## **Biomedicine Advances**

**Biomedicine Advances**. 2025;2(4):171-172

doi: 10.34172/bma.33 https://biomedad.ae

#### **Editorial**



# Mitochondria refine mesenchymal stem cell-based therapies

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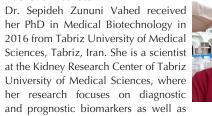
Received: June 6, 2025, Revised: June 23, 2025, Accepted: July 19, 2025, ePublished: October 20, 2025

esenchymal 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.<sup>2</sup> 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

### **Author's Biosketch**





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.

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.<sup>7,8</sup> The preconditioning of MSCs with mitochondria also boosts the efficacy of MSC-based cell therapy. Co-culturing of MSCs with cardiomyocyte-





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

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.<sup>12</sup> 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.

#### **Competing Interests**

None declared.

#### **Ethical Approval**

Not applicable.

#### **Funding**

None.

#### **Intelligence Use Disclosure**

This article has not utilized artificial intelligence (AI) tools for research and manuscript development, as per the GAMER reporting guideline.

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