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Research Progress in the Application of Exosomes for the Treatment of Intervertebral Disc Degeneration

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ABSTRACT
The pathological characteristics of patients with intervertebral disc degeneration are mainly manifested as the rapid degradation of the extracellular matrix, a reduction in nucleus pulposus cells, rupture of the annulus fibrosus, and inflammatory changes in the cartilage endplate. These changes lead to radicular pain in the lower limbs, as well as neck and back pain in patients. At present, the pathogenesis of intervertebral disc degeneration has not been clearly concluded in clinical practice. Treatment mainly focuses on alleviating clinical symptoms, preventing disease progression, and reversing the degenerative process. Therefore, it is necessary to further explore treatment methods for intervertebral disc degeneration. Exosomes have been a hot topic in the field of regenerative medicine in recent years. These active biological substances have a good control effect on inflammatory responses and can also improve the immune system. They can promote the rapid proliferation and regeneration of nucleus pulposus cells, and have a good therapeutic effect on intervertebral disc degeneration.

KEYWORDS
Exosomes; Intervertebral disc degeneration; Research progress

Intervertebral disc degeneration (IVDD) is very common in spinal surgery and is also a major factor causing neck and back pain. Statistics show that there are more than 700 million people with lower back pain worldwide, and 40% of them are closely related to IVDD. Under the influence of various factors such as obesity, aging, mechanical load, and chronic stress, the body's metabolic balance is disrupted, leading to changes in the components of the extracellular matrix, loss of nucleus pulposus cells, and triggering excessive oxidative stress and inflammatory responses in the body. These changes cause pathological changes in the intervertebral disc structure, microcalicification in the cartilage endplate, numbness in the lower limbs, and back pain in patients, which seriously affect the quality of life [1-2]. In recent years, with the change of people's lifestyle, the increasing severity of population aging, and the reduction of exercise due to long-term sitting, the incidence of IVDD has been rising continuously. However, there is currently no treatment that can reverse the process of IVDD. Therefore, it is necessary to further explore the mechanisms of IVDD and find more effective treatment methods. Exosomes, mainly derived from cell secretion, are lipid bilayer vesicles containing a variety of bioactive substances. Under the influence of these bioactive substances, damaged cells can improve the stability of the intervertebral disc structure [3-4]. This study analyzes the pathogenesis of IVDD and reviews the role of exosomes in the treatment of IVDD, hoping to provide more reference for the clinical treatment of IVDD.

1 Pathogenesis of Intervertebral Disc Degeneration

The intervertebral disc, composed of the nucleus pulposus and the outer fibrous annulus, can effectively cushion pressure. The center of the intervertebral disc is the nucleus pulposus, which includes nucleus pulposus cells and the extracellular matrix, and is a very important part of the intervertebral disc, as well as the main site where intervertebral disc degeneration occurs. Studies by Sima Xinli et al. [5] have shown that individuals with disc trauma, the elderly, obese individuals, long - term smokers, and those with a family history of intervertebral disc degeneration are at a higher risk of developing intervertebral disc degeneration. Excessive cell apoptosis and the accumulation of a large number of inflammatory factors can lead to a reduction in the extracellular matrix, thereby triggering intervertebral disc degeneration. Guo Sixu et al. [6] have found that the pathological characteristics of patients with intervertebral disc degeneration are mainly manifested as excessive apoptosis of nucleus pulposus cells and cartilage endplate cells, which is also the main reason for the accelerated progression of intervertebral disc degeneration. Due to changes in the biomechanics of the intervertebral disc, patients produce a large amount of inflammatory factors. The more severe the condition, the more evident the increased expression of inflammatory factors. In turn, the increase in inflammatory factors further exacerbates intervertebral disc degeneration, causing the patient's condition to enter a vicious cycle.

2 Analysis of Exosome Characteristics

Exosomes are nanoscale vesicles that can be secreted by cells, with a diameter ranging from 50 to 150 nanometers.

Due to their bilayer membrane structure, exosomes have higher stability in the extracellular environment, and bioactive molecules can be better protected. In the body's cells, the fusion of multivesicular bodies (MVBs) and the cell membrane leads to the release of exosomes into the extracellular space under the influence of proteins and lipids. Studies by Chen Shengcun et al. [7] have shown that although exosomes are small in size, they are rich in bioactive molecules. Exosomes play a very important role in the exchange of lipids, proteins, and RNA (including mRNA, lncRNA, and miRNA) between cells. Specifically, exosome proteins and lipids play a key role in cell adhesion, cell signaling, and the bilayer membrane structure. Additionally, the interaction between exosomes and target cells is also dependent on lipids, while RNA molecules play a crucial role in the gene expression and metabolic functions of target cells. mRNA, which encodes proteins, along with miRNA, complements target mRNA in the translation process and can inhibit and regulate gene expression in target cells. There are various ways for target cells to take up exosomes, and the transfer of bioactive molecules plays an important role in the metabolism and function of target cells. Yuan Xuemei et al. [8] have found that when target cells fuse with exosomes, the bioactive molecules are mainly integrated into the target cell membrane through the bilayer membrane of the exosomes. Additionally, target cells can internalize exosomes through membrane invagination, allowing them to enter the cell and undergo further processing. The surface ligands of exosomes can also bind to receptors on the surface of target cells, and exosomes are taken up by target cells through receptor - mediated endocytosis. Through these various uptake mechanisms, exosomes can deliver their bioactive molecules to target cells, which is an essential step in cell - to - cell communication and information transfer.

3 Mechanisms of Exosomes in Intervertebral Disc Degeneration

3.1 Promotion of Nucleus Pulposus Cell Functional Transition

The intervertebral disc relies primarily on nucleus pulposus cells to maintain its normal structure and function. Proteoglycans, which are crucial for disc hydration and elasticity, are synthesized and secreted mainly by these cells. An increase in disc water content due to nucleus pulposus cells helps enhance disc elasticity. However, when the disc degenerates, the function of nucleus pulposus cells is impaired, leading to cell apoptosis and inhibition of proteoglycan synthesis. Consequently, this results in a decrease in disc water content and elasticity. Bioactive molecules in exosomes can improve the function of nucleus pulposus cells. Morrison et al. [9] found that exosomes have a positive effect on nucleus pulposus cells, effectively enhancing their proliferation ability and providing a favorable environment for their survival. Mesenchymal stem cells, which can self - renew and differentiate into multiple lineages, can promote the secretion of bioactive factors in exosomes. Growth factors and antioxidant proteins, both present in mesenchymal stem cell - derived exosomes, can prevent nucleus pulposus cell apoptosis and exert a good inhibitory effect on oxidative stress responses. Under the influence of proteins and various growth factors, the proliferation rate of nucleus pulposus cells increases, promoting proteoglycan synthesis. Jin Fangquan et al. [10] found that after the signal pathways of nucleus pulposus cells are activated by growth factors, cell differentiation and proliferation are accelerated. Meanwhile, free radicals in cells are cleared under the influence of antioxidant proteins, better protecting the cells from oxidative stress. Additionally, under the influence of exosomes, nucleus pulposus cells can regulate autophagy and inflammatory responses effectively, preventing the further progression of intervertebral disc degeneration. During the self - degradation process of autophagy, cells can clear damaged organelles and proteins, maintaining a stable environment. After regulation, autophagy in nucleus pulposus cells can further enhance their ability to cope with stress and damage, helping to reduce inflammatory damage.

3.2 Inhibition of Inflammatory Response in the Body

Common inflammatory factors include Tumor Necrosis Factor - α (TNF - α) and Interleukin - 1 (IL - 1). In the progression of intervertebral disc degeneration, inflammatory responses are the main cause of disc cell apoptosis and extracellular matrix degradation. Exosomes can inhibit inflammatory signaling pathways through anti - inflammatory factors, thereby controlling the body's inflammatory response. Studies by Pan Yujun et al [11] have shown that exosomes have a good inhibitory effect on the inflammatory response of disc cells. This is mainly because exosomes contain effective anti - inflammatory factors, such as Transforming Growth Factor - β and IL - 10, which can effectively inhibit the expression and activity of inflammatory factors, preventing disc cells from being further damaged by the inflammatory response. Research has shown that IL - 10 can inhibit IL - 1 and TNF - α, thereby reducing the body's inflammatory response in patients. TGF - β can effectively regulate the degradation and synthesis of the extracellular matrix. Under the influence of exosomes, the body's inflammatory response can be effectively controlled.

3.3 Regulation of Extracellular Matrix Metabolism

Feng Shuaihua et al [12] found that the main reason for intervertebral disc degeneration is the disruption of the balance of extracellular matrix metabolism. In patients with intervertebral disc degeneration, the degradation and remodeling of proteoglycans and collagen fibers in the extracellular matrix affect the structure and function of the intervertebral disc. Exosomes can regulate the metabolism of the extracellular matrix by containing growth factors and enzymes, which can accelerate the synthesis of proteoglycans and collagen fibers and prevent their degradation. Zhang Hexing et al[13] found that growth factors in exosomes stimulate nucleus pulposus cells to secrete a large amount of proteoglycans, thereby increasing the water content of the intervertebral disc and enhancing its elasticity. Some enzymes can also promote the reconstruction of damaged collagen fibers, improving the structure of the intervertebral disc. Moreover, by regulating the metabolism of the extracellular matrix, the further progression of intervertebral disc degeneration can be prevented.

3.4 Promotion of Intercellular Interaction

The intervertebral disc contains the annulus fibrosus, nucleus pulposus, and cartilage endplate. The coordinated action of these cells helps maintain the normal structure and function of the intervertebral disc. Exosomes can act as a medium for communication between these cells. Under the influence of bioactive molecules, disc cells can maintain a balanced state. Gong Dongliang et al[14] found that exosomes can effectively regulate cell metabolism and function. This is mainly because annulus fibrosus cells, under the influence of exosome - derived growth factors and cytokines, proliferate and migrate, promoting the stability and integrity of the intervertebral disc. Additionally, the activation of annulus fibrosus cell signaling pathways under the influence of growth factors and cytokines can also regulate the function and metabolism of nucleus pulposus cells, promoting the regeneration and repair of damaged intervertebral discs. Exosome - derived factors can also regulate autophagy in nucleus pulposus cells, stimulating them to secrete a large amount of proteoglycans and other extracellular matrix components. This helps maintain the balance of disc cells and improves their function.

3.5 Inhibition of Angiogenesis

Studies have shown that in healthy individuals, the intervertebral disc lacks nerve tissue and blood vessels. However, as the condition progresses in patients with intervertebral disc degeneration, the annulus fibrosus is damaged, further affecting the physical barrier of the intervertebral disc. This leads to the growth of blood vessels and nerves. Under the influence of immune cells and inflammatory factors, the stability of the intervertebral disc decreases, further exacerbating the patient's condition and causing back pain. Therefore, in the clinical treatment of patients with intervertebral disc degeneration, controlling the growth of blood vessels in the intervertebral disc is very important. Exosomes can regulate the Wnt11/β - catenin pathway and have a good inhibitory effect on angiogenesis[15]. Moreover, exosomes are rich in bioactive substances, which play a role as a carrier in cell - to - cell communication, collectively inhibiting angiogenesis, thereby preventing the further progression of the patient's condition and improving the patient's quality of life.

4 Conclusion

Exosomes play a crucial role in inhibiting apoptosis of cartilage endplate, nucleus pulposus, and annulus fibrosus cells in intervertebral discs. They can promote intercellular communication and, through the transfer of bioactive molecules, effectively regulate the function and metabolism of disc cells. Additionally, exosomes can control the secretion of inflammatory factors and maintain the balance of extracellular matrix metabolism, thereby preventing the further progression of intervertebral disc degeneration. However, further research is needed on exosome - based treatment for intervertebral disc degeneration. The composition and function of exosomes can vary significantly depending on the type of source cells and culture conditions. To ensure the effectiveness of exosomes, it is necessary to standardize their production, purification, separation, storage, and transportation. Before clinical application, the safety and efficacy of exosomes must be verified through rigorous testing to create better conditions for exosome - based treatment of intervertebral disc degeneration.

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