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Evaluating the Efficacy of Intervertebral Disk Regeneration With Stem Cells in Animals

Low back pain and neck pain are the first and fourth most common causes for disability in the United States. Costs associated with these disabilities range from $80.1 billion to $91.8 billion a year. More than 70 percent of people age 50 or younger and more than 90 percent of people older than 50 experience intervertebral disk (IVD) degeneration. Although IVD can be asymptomatic, the pain associated with it, often called discogenic pain, accounts for 25 to 80 percent of all low back and neck pain.

"Degenerative IVD is the result of a series of changes in metabolism, biomechanics and morphology," explains Wenchun Qu, M.D., M.S., Ph.D., a specialist in physical medicine and rehabilitation and pain at Mayo Clinic's campus in Rochester, Minnesota. IVD is characterized by cell death and degeneration of extracellular matrix. Resulting microenvironmental changes include neovascularization and nerve growth, which can lead to pain and altered biomechanical function.

Current treatment modalities for IVD include pain medication, therapies, injections, nucleoplasty and surgical diskectomy. But none of these strategies addresses the IVD degeneration. Because the extracellular matrix is synthesized and modulated by IVD cells, researchers are exploring the use of stem cells and mesenchymal stem cells (MSCs) for IVD regeneration.

In animal studies, stem cell transplantation to the disk has shown promise in decelerating or arresting the degenerative process. However, small sample size, varying study designs and conflicting outcomes in preclinical animal trials have made it difficult to assess the effectiveness of this treatment. To address this challenge, Dr. Qu and a team of Mayo researchers recently performed and published a systematic review and meta-analysis of controlled trials exploring the strategy of cell-based IVD regeneration by means of stem cell transplantation in different animal models.

Wenchun Qu, M.D., M.S., Ph.D.

Study methods

Mayo researchers conducted a comprehensive search of seven databases and included preclinical controlled trials (randomized controlled trials, or RCTs) and nonrandomized controlled trials (N-RCTs) that evaluated stem cell transplantation on experimental regeneration of the intervertebral disk in animals.

Mayo researchers focused on the outcomes related to the effect and mechanism in IVD regeneration, which includes disk height index, MRI T2 signal intensity, type II collagen expression and histologic disk degeneration grade. Animals of any species or breed with any type of model in IVD degeneration secondary to IVD trauma were included. Control group animals included any type of intervention. Studies that combined multiple treatments, studies that used models of nontraumatic spinal cord injury, and studies lacking original data or outcomes of interest were excluded.

Using these criteria, 22 studies were culled from the 642 unique citations identified. This pool contained nine RCTs and 13 N-RCTs. Overall, 626 disks were studied, of which 313 were transplanted with stem cells and 313 were controls.

Study results

Among the 22 studies included, stem cell transplantation was associated with significantly increased disk height index, T2-weighted MRI signal intensity, type II collagen expression and significantly reduced histologic disk degenerative grade.

"We also noted that the regeneration processes after stem cell transplantation seem to follow a cascade of events reflecting the cell and molecular processes that maintain disk functions," explains Dr. Qu. These changes included increased production of extracellular matrix that leads to increased nucleus pulposus hydration, and subsequent prevention of loss of disk height.

Although the meta-analysis of animal studies suggests that stem cells halt the degeneration processes in IVD and promote IVD regeneration, Dr. Qu acknowledges some study limitations and that additional work must be done to provide a better understanding of the genome composition and phenotypical expression of MSCs and the nucleus pulposus-like cells involved in this process. Additional clinical trials also will be needed to understand if the benefits observed in animals can be translated to humans.

For more information

Wang Z, et al. Efficacy of intervertebral disc regeneration with stem cells — A systematic review and meta-analysis of animal controlled trials. *Gene*. 2015;564:1.

Other interesting findings:

- In 13 studies, Mayo researchers found that disk height index in the stem cell transplantation group was significantly higher than the control group (SMD = 3.64, 95% CI: 2.49, 4.78, $p < 0.001$, $I^2 = 91.3\%$).
- The 14 studies that reported MRI T2 signal intensity outcomes showed a significant increase of MRI T2 signal intensity in the stem cell transplantation group when compared with the control (SMD = 2.28, 95% CI: 1.48, 3.08, $p < 0.001$, $I^2 = 88.5\%$).
- In 11 studies, stem cell transplantation was associated with significantly reduced histologic disk degeneration grades when compared with the control group (SMD = -2.97, 95% CI: -3.97, -1.97, $p < 0.001$, $I^2 = 80.1\%$).
- Increased expression of type II collagen was identified in nine studies (SMD = 3.68, 95% CI: 1.66, 5.70, $p < 0.001$, $I^2 = 95.8\%$).

Mayo researchers also found no significant changes between subgroups.