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Review

Exosomes: A promising therapeutic strategy for intervertebral disc degeneration

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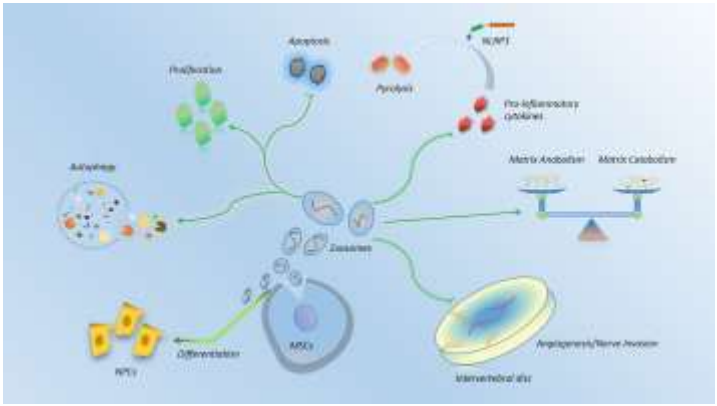
Abstract

As a common problem all over the world, low back pain (LBP) places a huge social and economic burden on people. Intervertebral disc degeneration (IDD) is often considered to be the main cause of low back pain. The current methods of treating disc degenerative diseases mainly focus on relieving symptoms, including surgery and conservative treatment, but none of them can be treated with the etiology, which means that the normal structure of the intervertebral disc cannot be fundamentally restored. With the development of tissue engineering and regenerative medicine, exosomes from different sources, especially mesenchymal stem cell-derived exosomes (MSC-exos) as active biological substances for intercellular communication have made rapid progress due to their potency in promoting tissue regeneration. The study of exosomes in the field of treatment of IDD has yielded many surprising results. This paper mainly reviews the mechanism and function of exosomes in the study of delaying or reversing IDD, as well as gives the prospects and challenges of exosomes.

Graphical abstract



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Introduction

IDD is considered to be the main cause of LBP and places a heavy burden on the global healthcare system (Hartvigsen et al., 2018). The intervertebral disc is composed of internal jelly-like nucleus pulposus (NP) and surrounding annulus fibrosis (AF), which can bear and reduce spinal pressure together. Generally speaking, in the degenerative process, the intervertebral disc has undergone complex biochemical and molecular changes, including the reduction of proteoglycan content, the conversion of type II collagen (COL II) to type I collagen (COL I), and the decrease of nucleus pulposus cells (NPCs) density, which can directly lead to decrease of the mechanical action of the intervertebral disc and structural damage, such as rupture of AF, herniated NP, etc. (Roberts et al., 2006) There are many factors that can promote or accelerate IDD, such as genes, age, and bad lifestyle habits, including occupational factors, smoking, and alcoholism (Williams and Sambrook, 2011). While genetic factor play a major role in IDD process as a potential regulator. Study on twins in IDD shows that genetic factors are involved in more than 70% (Videman et al., 2009; Battié et al., 2008). Previous studies have found that many genes are associated with IDD, including COL (I, IX, XI), IL-(1,6), aggrecan, Vitamin D4 receptor, matrix metalloproteinase-3(MMP-3), and microRNA etc.. They can cause intradiscal inflammatory response, lead to intradiscal metabolic imbalance, and can even be considered as biomarkers for the diagnosis or treatment of IDD as the main components in the intervertebral disc (Teles Filho et al., 2020). Due to the complex and unclear pathology of IDD, the options of treatment for LBP caused by intervertebral disc degeneration are very limited. Conservative treatment of LBP includes non-drug therapy and drug therapy. If conservative treatment fails to relieve pain, surgery can be considered. However, surgical procedures such as spinal fusion are invasive and often require long postoperative recovery times, with a non-negligible risk of surgical complications and high postoperative recurrence rates (X. Sun et al., 2020). Even if conservative and surgical treatment relieves LBP, it does not restore healthy discs and spine, which means that the IDD process will persist and cause LBP again or more at some point in the future. According to the current research progress, we found that the reduction of NPCs density, imbalance of

synthesis/degradation of nucleus pulposus extracellular matrix (ECM), AF degeneration (including cells apoptosis, collagen reduction and tissue rupture), inflammatory reaction, abnormal nerve invasion and angiogenesis in the intervertebral disc all lead to IDD. Due to the above reasons and gradually clarified degenerative mechanisms, a large number of studies aimed at delaying or reversing IDD have been carried out and have achieved promising results. As excellent candidate for tissue regeneration and anti-aging, MSC-exos, has made breakthroughs in many diseases nowadays, and many products have been approved for marketing. Of course, MSC-exos have also attracted the attention of researchers in delaying IDD. However, the complex mechanism of IDD makes it difficult to achieve comprehensive and in-depth studies. In view of the one-sidedness of the current research, we summarize the functions and mechanisms of MSC-exos in delaying IDD, which can give us a deeper understanding to draw up therapeutic strategies in theory. At the same time, it can also provide as comprehensive guidance as possible for the future search for reliable treatment options for IDD.

Section snippets

Searching strategy

Articles mainly come from the PubMed and Medline database (January 2016 to December 2021). The following keywords are used: (Intervertebral disc degeneration) OR (Degenerative disc disease) AND (Exosomes). Total of 48 publications were searched. Six review articles were ruled out and 12 articles were excluded for not being related to exosomes or intervertebral disc degeneration & degenerative disc disease. Ultimately, 30 articles were included (Fig. 1)....

Mesenchymal stem cells and exosomes

As the members of the stem cells family, mesenchymal stem cells (MSC) are derived from the early mesoderm and belong to pluripotent stem cells. MSC was first found in bone marrow, and has attracted increasing attention because of its multi-directional differentiation potential, hematopoietic support and promotion of stem cell implantation, immune regulation and self-replication (Galipeau and Sensébé, 2018). With the deepening of the research, encouraging results have confirmed that MSC can...

Apoptosis

Normal apoptosis can maintain the stability of the internal environment, which is autonomous programmed cell death controlled by genes (Tower, 2015). Research has confirmed that both exogenous and endogenous pathways participate in the process of human NPCs apoptosis (Sudo and Minami, 2010; Chong et al., 2020; Seyrek et al., 2020). The high rate of apoptosis and

senescence leads to a decrease of NPCs, which means that the excessive apoptosis can reduce the density of NPCs in the intervertebral...

Inflammation and pyrolysis

As one of the signs of intervertebral disc degeneration, inflammation, always accompanied by release of pro-inflammatory cytokines, is considered to be a key factor leading to discogenic pain. The interaction and abnormal expression of inflammatory cytokines (such as tumor necrosis factor-α, interleukin, nitric oxide and prostaglandin E2) can cause inflammation and accelerate IDD (Lyu et al., 2021). As the inflammatory response progresses, immune cells and pain-sensing nerve fibers from the...

Proliferation and autophagy

Cell proliferation is one of the crucial physiological functions of living cells and an important life characteristic of organisms, which mean that cell proliferation keeps the basis of organism growth, development, reproduction and heredity (Zhu and Thompson, 2019). While autophagy is an essential evolutionary conserved process of turnover of intracellular substances in eukaryotes. During this process, some damaged proteins or organelles are encapsulated by autophagic vesicles with a...

Extracellular matrix degradation

ECM is the microenvironment for cells production and survival, which is composed of collagen, proteoglycan, non-collagen, elastic fiber, water and glycoprotein. The main components glycoprotein and COL II combine with water to provide swelling force to resist the compression of the intervertebral disc and prevent excessive water loss. The main pathological feature of IDD is the loss of collagen and proteoglycan in the intervertebral disc (Ohnishi et al., 2020). Matrix metalloproteinase (MMP)...

Cell differentiation

Cell differentiation refers to the process in which cells from the same source gradually produce cell groups with different morphological structures and functional characteristics. When IDD occurs, the proliferative activity, cells density and extracellular matrix synthesis of NPCs in the intervertebral disc are reduced. So that it is difficult to obtain adequate autologous NPCs (Li et al., 2015). Nowadays, MSC has become a research hotspot due to its multi-directional differentiation and...

Angiogenesis and nerve invasion

As we all know, there are more blood vessels in the intervertebral disc in childhood than in adults, and the blood vessels can reach the deep layer of the intervertebral disc. Nevertheless, as human beings age, the blood vessels in the deep layers of the intervertebral discs gradually become less and thinner. And the nerves of the intervertebral disc are only distributed in the superficial layer of the annulus fibrosus, and there is no nerve distribution in the deep layer and nucleus pulposus....

Prospects and challenges

As we all know, like many human organs, the intervertebral disc will gradually degenerate with age, which is a normal senescence process that almost none can avoid it. Degenerative disc disease seriously affects people's quality of life and brings a heavy economic burden on the society. In the past, symptomatic treatment (such as non-selective NSAIDs and selective COX-2 inhibitors) and surgical treatment were mainly used for low back pain caused by lumbar disc degeneration, but this did not...

Declaration of competing interest

All authors report no conflicts of interest....

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