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Clinical Research Progress and Challenges of Biological Repair of Degenerative Intervertebral Disc Stem Cells

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Abstract: In theory, biological therapy can not only reverse or delay the process of intervertebral disc degeneration to a certain extent, but also preserve and restore the normal physiological function of intervertebral disc to the maximum extent, which is a research hotspot in recent years. Inhibiting inflammatory reaction, promoting the proliferation and division of residual cells, stem cell transplantation, cell scaffold and research and development of new biomaterials all provide new ideas and directions for the treatment of intervertebral disc degeneration. In this paper, the biological repair treatment scheme of intervertebral disc degeneration stem cells is reviewed.

1. Introduction

Intervertebral disc degeneration (IVDD) is one of the common causes of back pain and neck pain, especially in middle-aged and elderly people [1]. Intervertebral disc degeneration is due to the gradual deterioration of the structure and function of the intervertebral disc, which leads to the loss of its normal elasticity and height, and then causes the biomechanical changes of the spine and the compression of nerve roots or spinal cord. At present, the treatment of intervertebral disc degeneration mainly depends on conservative treatment (such as physical therapy and drug therapy) and surgical treatment (such as discectomy and spinal fusion), but these methods can not reverse the degeneration process or completely restore the function of intervertebral disc. Biological repair of stem cells is a new therapeutic strategy, which uses the self-renewal and multi-directional differentiation potential of stem cells to try to repair or regenerate damaged intervertebral disc tissue [2]. Stem cells are a kind of undifferentiated cells with self-replication ability, which can differentiate into many types of cells, including chondrocytes and osteocytes, which are very important for the repair of intervertebral discs.

2. Intervertebral Disc Degeneration

Intervertebral disc degeneration refers to the natural aging process of intervertebral disc with age, which leads to the gradual degradation of its structure and function. Intervertebral disc is located between adjacent vertebral bodies of the spine, which plays the role of connecting vertebral bodies, absorbing impact and maintaining the flexibility and stability of the spine. Intervertebral disc consists of fibrous ring (tough tissue at the periphery) and nucleus pulposus (gelatinous substance at the center).

The characteristics of intervertebral disc degeneration include: (1) With the increase of age, the water in the intervertebral disc gradually decreases, which leads to the loss of elasticity and fragility of the intervertebral disc. (2) There will be cracks or tears in the annulus fibrosus, which will cause the nucleus pulposus to protrude into the cracks, resulting in disc herniation or disc herniation. (3) The content of collagen fibers in the nucleus pulposus increases and the water content decreases, which makes the nucleus pulposus hard and lose its elasticity. (4) Due to water loss and structural changes, the height of the intervertebral disc will gradually decrease, which will lead to the shortening of the length of the spine and the decline of the stability of the spine. (5) Degeneration of intervertebral disc leads to pain, stiffness, limited movement and other symptoms, especially when the spine is active. Pain radiates along nerve roots, causing radiation pain. (6) In order to compensate for the loss of intervertebral disc function, extra bone, called osteophyte or spur, will be formed at the edge of the spine, which will compress the nerve root or spinal cord and cause pain or neurological symptoms.

Intervertebral disc degeneration is a common cause of spinal degenerative diseases, which is usually related to age, genetic factors, occupational factors, lifestyle and trauma. Although intervertebral disc degeneration is a part of natural aging, proper exercise, good posture, weight loss and avoiding excessive load can slow down the degeneration process and relieve symptoms to some extent. In some cases, medication, physical therapy or surgical treatment are needed to manage symptoms.

3. Biological repair of stem cells

Biological repair of stem cells refers to using the characteristics of stem cells to repair or replace damaged tissues and organs. Stem cells are a kind of primitive cells with the ability of self-renewal and differentiation into many different types of cells. They play a key role in the development and tissue repair of organisms.

The principles of stem cell biological repair include: (1) self-renewal, stem cells can produce more stem cells through division and maintain the stability of stem cell pool. (2) Multi-directional differentiation, stem cells can differentiate into many types of cells, including muscle cells, nerve cells, blood cells, etc., which makes them can be used to repair many types of tissues. (3) Immunoregulation. Some types of stem cells, such as mesenchymal stem cells (MSCs), have immunomodulatory function, which can reduce inflammatory reaction and promote tissue repair. (4) Tissue regeneration: Stem cells can migrate to damaged tissues, participate in the process of tissue regeneration, and promote the repair and functional recovery of damaged tissues.

The methods of biological repair of stem cells include: (1) Transplanting stem cells directly into damaged tissues to promote tissue repair. This method can be used to treat various diseases, such as heart disease, diabetes, nervous system diseases and so on. (2) Using stem cells and biomaterials to construct artificial tissues for repairing or replacing damaged tissues.

This method can be used to treat bone defects, skin defects, cartilage defects and so on. (3) Genetic modification of stem cells by gene editing technology, such as CRISPR/Cas9, to improve their repair ability or reduce immune rejection. (4) The activation and differentiation of stem cells in vivo are induced by drugs to promote tissue repair. This method can be used to treat osteoporosis, myocardial infarction and other diseases.

Although the biological repair of stem cells has great potential, it still faces many challenges, such as the source of stem cells, differentiation efficiency, immune rejection and ethical issues [4]. Future research needs to further solve these problems in order to realize the wide application of stem cell biological repair in clinical application.

4. Clinical research progress of biological repair of degenerative intervertebral disc stem cells

In May 2019, Japan approved a cell therapy technology called IDCT to treat intervertebral disc degeneration and entered the clinical trial stage. In January 2020, DiscGenics, a biopharmaceutical company, announced that the therapy showed positive efficacy and safety in preliminary double-blind clinical trials. This therapy belongs to a homologous allogeneic injection cell therapy, which adopts progenitor cells that have been transformed by biomedical engineering, and these cells are taken from intervertebral disc tissue, aiming at providing a non-surgical regenerative treatment option for mild to moderate degenerative intervertebral disc diseases. At present, six well-known universities in Japan are participating in this study, aiming at exploring the safety and preliminary treatment effect of two different doses. In recent years, many studies have verified that transplanting cells from autologous intervertebral disc or articular cartilage can effectively slow down the degeneration of intervertebral disc and promote the regeneration of intervertebral disc tissue [5]. In the research report in 2012, scholars used the whole culture technique in vitro to process the bovine intervertebral disc samples, and observed that human mesenchymal stem cells could cross the cartilage endplate and enter the intervertebral disc, effectively resisting the intervertebral disc degeneration caused by hunger, oppression or injury. In another study dating back to 2010, in the experiment of co-culture of human nucleus pulposus cells and mesenchymal stem cells, researchers found that the proliferation of nucleus pulposus cells and DNA synthesis activities were significantly improved, thus verifying the role of mesenchymal stem cells in promoting the viability of nucleus pulposus cells. Recently, the biological repair therapy with stem cell transplantation as the core has opened up a new way to treat degenerative diseases of intervertebral disc. This technology has made progress in laboratory research and gradually transited to the clinical trial stage, showing positive effects. In 2010, Spine magazine published a study, in which two cases with low back and leg pain and obvious degeneration of lumbar intervertebral disc were treated by clinical experiment. The researchers extracted bone marrow fluid from the patient's ilium, then isolated bone marrow mesenchymal stem cells and cultured them in vitro with the patient's own serum. Subsequently, gelatin sponge rich in autologous bone marrow mesenchymal stem cells was implanted into the degenerated intervertebral disc. After two years of follow-up, the patient's initial symptoms have been significantly alleviated, the degeneration of intervertebral disc has improved, and the stability of the spine has also been enhanced. This study confirmed that the transplantation of autologous bone marrow mesenchymal stem cells is helpful to the repair and regeneration of degenerated intervertebral disc tissue.

In a clinical trial in 2011, researchers treated 10 patients with degenerative intervertebral

disc accompanied by chronic low back pain by implanting their own bone marrow mesenchymal stem cells into degenerative intervertebral disc tissue. After a year's observation, all patients' symptoms of low back pain have been effectively alleviated, and their spinal function has recovered significantly. Compared with traditional spinal fusion or vertebroplasty, this treatment has shown more outstanding advantages. Based on these positive results, the researchers concluded that stem cell therapy is an effective and safe treatment for degenerative disc diseases.

Based on these positive therapeutic effects, another study in 2016 also pointed out [5] that autologous bone marrow mesenchymal stem cells cultured under hypoxia were injected into the intervertebral discs of five patients with discogenic low back pain. Follow-up investigation shows that four patients have improved their lumbar mobility in different degrees, and no tumor or other complications have been found near the injection area in the examination of 4 to 6 years after injection, which shows that transplantation of bone marrow mesenchymal stem cells is a reliable and safe method in clinical treatment of discogenic low back pain.

In 2017, a clinical trial involving 24 patients with lumbar discogenic pain was carried out by researchers in Valladolid Medical Center. The trial adopted a randomized controlled design, and allogeneic bone marrow mesenchymal stem cells were transplanted to the subjects. After a year of follow-up, the researchers found that the symptoms and intervertebral disc degeneration of patients treated with stem cells improved, which confirmed the effectiveness of this treatment.

At the same time, American stem cell experts engaged in regenerative medicine conducted a study on 26 patients who needed lumbar fusion or total disc replacement [6]. These experts injected 2 ml of autologous bone marrow mesenchymal stem cells into the nucleus pulposus of the patient's lumbar intervertebral disc. After 12 months of injection treatment, the degree of intervertebral disc degeneration has been improved. However, after 36 months, only 6 patients needed surgery, and the symptoms of the remaining 20 patients were significantly relieved, and no serious complications related to injection occurred in all patients during the treatment. This discovery provided a wider indication for the clinical application of bone marrow mesenchymal stem cells in the treatment of intervertebral disc degenerative diseases.

5. The clinical research challenge of biological repair of degenerated intervertebral disc stem cells

Biological repair of stem cells is a new therapeutic strategy, which aims to use the self-renewal and multi-directional differentiation potential of stem cells to repair or regenerate damaged intervertebral disc tissue. Stem cells can be derived from a variety of tissues, such as bone marrow, fat, cord blood and so on [7]. In the treatment of intervertebral disc degeneration, stem cells can be induced to differentiate into intervertebral disc cells to replace or repair degenerated intervertebral disc tissue. Although stem cell therapy has potential advantages in the repair of intervertebral disc degeneration, it still faces many challenges in clinical research: (1) Safety, and the safety of stem cell therapy is the primary consideration in clinical research. It is necessary to ensure that the use of stem cells will not cause immune rejection, tumor formation or other adverse events. (2) Effect evaluation. How to accurately evaluate the effect of stem cell therapy is a challenge. It is necessary to develop standardized evaluation methods to measure the structural and functional changes of intervertebral discs before and after treatment. (3) The origin and differentiation of cells, and the origin, purity, differentiation potential and stability of stem cells are very important to the therapeutic effect. It is necessary

to determine the best stem cell types and differentiation conditions to ensure the success of treatment. (4) Clinical trial design, in which rigorous clinical trials are designed to evaluate the effectiveness and safety of stem cell therapy. This includes selecting the appropriate patient group, determining the appropriate dosage and route of administration, etc. (5) Regulatory and ethical issues. Stem cell therapy involves many ethical and regulatory issues, including the acquisition, use and commercialization of stem cells. It is necessary to ensure that the research follows the relevant ethical standards and regulatory requirements. (6) Cost-effectiveness. The cost of stem cell therapy is relatively high, so it is necessary to evaluate its cost-effectiveness ratio to determine its feasibility in clinical practice. (7) Long-term effect and follow-up, patients need to be followed up for a long time to evaluate the long-term effect and potential complications of stem cell therapy. With the development of research and technology, these challenges are expected to be gradually solved, and the application prospect of stem cell biological repair in the treatment of intervertebral disc degeneration will be more clear.

6. Concluding remarks

To sum up, intervertebral disc degeneration is a common cause of back pain and neck pain, especially in the elderly. With the increase of age, the water content and elasticity of intervertebral disc decrease, which leads to the degeneration of intervertebral disc structure and function. More and more clinical trials have confirmed that stem cell transplantation is effective in the treatment of intervertebral disc degeneration, which can not only effectively relieve low back pain and restore spinal function, but also gain more and more recognition for its safety. With the further research, stem cell transplantation technology may become another choice to treat intervertebral disc degeneration.

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