Degenerative Disc Disease: A Review of Cell Technologies and Stem Cell Therapy

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Abstract

Background & Aim: Low back pain is broadly documented as one of the most widespread pathologies in the advanced domain. Although the reasons of low back pain are uncountable, it has been meaningfully related to intervertebral disc degeneration. Present therapies for Intervertebral Disc (IVD) degeneration such as physical therapy and spinal fusion reduce symptoms' severity, but do not treat the source of degeneration. The use of tissue engineering to treat disc degeneration offers a chance to control the pathological course. New methods are presently being examined and have exposed mixed results. One major way of study has been stem cell injections. We go on to define the course of stem cell-mediated modalities in treatment of degenerative lumbar disc herniation

Methods & Materials/Patients: Literature search was performed in electronic databases PUBMED and EMBASE by means of Mesh terminologies (Nucleus pulposus, therapeutics, annulus fibrosus, intervertebral disc) and keywords (Degenerative disk disease, Stem Cells, Therapy).

Results: The intervertebral disc organization, developing treatments, mesenchymal stem cells, embryonic stem cells, practice in disc degeneration were some sections that were found in analysis for study review design.

Conclusion: Mesenchymal stem cells (MSCs) have revealed potential in small animal models, nonetheless consequences in greater vertebrates have been varied.

Keywords: Intervertevral Disc; Degeneration; Stem cells

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Introduction

At this time, degenerative disk disease (DDD) and the following chronic back pain characterize an important cause of morbidity and mortality universally (1,2). The purpose of accessible treatment modalities such as pain treatment and operations is to offer symptomatic relief; but they do not reduce the original pathophysiology of DDD. The disease itself has high social health care expences (3). Magnetic resonance imaging (MRI) is a noninvasive and choice method to evaluate lumbar disc herniation and to exclude the different differential diagnosis in spine and other organs of body (4,5).

Numerous modalities are for symptomatic handling of this disorder, containing bed rest, massage, stretching, exercises, physical therapy, epidural injections and additional pain organization therapies, and spinal surgery by discectomy via laminotomy or laminectomy and spinal fusion with pedicular screw (6-9). Most conventional therapies are tried before surgery to reduce the probable complications due to surgical intervention. Though, these conservative actions and even operation itself with its linked dangers only reduce the symptoms with no influence on the disease procedure in the disc itself. New investigation has given additional vision into the pathogenesis of DDD, which has borne out a transformed attention in biologic therapies positioned on the nucleus pulposus (NP) and the annulus fibrosus and the potential of stem cells to converse the disease course at a histological and cellular level (10,11).

In this study, we reviewed the existing literature concerning biologic therapies in the regeneration of the intervertebral disc (IVD). We defined the course of stem cell-mediated modalities in treatment of degenerative lumbar disc herniation.

Methods and Materials

Literature search was performed in electronic databases PUBMED and EMBASE by means of Mesh terminologies (Nucleus pulposus, therapeutics, annulus fibrosus, intervertebral disc) and keywords in English (Degenerative disk disease, Stem Cells, Therapy). Papers published from 1869 to 2016 were considered in this study. Exclusion criteria were trainings available in every language other than English. We studied 61 articles from January 1976 to December 2015.

Results

The intervertebral disc: Organization and Degeneration

The IVD is avascular and contains predominantly of a macromolecular extracellular matrix (ECM) through a low-

density populace of cells aid to preserve this ECM. Obviously, a usual IVD involves a dominant NP enclosed by the annulus fibrosus (AF), all of which intersect each other among two cartilaginous endplates (EPs) (12). The NP is comparatively fluid, collected mainly of an ECM of collagen type II and proteoglycans. Functionally, the collagen informs tensile strength, whereas the proteoglycans entice and bind water, providing flexibility to compression. Postponed through this ECM are chondrocyte-like cells (13).

Frequently, the constancy of the NP is defined as "gell mass." In turn, the AF is collected of a sequence of concentric rings (lamellae) which are chiefly collagen I. The high fraction of collagen marks the AF rigid, a possession that assists to comprise more fluid NP and donate to the integrity of the disc. Lastly, the endplates distinct the NP and AF from the contiguous vertebral bone. Histologic valuation has revealed that disc degeneration ultimately initiates in the early teenage years (14,15). The discs of the lumbar spine tolerate an unequal quantity of this wear (14). Far from being static, the disc ECM is topic to nonstop synthesis and degradation (16). In IVD degeneration, the rate of matrix anabolism reduces, while matrix catabolism increases. This leads to an amount of variations. Proteoglycan contents in the NP drops meaningfully as well as the capability of the ECM to attract and recollect water (16). The amount of chondrocytes in the ECM drops (15,17). Macroscopically, fibrous tissue forms in the NP, resulting in a loss of gel-like personality and eventually leading to a disbanding of the distinction between NP and AF (2). Repetitive mechanical loading (18,19) and deteriorating nutrition (18,20,21) have been concerned as the two most critical influences in degeneration. Inadequate nutrition is important in slowing matrix anabolism. Because the IVD is avascular, it needs to obtain nutrients through diffusion. Blood vessels terminate at the EP and nutrients then move based on gradients across the plate and through the ECM to spread embedded cells. It is well recognized that the EPs developes less permeable by age (21,22), and Boos et al. (2002) found histologic confirmation that a reduction in endplate blood vessels accords with a growth in disc ECM failure. Educations on disc nutrition have recommended that glucose is the serious nutrient for preserving cell viability, with oxygen and pH acting as secondary factors (19,23). Once nutrition of the disc is adequately impaired, disturbance of matrix synthesis and cell death can happen (24,25). The additional constituent in disc degeneration is collapse of the matrix. Matrix metalloproteinases (MMPs) and aggrecanases are two curricula of enzymes complicated in both normal matrix turnover and degeneration. These enzymes destroy the components of the ECM and have been originate at raised levels in degenerated discs (26,27).

Developing Treatments. A growing sympathetic of the molecular variations related with IVD degeneration has run to an increasing investigation of numerous treatments planned to straight discourse these changes (17). In current years, treatments directing numerous molecular and cellular features of degeneration have been discovered. One method has been the direct injection or stimulation through gene therapy of an amount of growth factors intricate in regulating matrix anabolism (28,29). This practice has revealed hopeful consequences alternative major path of study has been cell therapy. The main objective of cell therapy is to grow ECM synthesis via rebuilding the degenerated NP. To achieve this, one of numerous types of cells is injected directly into the NP. Cell kinds used thus far include NP cells (32), chondrocytes (33), and MSCs (34), all of which have showed potential for decelerating and repairing degeneration.

Mesenchymal Stem Cells

Transforming growth factor-β3 (TGF-β3) is a factor that has been shown in multiple studies to stimulate cells to differentiate into chondrocytes (35). Several studies have shown that after TGF-β3 stimulation, MSCs turned positive for collagen type II protein and expressed a large panel of genes characteristic for chondrocytes, such as aggrecan, decorin, fibromodulin, and cartilage oligomeric matrix protein (35). Shen et al. () have shown that bone morphogenic protein-2 (BMP-2) can help to enhance TGF-β3-mediated chondrogenesis in MSCs (36). The combination of BMP-2 and TGF-β3 in alginate culture was found to be superior to the standard differentiation method using TGF-β3 alone as evinced by increased mRNA expression of aggrecan, type II collagen, Sox-9, BMP-2, and BMP-7, all of which are chondrocyte markers. This effect was even more pronounced when TGF-β3 and rhBMP-2 were both added (37). This synergistic effect was consistently found in the study, providing further support as yet unknown pathway towards chondrocytic differentiation.

Embryonic Stem Cells

Hoben et al. (2009) performed a similar characterization study using human ESCs (38). Growth factors were studied with a coculture method for 3 weeks and evaluated for collagen and glycosaminoglycan (GAG) synthesis. The growth factors studied were TGF-β3, BMP-2, BMP-4, BMP-6, and sonic hedgehog protein. The investigators found that the combination of BMP-4 and TGF-β3 within th fibrochondrocyte coculture led to an increase in cell proliferation and GAG production compared to either treatment alone. Koay et al. (2007) had similar results with BMP-2 and TGF-β3 leading human ESCs down a differentiation path that produced an end product with high type I collagen content (39). However, they also found that human ESCs treated with TGF-β3 followed by TGF-β1 and IGF-1 produced constructs with no collagen I, showing that different growth factor application in different temporal sequences can have a marked impact on end-product composition and biomechanical properties.

Practice in disc Degeneration

Some in vivo studies have indicated the usage of MSCs to deliberate the course of IVD degeneration and redevelop the matrix. In 2003, Sakai et al. conducted the first study of using the MSCs to restoration of IVD degeneration in vivo using a rabbit model (40). Incomplete aspiration of the NP was used to encourage degeneration, and autologous MSCs fixed in an atelocollagen gel stayed then inserted into discs. This process was established to avoid histological and morphological disc degeneration while matched to a nontreated, degeneration-induced controller. General NP and AF construction, cell volume, and matrix development were kept up to 8 weeks after injection,

and fixed MSCs were found to have differentiated into cells approximating original disc cells.
By a rabbit model, Zhang et al. (2008) established that transplanted allogenic MSCs survived and augmented proteoglycan and collagen II synthesis in the NP (41). Wei et al. (2009) used a rat model to evaluate the capability of human MSCs to proliferate and function inside the IVD (42). After 6 weeks, MSCs confirmed survival and differentiation to disc cells. Extensive Success using allogeneic and xenogeneic MSCs may replicate the immune advantage of the IVD (43), like the immunosuppressive abilities of MSCs (44). Henriksson et al. (2009) inserted human MSCs into porcine discs which were then gathered at up to 6 months (45).
At follow-up, MSCs survived and differentiated toward disc cells, displaying matrix-producing functionality. Likewise, Hiyama et al. (2008) found MSC injection into degeneration-induced canine discs proliferated proteoglycan contents and successfully alleviated degeneration (46).

Future Instructions

Combination therapy, providing supportive matrix and bioactive materials, might almost be the finest solution required, improving cell survival, proliferation, and differentiation (47). Numerous growth factors labelled in earlier studies have been implicated in IVD degeneration and therapy. MSCs secreting transforming growth factor-beta (TGF-β), Insulin-like growth factor-1 (IGF-1), and platelet-derived growth factor (PDGF) have been established in cocultures with NP cells and have been revealed to be an actual stimulator on matrix metabolism and cell proliferation throughout biological reparation of IVDs (48). Growth and differentiation factor- 5 have been exposed to rise disc stature and stimulate proliferation and matrix synthesis in the NP and AF.
Additionally, Henriksson et al. (1997) found endogenous stem cell places in the AF boundary to the ligament zone and the perichondrium area (49). The application of growth factors can excite proliferation of these endogenous stem cells. Immunogenicity, architectural and mechanical possessions alongside with biocompatibility, biodegradability, and technique of graft transfer should be measured while selecting the scaffold (50). Pharmaceutical studies will similarly require to be complete in order to regulate the cell density and volume that need to be transplanted in order to gain the anticipated outcome though causing the least quantity of side effects. Given that the IVD is reflected immunoprivileged, the need to discover an autologous cell origin might not be essential (51).
Other important issue is the perfect culture circumstances of the MSCs. First of all, for clinical trials it must be done in GMP grade situations with xeno-free substances (48). It is significant to consider that in vitro development can lead to an accumulation of genetic and epigenetic fluctuations by an unknown result in vivo when transplanted. The changes might lead to augmented immunogenicity even in autologous or malignant transformation.

Conclusion

It is obvious that there are numerous problems left unanswered. In order to define an actual therapeutic choice for IVD - degeneration associated back pain, further designed studies are required. One of the chief problems is making an animal model that can sufficiently duplicate the microenvironment perceived in IVD degeneration. When an animal model is recognized, more preclinical records in a focused method will be available.

Conflicts of Interest

The authors have no conflicts of interest.

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Comments

Twenty first century would face an introduction to clinical translation of basic research regarding stem cell technology for various neuropathological situations.

Most of the available evidence regarding application of stem cells for intervertebral disc pathologies have been obtained experimentally working on animals. These studies have been performed on rat, rabbit, and dog species, and try to promote proteoglycan synthesis, as well as collagen type II in the nucleus pulposus. They have successfully reported reproduction of chondrocytes in the nucleus pulposus, from stem cell origin.

Also chemical macromolecules such as Insulin like Growth Factor 1 (IGF1), Platelet Derived Growth Factor (PDGF), have had important role in the metabolism of connective matrix and cellular proliferation.

Some recent studies have used degenerated human nucleus pulposus cells for disc matrix regeneration. Other studies have suggested percutaneous mesenchymal stem cell injects in to the nucleus pulposus, for the purpose of disc regeneration. Nevertheless the following questions still remain unanswered:

1-Which patients will benefit from cell therapies?

2-What is the temporal profile of biological repair of human discs?

3-Can cells be implanted safely into the disc?

4-What are the limitations arising from the nutrient supply for the implant cells?

5-Are conditions in the treated discs permissive for matrix production in the nucleus polposus?

Obtaining good results from preclinical studies, has led to FDA certificate for conduction of several clinical trials regarding application of stem cells for intervertebral disc regeneration.

It is important for surgeons to have knowledge of stem cell treatment results and indications when they become available to the patients for helping them to make informed decisions about the treatments they undertake.

Well controlled preclinical testing is needed to address their long term efficacy for using committed cells compare to adverse effects and concerns about the use of stem cells.

The accumulation of well-designed and case-controlled clinical trials in a step-wise manner in concert with expert discussions and regulatory institutions will be crucial to surmounting the obstacles to stem cell therapy for intervertebral disc degeneration.

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