, accompanied by changes in DNA damage responses[46].

Similarly, bone marrow–derived MSCs exposed to clinostat conditions inhibit osteogenic differentiation associated with F-actin depolymerization and reduced TAZ nuclear localization[17]. Additionally, NSCs under SMG display enhanced proliferation and shortened cell cycle duration compared to static controls[47]. These findings confirm that SMG systems can recapitulate the critical mechanobiological features of actual microgravity, including altered cytoskeletal tension, signaling dynamics, and lineage specification.

SMG serves as a beneficial tool for early research and hypothesis development. However, it fails to perfectly simulate both fluid dynamics and radiation exposure observed in spaceflight; therefore, the results require careful interpretation[48].

Spheroid formation, differentiation behavior, and oxygen and nutrient diffusion properties vary depending on the specific RPM or clinostat setup and the fluid dynamic environment. For example, simulations and empirical measurements have shown that the shape of a vessel and its fill volume significantly alter the microshear stress environment[45,49].

Microgravity in the space environment changes the fundamental physical and biochemical signals that control cellular function[50]. The space environment enables researchers to investigate mechanobiology and develop improved methods for stem cell culture and differentiation owing to the unique properties of stem cells. Knowledge of the cellular responses to space-specific stimuli establishes the foundation for transitioning orbital platforms from experimental models to next-generation biomanufacturing environments (Fig. 1).

Stem cell functional responses to microgravity

In space, stem cell behavior is modulated by microgravity in a context-dependent manner, which affects replication abilities, differentiation processes, mechanotransduction pathways, and genomic stability. The multifaceted physical and physiological challenges of spaceflight have revealed previously hidden cellular mechanisms, providing a novel understanding of stem cell behavior that surpasses what could be achieved on Earth. These cells exhibit lineage-specific behaviors in response to space-related stimuli[17,49,51–53].

Proliferation and self-renewal

Stem cell proliferation is affected by microgravity in a complex and cell-type-dependent manner. For example, PSCs can temporarily sustain self-renewal in microgravity owing to the upregulated expression of pivotal transcription factors such as Oct4 and Nanog[54]. Similarly, MSCs and NSCs frequently exhibit increased spheroid formation and proliferation[55,56]. However, other studies have reported decreased colony formation or increased apoptosis, particularly in HSCs whose ability to proliferate and engraft may be compromised[57].

Microgravity induces measurable alterations in the cell cycle of stem cells and their progenitors. Mouse embryonic stem cells exposed to clinostat-based SMG exhibited delayed progression through the G2/M phase and increased DNA damage signaling[46]. Similarly, murine embryonic stem cells cultured in microgravity-like conditions exhibited reduced expression of cell cycle regulators such as cyclin B1 and CDK1[30]. These findings suggest that microgravity influences proliferation kinetics by modulating checkpoint activation and genome maintenance pathways. These results suggest that, depending on niche mimicry and signaling support, microgravity may impair viability or cause stress in some situations, while stimulating proliferation in others.

Differentiation trajectories

One of the primary phenomena observed under microgravity is the alteration of stem cell differentiation preferences. Although microgravity conditions transiently increase the maintenance of PSC self-renewal, they also produce noticeable changes in the PSC differentiation pathways. Embryoid bodies created from PSCs when exposed to microgravity became larger and exhibited more varied germ layer marker expression, indicating changes in cell aggregation dynamics and paracrine signaling networks due to low-shear conditions[58]. A recurring theme in microgravity studies is the altered differentiation trajectory of the stem cells. PSCs show enhanced

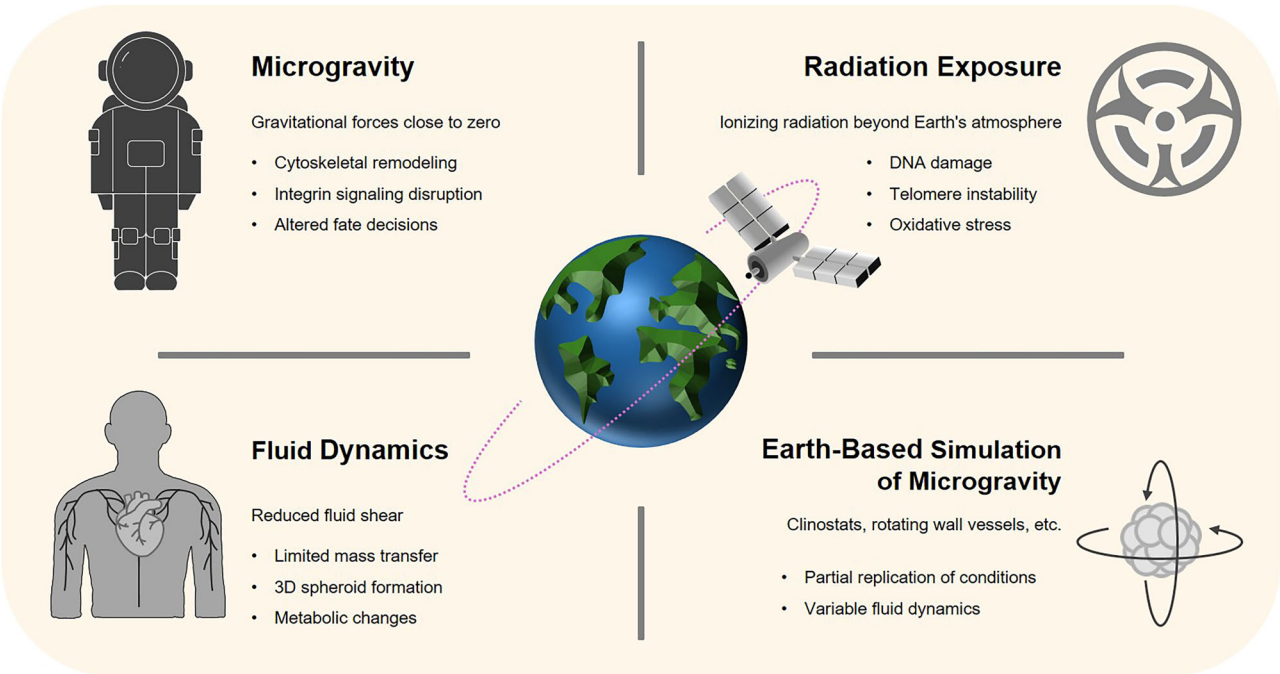


Fig. 1 | The space environment and its biological impacts. This infographic illustrates the multifactorial nature of the space environment, highlighting how microgravity, ionizing radiation, altered fluid dynamics, and temperature or atmospheric variation synergistically perturb cellular physiology. These physical factors influence stem cell morphology, cytoskeletal tension, nutrient diffusion, and genomic integrity, ultimately modifying fundamental cell functions such as proliferation, differentiation, and DNA repair.

mesodermal (e.g., cardiac) and endodermal (e.g., hepatic) differentiation, likely driven by the modulation of Wnt/β-catenin and transforming growth factor-β1 (TGF-β) signaling[54]. MSCs exhibit suppressed osteogenesis and enhanced chondrogenesis, whereas NSCs often display a posterior neural bias under microgravity[47,59]. In HSCs, lineage output is skewed toward myeloid cells at the expense of lymphoid cells. Rodent hindlimb unloading experiments, which simulate aspects of microgravity, have demonstrated a significant expansion of myeloid progenitors, including neutrophils, accompanied by a reduction in B and natural killer cells[60]. Moreover, spaceflight studies involving human CD34+ hematopoietic progenitors have shown accelerated maturation into macrophage-like cells and impaired erythroid lineage output under microgravity conditions[61]. These observations suggest that the space environment may disrupt hematopoietic balance, potentially favoring the production of innate immune cells, while compromising adaptive immunity components. Similar alterations have been observed in astronauts during and after space missions, providing a physiological context for in vitro and in vivo stem cell findings.

Long-duration astronauts frequently exhibit spaceflight-associated anemia characterized by reduced red blood cell mass and increased hemolysis[62]. These results suggest that the microgravity-induced suppression of erythropoiesis observed in human CD34+ progenitor cultures may contribute to the hematological adaptations observed in astronauts.

Additionally, spaceflight data indicate immune dysregulation, including reduced T-cell activation and altered cytokine profiles[63], which align with studies showing that microgravity mediates the skewing of HSC differentiation toward myeloid lineages.

Collectively, these astronaut-based findings support the hypothesis that hematopoietic and immune responses to spaceflight likely stem from cellular adaptations to altered mechanical and radiation environments, thereby bridging fundamental stem cell biology with human physiological outcomes in space. These shifts suggest that microgravity alters the mechanical and chemical signaling thresholds essential for fate decisions, possibly by removing substrate stiffness cues and enhancing sensitivity to soluble morphogens. Such lineage-level alterations imply that microgravity-induced changes at the stem cell stage may have downstream consequences across multiple organ systems, potentially affecting tissue regeneration, immune homeostasis, and even endocrine regulation in space environments.

Cytoskeletal remodeling and mechanotransduction

The cytoskeletal structure of stem cells undergoes substantial modifications during spaceflight. Actin stress fibers and microtubule networks are disassembled and reorganized in multiple cell types when subjected to microgravity conditions[64]. The Hippo pathway loses its function because these structural changes interfere with mechanotransduction via cytoskeletal tension, which controls YAP/TAZ localization and activation. Under microgravity conditions, the YAP/TAZ proteins remain in the cytoplasm, where they lose their ability to support cell proliferation and survival[28].

Multiple cell types (e.g., hMSCs, endothelial cells, melanoma cells) exposed to microgravity show decreased FAK signaling, consistent with observations of reduced substrate adhesion and integrin-mediated force transduction[14,27,65–68]. Mechanical disruptions within the microenvironment lead to downstream effects on cellular fate, as differentiation choices depend heavily on these mechanical attributes.

Secretome and paracrine signaling

In addition to inducing intrinsic cellular changes, microgravity modifies the secretory phenotype of stem cells. MSCs cultured in microgravity conditions show increased production of anti-inflammatory cytokines, including interleukin-10 and TGF-β1, as well as pro-regenerative factors such as vascular endothelial growth factor and hepatocyte growth factor[69]. Changes in the secretome during microgravity exposure can improve the immunomodulatory and angiogenic capabilities of these cells after they return from space, potentially increasing the therapeutic effectiveness of microgravity-conditioned cells.

The results of these studies have sparked interest in the development of cell-free therapies using a microgravity-modified secretome comprising exosomes and conditioned media as a safe and scalable alternative to stem cell transplantation[70]. Although other stem cell types, such as NSCs and PSCs, may undergo transcriptional reprogramming under microgravity, current evidence regarding their secretome modulation remains inconclusive. Therefore, therapeutic exploitation of space-conditioned secretory profiles is largely limited to stem cells.

Genomic stability and DNA damage responses

Microgravity-conditioned stem cells show functional benefits; however, concerns persist regarding their genomic and epigenomic stability[71]. The spaceflight environment exposes astronauts to increased radiation and oxidative stress, which can damage the integrity of DNA strands[35]. The NASA Twins Study demonstrated significant fluctuations in telomere length throughout spaceflight; telomeres lengthened during flight but rapidly shortened after returning to Earth, prompting important questions regarding long-term genomic stability[36]. Although somatic cell studies have provided the most information on genomic instability in space, mounting evidence suggests that stem cells may also be susceptible to genotoxic stress from radiation exposure and microgravity. For example, ESCs from the SJ-10 satellite exposed to spaceflight conditions demonstrate marked downregulation of DNA repair genes, suggesting weakened genome maintenance systems[72]. Similarly, in ESCs lacking Rad9, SMG enhances ROS production, resulting in severe double-strand breaks in DNA and apoptosis[73]. Additional studies have examined DNA damage and repair mechanisms in human and murine stem cells under combined exposure to microgravity and radiation. For example, murine embryonic stem cells exposed to SMG display reduced expression of genome maintenance regulators and telomerase-associated factors[30]. Moreover, clinostat-based microgravity simulations induce replication stress and increase DNA lesions in hematopoietic progenitor cells[74]. Reviews integrating these findings have emphasized the combined genotoxic impact of HZE ions and gravitational unloading on DNA integrity, highlighting the synergistic disruption of DNA repair efficiency and chromatin architecture[12,34]. After exposure to space, PSCs exhibit changes in telomerase activity and epigenetic remodeling, such as altered DNA methylation and chromatin accessibility, which may have long-term effects on their genomic integrity and lineage potential[36]. These results emphasize the necessity for a systematic evaluation of genotoxic and epigenetic risks in space-conditioned stem cell populations, as direct experimental data on adult stem cells, such as MSCs or HSCs, are lacking.

Epigenetic alterations

Space flight conditions can cause notable epigenetic changes. Microgravity exposure leads to alterations in histone methylation and global DNA methylation within stem cells, thereby affecting gene silencing, cellular memory, and reprogramming efficiency[75]. The adaptability benefits of this plasticity highlight the need for strict quality control measures in stem cell applications used in space[51].

Cancer stem cells in microgravity

In addition to normal stem cell populations, cancer stem cells (CSCs) also display distinct adaptations to microgravity. Breast cancer cells exposed to SMG undergo cytoskeletal remodeling with reduced focal adhesion signaling, suggesting that mechanical unloading alters CSC survival pathways[76]. Microgravity further enhances the assembly of CSCs into 3D spheroids and organoids, which more accurately reflect the in vivo tumor microenvironment than standard 2D cancer cell cultures[77]. Colorectal cancer organoids exhibit altered proliferation and therapeutic response profiles under SMG[78]. Moreover, Wise et al. reported that breast cancer cells exposed to SMG displayed altered small extracellular vesicle release[79]. Although they did not directly examine cancer stem cells, vesicle-mediated signaling influences CSC maintenance and drug resistance, suggesting that microgravity-induced vesicle alterations in tumor cells may indirectly affect CSC behavior.

Table 1 | Functional responses of various stem cell types under microgravity

Stem cell type	Self-renewal and proliferation	Differentiation bias	Cytoskeletal/ mechanotransduction	Potential applications
MSCs	Proliferation ↑ Spheroid formation ↑	Osteogenesis ↓ Chondrogenesis ↑	Focal adhesion kinase ↓ YAP/TAZ ↓ Cytoskeletal remodeling	Cartilage repair Bone loss countermeasures
Pluripotent (ESCs/iPSCs)	Transient ↑ Oct4/Nanog Variable proliferation	Mesoderm (cardiac) ↑ Endoderm (hepatic) ↑ Neuroectoderm ↓	Actin stress fiber loss YAP/TAZ nuclear exclusion	Cardiomyocyte production Hepatocyte production Organoids
NSCs	Spheroid growth ↑ Regional proliferation bias ↑	Caudalization of neural fate Variable gliogenesis	Planar polarity loss	Brain organoids Neurodevelopmental modeling
HSCs	Quiescence ↓ Engraftment ↓ Variable apoptosis	Myeloid lineage ↑ Lymphoid output ↓	-	Immune system modeling Leukemia risk studies

A comparative summary of stem cell responses to microgravity across different cell types, including pluripotent stem cells (ESCs/iPSCs), mesenchymal stem cells (MSCs), neural stem cells (NSCs), and hematopoietic stem cells (HSCs). Each cell type is evaluated for its behavior in self-renewal, differentiation, mechanotransduction, and its potential applications. Data are derived from spaceflight and ground-based simulation studies.

These findings highlight CSCs as a critical extension of microgravity stem cell research, offering unique platforms for tumor modeling, anticancer drug screening, and radiobiology studies in space. Beyond oncology, these observations reinforce a broader concept that stem cell alterations in microgravity can influence multiple physiological systems. The mechanobiological and epigenetic changes observed in stem cells under space conditions may contribute to tissue-specific dysfunctions, including musculoskeletal atrophy, alterations in neuroplasticity, and impaired hematopoiesis, which have been documented in astronauts.

These functional reactions indicate that microgravity is an active modulator of stem cell biology, rather than a passive environment. Microgravity alters lineage commitment and differentiation potential in a context-dependent manner, with some stem cells showing restricted capacity for certain fates, while others display enhanced plasticity. Stem cell expansion, lineage restriction, and altered secretory activity observed in multiple studies emphasize that microgravity influences cell-intrinsic pathways and interacts with surrounding niches (Table 1).

Current and future applications

Current applications

Stem cell investigations in space and under SMG conditions have revealed biological behaviors that directly influence biomedical research and regenerative medicine. Microgravity-induced changes in differentiation, gene expression, and self-organization have contributed to advancements in tissue engineering, immunomodulation, and disease modeling.

In tissue engineering, microgravity culture promotes the formation of complex 3D structures[42]. For instance, enhanced extracellular matrix production and cellular organization have been observed in bone and cartilage tissues, where cytoskeletal remodeling compensates for the absence of mechanical loading[30]. Neuronal stem cells also benefit from exposure to microgravity, displaying enhanced neurite outgrowth, synaptic connectivity, and network assembly that resemble physiologically accurate neural tissues[11]. These properties advance the development of implantable tissue constructs and provide relevant models for degenerative conditions, including osteoporosis, osteoarthritis, Parkinson's disease, and Alzheimer's disease[80–83].

Microgravity augments the immunomodulatory potential of stem cells. MSCs cultured under microgravity exhibit an increased release of anti-inflammatory cytokines and exosomes, which could address one of the primary limitations of MSC-based therapies: variability in clinical efficacy[69,79,84]. Preconditioning MSCs in SMG environments has been proposed as a strategy to enhance their therapeutic robustness for inflammatory and autoimmune disorders, as well as for managing immune dysregulation during long-term spaceflight.

Disease modeling and drug discovery represent other immediate applications. Microgravity promotes self-organization and maturation of stem cell-derived organoids, resulting in physiologically relevant models of human tissues[79]. Tumor spheroids generated in space closely mimic the in vivo cancer microenvironment, enhancing the predictive accuracy of anticancer drug testing[54,78,85]. Similarly, liver and cardiac organoids produced under microgravity conditions demonstrate advanced phenotypes, enabling the assessment of drug metabolism and cardiotoxicity. These models provide improved preclinical platforms for the development of precision medicines and pharmaceuticals.

Future prospects

Although current applications highlight the translational potential of microgravity, future opportunities lie in space-based biomanufacturing, regenerative medicine, and long-term safety assessments.

Microgravity induces distinct epigenetic and transcriptional changes in stem cells, including global DNA hypomethylation, altered histone marks, such as H3K27me3, and shifts in chromatin structure[86,87]. These modifications may provide advantageous plasticity and stress adaptation but raise concerns regarding lineage fidelity, genomic stability, and long-term safety[46,49,88,89]. Therefore, epigenetic monitoring will be crucial in evaluating space-conditioned stem cell products prior to clinical translation.

The development of orbital biomanufacturing platforms is promising. Microgravity enables uniform suspension cultures with reduced shear stress, improving scalability and product consistency[43]. Space-based bioreactors can generate therapeutic cells, extracellular vesicles, and engineered tissues[90]. Initiatives such as NASA's *Tissue Chips in Space* program, ESA's on-orbit bioreactor experiments, and private ventures such as Space Tango highlight the feasibility of building "cell factories" in LEO[19,21,22]. These facilities could eventually outperform Earth-based production systems by providing higher purity, yield, and reproducibility of stem cell-derived products.

Future research should investigate the combined effects of microgravity and cosmic radiation, particularly for extended space missions. HSCs under SMG exhibit impaired resolution of DNA double-strand breaks after genotoxic stress, whereas ESCs show reduced efficiency in DNA damage repair[46,91]. These synergistic stressors present unique safety challenges for space-based stem cell applications, highlighting the need for a more comprehensive investigation into DNA repair dynamics and long-term genomic integrity.

Overall, microgravity research has progressed from fundamental biology to early translational applications, with an expanding potential for regenerative medicine. This field is positioned to develop innovative therapeutic strategies by integrating current findings with biomanufacturing technologies, omics-driven analyses, and spaceflight platforms. Although most of these applications remain exploratory, the trajectory of space-based stem cell research highlights their potential to transform regenerative medicine, both in space and on Earth (Fig. 2).

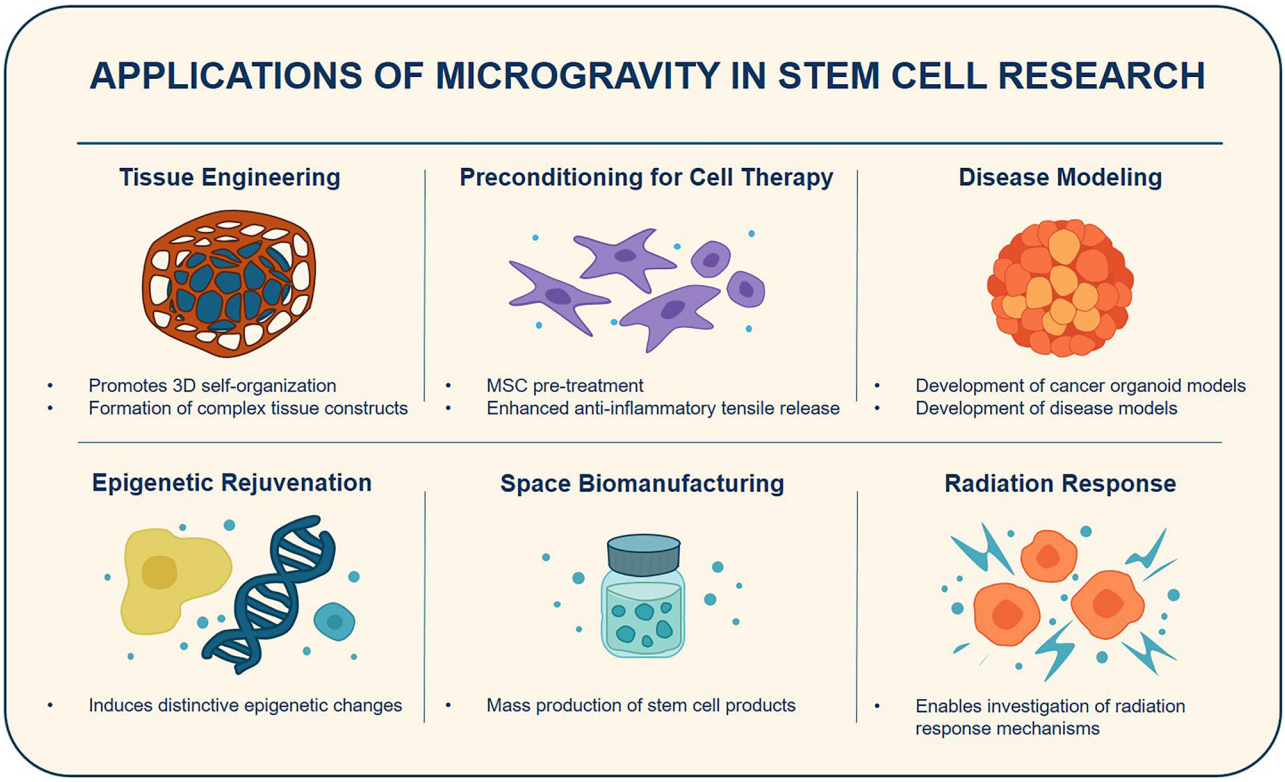


Fig. 2 | Biomedical applications of microgravity-conditioned stem cells. The diagram summarizes key biomedical and translational applications of stem cells cultured in space or simulated microgravity environments. These include enhanced tissue engineering via 3D self-organization, improved disease modeling through organoid maturation, augmented immunomodulatory functions in mesenchymal stem cells (MSCs), and potential deployment in space-based biomanufacturing. Such adaptations offer novel therapeutic and industrial opportunities.

Challenges and perspectives

Space-based stem cell research holds great potential but must overcome significant technical, ethical, and regulatory challenges before its capabilities can be fully realized. The transformative potential of this field necessitates a visionary approach that combines scientific breakthroughs, social accountability, and international collaboration. This section reviews the current challenges within the field while identifying possibilities for sustainable and ethical development that will create a meaningful impact.

Technical barriers

Limited access to spaceflight opportunities is the most significant obstacle to widespread progress in this field. Current research relies heavily on occasional space missions conducted by the government or commercial entities, which impose rigid restrictions on payloads and offer brief experimental times, along with inadequate real-time monitoring features. Despite their usefulness as partial analogs of microgravity conditions, parabolic flights and ground-based simulators, such as clinostats, cannot fully replicate the biological effects of actual spaceflight[92]. The ability to validate the findings on a large scale remains challenging. Commercial space stations and reusable launch systems could address this issue within the next decade; however, consistent access to orbital and deep-space environments remains a fundamental obstacle owing to reliability and affordability issues.

The rapid expansion of commercial space enterprises will transform the accessibility and scalability of research. Private sector initiatives, such as Axiom Space's development of the first commercial space station[93] and SpaceX's reusable launch systems, lower logistical barriers and enable more frequent biological experimentation. These platforms will support continuous microgravity-based studies involving stem cell culture, tissue engineering, and drug testing, extending beyond government-sponsored missions. The integration of public–private partnerships is essential for establishing standardized research frameworks, ensuring biosafety compliance, and accelerating the translation of space-enabled stem cell technologies into biomedical innovation[94,95].

The intense radiation in space presents scientific possibilities and potential biological dangers to researchers. Ionizing radiation induces DNA strand breaks, chromosomal aberrations, and epigenetic modifications in stem cells, compromising their genomic integrity and safety during therapy[96]. Radiation exposure encountered in space enables the study of aging and cancer growth; however, it also poses potential safety risks regarding genetic mutations and the clinical applications of stem cells. Future space missions should implement strict dosimetry procedures, along with genomic monitoring and comprehensive post-flight quality assessments to confirm that therapeutic cells developed in space adhere to clinical-grade safety requirements.

Ethical and regulatory considerations

As distinct space agencies and governmental bodies maintain their own biosafety standards and ethical guidelines for clinical translation, space biotechnology research lacks a universal regulatory framework[97]. Variations between agencies create obstacles for joint ventures and hinder the development of unified stem cell-use protocols for space exploration. The growing international scope of space biology requires the development of universal standards for stem cell management and medical applications. Data sharing methods, material transfer systems, and post-mission validation protocols require standardization across both institutional and national borders.

Opportunities for commercial and international collaboration

Future studies must address the existing limitations and strategically incorporate new technologies and conceptual developments to unlock the full potential of space-based stem cell research. Autonomous miniaturized bioreactor systems for long-duration missions represent a crucial area that

requires further development to function without human oversight. Using these systems, researchers can conduct high-throughput stem cell culturing and monitoring while performing real-time analysis in space, thereby minimizing dependency on astronauts and reducing experimental variation.

The concurrent fusion of multi-omics technologies, such as transcriptomics and proteomics, with artificial intelligence systems enhances the mapping of biological changes during spaceflight. Data-driven methodologies reveal new regulatory mechanisms while assisting in optimizing culture environments and accelerating the clinical application of stem cell products adapted to space conditions.

The on-demand creation of tissue constructs using stem cells adapted to space conditions is a promising new approach. The ability to generate medical solutions in situ is crucial in extraterrestrial or remote terrestrial locations because of the limited availability of immediate medical resources. These systems can produce functional tissues as needed, enabling them to support immediate regenerative treatments and customized therapy applications.

Building societal trust and ethical transparency are equally significant. Public engagement needs to be enhanced through inclusive dialogue, accessible education, and international cooperation as space biology approaches clinical relevance and commercial deployment. The manipulation and ownership of biological materials in space raise significant ethical concerns that necessitate proactive responses, which must be coordinated on a global scale.

The successful advancement of space-based stem cell platforms depends on their integration into earthbound biomedical applications. This emerging field offers a transformative vision for healthcare in the next generation by enabling improved disease modeling, efficient therapeutic production, and regenerative care during deep-space missions. However, this transformative vision requires ongoing scientific breakthroughs, accompanied by robust ethical oversight and international collaboration, to achieve shared progress.

Data availability

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Received: 8 August 2025; Accepted: 19 November 2025;
Published online: 02 December 2025

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Acknowledgements

This work was supported by the Bio&Medical Technology Development Program (RS-2023-00220207) of the National Research Foundation of Korea (NRF) and the Korean Fund for Regenerative Medicine (KFRM) grant (25A0203L1) funded by the Ministry of Science and ICT, the Ministry of Health & Welfare, Korean government (Republic of Korea). This work was also supported by a Chung-Ang University Graduate Research Scholarship (Academic scholarship for the College of Biotechnology and Natural Resources, 2023). The authors employed GPT-5, OpenAI to assist in drafting an initial outline and for language editing during manuscript preparation. The authors independently verified all cited literature, interpretations, and conclusions. The final version of the manuscript was written, critically revised, and approved by all human authors, who take full responsibility for its content.

Author contributions

S.K. conceptualized, drafted, reviewed, and edited the manuscript. K.H.M. conducted the literature search, visualization, and editing. Y.G.P. provided visualization and editing. S.H.M. provided funding, resources, reviewed the manuscript, and supervised the writing. All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

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