UTILIZATION OF STEM CELL RESEARCH IN MICROGRAVITY FOR INNOVATION IN CELLULAR THERAPY ON EARTH

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ABSTRACT

Recent advancements in stem cell biology, coupled with developments in space exploration, have opened new avenues for regenerative medicine. Microgravity environments in space induce significant physiological changes in the human body, such as muscle atrophy, decreased bone density, and immune system impairments, mimicking accelerated aging and chronic disease progression. These conditions offer a unique opportunity to study stem cell behavior, proliferation, and differentiation, which occur at a faster pace in space compared to Earth. The three-dimensional (3D) microgravity environment provides a more accurate representation of the human body's natural state than traditional two-dimensional culture systems, fostering enhanced stem cell development. Among the various stem cells studied in space, mesenchymal stem cells (MSCs) have shown promise for therapeutic applications, including the treatment of stroke, cancer, and neurodegenerative diseases. Research aboard the International Space Station (ISS) has demonstrated that MSCs maintain their properties, proliferate, and differentiate under microgravity conditions, offering potential for future therapies. Additionally, MSCs exhibit resistance to space radiation, protecting astronauts from its harmful effects by promoting tissue repair and releasing regenerative factors. This radiation resistance, coupled with cryopreservation techniques, enables MSCs to be used in long-duration space missions. The ongoing research on MSCs in space not only supports astronaut health but also holds the potential to revolutionize regenerative medicine on Earth. By understanding how microgravity influences stem cell behavior, scientists are uncovering critical insights into tissue repair and cell function, paving the way for innovative treatments for aging-related diseases and other medical conditions. These findings highlight the broader implications of space-based stem cell research for advancing human health both in space and on Earth.

Keywords : Stem cell biology; regenerative medicine; microgravity

INTRODUCTION

Over the past two decades, significant advancements in the field of stem cell biology have opened up tremendous opportunities for regenerative medicine, alongside groundbreaking innovations in space exploration technology (Ghani & Zubair, 2024). In a microgravity environment, the human body undergoes various significant changes, such as a decline in cardiovascular function, weakening of skeletal muscles, reduced bone density, and impairments in the immune system, among other effects. These conditions resemble health issues typically associated with aging and chronic diseases but occur at a much faster rate. While these effects might take years to manifest on Earth, in microgravity, symptoms can develop within just a few weeks. Studies on microgravity have provided profound insights into cell behavior, intercellular interactions, tissue development and repair processes, as well as the functioning of various components within the organism as a whole (Baio et al., 2018). Bioengineering research conducted on the ISS, supported by Earth-based experiments, indicates that microgravity offers opportunities to observe unique phenomena that cannot be studied under normal gravity conditions, including changes in the ability of stem cells to proliferate and differentiate (Yuge et al., 2006; Blaber at al., 2015; Jha et al., 2016; Imura et al., 2019).

The long journey into space can pose a threat to astronauts' health due to low gravity and exposure to harmful radiation. The negative impacts include damage to various bodily systems, such as muscle function, the circulatory system, the immune system, as well as an increased likelihood of genetic mutations and cancer (Giri & Moll, 2022). To mitigate these dangers, various approaches such as exercise, the use of medications, and protection through shielding have been developed. The use of ready-to-use MSC therapy can withstand space conditions due to the extremely low temperatures. Additionally, cryorecovery techniques and the cultivation of MSCs in a gravity-free environment have also been successfully demonstrated (Giri & Moll, 2022).

MATERIALS AND METHODS

This study employs a literature review approach to explore, analyze, and synthesize research findings relevant to the topic under investigation. The process is systematically designed to ensure that the sources used are highly valid and relevant. The first step in this research involves formulating research questions that focus on the core issue. Subsequently, literature is sought from various credible academic databases, such as PubMed, Scopus, ScienceDirect, and Google Scholar. To enhance search accuracy, a combination of relevant keywords, including synonyms and Boolean operators, is used. Once the literature is collected, the selection process is conducted in two stages. The initial stage involves screening titles and abstracts, while the subsequent stage entails evaluating the full text. During this process, inclusion and exclusion criteria are applied to ensure that only literature aligned with the research objectives is selected. Some inclusion criteria used include a specific publication time range, the language of the articles is English, and relevance to the topic. After selection, the quality of the chosen articles is assessed using standard tools such as the PRISMA checklist. This evaluation aims to assess the reliability, validity, and credibility of each article. The final stage involves data analysis and synthesis, where data from the selected literature are analyzed using qualitative or quantitative approaches depending on the data type. The synthesis process is conducted to identify patterns, themes, and gaps in previous research. Through this approach, the study aims to provide a comprehensive understanding of the topic under investigation while offering a solid foundation for future research.

RESULT AND DISCUSSION

Research on Stem Cells in Outer Space and Their Potential Applications in The Future

Therapeutic approaches using stem cells are considered an alternative for addressing various aging-related conditions, such as stroke, dementia, neurodegenerative diseases, and cancer, as well as other disorders or injuries. However, these treatments often require a large number of stem cells, which are difficult to obtain due to challenges in developing stem cells for therapeutic purposes (Chen et al., 2012). A crucial factor influencing the effectiveness of stem cell therapy is the culture conditions in which the cells are grown, including the impact of gravity. Microgravity environments have been identified as an innovative culture method for stem cells because they can induce unique changes in the culture process (Imura et al., 2019).

Conditions in space offer unique opportunities for stem cell development by creating a three-dimensional (3D) environment that more closely resembles the natural state within the human body, unlike the two-dimensional (2D) culture systems on Earth, which are less capable of accurately replicating biological tissue structures (Ma et al., 2023). The 3D cell culture model offers superior capabilities in mimicking in vivo cell activity and responses compared to 2D models, as it can better represent natural cell-to-cell interactions and dynamics (Park et al., 2021).

Research in Outer Space Encompasses Various Types of Stem Cells

Cells such as mesenchymal stem cells (MSC), hematopoietic stem cells (HSC), cardiomyocytes derived from hiPSC-CM, cardiovascular progenitor cells (CPC), and neural stem cells (NSC) have been sent to the International Space Station (ISS) and later returned for further analysis. Successfully developing stem cells in space and maintaining their stem cell properties without differentiating into other cell types, as well as returning them to Earth in an intact state, will make these cells potentially useful for patient therapies in the future (Ghani & Zubair, 2024).

Table 1. Research Conducted in Space to Study The Growth and Development of Human Stem Cell Cultures during Space Missions

Type of stem cells	Duration of cell culture in the ISS	Key findings
Mesenchymal Stem Cells (MSCs)	14 days	During the cultivation process, MSCs maintain their morphological and phenotypic characteristics
		MSCs continue to maintain their ability to proliferate
		The decreased expression of PLK1 indicates that μG may inhibit the progression of MSCs at certain phases in the cell cycle during prolonged culture periods
		MSCs maintain their ability to differentiate
		MSCs demonstrate a greater ability to suppress immune responses
		There is no evidence indicating any transformation into tumors
Hematopoietic stem cells (HSC)	11 days	CD34+ cells maintain cell viability of more than 95%
		There is a significant decrease in the proliferative capacity of multilineage hematopoietic progenitor cells, particularly in

Type of stem cells	Duration of cell culture in the ISS	Key findings
		the erythroid lineage
		The reduction in the number of progenitor cells is accompanied by an increase in the number of fully differentiated macrophages
Neural stem cells (NSC)	39,3 days	NSCs successfully maintained the integrity of their stemness despite being in space
		The proliferative ability of NSCs is maintained
		Metabolic activity in NSCs in space appears more intensive, with an increase in oxygen consumption and glycolysis processes
		NSCs are able to maintain their function as neurons under appropriate conditions

The Microgravity Conditions in Space can Stimulate an Increase in The Number of Cardiomyocytes Derived from Human iPSCs

In microgravity conditions, cells undergo significant changes in their characteristics. A study found that exposure to microgravity conditions in space can trigger an increase in cell proliferation activity. For example, there is an upregulation of genes involved in regulating cell division, such as KIF14, IGF2, KIF18B, SUSD2, RBL1, and AURKB. Additionally, although not classified under specific GO terms for proliferation, an increase in the expression of cell cycle regulatory genes like CCND1, CCND2, IGF2, and TBX3 was also observed. Cryopreserved 3D heart progenitors were cultured for three weeks aboard the International Space Station (ISS). Compared to cultures under 1G gravity, microgravity cultures showed a threefold increase in cell spheroid size, with the number of cell nuclei increasing by up to 20 times and higher expression of proliferation markers. Cardiomyocytes enriched in the microgravity environment exhibited better calcium handling and increased expression of genes related to muscle contraction. A brief three-day exposure to microgravity also enhanced the expression of genes related to cell proliferation, survival, heart differentiation, and contraction, supporting better outcomes in microgravity cultures at later stages. These findings suggest that the microgravity conditions in space support the proliferation of hiPSC-derived cardiomyocytes, exhibiting optimal structure and function (Rampoldi et al., 2022).

Therapeutic approaches using stem cells are considered an alternative for addressing various aging-related conditions, such as stroke, dementia, neurodegenerative diseases, and cancer, as well as other disorders or injuries. However, these treatments often require a large number of stem cells, which are difficult to obtain due to challenges in developing stem cells for therapeutic purposes (Chen et al., 2012). A crucial factor influencing the effectiveness of stem cell therapy is the culture conditions in which the cells are grown, including the impact of gravity. Microgravity environments have been identified as an innovative culture method for stem cells because they can induce unique changes in the culture process (Imura et al., 2019).

The Use of MSCs in The Context of Cellular Pharmacology in Space Environments

MSCs show potential as a preventive solution against harmful radiation exposure in animal models and the first clinical research in humans, such as in the treatment of radiation injuries and radiation sickness. For the use of MSCs as a cell-based therapy in space missions to be successful, understanding the needs of living therapeutic cells is crucial, with attention to ideal storage conditions, mechanisms of action (MoA), as well as pharmacokinetic and pharmacodynamic aspects in the context of that environment (Caplan et al., 2019; Moll et al., 2019; Moll et al., 2020; Giri & Galipeau, 2020; Moll et al., 2022).

Initial research on the use of stem cell therapy in space studies has begun, including experiments and its potential applications to address diseases related to space conditions (Huang et al., 2020; Chinnadurai et al., 2020; Zubair, 2020; Chinnadurai et al., 2021). MSC cells exhibit resistance to radiation, which is further explained in this article, along with the cellular and molecular mechanisms underlying this radioresistant property and their potential clinical applications (Nicolay et al., 2015). The ability of MSCs to differentiate into various types of mesodermal cells, along with their immunomodulatory capabilities and strong paracrine secretion, makes them an ideal choice for tissue recovery therapy in organs damaged by radiation, such as skin, intestines, brain, lungs, liver, and heart (Wang et al., 2021).

MSCs can create a protective environment for damaged tissues by releasing a large number of immunomodulatory mediators and regenerative factors (Doorn et al., 2012; Ankrum et al., 2014). The presence of MSCs in vitro remains stable despite exposure to high doses of radiation (Chinnadurai et al., 2020). This radiation resistance is more pronounced under hypoxic conditions, as shown by increased proliferation, better DNA repair, and enhanced long-term survival after exposure to ionizing radiation (Sugrue et al., 2014).

MSCs maintain their stem cell properties, such as the ability to adhere to substrates and the potential to differentiate into adipocytes, osteocytes, and chondrocytes, even when exposed to high doses of ionizing radiation or carbon ions (Li et al., 2007; Nicolay et al., 2013). Therapeutic doses of MSCs can be maintained in space conditions using low-temperature cryopreservation techniques and appropriate radiation protection to prevent mutations and preserve functionality until needed for clinical therapy (Moll et al., 2016). MSCs exhibit resistance to double-strand DNA damage caused by high radiation, both photon and 12C particle radiation, through non-homologous end joining and homologous recombination mechanisms (Sugrue et al., 2014; Nicolay et al., 2015). This protective potential and radiation resistance could be leveraged to reduce tissue damage from radiation exposure during long-duration space missions.

SUMMARY

Stem cell research in space opens up significant opportunities for medical therapies, particularly in addressing aging-related diseases such as stroke, dementia, and cancer. The microgravity environment allows for the development of cells in a three-dimensional

(3D) system that more closely resembles the human body's conditions, producing cells with optimal properties and enhancing their regenerative capabilities. Various types of stem cells, such as MSCs and cardiomyocytes, have been successfully developed on the International Space Station (ISS), maintaining their original properties and demonstrating increased proliferation and biological functions. MSCs, in particular, exhibit high resistance to radiation, immunomodulatory abilities, and differentiation potential for tissue repair. With cryopreservation techniques and radiation protection, MSCs can be utilized in long-term space missions, supporting astronaut health and offering breakthroughs in regenerative therapy for humans on Earth.

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