Letter to Editor

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Mitochondrial Transfer from Menstrual Blood Stromal/Stem Cells Promotes Survival of Cardiomyocytes Following Myocardial Infarction

Dear Editor,

Recently, Mitochondrial Transfer (MT) from stem cells to injured cells has been proposed as a novel therapeutic strategy that could restore the bioenergetics requirement of damaged tissues [1]. This organelle is essential for cellular homeostasis, cell survival, cell growth, cell death induction, calcium storage, cell signaling, and energy supply, especially in energy-demanding cells like cardiomyocytes [2,3]. Mitochondrial dysfunction is contributed to a majority of pathologic conditions like Myocardial Infarction (MI) and cardiomyopathies [4]. Mitochondrial impairment results in reduction of Adenosine Triphosphate (ATP) production, induces the generation of intracellular Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS), and activates the caspase cleavage pathway [5]. It has been confirmed that Mesenchymal Stem Cells (MSCs) could transport mitochondria to a range of cells including endothelial cells and cardiomyocytes [6]. It appears that healthy mitochondrial donation by MSCs is a unique phenomenon that leads to replacement of dysfunctional mitochondria in injured cells. It has been designated that the transfer of even a small number of Multipotent Mesenchymal Stem Cells (MMSC)-derived mitochondria resulted in enhanced oxidative phosphorylation and promotion of cell proliferation in the recipient damaged cells [7]. Although mitochondrial transmission from various sources of stem cells like Bone Marrow Mesenchymal Stem Cell (BM-MSCs), induced Pluripotent Stem Cells (iPSCs), and Dental Pulp Derived Mesenchymal Stem Cell (DP-MSCs) has been stated, there is no report about MT from menstrual blood Stromal/Stem Cells (MenSCs). Recently we have perceived that, transepicardial MenSCs administration could improve cardiac function, prevent metaplastic development, and promote survival of cardiomyocytes following MI conceivably by transfer of their mitochondria to preserved cardiomyocytes and endothelial cells. We tracked the injected MenSCs 28 days' post-transplantation by anti-human mitochondrial antibody in MI site in rat model and demonstrated successfully transferred human mitochondria from MenSCs into the targeted cells.

Researchers have showed that mitochondrial dysfunction plays critical role in the loss of cardiomyocytes during MI [8]. Although exact mechanisms of MT have not been clarified yet, it has indicated that the local microenvironment of injured tissue releases physiological signals that trigger MT [9]. For instance, mitochondrial DNA (mtDNA) released by damaged cells is engulfed by MSCs and that later, prompts the cytoprotective function of MSCs and boosts mitochondrial biogenesis [10]. Furthermore, ROS and RNS can also stimulate mitochondrial donation [11]. It is assumed that, transmission of mitochondria derived from MenSCs may lead to maintenance of cellular homeostasis, preservation of aerobic respiration, reduction the level of ROS, prevention of cell death, and upregulation of cardio-protective cytokines in the cardiomyocytes [12]. Mitochondria in MSCs like MenSCs is in dormant state due to lesser energy demands. However upon differentiation, increase in levels of respiratory enzymes, greater oxygen consumption rate, augmented levels of intracellular ATP, increase in mtDNA copy number and mRNA levels may occur [13,14]. Interestingly, it has been indicated that the MT phenomenon from MSCs not only results in protection of injured targeted cells, but also, it can lead to more MSCs survival due to decreasing their partially depolarized and dysfunctional mitochondria [15].

Researchers indicated that transmission of mitochondria from BM-MSCs to cardiomyocytes can inhibit apoptosis and reprogrammed differentiated cardiomyocytes to progenitor-like cells [16]. Furthermore, iPSC-MSCs directly protects cardiomyocytes against induced cardiomyopathy through bioenergetic preservation by functional MT [17]. Also MT from MSCs to endothelial cell rescued the injured endothelial cell by reducing apoptosis and promoting proliferation [18].

Meanwhile, some resident cells in injured site could transfer mitochondria to injured cells; we believe that only endogenous transfer is transient and cannot inhibit progressive injuries following MI. Our studies have shown that; administration of MenSCs post-MI modifies the metabolism and restores the functionality of heart, and also protect myocardium from further subsequent injuries mainly with donation of their healthy mitochondria to cardiomyocytes and endothelial cells. It is likely that the donor mitochondria fuse with mitochondria in the recipient cell, and restore bioenergetic requirements; or the recipient cell removes its injured mitochondria and gets the donated healthy mitochondria [19]. Researchers revealed that human mitochondrial DNA from MSCs could be found in mice 28 days after MSC administration. However, MSC nuclear DNA was not detected 3 days post administration and suggesting that the long-term therapeutic effects of MSCs administration may be related to MT [15]. So, the stem cell-based mitochondria transfer approach from MenSCs can be considered as a newly effective therapeutic strategy to treat cardiomyopathies. However, more in-

vestigation is needed to explore the exact mechanism of the MenSCs-derived mitochondria communication with the recipient cells, restoration of mitochondrial bioenergetics in these cells, cell-signaling pathways involved to this phenomenon, and understand how this organelle donation would lead to regeneration.

Keywords: Donation, Mitochondria, Myocardial infarction, Stem cells

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Mahmood Manshori, Somaieh Kazemnejad, and Hannaneh Golshahi *

Nanobiotechnology Research Center, Avicenna Research Institute, ACECR,Tehran, Iran

*** Corresponding author:** Hannaneh Golshahi, DVSc., Nanobiotechnology Research Center, Avicenna Research Institute, ACECR, Tehran, Iran
Tel: +98 21 22432020
Fax: +98 21 22432021
Email: h.golshahi@avicenna.ac.ir

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