

STEM-CELL TREATMENT IN DISC DEGENERATION: WHAT IS THE EVIDENCE?

*CÉLULAS TRONCO NO TRATAMENTO DE DOENÇA DEGENERATIVA DISCAL:
QUAL É A EVIDÊNCIA?*

*CÉLULAS MADRE EN EL TRATAMIENTO DE DEGENERACIÓN DE DISCO:
¿CUAL ES LA EVIDENCIA?*

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ABSTRACT

To review the potential role of stem cells in treating degenerative disc disease of the intervertebral disc (IVD). A review was performed of articles from the Medline database concerning stem cells and degenerative disc disease (DDD). To discuss the data, the papers were classified as: review, in vitro, experimental, and clinical. The currently available treatments were basically for symptom reduction, not to revert the IVD degenerative process. The use of mesenchymal stem cells (MSC) is being proposed as an option of treatment for DDD. In vitro studies have shown that the MSC are able to differentiate into NP cells and that the MSC also reduce the inflammatory levels of the degenerated IVD. Besides, experimental studies demonstrated that the MSC remained viable when injected into the IVD, and that they were able to regenerate partially from the degenerated IVD and its structure. The few clinical studies found in the literature presented diverging results. The use of MSC is being widely studied and shows promising results for the treatment of DDD. Although many advances are being achieved in studies in vitro and experimental, there is a lack of clinical studies to prove the role of MSC in DDD management.

Keywords: Stem cells; Intervertebral disc degeneration; Spine; Mesenchymal stem cells; Intervertebral disc.

RESUMO

Revisar o potencial papel das células-tronco para o tratamento de doença degenerativa do disco intervertebral (IVD). Foi realizada uma revisão dos trabalhos da base de dados Medline em relação a células-tronco e doença degenerativa discal (DDD). Para fins de discussão dos dados, os trabalhos foram divididos em: revisão, in vitro, experimentais e clínicos. Os tratamentos disponíveis atualmente focam basicamente na redução dos sintomas, e não na reversão do processo degenerativo do DIV. O uso de células-tronco mesenquimais (CTM) vem sendo proposto como uma opção de tratamento para DDD. Estudos in vitro demonstraram que as CTM são capazes de se diferenciarem em células do NP e que as CTM também diminuem os níveis inflamatórios do DIV degenerado. Além disso, estudos experimentais demonstraram que as CTM permaneciam viáveis quando injetadas no DIV e que eram capazes de regenerar parcialmente do DIV degenerado e sua estrutura. Os poucos estudos clínicos presentes na literatura apresentam resultados divergentes. O uso de CTM esta sendo amplamente estudado e mostra resultados promissores para o tratamento da DDD. Embora muitos avanços venham sendo alcançados em estudos in vitro e experimentais, ainda faltam estudos clínicos para comprovar o papel das CTM no manejo da DDD.

Descritores: Células-tronco; Degeneração do disco intervertebral; Coluna vertebral; Células-tronco Mesenquimais; Disco intervertebral.

RESUMEN

Revisar el papel potencial de las células madre en el tratamiento de la enfermedad degenerativa del disco intervertebral (IVD). Se realizó una revisión de los artículos de la base de datos Medline sobre células madre y la enfermedad degenerativa del disco (DDD). Para fines de discusión de los datos, los trabajos se dividieron en: revisión, in vitro, experimentales y clínicos. Los tratamientos disponibles actualmente enfocan básicamente la reducción de los síntomas, y no la reversión del proceso degenerativo del IVD. El uso de células madre mesenquimales (MSC) se propone como una opción de tratamiento para DDD. Estudios in vitro demostraron que las MSC son capaces de diferenciarse en células NP y que las MSC también reducen los niveles inflamatorios de la IVD degenerado. Además, estudios experimentales demostraron que las MSC se mantuvieron viables cuando inyectadas en el IVD y que eran capaces de regenerarse parcialmente del IVD degenerado y su estructura. Los pocos estudios clínicos presentes en la literatura presentan resultados divergentes. El uso de MSC se está estudiando ampliamente y muestra resultados prometedores en el tratamiento de la DDD. Aunque se hayan logrado muchos avances en estudios in vitro y experimentales, aún faltan estudios clínicos para comprobar el papel de las MSC en el manejo de la DDD.

Descritores: Células Madre; Degeneración del disco intervertebral; Columna vertebral; Células madre mesenquimales; Disco intervertebral.

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INTRODUCTION

Degenerative disc disease (DDD) is a common and natural process in the human spine. This degeneration occurs progressively and can affect the biomechanics, stability, and neurological function of the spine¹. In the United States (US) almost 300,000 surgeries are performed every year due to DDD, with the costs related to the surgical procedures rising to 50 billion dollars annually². Overall, 1.5 million disc surgeries are performed worldwide every year³. Annually, approximately 5 of 1000 persons will present sciatica due to disc disorders⁴, which are the major cause of chronic low-back pain in the modern world⁵.

Nowadays, degeneration of the intervertebral disc (IVD) is regarded as an irreversible phenomenon. The treatment options involve basically non-surgical (physical therapy, nerve root blocks) and surgical strategies (disc excision and arthrodesis), which are effective only in symptomatic relief and may actually accelerate the degenerative process in adjacent levels⁶. Recent studies demonstrated the potential of stem cell treatment to regenerate or repopulate the degenerated IVD⁷⁻⁹.

The goal of this study is to review the potential of stem cells as a treatment option for DDD, discussing the actual role of the stem cell treatment.

Physiopathology of Disc Degeneration

The human spine is composed by 23 IVD that separate the vertebrae and provide flexibility. They account for 20 to 30% of the length of the spine and increase in size on progression from the cervical to the lumbar spine¹⁰. In addition to flexibility the IVD have the function of stability and support loads during exercise. The IVD structure consists basically in a central part called the nucleus pulposus derived from notochord, which is surrounded by the annulus fibrosus derived from mesenchymal tissue¹⁰. The nucleus pulposus (NP) is rich in proteoglycan and water whereas the annulus fibrosus is rich in collagen, especially type I, II, VI and IX^{11,12}.

The composition of the IVD varies with the level of the spine, the collagen content in the nucleus being highest in the cervical discs and lowest in the lumbar discs, whereas the proteoglycan content shows the opposite trend¹³.

In the mature NP, the proteoglycan aggregates are important to retain water and restricting the water flux influences the response of the tissue to loads delivered in the spine¹¹. With ageing principally in the nucleus there is a decrease of proteoglycan aggregates and an increase of nonaggregating aggrecan because of proteolytic degradation^{14,15}. Thus, with age the ability of resist compressive loading declines.

In the annulus fibrosus the collagen fibrils are oriented in sheets around the NP. The key function of this structure is to retain the NP, taking up and distributing the load exerted by this tissue during various types of exercise¹¹.

During life many changes occur in the composition of the extracellular matrix including notochordal cell loss, mesenchymal cell senescence, loss of the vasculature and calcification of the vertebral endplates, which alter or decrease the synthetic capabilities of the disc cells¹⁰. Nuclear cell density decreases with age throughout life, whereas annular cellularity reaches a plateau after the age of 50 years¹⁶. The normal turnover capability is impaired in the disc matrix and degeneration products accumulate¹⁰.

The IVD degeneration and its structural changes result from this continuum catabolism occurring in the extracellular matrix associated with the incapacity of replace the impaired collagen fibers and aggrecan with new molecules during life. The IVD appears incapable of intrinsic repair in the adult, but it is the dream of physicians to be able to induce such biologic repair¹⁷.

Cell-Based Therapy for Intervertebral Disc Degeneration

Nowadays, surgical and non-surgical therapies to manage IVD degeneration focus only on symptom relief. In recent years, as the understanding of the molecular and cellular events involved in disc degeneration has improved, the idea of manipulating the cellular content of the disc to achieve a beneficial outcome has grown^{6,18}.

One treatment option is the use substances in order to stimulate the existing disc cells to increase production of proteoglycan. However, due to the relative acclularity of the degenerated disc it may not be sufficient to achieve a good result. An option for that issue is to introduce

in the degenerated disc cells capable of producing appropriate matrix in an attempt to recover the biomechanical properties of the disc⁶.

Nishimura et al.¹⁹ performed the transplantation of autologous NP tissue into denucleated rat discs, where it was shown to slow the progression of degeneration. However, this cell source has practical limitations in the clinical setting due to the necessity of damaging an adjacent disc, likely inducing degeneration in this level. By contrast, adult mesenchymal stem cells (MSC) are easily procured by bone marrow aspiration, and are more capable of adapting successfully to the environment of the disc and therefore of achieving a differentiated state appropriate for long-term matrix synthesis⁶.

Characteristics of Mesenchymal Stem Cells

MSC are undifferentiated, multipotent cells that have the ability to differentiate into a number of cell types, including bone, cartilage, fat, muscle and tendons, depending on the environment and biologic signals provided. It has already been established that MSC can be pushed into chondrogenic or perhaps even discogenic pathways and are capable of expressing aggrecan and Type II collagen in large quantities²⁰. Another advantage is the fact that MSC can be obtained from many autologous sources including bone marrow and fat without significant morbidity or immunogenic response and can be easily expanded in cultures²¹.

In Vitro Studies with Stem Cells and Disc Degeneration

It was already known that MSC were able to differentiate into chondrocyte-like cells²². Due to the fact that NP and chondrocytes have similar characteristics, it is reasonable to assume that MSC could also be able to differentiate into NP-like cells^{23,24}.

Risbud et al.¹² demonstrated that rat MSC when exposed to hypoxia and transforming growth factor- β are able to differentiate into a phenotype consistent with that of the NP via mitogen-activated protein kinase signaling pathways. Using different methods, other authors also demonstrated that MSC are able to differentiate into NP-like cells that could be used in cell-based tissue engineering therapies for IVD regeneration²⁵⁻³².

Blanco et al.³³ performed the isolation and characterization of MSC from human degenerated disc. They found that the degenerated NP contains MSC and that those cells are extremely similar to those found in the bone marrow. These findings suggest that DDD could be treated by cell therapy, injecting differentiated cultured MSC into NP-like cells, and stimulating the MSC already present in the NP.

One of the possibilities to explain why some patients with DDD present more pain than others is the development of intradiscal inflammation. Bertolo et al.³⁴ studied the immunosuppressive influence of the MSC in fragments of the IVD of patients with DDD. They found that 70% of the patients had a reduction in IgG production and the proliferation of peripheral blood lymphocytes was also reduced when MSC were present. This effect in reducing inflammation shows that the potential role of MSC for DDD goes beyond the ability to repopulate the IVD.

Experimental Studies with Stem Cells and Disc Degeneration

After demonstrating that MSC are able to differentiate into NP-like disc cells, *in vivo* studies were necessary to evaluate the efficacy and safety of this therapeutic option in degenerated discs.

Crevensten et al.³⁵ studied the viability of MSC injected in rat coccygeal discs; 14 days after injection a decrease in the number of MSC labeled with fluorescence was observed. However, twenty-eight days after injection the number of MSC rose to the initial number of cells with 100% viability.

Bendtsen et al.³⁶ induced disc degeneration in minipigs and injected hydrogels without MSC and hydrogels loaded with autologous MSC. They found that MSC and hydrogel therapy are able to partly regenerate the IVD and maintain perfusion and permeability of the vertebral endplate and subchondral bone. Another author performed the transplantation of human MSC into minipigs with DDD and found that those cells survived in the porcine disc for at least 6 months and expressed typical chondrocyte markers suggesting differentiation toward disc-like cells, demonstrating the possibility of xenotransplantation³⁷. Some authors also reported the increase in disc height with the use of MSC compared to control groups³⁸⁻⁴⁰.

The *in vivo* studies performed in rats and minipigs were able to

demonstrate that MSC are able to survive and differentiate when injected into the degenerated IVD and have the potential to restore its normal function and structure. However, those results are limited by its models of degeneration that trigger rapid degeneration of the IVD which are not equivalent to slow degeneration that occurs in human disc degeneration⁴¹. Also, the tail disc of rats and pigs is not submitted to the same static and dynamic load to which human discs are exposed^{42,43}.

Clinical Studies with Stem Cells and Disc Degeneration

There are a few clinical studies using stem cells in DDD in the literature.

Haufe and Mork⁷ found no improvement in the lower back after one year in 10 patients with DDD submitted to injection of hematopoietic precursor stem cells obtained from the patient's bone marrow. However, those authors did not perform any culture or expansion of the stem cells prior to the injection. In addition, they also submitted the patients to a 2-week course of hyperbaric oxygen therapy after the cells were injected.

Yoshikawa et al.⁹ studied the effect of MSC in two patients with DDD; they found that two years after the initial procedure the symptoms had improved in both patients and the rates of the Visual Analog Scale score for low back pain have decreased 38% in one case and 18% in the second patient. In both patients after two years radiograph and computed tomography confirmed that the intervertebral vacuum phenomenon improved.

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