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Operative Techniques in
Orthopaedics

Cell-Based Therapies for Degenerative Disc Diseases ☆

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Intervertebral discs degeneration are responsible for most of cases of low back pain, which affects millions of people worldwide. Current clinical therapies for degenerative disc diseases involve medications or physiotherapy for mild to moderate degeneration, and surgeries for severe degeneration. However, current treatments aim to remove symptoms sometimes at the cost of mobility instead of restoring the biological function. Future therapy for disc repair is in development by biological strategies, including protein or growth factor injections, gene therapy or cell therapy approaches. Cell-based therapies provide the greatest hope, as it is a continuous source of cells and cytokine production, and the safety is superior compared to gene therapy. The choice of cell source includes chondrocytes, disc cells, embryonic stem cells, hematopoietic stem cells, and mesenchymal stem cells. Results of several clinical trials suggest that mesenchymal stem cells are the best choice of cell source for intervertebral discs regeneration. The remaining concern is that the harsh environment of the degenerated disc may have effect on the engraftment and differentiation of implanted cells. The timing of cell implantation may also have effect on the degree of disc regeneration, which may require an earlier intervention at mild to moderate level of disc degeneration to achieve satisfactory surgical outcome.

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Introduction

Intervertebral discs (IVDs) are fibrocartilaginous tissues connecting the vertebral bodies, contributing about one-third of spinal length. IVDs are important to spinal function by providing stability while permitting motion between the vertebrae. Importantly, the complex structural features of IVDs also enable them to absorb and disperse loads from physical activities. IVD degenerates during time. Degenerative disc diseases (DDD) are progressive disorder correlated with age. The prevalence is more than 70% in the age group of 50 years or younger and more than 90% in those older than 60 years.[1] IVD degeneration may not necessarily cause pain. Depending on individual difference, it may sometimes be asymptomatic, but it can also be painful, which is termed discogenic pain. Discogenic low back pain (LBP) accounts for 26%-42% of chronic LBP patients,[2] which affects approximately 70% of the population at some point in their lives. DDD is a musculoskeletal disorder and can be indicative of severe conditions such as disc herniation or prolapse, radiculopathy, or spinal stenosis. It imposes an enormous socioeconomic burden on the affected individual and the health care services, with increased medical expenditure and reduced productivity owing to loss of working hours.

Current clinical therapies for DDD involve symptomatic relief from pain by medications or physiotherapy for mild to moderate degeneration. For severe degeneration, surgeries such as disc arthroplasty, spinal fusion, and disc decompression are often employed as a last resort. However, the effect is controversial[3,4] and it may cause complications such as

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adjacent level disease[5] that often warrants further surgical procedures. Such treatment modalities, however, neither arrest the progression of degeneration nor restore the native functional state of the IVD. Recent years, the advances in gene delivery techniques and the identification of adult stem cells have promoted the research on the possibility to treat disc degeneration with the transplantation of viable cells, especially stem cells. Expanding knowledge has enabled diverse therapeutic development and various techniques to manipulate and direct them to specific fates has promoted a stem cell-based regenerative approach to DDD.

IVD Structure and Cell Biology

A healthy adult IVD is composed of 3 morphologically distinct components: the central gelatinous nucleus pulposus (NP), which contains chondrocyte-like cells, surrounded by a lamellated fibrous annulus fibrosus (AF) containing fibroblast-like cells, and capped by 2 cartilaginous endplates (EP) that anchor into the adjacent vertebrae. The IVD is rich in extracellular matrix predominantly represented by collagen and proteoglycans with distinct differences in each compartment.[6] NP is rich in aggrecan and type II collagen, whereas AF contains type I collagen with little proteoglycans. In fact, collagenous proteins comprise 70% of the outer annulus dry weight, but only 20% are located in the central NP, whereas proteoglycans make up 50% of the NP.[7] Although the component of NP matrix is similar to that of articular cartilage, there are much differences in the gene expression profile and matrix synthesis.[8] The density within the NP tissue is quite lower at approximately 5000-6000 cells/mm^3[9] compared with 15,000 cells/mm^3 in cartilage.[10] The proteoglycan—collagen ratio is also different, it is 27:1 in the NP, and 2:1 in the cartilage.[11] High proteoglycan content is an important feature of the NP. The high positive charge of proteoglycans gives the NP a high osmotic potential, which draws in water and enable the NP to absorb mechanical shock and deliver it horizontally to AF. It also inhibits the ingrowth of nerve.[12] Evidence has shown that the loss of proteoglycan lead to nerve and blood vessel ingrowth in an ovine annular lesion model of experimental disc degeneration.[13] Owing to the aforementioned reasons, NP is the most critical component of the IVD and is the region where degenerative changes first occurs. It is also the focus of IVD regeneration researches.

The Etiology of DDD

The etiology of DDD is complicated in origin. It can include occupational exposure, mechanical influences, injury, lifestyle, and genetic predisposition. Moreover, strong evidences have confirmed that the disturbance in the biology of the cells in the NP, AF, and EP, which are significantly affected by the diffusion of nutrients and oxygen from the blood vessels,[14,15] the soluble factors in the niche,[16] the mechanical loads[17] as well as ageing or senescence,[18,19] plays a key role in the regulation of the IVD degeneration. However, in spite of the predisposition factors and secondary causes, it is believed that mechanical overload is one of the initiating factors of the disorders of the IVD. The normal adult IVD is avascular and aneural with the exception of the outer third of the AF. When IVD degenerates, the NP is disorganized, and the proportion and types of extracellular matrix proteins changes which makes the NP more eosinophilic. Overload leads to breakdown of the matrix of the NP with the formation of fissures that eventually extend into the AF. There is often also disruption of the collagen fiber orientation in the AF, traumatic damage to the EP, and blood vessel[20] and nerve ingrowth[21,22] into the inner AF and NP, which is normally avascular and aneural.

Molecular Changes in the Degenerated IVD

Molecularly, DDD is characterized by cell death and degeneration of extracellular matrix. Normal NP cells are characterized by expression of type II collagen and proteoglycans. In disc degeneration, matrix remodeling[23] leads to an increase in collagens I and III and decreased production of aggrecan. In degeneration, the anabolic:catabolic balance is broken, there is a net increase in matrix-degrading enzyme activity over natural inhibitors of such activity, which leads to loss of disc matrix. Increased degraded fragments of proteoglycan[24,25] and other matrix proteins[26] was reported, which has the potential to trigger further inflammatory changes[27] (summarized in Ref. 28). Aggrecan has 2 cleavage sites, one acted upon by matrix metalloproteinase (MMPs) and the other by members of a group of enzymes called the ADAMs family.[29] MMPs and ADAMs have both been implicated in disc degeneration.[30,31]

Degenerated IVDs are demonstrated to be in a chronic inflammatory state with increased expression of multiple proinflammatory cytokines, including interleukin 1 (IL-1), matrix metalloproteinase 10 (MMP10),[32] IL-8, tumor necrosis factor-α (TNF-α),[33] IL-10,[34] IL-2, IL-4, IL-17, monocyte chemotactic protein-1 (MCP-1), and prostaglandin E2 (PGE2).[35,36] Of these, IL-1 is particularly interesting, because IL-1 plays more important role in mediating disc matrix degradation than TNF-α.[16] IL-1β also leads to production of MMPs and pain mediators, such as the eicosanoid prostaglandin E2, by human IVD cells.[37]

Potential Developing Treatments for Disc Degeneration

One of the problems of current treatments is their inability to repair the disc. Instead the aim of current treatments is more about removing symptoms such as pain and sometimes this is realized at the cost of mobility in the case of spinal fusion. As the future therapy for disc repair, protein or growth factor injections, gene therapy or cell therapy approaches is in continuous development.

Growth factors are small proteins with pleiotropic effects on cells, including stimulation of cell differentiation and division.