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Research progress of transferring mitochondria application in nanotubes in treatment of acute lung injury sepsis

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ABSTRACT

Acute lung injury (ALI) is a common complication of sepsis with characteristics of acute onset, rapid change in the disease and high mortality. Since current clinical treatment can only alleviate the unfavorable condition to a certain extent but cure, we urgently need to find an effective treatment. Most scholars believe that sepsis-induced ALI is associated with extensive mitochondrial damage. In recent years, a widely studied pluripotent stem cell that is mesenchymal stem cell has been proved to alleviate and treat sepsis-induced ALI by transporting mitochondria via nanotubes in a microtubule-dependent manner. Research progress in this field will be reviewed in this study.

1. Introduction

Sepsis is a systemic inflammatory response syndrome (SIRS) mediated by the inflammatory mediators of the body after being infected with various pathogens. It has high mortality rate and painful process. Patients with sepsis usually have complications of multiple organ failure and septic shock[1]. Lungs are the first organs to be attacked in sepsis, therefore acute lung injury (ALI) is the most common complication of sepsis, which may deteriorate into acute respiratory distress syndrome (ARDS) with an extremely high case fatality rate and be the leading cause of mortality in sepsis patients[2]. How to reduce the high mortality

and improve the prognosis of patients has become a hot topic. In recent years, more and more experimental studies have shown that bone marrow-derived mesenchymal stem cells (MSCs) can effectively treat ALI caused by sepsis[3,4]. The most important mechanism is a new type of ubiquitous cell junctions membrane nanotubes[5]. Mitochondria can be directly transmitted in nanotubes through microtubules so as to reduce endothelial cell damage. This article will review the pathogenesis of mitochondria associated with sepsis-induced ALI and how mitochondria transport through microtubules in nanotubes.

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2. Role of mitochondria in sepsis-induced ALI

ALI is a syndrome of progressive respiratory distress induced by various extrapulmonary causes of pulmonary alveolar epithelial cells and capillary endothelial cells, which in turn causes ARDS and finally result in respiratory failure[6]. Currently, most scholars believe that mitochondria play a key role in the inflammatory response, and mitochondrial dysfunction is related to the severity degree and outcomes of sepsis and ALI[7,8]. When the body has sepsis, it will cause oxidative stress response and produce so many high-activity molecules like reactive oxygen species, which will induce oxidation/anti-oxidation system imbalance and result in mitochondrial structure damage, causing the decline of mitochondrial number and function[9]. On the other hand, the opening of the mitochondrial permeability transition pore causes a large increase in cytochrome C, NO, Ca^{2+} and so on, leading to ion imbalance in the intima, matrix edema and membrane rupture, eventually results in a halt in energy synthesis, activation of apoptosis factors and apoptosis[10].

3. Mitochondrial metastasis in MSCs for treatment of ALI

There was not a good clinical treatment for sepsis-induced ALI. In recent years, some experimental studies have provided us with a new direction of treatment: bone marrow-derived MSCs. MSCs are pluripotent stem cells with the capacity of self-renewing and self-reproducing, which can be isolated and cultured from bone marrow and many other tissues and organs such as the placenta, umbilical cord, and amniotic fluid[11]. MSC can be 'self-sufficient', so it does not create rejection and ethical issues. It has a strong fertility with the potential to differentiate in multiple directions, which can repair tissue damages caused by aging or other lesions. Purified and amplified MSCs can be injected into the vein of patients, so that they can reduce bleomycin-induced ALI mortality and the degree of lung injury, as well as improve the ability of alveolar epithelial repair[12]. Mitochondrial transfer plays an important role in the mechanism of MSCs treatment of lung injury[13].

4. Discovery of mitochondrial transfer phenomenon

As early as 2012, foreign scholars discovered the phenomenon of mitochondria transfer. Researchers constructed an ALI

model by injecting a certain dose of endotoxin into the airway of a mouse. In the control group, the same dose of phosphate buffered saline was injected. And then mice and human MSCs were injected, respectively. MSCs transferred mitochondria to alveolar epithelial cells via connexin 43. Later, mouse mitochondrial DNA was found in mouse MSCs-injected lung, while human mitochondrial DNA was found in human MSCs-injected lung. Transferred mitochondria can not only increase energy supply, but also promote the secretion of surfactant type II alveolar cells; meanwhile, leukocyte count and albumin content in bronchoalveolar lavage fluid reduced significantly, thus the mice can survive longer[14]. This experiment not only found the mitochondrial transfer phenomenon, but also demonstrated that MSCs can repair the lung epithelial cells through mitochondrial transfer. Further studies showed that mitochondrial metastasis can also exist in the MSC model of myocardium, vascular smooth muscle, cancer, osteosarcoma and so on[15-18]. Mitochondrial metastasis is not disordered. Mitochondrial transfer from the MSC to airway epithelial cells can be observed in the model of MSC and airway epithelial cell[19].

5. Way of mitochondrial transfer

Intercellular communication is a key to the development and maintenance of multicellular organisms. To date, different mechanisms have been documented for exchange of information between cells including chemical synapses, gap junctions and plasmodesmata. Such plasmodesmata are highly sensitive nanotube structures that form complex networks among cells, which facilitates the selective transfer of membrane vesicles and organelles and prevents the flow of small molecules. Mitochondria transfer among cells through the nanotube structure[20].

Membrane nanotube is a ubiquitous structure in nerve cells, immune cells, cancer cells and epithelial cells, which is an effective transfer pathway of organelle[21]. Numerous reports have already demonstrated that nanotubes can promote the exchange between signaling molecules and organelles, including mitochondria[22-25]. Mitochondrial transfer from MSCs to bronchial epithelial cells through nanotubes has been proved to work in asthma and COPD models[5]. Some data indicate that MSCs can transfer their mitochondria to the damaged alveolar epithelium and then recover adenosine triphosphate to normal levels, and the transferred key is the connexin 43[14].

6. Mitochondrial transfer process

It has been demonstrated that mitochondrial transfer of MSCs using extracellular vesicles has a good effect on metabolomics. In the lipopolysaccharide-induced ALI model, direct ATP levels can be restored through mitochondrial transfer using connexin 43[14]. When use of MSCs in the intervention of lipopolysaccharide-induced ALI, it can be found that useless MSCs in gap junction and dysfunctional mitochondria would be removed. MSC treatment can also prevent silica-induced pneumonia and pulmonary fibrosis[26]. MSC can control the level of oxidative stress in cells by transferring depolarized mitochondria. Vesicles are phagocytosed and reused by macrophages to enhance bioenergetics. To accomplish these transfers, MSCs loaded the mitochondria in the cytoplasm into microbubbles with microtubule-associated protein 1 light chain 3. These microvesicles express the transport-associated tumor suppressor gene 101 and the inhibitory protein domain including protein 1 and endosomal sorting complex required for transport. The protein would be squeezed from the cells in the microvesicles mediated by protein 1, and germinated directly on the plasma membrane, on which it was identified by macrophages. In the model of *Escherichia coli* pneumonia, mitochondrial transfer from MSCs to alveolar macrophages via nanotubes is necessary to enhance macrophage bioenergetics and phagocytosis, as well as MSC antimicrobial activity *in vivo*[27].

7. Kinetic energy of nanotubes for mitochondrial transfer

Nanotubes, as an important fundamental structure in the cell, can not only maintain the spatial order to some extent of cells inside and outside, but also play an important role in the normal life activities of cells. Nanotubes are involved in cellular activities including gene expression, cell differentiation, division and apoptosis, as well as transport of material, energy and information[28]. Some experiments were done to explore the movement characteristics of mitochondria in nanotubes[29,30]. Laser confocal instrument was used for real-time observation of mitochondrial motility and transmission. Immunofluorescence method was used to observe the position of mitochondria, microtubules and microfilaments. Microtubule inhibitor of nocodazole was used to block the polymerization of microtubules so as to observe the role of nanotubes in mitochondrial transfer. KIF5B protein expression was detected by methods of Western

blotting and fluorescent quantitative RT-PCR. By transfecting KIF5B-siRNA lentivirus, KIF5B protein expression was knocked down to observe the KIF5B function. TUNEL was used for detection of myocardial apoptosis. These results demonstrated that: 1) the existence of mitochondrial transfer; 2) the transfer way of nanotubes; 3) microtubules was the key for transporting mitochondria via the nanotubes; 4) KIF5B protein allowed mitochondria to be transported from MSCs into damaged cells.

8. Conclusion

Sepsis-induced ALI can not only lead to disorganization of mitochondria, but also dysfunction. Mitochondrial dysfunction often leads to oxidative-stress injury, increased reactive oxygen species, activation of apoptotic pathway, and apoptosis. All reactions, in turn, will cause changes of structure and function in other organelles around or even the whole cell, thus aggravate ALI degree. MSC can deliver mitochondria in a microtubule-dependent manner through membrane nanotubes, which brings great opportunities and challenges for early intervention and treatment of sepsis-induced ALI.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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