

Effects of Weightlessness on Molecular Changes in Cellular Organisms, Animals and Plants

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1. Introduction

Space travel is a dream of humankind. Planned deep space exploration adventures will increase the time which humans or animals will spend in weightlessness. Space travelers will be exposed to microgravity (μg), cosmic radiation, isolation and other stresses. Unfortunately, a long-term spaceflight has large well-known effects on our health [1]. To counteract these health problems, studies supported by NASA, ESA and other space agencies focusing on cardiovascular changes, bone loss, muscle atrophy or the immune system, among others, have been performed in recent years [2,3]. Space research is a hot topic at present. To perform research in weightlessness, several platforms with diverse durations of μg exposure for experiments in real μg are available [4]. A drop tower provides about 4.74 s of weightlessness up to three times a day. The time in μg can be doubled with a catapult system. With the catapult, the experimental subjects are flung from the bottom to the top and then fall back. A drop tower is mainly used for experiments in science and physics under space conditions [5,6]. Short-term experiments in μg can be realized during a parabolic flight [7]. A parabola provides 22 s of μg and two phases of hypergravity lasting 20 s. Researchers can study the early responses to gravitational changes in humans, microorganisms, cells and plants, among others. Parabolic flights are used for astronauts' training and human physiological experiments, as well as in physics and material sciences. Other platforms, like sounding rockets, can provide, depending on the rocket type, from 3 min up to 15 min of μg . These rockets carry scientific instruments and experiments into space along a parabolic trajectory [8]. Sounding rocket flights are used for short-term studies in medical, biological, physical, chemical, atmospheric or material sciences [8–10]. To perform long-term studies (days), biosatellites like the Russian Bion spacecraft or the Shenzhou spaceships can be used. The International Space Station (ISS) and the Chinese Space Station (CSS) provide the possibility to perform experiments lasting more than six months [11,12].

Unfortunately, experiments in real μg on the ISS and CSS are expensive and rare. It is difficult to obtain the opportunity to perform studies in space. Therefore, so-called ground-based facilities (GBFs) to simulate μg have been developed. NASA and ESA have acknowledged various GBFs. Examples include the NASA-developed rotating wall vessel (RWV) and the 2D and 3D clinostat, among others such as the Random Positioning Machine (RPM). All devices are able to create μg on Earth. Researchers use these machines to prepare space missions, or to investigate the cell- and molecular-level biological effects of μg on cells, microorganisms, bacteria or plants [13]. Frequent research objectives in the field of space biology are to study changes in protein and gene expression or the cell metabolism of



Received: 10 August 2025

Accepted: 19 August 2025

Published: 21 August 2025

Citation: Grimm, D. Effects of Weightlessness on Molecular Changes in Cellular Organisms, Animals and Plants. *Biomolecules* **2025**, *15*, 1207.

<https://doi.org/10.3390/biom15081207>

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cells, animals and humans, or plants exposed to μg . Omics investigations in weightlessness focusing on the human and animal organism or on cells aim to characterize and quantify the biological factors responsible for the observed changes in morphology, structure, function, metabolism and dynamics of cells exposed to μg conditions. Weightlessness has been demonstrated to influence various biological processes in vitro and in vivo. Increasing our knowledge in this research field could help us find countermeasures against various space stressors and may improve our understanding of various diseases on Earth.

2. An Overview of Published Articles

This Special Issue (SI), “*Effects of Weightlessness on Molecular Changes in Cellular Organisms, Animals and Plants*”, comprises research articles in the field of gravitational biology, space medicine, translational regenerative medicine and molecular oncology. This issue contains nine research articles [14–22] and one review [23] (Table 1). It addresses the impact of μg on benign human [14,17] and animal cells [22], stem cells [15,18], cancer cells [21], freshwater protists (*Euglena (E.) gracilis*) [19], mice [16] and rats [20].

Table 1. Contributions to the Special Issue “Effects of Weightlessness on Molecular Changes in Cellular Organisms, Animals and Plants”.

Author	Title	Topics and Results	Type	Reference
Jokšienė J. et al.	Effects of high glucose on human endothelial cells exposed to simulated microgravity	- Human EA.hy926 endothelial cells exposed to a 3D clinostat and to NG or HG for 14 d. - Glucose concentrations had a weaker effect than clinorotation. μg downregulated the ECM gene and protein expression and had a stronger influence on glucose metabolism than HG. - HG caused more pronounced changes in 3D cultures than in 2D cultures, including an increase in the size and number of spheroids, upregulation of NOX4 and NF-κB and CASP3, and downregulation of fibronectin and transglutaminase-2.	Research article	[14]
Tran V. et al.	Oligodendrocyte progenitors display enhanced proliferation and autophagy after space flight	- Behavior of oligodendrocyte progenitors (OLPs) after spaceflight using time-lapse microscopy. - Space-flown OLPs presented a significant increase in autophagic cell death. - Secretomics: heat shock protein-90 beta was the fifth most enriched (6.8 times) and the secreted protein acidic and rich in cysteine “SPARC” was the seventh most enriched (5.2 times) relative to ground control cells.	Research article	[15]

Table 1. Cont.

Author	Title	Topics and Results	Type	Reference
Veliz A. et al.	Transcriptomic effects on the mouse heart following 30 days on the international space station	• Transcriptomic changes (RNA sequencing): hearts of female C57BL/6J mice flown on the ISS for 30 days. • A total of 1147 transcripts were significantly regulated after spaceflight: MAPK, PI3K-Akt and GPCR signaling pathways were predicted to be activated. Transcripts related to cytoskeleton breakdown and organization were upregulated. • No significant change in ECM components or oxidative stress pathway-associated transcripts. • Absence of cellular senescence and upregulation of cell cycle genes. • Cellular maintenance and survival were most affected, suggesting that cardiovascular transcriptome initiates an adaptive response to long-term spaceflight.	Research article	[16]
Steinwerth P. et al.	Structural and molecular changes in human chondrocytes exposed to the rotating wall vessel bioreactor	• RWV bioreactor to culture primary human chondrocytes and cells from the immortalized line C28/I2 for up to 14 d. • Spheroid formation starting on day 3. After 14 d, size of C28/I2 spheroids: 5 mm, primary chondrocyte spheroids 3 mm, characteristic cartilage morphology with collagen-type 1, -type 2 and -type 10 positivity. • Primary chondrocytes: significant changes in <i>IL6</i>, <i>ACTB</i>, <i>TUBB</i>, <i>VIM</i>, <i>COL1A1</i>, <i>COL10A1</i>, <i>MMP1</i>, <i>MMP3</i>, <i>MMP13</i>, <i>ITGB1</i>, <i>LAMA1</i>, <i>RUNX3</i>, <i>SOX9</i> and <i>CASP3</i> gene expression. C28/I2 cells: No changes in gene expression. • The RWV bioreactor is suitable for engineering dense 3D cartilage-like tissue without any scaffolds.	Research Article	[17]

Table 1. Cont.

Author	Title	Topics and Results	Type	Reference
Carpo N. et al.	Space flight enhances stress pathways in human neural stem cells	- Space (SPC)-flown neural stem cells (NSCs) cultured on the ISS for 39.3 d and then returned to Earth. - Postflight: Most of these cells survived the spaceflight and self-renewed. - Some NSCs showed enhanced stress responses and autophagy-like behavior. - The secretome from SPC-flown NSCs contained molecules inducing these responses. Incubation of NSC resulted in a four-fold increase in stress responses. - Proteomic analysis of the secretome: elevated SPARC protein.	Research Article	[18]
Krüger J. et al.	Changes in gravitaxis and gene-expression in an <i>Euglena gracilis</i> culture over time	- Microarray analysis of 5-day-old <i>E. gracilis</i> cells with positive gravitaxis, 6-day-old cells without gravitactic orientation (controls) and older cells (9- and 11-day-old with negative gravitaxis). - A total of 2779 transcripts were differentially expressed. Positive gravitactic cells (5-day-old culture) showed only minor differences in gene expression compared to controls. mRNAs changes were found in older cells. Genes coding for adenylyl cyclases, photosynthesis, and metabolic enzymes were differentially expressed. <i>E. gracilis</i> is important for biotechnology and life-support systems.	Research Article	[19]
Ru M. et al.	Integration of proteomic and metabolomic data reveals the lipid metabolism disorder in the liver of rats exposed to simulated microgravity	- S-μg rat model: standard rodent tail suspension model; focus on liver tissue. - Proteomics and metabolomics: 63 proteins and 150 metabolites between the S-μg and controls. - S-μg: dysregulation of major metabolic pathways (biosynthesis of unsaturated fatty acids, linoleic acid metabolism, steroid hormone biosynthesis and butanoate metabolism).	Research Article	[20]

Table 1. Cont.

Author	Title	Topics and Results	Type	Reference
Barkia B. et al.	The formation of stable lung tumor spheroids during random positioning involves increased estrogen sensitivity	• Cancer research under s-μg (RPM): Spheroid formation to study metastasis in vitro. • Two cell types of lung cancer (NCI-H1703 squamous cell carcinoma cells and Calu-3 adenocarcinoma cells). NCI-H1703: spheroids after 3 d, Calu-3: 2D cell layer after 3 d. Two-dimensional growing Calu-3 cells have less mucin-1, further downregulating their expression on the RPM. • Calu-3 cells form unstable spheroids due to an imbalanced ratio of adhesion proteins (β1-integrin and E-cadherin) and mucin-1. • RPM-exposed Calu-3 cells showed a strongly upregulated ESR1. 17β-estradiol or phenol red induced more stable Calu-3 spheroids.	Research Article	[21]
Kahlert S. et al.	Dynamic mechanical load as a trigger for growth and proliferation in porcine epithelial cells	• Porcine epithelial cells (IPEC-1 and IPEC-J2) exposed to dynamic cultivation systems to mimic the load changes and the resulting mechanical forces. • Changes in morphology in IPEC-1 but not in IPEC-J2. • IPEC-1 changes in the distribution and structure of F-actin cytoskeleton. • Apical brush border and tight junctions were unaffected; decrease in transepithelial resistance in IPEC-1 and partially affected IPEC-J2; increase in Ki67. • Doubling of cellular mitochondrial respiration. • No signs of senescence.	Research Article	[22]
Fava M. et al.	Cellular and molecular effects of microgravity on the immune system: A focus on bioactive lipids	• Focus on the effects of real and simulated μg on the metabolism and signaling of bioactive lipids in the context of immune and inflammatory homeostasis.	Review	[23]

It has long been known that mammalian cells change their growth behavior, differentiation, proliferation, adhesion, etc., when cultured under μ g conditions in space and on Earth [24,25]. This SI presents three publications supporting these findings and demonstrating the three-dimensional (3D) growth of different cell types exposed to s- μ g [14,17,21]. Jokšienė et al. [14] studied endothelial cells under s- μ g using a 3D clinostat for 14 d in high-glucose (HG) and normal-glucose (NG) media. The authors found changes in growth. One portion of the endothelial cells grew in the form of 3D aggregates (spheroids), the other as a monolayer. The HG medium induced bigger and more spheroid growth compared to

NG medium. An earlier study showed that 3D tissue-like aggregates can be engineered on the RWV [26]. In addition, angiogenic activity was also observed when adipose-derived mesenchymal stem cells were exposed to an RPM [27].

Tissue engineering in μg is currently a hot topic [28]. Culturing human cells like chondrocytes, under μg conditions, are suitable for the tissue engineering of cartilage [29]. Steinwerth et al. [17] demonstrated that the RWV is suitable for engineering cartilage tissues without any scaffolds. At present, experiments in space and studies using μg -simulating devices are increasingly performed in the field of cancer research [30–33].

The lessons learnt from cancer research in space, among other things, showed that cancer cells exposed to μg reveal changes in growth behavior. The μg environment induces multicellular spheroids and organoids, with the potential to study the processes of cancer progression and metastasis on a molecular level. Barkia et al. [21] investigated two types of lung cancer cells on the RPM and demonstrated that NCI-H1703 squamous cell carcinoma cells and Calu-3 adenocarcinoma cells exhibit a different growth behavior after 3 d. A 3-day RPM exposure induced stable spheroid formation in NCI-H1703 cells but not in Calu-3 cells. Mucin-1 was reduced in Calu-3 cells and further decreased under μg conditions. RPM-exposed Calu-3 demonstrated sensitivity to 17β -estradiol or phenol red, allowing for the formation of more stable spheroids.

Moreover, this SI covers three publications reporting on studies performed on the ISS [15,16,18]. One group reported two different stem cell experiments [15,18]; another one reported the results of an animal study [16]. The group of Dr. Espinosa-Jeffrey investigated oligodendrocyte progenitors on the ISS and found that the proliferation and autophagic death of the cells were enhanced after spaceflight [15]. The secretome of space-flown cells revealed that HSP-90 and SPARC proteins were clearly elevated, indicating their key role in the mitigation of intracranial hypertension and the visual impairment intracranial pressure of space travelers during and after a space mission [15]. In a second ISS experiment, neural stem cells were studied. The authors demonstrated that spaceflight enhances stress pathways in human neural stem cells [18]. Interestingly, they found an increased secretion of the ER stress-related proteins SPARC, calreticulin and endoplasmic reticulum following spaceflight and the induction of autophagy-like behavior in neural stem cells was detected after spaceflight [18]. The third ISS experiment is an animal study [16]. The authors focused on the transcriptomic changes in the hearts of female C57BL/6J mice flown on the ISS for 30 d. Only 1147 transcripts (1.3%) were significantly regulated in the flight group, suggesting that by 30 d the heart successfully adapted to the stressful space conditions. Activated biological processes in the flight group contributing to adaptation and survival included the PI3K-Akt pathway, GPCR signaling pathway and MAPK signaling pathway. Transcriptomic analyses predicted the activation of these pathways. The authors concluded that the heart adapts to μg during and after long-term spaceflight [16].

A second animal study investigated rats under s- μg conditions [20]. For this purpose, the authors used the standard rodent tail suspension model and focused on liver tissue. Proteomics and metabolomics results revealed lipid metabolism disorder in the rat liver [20]. S- μg induced abnormal changes in proteins and metabolites involved in the PPAR signaling pathway. These changes may be the primary cause of lipid metabolism disorders in rat livers [20].

A further study examined porcine epithelial cells (IPEC-1 and IPEC-J2) under dynamic mechanical load [22]. The results demonstrate the impact of motion on the intestinal epithelial border cells in vitro. The cultivation conditions obtained by a rotating vessel within 3 d were sufficient to trigger significant morphological and cell physiological modifications (growth and proliferation), which improved the expressiveness of the IPEC cell culture model [22].

Krüger et al. examined the transcription levels of four independent *E. gracilis* cultures [19]. The gene expression and phenotype of *E. gracilis* cells change depending on

age. mRNAs changes were measured in older cells. DEGs were detected for adenylyl cyclases, photosynthesis and metabolic enzymes. Regarding the significance of *E. gracilis* for biotechnological, pharmacological and space applications like biological life-support systems, the determination of such shifts is very important [19].

Finally, Farva and coauthors reviewed the current knowledge regarding the effects of real and simulated μg on the metabolism and signaling of bioactive lipids in the context of immune and inflammatory homeostasis [23].

3. Conclusions

The excellent papers included in this SI report novel findings in the field of space research and space medicine. Space stressors like μg , radiation, isolation and psychological problems are known to impact the health of humans and animals traveling to space. Therefore, it is necessary to study the mechanisms of these health problems and to find suitable countermeasures [34,35].

This SI covers new publications focusing on omics studies of cells and tissues exposed to conditions of real and simulated weightlessness, with a focus on the transcriptome, proteome, secretome and metabolome. In addition, new data regarding the tissue engineering of cartilage, vessels and lung cancer spheroids have been published. Dynamic mechanical load serves as a trigger for growth and proliferation in porcine epithelial cells. Furthermore, novel ISS results with respect to the stressors for intracranial hypertension and visual impairment intracranial pressure, as well as adaptation of the mice heart to long-term spaceflight, are provided. Data regarding lipid metabolism disorders in the liver of rats exposed to tail suspension increase our knowledge of the hepatic changes in rodents and humans in space. Furthermore, new results regarding *E. gracilis* and its impact on life support systems are published. Finally, the importance of bioactive lipids for the known dysfunctional immune homeostasis and inflammatory damage were reviewed.

I am convinced that space research using the ISS, as well as devices for s- μg in combination with OMICS technologies, will be useful in protecting human health in space during deep space exploration missions and will also be applicable to translational regenerative medicine on Earth.

Funding: This work was supported by the German Space Agency at DLR (Deutsches Zentrum für Luft- und Raumfahrt, grant number 50WB2519).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: As Guest Editor of the Special Issue “Effects of Weightlessness on Molecular Changes in Cellular Organisms, Animals and Plants”, I would like to express my deep appreciation to all authors whose valuable work was published in this issue and thus contributed to the success of the edition. I would like to thank Marcus Krüger, Otto-von-Guericke-University-Magdeburg for his help with Endnote and for editing this manuscript.

Conflicts of Interest: The author declares no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

<i>ACTB</i>	Actin Beta gene
2D	Two-dimensional
3D	Three-dimensional
<i>CASP3</i>	Caspase-3 gene
<i>COL1A1</i>	alpha-1 chain of type I collagen gene
<i>COL10A1</i>	alpha-1 chain of type I0 collagen gene
D	Days
<i>E.</i>	Euglena
ECM	Extracellular matrix
ESA	European Space Agency
ESR1	Estrogen receptor 1
GBFs	Ground-based facilities
GPCR	G protein-coupled receptors
HG	High-glucose medium
HSP-90	Heat shock protein 90
<i>IL6</i>	Interleukin-6 gene
ISS	International Space Station
<i>ITGB1</i>	Integrin beta 1 gene
<i>LAMA1</i>	Laminin subunit alpha-1 gene
MAPK	Mitogen-activated protein kinase
μg	Microgravity
min	Minutes
<i>MMP1</i>	Matrix Metalloproteinase 1 gene
<i>MMP3</i>	Matrix Metalloproteinase 3 gene
<i>MMP13</i>	Matrix Metalloproteinase 13 gene
NASA	National Aeronautics and Space Administration
NG	Normal glucose medium
NSC	Neural stem cells
OLPs	Oligodendrocyte progenitors
PI3K-Akt	Phosphoinositide 3-kinase-protein kinase B
PPAR	Peroxisome proliferator-activated receptor
RPM	Random Positioning Machine
<i>RUNX3</i>	Runt-related transcription factor 3 gene
RWV	Rotating Wall Vessel
SI	Special Issue
s-μg	Simulated microgravity
SOX9	SRY-Box Transcription Factor 9
SPARC	Secreted protein acidic and rich in cysteine (osteonectin)
<i>TUBB</i>	Tubulin Beta gene
<i>VIM</i>	Vimentin gene

References

1. White, R.J.; Averner, M. Humans in space. *Nature* **2001**, *409*, 1115–1118. [[CrossRef](#)]
2. Krittanawong, C.; Singh, N.K.; Scheuring, R.A.; Urquieta, E.; Bershad, E.M.; Macaulay, T.R.; Kaplin, S.; Dunn, C.; Kry, S.F.; Russomano, T.; et al. Human health during space travel: State-of-the-art review. *Cells* **2022**, *12*, 40. [[CrossRef](#)]
3. Pramanik, J.; Kumar, A.; Panchal, L.; Prajapati, B. Countermeasures for maintaining cardiovascular health in space missions. *Curr. Cardiol. Rev.* **2023**, *19*, 57–67. [[CrossRef](#)]
4. ElGindi, M.; Sapudom, J.; Ibrahim, I.H.; Al-Sayegh, M.; Chen, W.; Garcia-Sabate, A.; Teo, J.C.M. May the force be with you (or not): The immune system under microgravity. *Cells* **2021**, *10*, 1941. [[CrossRef](#)]
5. Trittel, T.; Puzyrev, D.; Harth, K.; Stannarius, R. Rotational and translational motions in a homogeneously cooling granular gas. *NPJ Microgravity* **2024**, *10*, 81. [[CrossRef](#)] [[PubMed](#)]

6. Moura, W.d.M.; dos Santos, C.R.; Freitas, M.J.d.S.; Pinto, A.C.; Simões, L.P.; Moraes, A. Microgravity explorer kit (mgx): An open-source platform for accessible space science experiments. *Aerospace* **2024**, *11*, 790. [[CrossRef](#)]
7. Shelhamer, M. Parabolic flight as a spaceflight analog. *J. Appl. Physiol.* **2016**, *120*, 1442–1448. [[CrossRef](#)] [[PubMed](#)]
8. Heatwole, S.E. Current usage of sounding rockets to study the upper atmosphere. *Proc. Natl. Acad. Sci. USA* **2024**, *121*, e2413285121. [[CrossRef](#)]
9. Zeger, L.; Barasa, P.; Han, Y.; Hellgren, J.; Redwan, I.N.; Reiche, M.E.; Florin, G.; Christoffersson, G.; Kozlova, E.N. Microgravity effect on pancreatic islets. *Cells* **2024**, *13*, 1588. [[CrossRef](#)]
10. Luna, A.; Meisel, J.; Hsu, K.; Russi, S.; Fernandez, D. Protein structural changes on a cubesat under rocket acceleration profile. *NPJ Microgravity* **2020**, *6*, 12. [[CrossRef](#)] [[PubMed](#)]
11. Greshko, M. Panel calls for giant boost to space station research. *Science* **2023**, *381*, 1144–1145. [[CrossRef](#)]
12. Pei, W.; Hu, W.; Chai, Z.; Zhou, G. Current status of space radiobiological studies in china. *Life Sci. Space Res.* **2019**, *22*, 1–7. [[CrossRef](#)]
13. Herranz, R.; Anken, R.; Boonstra, J.; Braun, M.; Christianen, P.C.; de Geest, M.; Hauslage, J.; Hilbig, R.; Hill, R.J.; Lebert, M.; et al. Ground-based facilities for simulation of microgravity: Organism-specific recommendations for their use, and recommended terminology. *Astrobiology* **2013**, *13*, 1–17. [[CrossRef](#)]
14. Joksiene, J.; Sahana, J.; Wehland, M.; Schulz, H.; Cortes-Sanchez, J.L.; Prat-Duran, J.; Grimm, D.; Simonsen, U. Effects of high glucose on human endothelial cells exposed to simulated microgravity. *Biomolecules* **2023**, *13*, 189. [[CrossRef](#)] [[PubMed](#)]
15. Tran, V.; Carpo, N.; Cepeda, C.; Espinosa-Jeffrey, A. Oligodendrocyte progenitors display enhanced proliferation and autophagy after space flight. *Biomolecules* **2023**, *13*, 201. [[CrossRef](#)] [[PubMed](#)]
16. Veliz, A.L.; Mamoun, L.; Hughes, L.; Vega, R.; Holmes, B.; Monteon, A.; Bray, J.; Pecaut, M.J.; Kearns-Jonker, M. Transcriptomic effects on the mouse heart following 30 days on the international space station. *Biomolecules* **2023**, *13*, 371. [[CrossRef](#)] [[PubMed](#)]
17. Steinwerth, P.; Bertrand, J.; Sandt, V.; Marchal, S.; Sahana, J.; Bollmann, M.; Schulz, H.; Kopp, S.; Grimm, D.; Wehland, M. Structural and molecular changes of human chondrocytes exposed to the rotating wall vessel bioreactor. *Biomolecules* **2023**, *14*, 25. [[CrossRef](#)]
18. Carpo, N.; Tran, V.; Biancotti, J.C.; Cepeda, C.; Espinosa-Jeffrey, A. Space flight enhances stress pathways in human neural stem cells. *Biomolecules* **2024**, *14*, 65. [[CrossRef](#)]
19. Krüger, J.; Richter, P.; Stoltze, J.; Prasad, B.; Strauch, S.M.; Krüger, M.; Nasir, A.; Lebert, M. Changes in gravitaxis and gene-expression in an euglena gracilis culture over time. *Biomolecules* **2024**, *14*, 327. [[CrossRef](#)] [[PubMed](#)]
20. Ru, M.; He, J.; Bai, Y.; Zhang, K.; Shi, Q.; Gao, F.; Wang, Y.; Li, B.; Shen, L. Integration of proteomic and metabolomic data reveals the lipid metabolism disorder in the liver of rats exposed to simulated microgravity. *Biomolecules* **2024**, *14*, 682. [[CrossRef](#)]
21. Barkia, B.; Sandt, V.; Melnik, D.; Cortes-Sanchez, J.L.; Marchal, S.; Baselet, B.; Baatout, S.; Sahana, J.; Grimm, D.; Wehland, M.; et al. The formation of stable lung tumor spheroids during random positioning involves increased estrogen sensitivity. *Biomolecules* **2024**, *14*, 1292. [[CrossRef](#)] [[PubMed](#)]
22. Kahlert, S.; Nossol, C.; Krüger, M.; Kopp, S.; Grimm, D.; Wuest, S.L.; Rothkotter, H.J. Dynamic mechanical load as a trigger for growth and proliferation in porcine epithelial cells. *Biomolecules* **2025**, *15*, 455. [[CrossRef](#)] [[PubMed](#)]
23. Fava, M.; De Dominicis, N.; Forte, G.; Bari, M.; Leuti, A.; Maccarrone, M. Cellular and molecular effects of microgravity on the immune system: A focus on bioactive lipids. *Biomolecules* **2024**, *14*, 466. [[CrossRef](#)]
24. Van den Nieuwenhof, D.W.A.; Moroni, L.; Chou, J.; Hinkelbein, J. Cellular response in three-dimensional spheroids and tissues exposed to real and simulated microgravity: A narrative review. *NPJ Microgravity* **2024**, *10*, 102. [[CrossRef](#)]
25. Lopez Garzon, N.A.; Pinzon-Fernandez, M.V.; Saavedra, T.J.; Nati-Castillo, H.A.; Arias-Intriago, M.; Salazar-Santoliva, C.; Izquierdo-Condoy, J.S. Microgravity and cellular biology: Insights into cellular responses and implications for human health. *Int. J. Mol. Sci.* **2025**, *26*, 3058. [[CrossRef](#)]
26. Sanford, G.L.; Ellerson, D.; Melhado-Gardner, C.; Sroufe, A.E.; Harris-Hooker, S. Three-dimensional growth of endothelial cells in the microgravity-based rotating wall vessel bioreactor. *In Vitro Cell. Dev. Biol. Anim.* **2002**, *38*, 493–504. [[CrossRef](#)]
27. Ratushnyy, A.; Ezdakova, M.; Yakubets, D.; Buravkova, L. Angiogenic activity of human adipose-derived mesenchymal stem cells under simulated microgravity. *Stem. Cells Dev.* **2018**, *27*, 831–837. [[CrossRef](#)]
28. Cui, Y.; Liu, W.; Zhao, S.; Zhao, Y.; Dai, J. Advances in microgravity directed tissue engineering. *Adv. Healthc. Mater.* **2023**, *12*, e2202768. [[CrossRef](#)]
29. Jeyaraman, M.; Ramasubramanian, S.; Yadav, S.; Jeyaraman, N. Exploring new horizons: Advancements in cartilage tissue engineering under space microgravity. *Cureus* **2024**, *16*, e66224. [[CrossRef](#)] [[PubMed](#)]
30. Akbarialiabad, H.; Jamshidi, P.; Aminzade, Z.; Azizi, N.; Taha, S.R.; Sadeghian, N.; Varghese, L.J.K.; Kouhanjani, M.F.; Niknam, N.; Babocs, D.; et al. Leveraging space innovations for cancer breakthroughs on earth. *Trends Cancer* **2025**, *11*, 433–440. [[CrossRef](#)]
31. Chen, Z.Y.; Guo, S.; Li, B.B.; Jiang, N.; Li, A.; Yan, H.F.; Yang, H.M.; Zhou, J.L.; Li, C.L.; Cui, Y. Effect of weightlessness on the 3d structure formation and physiologic function of human cancer cells. *Biomed. Res. Int.* **2019**, *2019*, 4894083. [[CrossRef](#)]

32. McKinley, S.; Taylor, A.; Peeples, C.; Jacob, M.; Khaparde, G.; Walter, Y.; Ekpenyong, A. Simulated microgravity-induced changes to drug response in cancer cells quantified using fluorescence morphometry. *Life* **2023**, *13*, 1683. [[CrossRef](#)]
33. Niknam, N.; Akbarialiabad, H.; Farjoud Kouhanjani, M.; Kolaparambil Varghese, L.J.; Berrington de González, A.; Melin, M.M.; Shafie'ei, M.; Mousavi, S.M.; Hosseini, S.A.; Taha, S.R.; et al. Space oncology: A comprehensive scoping review. *Wilderness Env. Med.* **2025**, *36*, 148s–171s. [[CrossRef](#)] [[PubMed](#)]
34. Rosenthal, R.; Schneider, V.S.; Jones, J.A.; Sibonga, J.D. The case for bisphosphonate use in astronauts flying long-duration missions. *Cells* **2024**, *13*, 1337. [[CrossRef](#)] [[PubMed](#)]
35. Venugopalan, S.K.; Harikrishnan, N.; Pavithra, T.; Maheshwari, U.; Sharon, E.; Singh, A. Challenges and countermeasures for ensuring health and drug stability during long-term space missions. *Curr. Drug Discov. Technol.* **2025**. [[CrossRef](#)] [[PubMed](#)]

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