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Research progress in the treatment of cardiovascular diseases with extracellular vesicles

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Abstract. Extracellular vehicles (EVs) are small lipid vesicles that can release signaling substances containing proteins, nucleic acids, and other bioactive molecules. Recent research shows that EVs have potential application prospects in the treatment of cardiovascular diseases. EVs can alter the function of damaged cells and promote the repair and regeneration of cardiovascular tissue by transmitting bioactive molecules. In addition, EVs have the characteristics of low immunogenicity and high stability, making it a potential therapeutic strategy for cardiovascular diseases. Although the current research is still in the pre-clinical stage, with the further revelation of the mechanism of cardiovascular disease treatment using EVs, the treatment of cardiovascular diseases by EVs is bound to enter the clinical stage. This review expounds the advantages of EVs in cardiovascular diseases, and systematically lists the current application progress of EVs in a variety of cardiovascular diseases.

Keywords: Extracellular vesicles; cardiovascular diseases; non cellular therapy.

1. Introduction

Cardiovascular disease encompasses both heart and peripheral vascular diseases. Patients who suffer from high blood fat, blood viscosity, atherosclerosis, hypertension, and other conditions can experience ischemia or bleeding disease in their heart and peripheral blood vessels. Cardiovascular disease is a common disease that seriously threatens the health of human beings, especially the middle-aged and elderly over 50 years old, with a high incidence rate, high disability rate and high mortality.

In the past decades, cardiovascular disease has been one of the diseases which is hardest to cope with in the world. The traditional treatment methods include medication, surgery, and cardiac rehabilitation. However, these methods are limited by drug side effects, efficacy, recurrence risk, and treatment costs. Although some breakthroughs have been made in the treatment and new methods have been found, such as the use of cell therapy for intervention. It has been shown that human pluripotent stem cells (hPSCs), including human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs), are expected to promote the healing of myocardial infarction, because they can differentiate into cells of any lineage, including myocardial cells. However, the application of cell therapy in heart disease has been limited. First of all, cardiac myocytes and stem cells are not easy to obtain, and there are resource constraints and ethical issues [1]. Secondly, cells may be affected by factors such as mechanical trauma and ischemia after injection, leading to a decrease in survival rate [2], which limits its long-term therapeutic effect. In addition, exogenous cells may trigger immune system rejection when injected into the patient's body. This may lead to inflammatory reactions and cell death, thereby affecting the therapeutic effect [3]. At the same time, cell therapy is often a non-specific treatment method, which is difficult to control the location and distribution of cells in the human body.

To overcome the limitations of cell therapy, people began to explore cell derivatives therapy in recent years. Extracellular vesicles (EVs)-based therapies have been shown to be one of the attractive candidates for treating cardiovascular diseases. This review introduces the research progress of EVs in the treatment of cardiovascular diseases, and systematically summarizes the current exploration in this field. Although most studies are still in the early stages of animal experiments and there is still a certain distance from clinical research, with the progress of technological development, this treatment method may be more widely applied in the future.

2. Extracellular vesicle therapy

2.1. Extracellular vesicles

Extracellular vesicles EVs are cell-secreted vesicles and are one of the important secretions in cellular tissue. Its diameter is usually between 30 and 1000 nanometers [4]. EV can be secreted by most cells, and the secreted EV typically contains different goods, including proteins, DNA, RNA, and lipids, which can be used to construct intercellular signaling pathways. EVs play an important role in intercellular communication and signal transduction. They can carry pre-programmed signal programs to transmit signals to receptor cells to regulate their behavior and trigger diverse responses.

Given the support of intercellular mediators for non-autonomous cellular activities, intercellular communication can be influenced by EVs, which are considered an important mode of communication in both physiological and pathological conditions [5]. They participate in various biological processes, such as immune response, cell growth and proliferation, angiogenesis, and tumor metastasis. In addition, EVs are widely used in biomedical research and clinical medicine and are considered as potential biomarkers and therapeutic targets.

2.2. The advantages of EVs therapy

EVs, as carriers for transmitting cellular information and substances, can treat diseases by repairing or improving abnormal cells or tissues in patients' bodies. In cardiovascular diseases, EVs therapy may promote vascular repair and cardiac function recovery by transferring the active substances in EVs, while cell therapy may repair damaged heart tissue by transplanting cardiac cells[6]. Compared with cell therapy, EVs do not require a large number of cells to be transplanted, which reduces the problems of implantation restrictions and low cell survival rate. In addition, EVs have good biocompatibility due to their natural small vesicles released by cells[7]. This reduces the patient's immune response to EVs treatment and reduces the risk of adverse reactions. Growth factors and anti-inflammatory factors are abundantly present in the EVs secreted by cardiac cells, which can assist in the repair and regeneration of cardiovascular cells. Injecting EVs into the damaged area of heart disease patients can improve heart function and promote the regeneration of heart tissue.

2.3. Mesenchymal stem cells-derived EVs

Among many sources of EVs, EVs derived from mesenchymal stromal cells (MSCs) are one of the most-commonly-used extracellular vesicles. Mesenchymal stromal cells are a type of pluripotent stem cells, and some evidence suggests that they have immune regulatory effects. Therefore, MSC has been widely used in cell therapy for inflammatory diseases and tissue repair and rehabilitation. EV derived from MSCs is believed to have the same therapeutic effects as MSCs, such as anti-inflammatory, immune regulation, promoting tissue repair and regeneration[8] At the same time, he also addressed the high cost, low efficiency, immunogenicity and other defects of MSC itself. MSC EVs have been shown to replace MSCs in certain situations to achieve therapeutic effects. For example, in the model of type I diabetes and retinitis, MSC EVs are as effective as MSCs in inhibiting autoimmunity. In addition, the effect of MSC-EVs on acute kidney injury is similar to that of MSCs [9]. These observations indicate that MSC EVs can serve as substitutes for MSC based cell therapy.

MSC EVs can carry factors from mother cells, such as microRNAs, mRNA, proteins, etc. Once absorbed by the receptor cells, the membrane structure of EVs will be internalized or directly fused with the cell membrane, thereby activating a series of signals for transmission. For example, regulating immune responses, promoting cell proliferation and differentiation, and reducing inflammatory reactions. There have been many studies supporting the impact of microRNAs in MSC-EVs on the level of transcripts of specific pathways within cells, demonstrating their similar functions to MSCs. Compared with direct use of MSC therapy, the use of MSC-EV has the advantages of good compatibility, high delivery efficiency, and ease of preparation, storage, and transportation. Currently, research on MSC EVs is still in its early stages and further research is needed to verify their therapeutic efficacy, safety, and optimal use.

MSC EVs have made some progress in the treatment of cardiovascular diseases. Research has demonstrated the potential of MSC EVs in the treatment of cardiovascular diseases. Researchers have found in animal models that injecting MSC-EVs into myocardial infarction areas can promote the regeneration and repair of myocardial tissue, improve cardiac function, and reduce myocardial damage [10]. Meanwhile, some EV treatment experiments based on animal models have observed significant improvements in cell activity. Of course, there are currently no clinical trials conducted in humans. Overall, the progress of MSC-EVs in treating cardiovascular diseases is still in its early stages, but it shows great potential. With more research and clinical trials, it is believed that MSC-EV will become an effective treatment method, bringing better therapeutic effects to patients with cardiovascular diseases.

2.4. Engineering EVs

In recent years, artificial vesicles generated through genetic engineering or chemical modification of natural EVs have emerged, known as engineering EVs. The core specificity of Engineering EV is to add specific molecules to EV through different pathways, enabling it to perform specific functions. In terms of preparation form, Engineering EVs can be divided into two categories: one is to express endogenous target factors in EVs, and the other is to manually add target factors after isolating and purifying EVs [11]. In terms of purpose, Engineering EVs can be roughly classified into three categories. The first type is a drug carrier engineering electric vehicle, mainly used as a container for delivering drugs, allowing drug molecules to easily enter the target cell membrane. By modifying the membrane receptors or surface proteins, these EVs can specifically target disease tissues or cells and release the contents. The second type is gene delivery engineered EVs, which are designed to transmit genes to target cells. Through designing the nucleic acid inside the vesicles, specific DNA or RNA sequences can be delivered into cells to achieve gene therapy or gene expression regulation [12]. The third type is diagnostic engineering EVs, which modify the surface proteins or membrane molecules of EVs to specifically bind to disease markers and detect their levels, thereby achieving early diagnosis and monitoring of diseases.

Engineered EVs also have a broad prospect in the treatment of cardiovascular diseases, in addition to traditional drug delivery. Engineered EVs carrying growth factors can promote vascular regeneration and repair, as well as vascular damage caused by cardiovascular disease or ischemia in dry mountains. Alternatively, engineered EVs with vesicle surface modification can be used to regulate the inflammatory response process. In recent years, new scaffold materials and preparation methods have also been used to prepare engineered EVs.

3. Application of EVs therapy in the treatment of cardiovascular diseases

3.1. Progress has been made in treating Cardiovascular diseases

Different EVs can be used to treat cardiovascular diseases, and have made great progress in recent years. Yu et al found that EVs loaded with miR-21 can decrease the apoptosis of primary mouse cardiomyocytes. In animal models, miRNA-EV can effectively complete delivery and inhibit cell apoptosis leading to improved cardiac function. In the chronic inflammatory injury model of human coronary artery endothelial cells (HCAECs), researchers carried out functional verification by loading miR-34c-5p or its analog into platelet extracellular vesicle (PLT-EVs) [13]. They found that PLT-EVs containing miR-34c-5p and its analogs alleviated the inflammatory factors of HCAECs by blocking the P38 MAPK signaling pathway. miR-34c-5p mediated Podocalyxin (PODXL) consumption helps prevent oxidized low-density lipoprotein (ox-LDL) induced inflammation. The findings observed in the mouse model further validate these in vitro findings. In addition, miR-34c-

5p in PLT-EVs showed a protective effect on atherosclerosis in the mouse model [14]. Structural and functional changes of the vascular wall can be caused by EVs from subcutaneous adipose stem cells or bone marrow MSCs. Besides, Evs form these cell and tissues also triggers regression of key coordination factors expression in endothelial dysfunction induced by atherosclerosis, and regression of inflammation mediated atherosclerosis process [15].

In the myocardial infarction model, EVs therapy also showed significant improvement in cardiac function. Using a permanent myocardial infarction mice model, injecting EVs from hESCs/hPSCs into injured myocardium can significantly improve cardiac function, reduce fibrosis, promote angiogenesis and myocardial cell activity [16]. Furthermore, EVs derived from human cardiovascular progenitor cells (hCVPC) can enhance the tube formation and migration of human umbilical vein endothelial cell (HUVECs), and hCVPC-EVs can promote infarct healing by improving myocardial cell survival and angiogenesis [10]. In addition, macrophages have been shown to be closely related to the pathogenesis of myocardial infarction and tissue repair after myocardial infarction. EVs secreted by M1 phenotype bone marrow-derived macrophages activate angiogenesis and myocardial regeneration after myocardial infarction through the MALAT1/miR-25-3p/CDC42 axis and MEK/ERK pathway. The above studies are all about exogenous EVs [17]. In 2022, researchers collected and studied endogenous EVs from patients with myocardial infarction. They found that endogenous EVs from patients with myocardial infarction, regardless of the severity of the myocardial infarction, affects TNF-α. When inducing cell death, it exerts a cardioprotective effect [18]. The above studies have demonstrated that EVs play a cardioprotective role after myocardial infarction, but the underlying mechanism has not been elucidated yet.

For heart failure, EVs also have significant therapeutic effects. The disruption of energy supply and demand balance is one of the main causes of heart failure. Therefore, researchers used EVs rich in mitochondria (M-EVs) to promote the transportation and expansion of its mitochondrial and non-mitochondrial mediators, in an attempt to improve intracellular energy. Injecting M-EVs into the myocardium of mice can enhance cardiac function after heart failure in vivo. In 2022, EVs derived from human bone MSCs was proved to alleviate myocardial fibrosis and inflammatory cell infiltration, promote angiogenesis in rats with heart failure [12].

3.2. Progress of EVs in the treatment of cardiovascular diseases

As early as the 1990s, scientists first discovered EVs, also known as MSC-EVs, released by MSCs. These small vesicles have been found to carry various bioactive molecules that can transmit signals and functions between cells. In 2013, researchers first demonstrated the therapeutic potential of MSC-EVs for myocardial infarction. They found that injecting MSC-EVs can promote myocardial repair and regeneration, and improve cardiac function after myocardial infarction. Subsequent studies have shown that MSC-EV also has potential for the treatment of Atherosclerosis. MSC-EVs can alleviate vascular wall damage and improve the pathological process of Atherosclerosis by regulating inflammatory response, promoting angiogenesis and antioxidant stress. In recent years, people have a deeper understanding of the key factors in MSC-EVs for the treatment of cardiovascular diseases, and have made breakthroughs in the mechanism.

In 2015, Yu et al first discovered that miR-19a in MSC-EVs can restore cardiac function and reduce infarct size in rats with myocardial infarction [19]. Cheng et al. evaluated the potential of MSC-EVs for cardiac repair, indicating that the use of MSC-EVs can transfer bioactive content and induce cardiac repair after myocardial infarction [20]. In 2017, Wang et al. found that MSC-EVs are sufficient to improve angiogenesis and cardiac function in myocardial infarction hearts [21]. The miR-210-Efna3 pathway may be involved in the mechanism of MSC-EVs promoting angiogenesis. In 2022, Tang et al. proposed a new method for delivering EVs to the surface of the heart to treat myocardial infarction [22]. In the same year, Marta et al. used artificial acellular heart stents to locally deliver porcine cardiac adipose tissue MSC-EVs in a pig model of acute myocardial infarction, demonstrating anti-inflammatory effects at both local and systemic levels, and promoting myocardial angiogenesis and reduced fibrosis [23]. Highlighting the immunomodulatory potential of cATMSC-

EVs in the long-term progression of ischemic injury and reducing the size of infarcted scars to cure cardiac healing after myocardial infarction. In 2023, Ning et al. found that MSC-EVs can promote macrophage polarization through miR-139-3p/Stat1 pathway, revealing a new mechanism of cardiac repair in acute myocardial infarction (AMI) [24].

4. Conclusion

As a new therapeutic strategy, EVs have great potential for the treatment of cardiovascular diseases. Although EVs have been proven effective in animal models, there are still some areas that need to be clarified and optimized. Firstly, the functions and mechanisms of EVs are not clear, especially the effects of EVs secreted by different cells. To reveal the detailed functions and mechanisms of action will help us optimize the treatment outcomes. Secondly, there are still challenges in the preparation and purification of EVs, such as unstable yield and low purity. Future research should focus on developing more effective, repeatable, and high-purity EVs preparation technologies for clinical application. Despite encouraging progress, the clinical application of EVs in the treatment of cardiovascular diseases is still in the pre-clinical phase. To provide patients with more precise and personalized treatment options, it is necessary to conduct more clinical research and trials to evaluate the safety, efficacy, and optimal treatment plan of EVs in the future.

In short, as a new therapeutic strategy, EVs have brought new hope for the treatment of cardiovascular diseases. We have reason to believe that EVs will play a more important role in the treatment of cardiovascular diseases in the future, bringing better quality of life and health to patients.

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