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Commentary

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Mitochondria Transference, a Fascinating Mechanism of Mesenchymal Stem Cells

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Abstract

Mitochondria are perhaps the most intriguing organelle within a cell, from an evolutionary perspective to a functional viewpoint. A variety of diseases and conditions have been reported to be linked to mitochondria malfunction, including type 2 diabetes, pulmonary associated conditions, ischemic stroke events, Parkinson´s and Alzheimer disease. Recently, the use of mesenchymal stem cells has drawn promising results due to its immunomodulatory and regeneration properties. However, mitochondria transference to deficient cells has been newly explored. This manuscript provides a concise overview of this fascinating mechanism and its implications in stem cell therapy.

Keywords: Cell-to-cell communication, Mesenchymal stem cells, Mitochondria transference, Stem cell therapy

Mitochondria Transfer, a Fascinating Mechanism of the Therapeutic Use of MSC

Mitochondria are perhaps the most intriguing organelle since it provides most of the energy needed for the metabolism and movement of the host cell through oxidative phosphorylation and the formation of adenosine triphosphate (ATP), while trying to balance out the generation of reactive oxygen species (ROS). Although, this secondary product is considered to be the primary source of mitochondrial dysfunction, it has been hypostatized that this mechanism could be an attempt to compensate cellular stress on a daily basis. Nevertheless, ROS formation along with a breach in mitochondrial integrity as well as mutations in quality-control-associated genes, are in the spotlight in regard to mitochondria malfunction [1]. This deficiency can be tracked not only to aging-related disorders but affect high-energy-demand cells, being observable in a variety of conditions including type 2 diabetes, pulmonary associated conditions, ischemic stroke events, Parkinson´s and Alzheimer disease [2].

Recently, the use of mesenchymal stem cells (MSC) *in vitro* has drawn interesting results, whereas *in vivo* studies have reported promising outcomes in a variety of diseases [3]. Immunomodulation along with regenerative properties appear as the two most investigated mechanisms behind the surprising results observed in MSC therapy. Interestingly, many studies have researched the influence MSC has on macrophage polarization either by cell-to-cell contact or paracrine communication, in order to produce ant-inflammatory soluble factors. Prostaglandin E2 (PGE), transforming growth factor β (TGF-β), indoleamine 2,3-dioxygenase (IDO), are reported as the main molecules to promote this process and downregulate the activation of the immune system [4]. Similarly, MSC's production of growth factors, such as epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and hepatocyte growth factor (HGF) are known to promote tissue regeneration and in some cases lead to long-term regain of normal function [5]. Nevertheless, there are still many other mechanisms behind MSC therapy not fully understood yet; recently, mitochondria transference appears as one of the most intriguing mechanisms waiting to be elucidated.

Mitochondria transference was first reported in 2005 by Koyanagui and colleagues, as they observed the formation of nanotubular connections and organelle transportation between endothelial progenitor cells and cardiac myocytes after cell-to-cell interaction [6]. One year later, investigations led by Spees, confirmed mitochon-

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dria transference from human MSC to mutated mtDNA A549ρ ◦ cells during cocultivation. Interestingly these defective cells not only acquired the organelle but displayed functional metabolic behavior, such as decreased levels of ROS, increased ATP production and active proliferation [7]. Various research indicates that this could be a potential mechanism of action during MSC therapy, especially on conditions affecting directly the mitochondria capability.

Although several studies *in vitro* and *in vivo* have been able to confirm partial cellular fusion as a route for this mechanism, one of the first investigations reported was led by Acquistapace and his team in 2011. Their research confirmed that fully differentiated cardiomyocytes were able to regain progenitor-like properties after being cocultured with MSC through partial cell fusion. Functional stem-cell-mitochondria trade was observed by time-lapse video microscopy; while the somatic reprogramming was confirmed after hybrid cells expressed progenitor markers, such as GATA-4, myocyte enhancer factor 2C and Ki67 [8]. Another explored hypothesis explaining mitochondria acquisition, was given by Islam and collaborators in 2012, during *in vivo* observations in mice with acute lung injury. Bone marrow derived MSC airway-instilled were able to donate functional mitochondria via the release of microvesicles. Internalization of these microvesicles by lung epithelium cells significantly restituted ATP production, improving overall alveolar bioenergetics [9].

Additionally, this interesting intracellular process has also been reported to occur via the formation of tunneling nanotubes after cell-to-cell communication. These cytoplasmatic channels enveloped by a membrane serve as a conduct through which mitochondria and other molecules are carried into the new host-cell. Besides paracrine mechanisms, this process provides new insight into how MSC therapy could be helping patients worldwide. On recent investigations, the role of Miro1, a GTPase on the outer membrane of the mitochondria, has been placed as an important motor protein adaptor and regulator of this trading. Remarkably, mitochondria transference from MSC to neurons in a co-culture system, has been recently studied. On a novel research, neurons underwent oxidative damage in order to simulate an ischemic stroke state before MSC interactions. Direct microscopic observations using MitoTracker along with FACS confirmed successful mitochondrial transference into defective cells. Furthermore, beneficial metabolic outcomes were also reported, as this interaction improved ATP production, general survival rate and overall cellular metabolism [3,10].

Although more research is needed to clarify the mechanisms aforementioned, as well as its occurrence *in vivo* during disease, it is clear that MSC not only contributes to the immunomodulation and tissue regeneration through paracrine communication. Cell-to-cell communication is currently being explored during MSC therapy since new evidence points out its occurrence during cell interactions. Local administration of MSC, especially during arthritis and spinal cord injuries, has been reported with promising outcomes, possibly because this application contributes to local mitochondria donation. Considering that a high portion of MSC is sequestered by the pulmonary system during IV infusion, the importance of local infiltrations in certain conditions could be an optimal way to promote this fascinating mechanism of action.

Acknowledgement

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Conflict of Interest

None.

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