Endogenous Cell Homing for Intervertebral Disk Regeneration

Intervertebral disk (IVD) degeneration is characterized by a gradual loss of cellular function and related breakdown of extracellular matrix. This process leads to a decrease in the mechanical stability of the spine and activation of nociceptive receptors that trigger painful back and neck symptoms. Implantation of mesenchymal stem cells (MSCs) has been shown to counteract the degenerative processes in animal models of disk degeneration and in some initial clinical studies. The regenerative activity of MSCs when injected into the disk may partially rely on their potential to differentiate toward an IVD-like phenotype upon exposure to the appropriate microenvironment. In addition, therapeutic MSCs also release trophic factors that may stimulate the metabolism of disk cells and suppress inflammatory reactions. However, in spite of these promising perspectives, clinical application of MSCs has certain limitations. Harvesting of autologous bone marrow for isolation of MSCs is an invasive procedure, and the cell processing can be complex and costly. Potential adverse events may occur, such as cell leaking and osteophyte formation.

Recruitment or homing of endogenous progenitor cells is being investigated as an alternative concept. As a reaction to cell or tissue damage, cells will release various signaling molecules, aiming to facilitate tissue repair. Certain chemokines efficiently attract progenitor cells from their niches within surrounding tissues, thereby enabling cell-mediated healing. Progenitor cell recruitment has primarily been investigated in the context of wound healing, myocardial infarction, and bone repair. For IVD regeneration, cell homing appears challenging, given that the disk is an avascular tissue and that circulating or bone marrow–derived stem cells need to migrate over longer distances to reach the inner annulus fibrosus or the nucleus pulposus tissue.

Using a whole-organ culture model of induced IVD degeneration, we have shown that human bone marrow–derived MSCs (hBMSCs) were capable of migrating through the end plate of a bovine coccygeal disk. While a low basal level of migration was observed in disks cultured under simulated physiologic conditions, the number of recruited cells was significantly enhanced by induced degenerative settings. Specifically, a degenerative state was achieved by culturing the disks under limited nutrition, exposing disks to high-frequency dynamic compressive loading and causing mechanical damage by annular needle puncture. Furthermore, the expression of certain chemokine receptors was significantly upregulated in MSCs cultured with degenerative disk-conditioned medium, confirming the responsiveness of the cells to the degenerative disk environment. The feasibility of MSC recruitment in the disk in vivo was recently evaluated on a mouse tail model of induced disk degeneration. However, only a limited number of bone marrow cells were recruited in the disk degeneration group, which is probably due to its avascular nature.
The finding that MSCs could migrate through the end plate of the IVD was further explored by injecting stromal cell-derived factor 1 (SDF-1, also known as CXCL12), into the cavity of a partially nucleotomized disk in organ culture. The chemoattractant was delivered using a hyaluronan-based thermoreversible injectable hydrogel, which had previously been shown to support disk cell growth, matrix production, and MSC differentiation toward the disk-like phenotype. Fluorescent-labeled hBMSCs were applied onto the end plate and incubated for 48 hours. Microscopic evaluation revealed a significantly enhanced migration of cells into the disks that had been treated with SDF-1 containing hydrogel compared with disks treated with the hydrogel alone or with SDF-1 in saline. Interestingly, recruited MSCs were identified in both the anulus fibrosus and nucleus pulposus tissues, indicating migration through both extracellular matrix structures.

These results indicate that recruitment of MSCs toward the center of a damaged disk is feasible and that MSC migration can be enhanced by a chemoattractant delivery system consisting of a suitable hydrogel and a potent chemokine. Yet, tissue-specific chemoattractants may be released by a damaged or degenerative disk. To identify the factors released by the disk cells in response to tissue damage, the proteomic profile of the conditioned medium of a whole disk maintained under induced degenerative settings was analyzed. Proteomic analysis revealed CCL5/RANTES (chemokine [C-C motif] ligand 5/regulated on activation, normal T cell–expressed and secreted) and CXCL6 (chemokine [C-X-C motif] ligand 6) as two main chemotactic factors secreted by the degenerative disk. Interestingly, depletion of CCL5/RANTES from degenerative disk–derived medium markedly reduced its chemoattractive activity toward MSCs, suggesting that CCL5/RANTES plays a major role in the recruitment of regenerative cells in the disk. Presence of CCL5/RANTES and its receptors was also confirmed in histologic sections of bovine and human degenerative disks and was associated with painful disk diseases.

In conclusion, there is clear evidence that homing of endogenous regenerative progenitor cells can occur in the disk and can be advanced by chemoattractant delivery systems. Further research is necessary to identify the most effective chemotactic factor and uncover potential side effects. Finally, recent studies have described the presence of progenitor cells at different locations of the healthy and degenerative IVD. Mobilization, augmentation, and activation of these endogenous progenitor cell populations represent attractive targets for future regenerative strategies.

References

(CCL5) by human disc cells and modulation by IL-1β and TNF-α in 3D culture. Exp Mol Pathol 2014;96(2):133-138.


Errata

Case Study: AAOS Clinical Practice Guideline: Management of Hip Fractures in the Elderly
Karl C. Roberts, MD, and W. Timothy Brox, MD
(Vol 23, No 2, February 2015, pp 138-140)

On page 139, column 1, in the paragraph beginning under Management, the parenthetical reference to the AAOS Guideline, which now incorrectly recommends the use of regional anesthesia, should correctly recommend the use of general or spinal anesthesia:

(The AAOS Guideline strongly recommends the use of general or spinal anesthesia “unless a clear and compelling rational for an alternative approach is present,” which is the situation in this case.)

Multiple Epiphyseal Dysplasia
Steven Anthony, DO, Richard Munk, MD, William Skakun, DO, and Michael Masini, MD
(Vol 23, No 3, March 2015, pp 164-172)

On page 164, in the author notes section in the right hand column, Dr. Skakun is noted as being affiliated with The Ohio State University. In fact, Dr. Skakun is affiliated with Ohio University.

The Journal regrets these errors.