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Cell-based therapy for disc repair

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Abstract

BACKGROUND CONTEXT: One of the most promising therapies for symptomatic disc degeneration involves the implantation of therapeutic cells into the degenerative disc.

PURPOSE: In this article, the rationale and approaches for cell-based tissue engineering of the intervertebral disc are discussed.

STUDY DESIGN: The scientific literature related to cell-based tissue engineering of the intervertebral disc is reviewed.

METHODS: A variety of cell types have been used in various research models to affect matrix repair of the intervertebral disc. The use of cellular scaffolds and growth factors or genes also appears promising for achieving meaningful tissue repair of the intervertebral disc.

RESULTS: Disc tissue engineering is a promising approach for achieving repair of the intervertebral disc. Using cell-based approaches, various research models suggest that improvements in the complex matrix of the disc may be achieved.

CONCLUSION: A cell-based approach to repair of the intervertebral disc appears promising. More research is needed to define the optimal cell type, cellular scaffold and mixture of growth factors that may allow meaningful repair of the human symptomatic degenerative disc.

Keywords: Cell therapy; Cell culture; Disc degeneration; Growth factor; Mesenchymal stem cells; Tissue engineering

Introduction

The effect of disc degeneration on society is well known [1,2]. Normal biomechanical functioning of the disc requires structural integrity of the semifluid nucleus pulposus and fibrous anulus that provides stress dissipation and allows motion of the intervertebral segment [3]. Disc degeneration leads to dramatic changes in the cellular and structural matrix components of the disc, ultimately resulting in failure of the disc to perform its biomechanical function.

As the disc degenerates, the structural characteristics of the nucleus pulposus transform from a highly hydrated gel toward a desiccated tissue, and the strong, multilayered anulus fibrosus develops internal fissures that slowly extend radially outward to the periphery. The cellular population of the disc changes dramatically during aging with a near or total loss of large, notochordal cells in the nucleus pulposus region and a shift toward a sparse chondrocyte-like population in the central region of the disc. As cells are lost by apoptosis, they are not able to maintain the large matrix macromolecules of the disc, resulting in a net loss of large proteoglycans and a shift in the expression of disc collagens [4–6]. Specifically, Type II collagen, the main collagen in the inner disc, is sharply down-regulated, and Type I collagen, which is not usually present in significant quantities in the nucleus pulposus, begins to be expressed [7–9]. Other matrix proteins such as fibromodulin also change significantly during the degenerative process [10]. Changes in the expression of disc extracellular proteins ultimately lead to a tissue that is not able to function biomechanically, resulting in mechanical failure [11,12].

FDA device/drug status: investigational/not approved (cell-based therapy).

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Luk et al. [13] used a rhesus monkey model to test the applicability of transplanting whole bone-disc-bone allogenic tissue to the spine. Unfortunately, by the 24-month time point, degenerative changes were evident in the transplanted tissue, suggesting that this radical method of treatment would not restore spinal function [13]. However, more sophisticated methods of tissue engineering for degenerative disc disease do appear promising. One potential strategy is to implant cells into the disc that can be used to repair the degenerating disc matrix. Although simple in principle, the achievement of meaningful tissue repair in the disc is not an easy task. The implanted cells must survive, replicate and function in the hostile, metabolically challenged environment within the disc [14–16]. This article reviews the ongoing efforts to achieve a successful cell-based repair of the intervertebral disc.

Cellular candidates for disc regeneration

To repair the matrix of the degenerating nucleus pulposus, transplanted cells must produce proteoglycans (eg, aggrecan), Type II collagen and other matrix proteins in large quantities [17]. Chondrocytes and disc cells from the central regions of the disc normally produce these matrix proteins, making them candidates for cell-based disc repair. In addition, mesenchymal stem cells (MSCs) are a primitive or resting cell population that resides in many mature skeletal tissues. MSCs are flexible and have the ability to differentiate toward several mature tissue types, including bone, cartilage, fat, muscle and tendon, depending on the environment and biologic signals provided to these resting cells [18,19]. By appropriate manipulation, MSCs can be pushed toward a chondrogenic or perhaps even discogenic pathway and made to express aggrecan and Type II collagen in large quantities.

MSCs have several theoretical advantages over mature cells for tissue engineering applications. These cells are available from many autologous sources, including bone marrow and fat, that can be harvested to isolate these cells without significant donor site morbidity or immunogenic response [20]. MSCs can easily be expanded in culture to produce adequate numbers of cells for tissue engineering strategies. Furthermore, MSCs as primitive cells may have a better potential to survive and produce significant quantities of matrix compared with terminally differentiated cells (eg, chondrocytes or disc cells), which tend to be relatively metabolically quiescent. MSCs do not have the same surface antigen profile as mature cells, increasing the potential application of allogeneic MSCs as a therapeutic cell source. Finally, the use of gene therapy to guide and stimulate MSCs toward the desired phenotype may be easier than with terminally differentiated mature cells [21,22]. Clinical trials using autologous MSCs for a variety of pathologic conditions are underway or being planned [23].

Characteristics of MSCs

In adult bone marrow, the concentration of MSC is between one per 10^4 to one per 10^6 total cells. The number of MSCs at a given site appears to decrease with age. MSCs express the CD44, CD71, CD90, CD105, CD120a, CD124 and CD166 surface antigens but do not express markers specific to the hematopoietic lineage [24]. MSCs secrete a distinct pattern of cytokines compared with hematopoietic cells, including interleukin 6 (IL−6), −7, −8, −11, −12, −14 and −15; leukocyte inhibitory factor (LIF); granulocyte-macrophage colony-stimulating factor (GM-CSF) and Flt-3 ligand [25]. MSCs can be separated, using specific culture techniques, from the heterogeneous cell population. In vitro, the culture conditions have dramatic effect on the differentiation of MSCs toward a particular lineage. Identification of MSCs in situ is difficult. As a result, identification of MSC-specific marker proteins is an important area of research.

Cellular scaffolds

In addition to an appropriate source of nutrition, cells require a conducive microenvironment to survive and flourish. This microenvironment must provide an attachment site for the cells and allow the diffusion of nutrients and cellular waste products. Nucleus pulposus cells establish cell-to-cell contact and possess gap junctions [26,27]. They are shown to prefer a three-dimensional environment, as opposed to a monolayer culture environment, to maintain their phenotype [28].

Three-dimensional scaffolds are used to provide a permissive microenvironment for cell growth, migration, communication and the synthesis of extracellular matrix by cells in vitro and in vivo. Ideally, the microenvironment of the scaffold should mimic closely the environment of the tissue that is desired. For clinical implantation, the scaffolds used to grow cells must be biocompatible to the spine and should provide initial mechanical stability and support a homogenous cell distribution after implantation.

Various cell culture techniques and scaffolds are available for growing disc cells. Three-dimensional culture scaffolds include gels and porous solid materials that can be permanent or biodegradable [29,30]. Scaffolds made of hyaluronic acid, collagen and chitosan provide a three-dimensional environment for cell growth and are able to provide a stable nucleus pulposus–like phenotype [31,32]. Polymeric preparations of chitosan gel and fibrin glue have been used successfully in tissue engineering applications [33].

Advanced culture techniques can play a role in the production of engineered tissues. Bioreactors are mechanical devices that affect the circulation of culture medium around the tissue constructs. Bioreactors are useful during the in vitro cellular expansion phase of a tissue engineering protocol. These devices improve the distribution of nutrients to the cells and thus increase the growth rate and matrix production