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Editorial

Mitochondria refine mesenchymal stem cell-based therapies

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Mesenchymal stem cells (MSCs) have become a focus of interest in cell therapy and regenerative medicine due to their ability to differentiate into multiple cell types, modulate the immune system, and promote tissue repair. To fully achieve their therapeutic capabilities, it is crucial to understand the internal signaling mechanisms that regulate their decisions to differentiate, proliferate, age, or survive. In this context, mitochondria play a major role and act far beyond their traditional role in energy production.

Mitochondrial metabolism and dynamics have direct impacts on MSC stemness, differentiation, migration, survival, paracrine functions, and therapeutic efficacy. In their undifferentiated state, the metabolism of MSCs depends on glycolysis for energy, which preserves reactive oxygen species (ROS) levels low and maintains a basic mitochondrial structure that supports their stem-like qualities. As MSCs begin to differentiate, their energy demands increase; a metabolic shift toward oxidative phosphorylation (OXPHOS), increased mitochondrial biogenesis, and the development of a more mature mitochondrial architecture occur.[1] The balance of mitochondrial dynamics, mediated by fission (Drp1/DLP1) and fusion (Mfn1/2, OPA1), controls the MSC differentiation. Forni et al. showed that during MSC adipogenesis and osteogenesis, mitochondrial networks become elongated and fused via upregulation of Mfn1/2, while knockdown of Mfn2 impaired respiration and differentiation.[2] Similarly, Feng et al. revealed that spontaneous differentiation is accompanied by reduced Drp1 and increased OPA1 expression.[3] In this line, mitophagy, a cellular process where dysfunctional or damaged mitochondria are recycled, preserves mitochondrial homeostasis that is critical for MSC proliferation and differentiation potential. These studies highlight a mechanistic pattern: mitochondrial fusion shifts MSCs toward OXPHOS, enabling differentiation, whereas fission maintains a glycolytic, stem-like state.

Beyond intrinsic dynamics, the most exciting discovery in MSC biology is their ability to transfer mitochondria to damaged or stressed cells spontaneously, providing bioenergy and survival for recipient cells. This mitochondrial trafficking occurs via tunneling nanotubes (TNTs), gap junctions (e.g., connexin 43 channels), and extracellular vesicles.[4] Both autologous and intercellular transfer of mitochondria impact the therapeutic potency of MSCs. In a study, Long et al. transferred autologous mitochondria into bone marrow MSCs (BM-MSCs). Mitochondria-recipient BM-MSCs exhibited enhanced proliferation, migration, osteogenesis, and ATP production; these effects were abolished by oligomycin, linking benefits directly to OXPHOS enhancement and translated into accelerated bone defect repair in rats.[5] Complementing this, Yao et al. demonstrated that adipose-derived MSCs receiving exogenous mitochondria exhibited a ~17 % rise in ATP, upregulation of cell-cycle genes, and enhanced migration and secretome factors.[6]

Intercellular mitochondrial transfer modulates the host environment with mixed outcomes. Studies in Achilles tendinopathy and lung injury models demonstrate that TNT-mediated mitochondrial transfer from MSCs to damaged cells protects injured tenocytes and alveolar epithelial cells by restoring aerobic respiration and preventing apoptosis.[7,8] The preconditioning of MSCs with mitochondria also boosts the efficacy of MSC-based cell therapy. Co-culturing of MSCs with cardiomyocyte-

Author's Biosketch

Dr. Sepideh Zununi Vahed received her PhD in Medical Biotechnology in 2016 from Tabriz University of Medical Sciences, Tabriz, Iran. She is a scientist at the Kidney Research Center of Tabriz University of Medical Sciences, where her research focuses on diagnostic and prognostic biomarkers as well as molecular pathways involved in disease development. She has gained notable recognition in the scientific community, being ranked among the top 2% most cited scientists worldwide, according to an annual analysis conducted by Stanford University and published by Elsevier.

derived mitochondria boosted their regeneration capacity by inducing ROS production and activating mitophagy.[9] However, tumor microenvironments exploit this mechanism: MSCs transfer mitochondria to glioblastoma stem cells (GSCs), boosting OXPHOS and chemoresistance against temozolomide.[10]

Finally, the MSCs' microenvironment impacts mitochondrial health and transfer. Pathological conditions such as hyperglycemia impair MSC mitochondria and trigger apoptosis; inhibiting their proliferation and differentiation.[11] Furthermore, the fate of donated mitochondria (mitophagy) and their effect on the function and metabolism of the recipient MSC should be considered. In preconditioning studies, the cellular source for mitochondrial isolation would be important, as it is reported that transferred mitochondria alter MSC properties based on their cellular origin.[12] This interplay among mitochondrial turnover, metabolic state, and environmental context suggests that optimizing mitochondrial dynamics and transfer protocols will be critical for ensuring safe and effective MSC-based therapies.

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References
1. Xi W, Chen W, Sun W, Li X, Suo Z, Jiang G, et al. Mitochondrial activity regulates the differentiation of skin-derived mesenchymal stem cells into brown adipocytes to contribute to hypertension. Stem Cell Res Ther. 2021;12(1):167. doi: 10.1186/s13287-021-02169-0.
2. Forni MF, Peloggia J, Trudeau K, Shirihai O, Kowaltowski AJ. Murine mesenchymal stem cell commitment to differentiation is regulated by mitochondrial dynamics. Stem Cells. 2016;34(3):743-55. doi: 10.1002/stem.2248.
3. Li X, Chaouhan HS, Yu SH, Wang IK, Yu TM, Chuang YW, et al. Hypoxia-induced metabolic and functional changes in oral CSCs: implications for stemness and viability modulation through BNIP3-driven mitophagy. J Cell Mol Med. 2025;29(3):e70400. doi: 10.1111/jcmm.70400.
4. Boukelmoune N, Chiu GS, Kavelaars A, Heijnen CJ. Mitochondrial transfer from mesenchymal stem cells to neural stem cells protects against the neurotoxic effects of cisplatin. Acta Neuropathol Commun. 2018;6(1):139. doi: 10.1186/s40478-018-0644-8.
5. Guo Y, Chi X, Wang Y, Heng BC, Wei Y, Zhang X, et al. Mitochondria transfer enhances proliferation, migration, and osteogenic differentiation of bone marrow mesenchymal stem cell and promotes bone defect healing. Stem Cell Res Ther. 2020;11(1):245. doi: 10.1186/s13287-020-01704-9.
6. Yao X, Ma Y, Zhou W, Liao Y, Jiang Z, Lin J, et al. In-cytoplasm mitochondrial transplantation for mesenchymal stem cells engineering and tissue regeneration. Bioeng Transl Med. 2022;7(1):e10250. doi: 10.1002/btm2.10250.
7. Wei B, Ji M, Lin Y, Wang S, Liu Y, Geng R, et al. Mitochondrial transfer from bone mesenchymal stem cells protects against tendinopathy both in vitro and in vivo. Stem Cell Res Ther. 2023;14(1):104. doi: 10.1186/s13287-023-03329-0.
8. Islam MN, Das SR, Emin MT, Wei M, Sun L, Westphalen K, et al. Mitochondrial transfer from bone-marrow-derived stromal cells to pulmonary alveoli protects against acute lung injury. Nat Med. 2012;18(5):759-65. doi: 10.1038/nm.2736.
9. Vignais ML, Levoux J, Sicard P, Khattar K, Lozza C, Gervais M, et al. Transfer of cardiac mitochondria improves the therapeutic efficacy of mesenchymal stem cells in a preclinical model of ischemic heart disease. Cells. 2023;12(4):582. doi: 10.3390/cells12040582.
10. Nakhle J, Khattar K, Özkan T, Boughlita A, Abba Moussa D, Darlix A, et al. Mitochondria transfer from mesenchymal stem cells confers chemoresistance to glioblastoma stem cells through metabolic rewiring. Cancer Res Commun. 2023;3(6):1041-56. doi: 10.1158/2767-9764.Crc-23-0144.
11. Abu-El-Rub E, Almahasneh F, Khasawneh RR, Alzu'bi A, Ghorab D, Almazari R, et al. Human mesenchymal stem cells exhibit altered mitochondrial dynamics and poor survival in high glucose microenvironment. World J Stem Cells. 2023;15(12):1093-103. doi: 10.4252/wjsc.v15.i12.1093.
12. Levoux J, Prola A, Lafuste P, Gervais M, Chevallier N, Koumaiha Z, et al. Platelets facilitate the wound-healing capability of mesenchymal stem cells by mitochondrial transfer and metabolic reprogramming. Cell Metab. 2021;33(2):283-99.e9. doi: 10.1016/j.cmet.2020.12.006.