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Contents

Monthly Volume 16 Number 3 March 26, 2024

EDITORIAL

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Study

Basic Study

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Contents

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EDITORIAL

Understanding host-graft crosstalk for predicting the outcome of stem cell transplantation

Luminita Labusca, Florin Zugun-Eloae

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Abstract

Mesenchymal stromal cells (MSCs) hold great promise for tissue regeneration in debilitating disorders. Despite reported improvements, the short-term outcomes of MSC transplantation, which is possibly linked to poor cell survival, demand extensive investigation. Disease-associated stress microenvironments further complicate outcomes. This debate underscores the need for a deeper understanding of the phenotypes of transplanted MSCs and their environment-induced fluctuations. Additionally, questions arise about how to predict, track, and comprehend cell fate post-transplantation. *In vivo* cellular imaging has emerged as a critical requirement for both short- and long-term safety and efficacy studies. However, translating preclinical imaging methods to clinical settings remains challenging. The fate and function of transplanted cells within the host environment present intricate challenges, including MSC engraftment, variability, and inconsistencies between preclinical and clinical data. The study explored the impact of high glucose concentrations on MSC survival in diabetic environments, emphasizing mitochondrial factors. Preserving these factors may enhance MSC survival, suggesting potential strategies involving genetic modification, biomaterials, and nanoparticles. Understanding stressors in diabetic patients is crucial for predicting the effects of MSC-based therapies. These multifaceted challenges call for a holistic approach involving the incorporation of large-scale data, computational disease modeling, and possibly artificial intelligence to enable deterministic insights.

Key Words: Mesenchymal stem cells; Phenotype; Transplantation; Host; Microenvironment; Cellular imaging; Diabetes mellitus

Core Tip: Deterministic methods for modeling stem cell–host interactions are needed to ensure the safety and efficacy of stem cell-based therapies. This requires an in-depth understanding of the mechanism of action of the transplanted cells for each and every host condition(s) and asks for the establishment of adequate methods to predict, follow-up and determine the safety profile of the respective therapies.

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INTRODUCTION

Mesenchymal stromal cells (MSCs) continue to be the most explored type of stem cell because of their regenerative impact on restoring organ and tissue structure and function. Such cell-based therapies are tested within various regenerative approaches in the hope of enabling the treatment of disabling diseases[1]. However, the consistent improvement in disease-associated biomarkers reported after MSC transplantation proved to be short-lived. This transitory effect could be related to a poor cell survival rate, which requires extensive investigation[2]. The disease environment is characterized by the presence of numerous stressors that include but are not limited to hypoxia, inflammation, and metabolic imbalances that can impact the duration and efficiency of MSC transplantation. To further complicate this matter, disease association and side effects of concurrent therapies result in an extremely complex and intricate situation for a specific individual or group of individuals potential recipients of MSC therapies. It has been proposed that in the context of cell therapies, host microenvironmental modulators can be used as therapeutics. This requires a deep understanding of the mechanism of action of the transplanted cells for specific host condition(s) and asks for the establishment of adequate, probably multi-biomarker panels to predict, follow-up and determine the safety profile of the respective therapies[3].

This largely open debate invites several considerations with respect to MSCs (and probably other stem cell types). therapies at large. What is known about the phenotype of transplanted MSCs, and what do they represent from an informational and physiological perspective?

The question of whether cultured expanded MSCs faithfully reflect any stage of natural *in vivo* MSCs or whether cells are present akin to developmental stages is prominent. It is essential to note the intricate embryological development of mesenchymal tissues that have double embryological origins within trunk and head mesenchymal lineages (neural crest-derived), with these origins intricately intertwined, particularly in tissues such as the myocardium or head and neck, including sensory organs[4]. In the natural context of a developing organism, cellular differentiation appears deterministic, allowing predictions about the fate of similar cells in subsequent generations even in unrelated species. However, embryological studies reveal that cells from one presumptive tissue, when implanted into another tissue, can assume a different fate[5]. The local regulation of their destiny by the new environment underscores the selective rather than directive development of implanted cells, a characteristic inherent to MSCs. The development of human mesenchymal tissues involves a sequence of precisely coordinated series of time-dependent events distinct from the tissue repair mechanisms observed in adults 15-80 years later[6]. A classic example of such a mismatch is the long-tested and highly argued approach in which MSCs from various sources are used for regeneration or tissue engineering of articular cartilage. Chondrogenic primed adult tissue-derived MSCs notoriously undergo hypertrophic ossification since endochondral bone repair appears to be the "default" function after organism maturation. Manipulation of the Wnt/β-catenin pathway or pulsed exposure to parathyroid hormone related protein, which are reportedly used to suppress or delay hypertrophic differentiation[7], involves the use of several attached strings. Challenges in describing the timing and duration of such pharmacological intervention are not negligible, while adding steps in cell manipulation complicates both prospective cell therapy manufacturing and regulatory approval altogether. Although insights from early development may offer insight into utilizing cultured MSCs for repairing and regenerating adult tissues, the precise underlying mechanisms remain unknown.

Another question refers to the ability to predict, track and monitor cell fate after transplantation. From a regulatory perspective, the ability to fully comprehend cell fate after delivery is vital for understanding safety and efficiency. Translation from animal models to clinical studies often requires an upgraded set of tests in an attempt to describe parameters such as biodistribution, cell survival or engraftment after transplantation[8]. Preclinical studies rely on data gathered through invasive sample collection for safety studies. Such assessments commonly utilize polymerase chain reaction or immunohistochemistry as standards for good laboratory practice to detect cell-specific markers *in vivo*. This approach involves the termination of *in vivo* experiments to enable sample collection. Time-series results and long-term follow-up require a substantial number of animals and are obviously impractical for clinical studies. Consequently, there is a critical demand for *in vivo* cellular imaging that facilitates both short- and long-term pharmacological studies, as well as monitoring of therapeutic response. Cellular imaging has become necessary in the context of short- and long-term

safety and efficacy of cell therapies. However, translation of imaging methods from preclinical studies is challenging. Clinically available imaging methods, such as computer tomography, single-photon emission spectroscopy computer tomography, and magnetic resonance imaging, need to be used to balance sensitivity, specificity, resolution and the need for cell labeling. Radiolabeling, positron-emitting isotopes and nanomagnetic tracers are intensely tested alone or in combination to enable imaging at the cellular level. Cell trackers themselves can modify both transplanted cells and the host environment, introducing another set of variables that need to be taken into account when predicting the behavior of the two intertwining systems. Notably, to date, no relevant modality for noninvasively imaging the viability of transplanted cells has made its way to clinical settings despite several smart solutions being proposed experimentally.

However, the most difficult question may be whether the fate and function of the transplanted cell population are predicted within the context of the host environment. In addition to the much-investigated issue of cell engraftment and direct involvement in tissue regeneration *vs* the so-called "trophic" role that MSCs are supposed to play in the quality of small molecules releasing "medicinal cells"[9], other crucial points require careful consideration. Specifically, molecular-level descriptions of therapeutic cell mechanisms of action, donor- and tissue-type-dependent MSC variability, consistent differences between preclinical data and existing results from available clinical trials are the only major challenges to be addressed. In addition, predicting the content of MSC-released cytokines "black box" and their environment-induced licensing after transplantation are still unresolved problems[3].

A significant challenge for stem cell therapy is cell survival and maintenance of the phenotype after transplantation. The harsh microenvironment of the host commonly includes ischemia, inflammation, oxidative stress, and mechanical stress, which contribute to important cell loss and to the release of proinflammatory cytokines, potentially increasing local damage[10].

The multifaceted aspects of these challenges point toward the necessity of approaching them by means of a holistic view where large amounts of data, computational disease modeling and perhaps the use of artificial intelligence could offer valuable insights. Several possible developments in this context consist of data-driven optimization of cell delivery. Thus, a large amount of data analysis can inform the optimization of cell delivery methods to increase the survival of transplanted stem cells in hostile microenvironments[11]. With respect to the existing knowledge regarding the use of biomaterial-based nanocarrier systems, tailored methods for cell delivery to fit a specific clinical situation (such as intraarticular or intracardiac), cell preconditioning or cell engineering can be used to inform decision-making regarding pharmacological aspects of cell transplantation for a given clinical need.

MSCs can display a bidirectional immune modulatory effect, as shown by numerous *in vivo* studies and clinical trials. MSCs are actually used to modulate the hyperactive immune response in coronavirus disease 2019 or graft-*versus*-host disease patients[12]. MSCs act through secretomes and exosomes *via* paracrine effects, promoting the production of regulatory T cells and preventing the infiltration of proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6[13].

Cell engineering strategies can be used to mitigate the immune response in the context of cell therapy. Genome editing strategies and immune checkpoint inhibitors, such as programmed cell death ligand 1, CD47, and human leukocyte antigen-G, are being explored to mitigate immune rejection caused by various cellular components of the immune system, either in the presence or absence of human leukocyte antigen, particularly in human induced pluripotent stem cells and progenitor-based therapies[14].

Despite the progress made in developing strategies to mitigate immune responses in patients receiving stem cell therapies, these approaches still have limitations. One of the main challenges is that none of the current treatment modalities are successful at abolishing the immune response in a manner that does not influence transplanted cell viability or therapeutic efficacy[15]. The human immune system is extremely accurate at identifying non-self cells, which poses a significant risk of antigraft immune responses resulting from allogeneic MSC sources. Another limitation is that the refinement of stem cell culture protocols, including cell engineering strategies to increase the "therapeutic phenotype", may increase the immunogenicity of the transplanted cells.

AI and large-scale data analysis could be used to identify methods for cell preconditioning as well as genetic engineering techniques that increase the survival and viability of transplanted stem cells, offering new possibilities for improving engraftment and functionality. A holistic view, informed by large amounts of data and computational modeling, can aid in understanding the complex interplay of factors affecting the survival and functionality of transplanted stem cells, leading to more effective therapeutic strategies.

Using artificial intelligence in stem cell research introduces a new set of challenges mostly related to ethical considerations, policy implications, and intellectual property, demanding a risk-based approach to balance the potential benefits and risks. Abu-El-Rub *et al*[16] discussed one important aspect of MSC transplantation within the survival-challenging environment of diabetes mellitus (DM) patients. MSC transplantation has been proposed as a potential treatment for type I and II DM mainly due to its immunosuppressive properties and anti-inflammatory effects. The authors present evidence that high glucose concentrations adversely affect MSC survival by disrupting mitochondrial regulatory factors, leading to apoptosis. These findings advance the idea that understanding and preserving factors such as the mitochondrial membrane potential, the NAD+/NADH pool, and the mechanistic target of rapamycin protein may enhance MSC survival in diabetic microenvironments. Future strategies could involve genetic modification, biomaterials, and nanoparticles aimed at overcoming poor MSC survival under high-glucose conditions. Additionally, studying the impact of other stressors in DM patients is crucial in the attempt to predict the effect of potential MSC-based therapies. The role of frequent fluctuations in glucose levels in DM patients, systemic inflammation and the possible uremic milieu still need to be considered.

CONCLUSION

The incoming field of MSC-based cellular therapies faces multifaceted challenges, including poor cell survival rates, complex host microenvironments, and immune responses. Addressing these challenges requires a holistic approach informed by large amounts of data, computational modeling, and possibly the use of artificial intelligence. Future strategies could involve genetic modification, biomaterials, and nanoparticles aimed at overcoming poor MSC survival in specific microenvironments, such as those found in diabetic patients. Awaiting the true potential of cell-based therapies to unfold, the need for comprehensive and multidisciplinary approaches to overcome these obstacles and to advance the field toward more effective and safer clinical applications appears to be more imperative.

FOOTNOTES

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