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LETTER TO THE EDITOR

Resilience and challenges: Evaluating the impact of stress conditions on mesenchymal stem cells across different passages

Yue Ding, Fang Lin, Xiao-Ting Liang

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Abstract

This article discussed a study by Almahasneh *et al*, which investigated how high glucose and severe hypoxia affected mesenchymal stem cells (MSCs) at different passages. This research provides insights into the resilience of higher-passage MSCs under stress conditions, challenging the common use of lower passage MSCs in clinical settings. While this study offers valuable perspectives on the adaptability of MSCs, it relies mainly on *in vitro* results from a single cell line, limiting broader applicability. It highlights the need for more comprehensive *in vivo* studies to validate these findings and better understand MSC behavior in clinical scenarios.

Key Words: Mesenchymal stem cells; High glucose; Hypoxia; Cellular senescence; Passages

Core Tip: This article discussed the research by Almahasneh *et al* on the resilience of mesenchymal stem cells (MSCs) under high glucose and severe hypoxia conditions at different passages. Highlighting the adaptability of higher passage MSCs, this study challenges traditional preferences for lower passage MSCs for use in clinical treatments, especially under conditions simulating diabetic or ischemic environments. While offering novel insights into MSC adaptability are offered, the research's reliance on *in vitro* tests from a single cell line highlights the need for more in-depth *in vivo* studies to ascertain the clinical relevance of these findings and broaden their applicability.

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TO THE EDITOR

Mesenchymal stem cells (MSCs) are widely applied in clinical contexts due to their strong potential for self-renewal, multipotency, and immunomodulation. However, as passage numbers increase, MSCs undergo phenotypic changes associated with aging, including reduced proliferative capacity, weakened immunomodulatory effects, and diminished paracrine and antioxidative abilities[1]. The senescence represents a significant challenge, limiting the therapeutic efficacy and clinical applications of MSCs[2]. Overcoming these age-related limitations is crucial for maximizing the regenerative potential of MSCs in clinical treatments. The article by Almahasneh *et al*[3], published in *World Journal of Stem Cells*, adds valuable insights to the field by examining how high glucose levels and severe hypoxia affect MSCs across various passages. This work significantly contributes to regenerative medicine by challenging the traditional preference for early-passage MSCs, showing that later-passage MSCs maintain adaptability and functionality under stress, particularly in conditions mimicking diabetic or ischemic environments. This opens new possibilities for their use in therapeutic applications.

Strength and limitation

This study[3] underscores the adaptability of higher-passage MSCs under challenging conditions, questioning the common clinical preference for lower-passage cells. However, expanding the discussion to highlight the significance of the cellular microenvironment in determining the therapeutic efficacy of MSCs could further enhance the insights. Emerging evidence suggests that beyond passage number, microenvironmental factors such as oxygen tension, mechanical forces, soluble signaling molecules, and the extracellular matrix provide essential cues that influence MSC behavior post transplantation. Preconditioning involves exposing MSCs to various external stimuli that mimic the harsh conditions they face in their therapeutic environment, such as acidic pH, oxidative stress, or hypoxia[4,5]. These stimuli simulate key aspects of the microenvironment within injured or diseased tissues, helping MSCs adapt to stressful conditions before they are transplanted. By replicating elements of the microenvironment *in vitro*, preconditioning enhances the resilience of MSCs, ensuring that they are better equipped to survive, migrate, and function in challenging environments post-transplantation. Strategies such as preconditioning MSCs under hypoxic conditions[6] or utilizing biomaterials that mimic the natural extracellular matrix[7] can significantly improve MSC performance post-transplantation. Preconditioning by treating with proinflammatory cytokines can activate the immunosuppressive capabilities of MSCs, allowing them to modulate immune responses more effectively in inflammatory disease settings[8]. Therefore, incorporating strategies to modulate the microenvironment may significantly improve the practical application of MSCs in regenerative therapies. Nevertheless, the study has certain limitations that should be addressed in future research.

The current study[3] primarily focuses on observational data, leaving room for further in-depth mechanistic insights. In the discussion section, the authors proposed that specific pathways might be involved in stress responses, such as the protein kinase B/mammalian target of the rapamycin and p53 signaling pathways. However, the molecular mechanisms underlying MSC responses to specific stressors indicated in the current study remain unexplored. A more comprehensive investigation into how MSCs adjust their gene expression profiles and undergo epigenetic modifications in response to stress conditions would provide valuable insights. For example, Zielniok *et al*[9] used RNA sequencing to compare the gene expression profiles of bone marrow-derived MSCs after 6 hours of either exposure to hypoxia (2% O_2) or treatment with 40 μM vadadustat, a hypoxia-inducible factor prolyl hydroxylase 2 inhibitor. Their findings revealed 1770 differentially expressed genes between the vadadustat and hypoxia-treated groups. Among these, genes related to autophagy, phospholipid metabolism, and the toll-like receptor signaling cascade were upregulated, while those involved in the cytoskeleton and global genomic nucleotide excision repair pathways were downregulated. Isik *et al*[10] reported that hypoxia preconditioning amediated DNA hydroxymethylation in adipose-derived MSCs from a swine model of atherosclerotic renal artery stenosis. The synergistic induction of hypomethylation and hypoxia significantly enhanced the therapeutic efficacy of extracellular vesicles derived from human bone marrow MSCs, as evidenced by improved osteogenic differentiation and proangiogenic effects[11]. Therefore, the authors should consider conducting in-depth research into gene expression and epigenetic modifications, which could offer valuable insights into the observed phenomena.

This study[3] used human adipose-derived stem cells sourced from Lonza, with all findings based on a single cell line, which may limit the broader applicability of the results to other cell types. Furthermore, the authors did not specify key

details about the donor characteristics, such as age or sex, both of which can significantly affect cellular properties. For instance, MSCs from older donors may exhibit signs of senescence as early as passage three[12], making such information crucial for evaluating their behavior and functionality.

This study[3] focused primarily on investigating the effects of single concentrations of high glucose and hypoxia on MSCs rather than systematically exploring the full range of concentration gradients that could more accurately reflect the variety of stress conditions MSCs may encounter. By examining only isolated concentrations, this approach may overlook critical subtleties in how MSCs respond to varying intensities of stress. For example, the cellular response to stress often involves time- and dose-dependent effects, where lower levels of stress may induce adaptive or protective mechanisms, while higher levels may trigger apoptosis or senescence[13,14]. While oxygen levels of approximately 5% enhance MSC proliferation, activate biosynthetic pathways, and support an overall hypermetabolic state, exposure to oxygen levels below 1% shifts MSCs toward a more quiescent state, where cellular metabolism depends predominantly on anaerobic glycolysis for energy production[15]. In the methodology section, the author describes using $CoCl_2$ to mimic a hypoxic condition and refers to this treatment as "severe hypoxia" throughout the manuscript. When $CoCl_2$ is used to simulate hypoxia, it's important to recognize that this chemical agent stabilizes hypoxia-inducible factor-1α, which then triggers a series of hypoxia-related cellular pathways[16]. Notably, $CoCl_2$-induced hypoxia is not an exact replication of true oxygen deprivation, as it mimics only part of the hypoxic response, with a primary focus on hypoxia-inducible factor-1α stabilization. To validate the effectiveness and severity of $CoCl_2$ treatment in inducing hypoxia, the manuscript should include data on the expression levels of hypoxia-inducible factor-1α together with other downstream hypoxia-responsive genes, providing a clearer picture of the extent to which the cells are experiencing true hypoxia.

While the focus on apoptosis and cellular senescence is valuable, the study[3] does not adequately explore other important factors such as the differentiation capacity and paracrine signaling. Furthermore, the reliance on *in vitro* models limits the applicability of the findings, as these controlled environments may not accurately reflect the complexity of *in vivo* interactions. This underscores the necessity for additional research using *in vivo* models to assess the clinical relevance of these results. Since MSCs exert their therapeutic effects largely through paracrine mechanisms - such as secreting growth factors, chemokines, and extracellular vesicles[17,18] - it is noteworthy that these aspects were not assessed in the study. Relying exclusively on *in vitro* data from one cell line may restrict the scope of conclusions, thereby constraining the broader applicability of the contexts. Moreover, there are some concerns with the presentation of data. For example, in Figure 4 of Almahasneh *et al*[3], the annexin V staining images do not include a total cell count, making it challenging to fully interpret the extent of apoptosis in the cell population. Improving data clarity would significantly enhance the robustness of the conclusions.

Future directions

The author of the study[3] proposed an innovative concept of 'passage-stress matching'. While low-passage MSCs are generally believed to possess greater therapeutic potential than high-passage MSCs because of their baseline fitness and regenerative capacity, this concept suggests that high-passage MSCs might outperform low-passage-MSCs under specific stress conditions. To validate this concept, future research should focus on systematically testing higher-passage MSCs across a range of *in vitro* and *in vivo* stress conditions that reflect clinical conditions, such as ischemia, inflammation, and oxidative stress. It would be essential to design experiments that not only compare MSCs at different passages but also map how they perform under varying degrees of stress, assessing key therapeutic attributes such as cell survival, immunomodulation, and paracrine signaling. Additionally, studies should explore the molecular and epigenetic changes that occur in higher-passage MSCs, as this will provide insights into how stress conditions influence their therapeutic effectiveness over time.

Moreover, the application of "omics" technologies (*e.g.*, transcriptomics, proteomics, and metabolomics) could help identify specific markers of passage-related stress resilience, offering a more detailed understanding of how different passages respond at the molecular level. These insights could guide the development of tailored preconditioning strategies that optimize MSC fitness for the microenvironments they may encounter post transplantation. Longitudinal studies following MSC transplantation, particularly in animal models that mimic human disease conditions, would further clarify how passage-stress matching can be harnessed to maximize therapeutic outcomes.

Conclusion

In summary, the study by Almahasneh *et al*[3] provides valuable insights into the selection of MSC passages for clinical applications. However, to improve its clinical applicability, the limitations of the study should be addressed. While the research offers foundational data, it lacks depth in exploring the complex *in vivo* interactions. The reliance on just one commercial cell line restricts the generalizability of the findings to MSCs from other sources. Additionally, the focus on *in vitro* findings does not adequately simulate the *in vivo* conditions. Moving forward, future research should incorporate a wider range of cell models and *in vivo* experiments to thoroughly validate the results. This would contribute to a deeper understanding of how to optimize MSCs for therapeutic applications across various disease conditions.

FOOTNOTES

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