20 DISC REPAIR AND DISC REPLACEMENT - INNOVATIONS "INTERVERTEBRAL DISC TRANSPLANTATION"

Rahsan Kemerdere MD, Murat Hancı MD

It is thought that intervertebral disc degeneration starts in the nucleus pulposus.[12] Reducing of glucosaminoglycan amount and the matrix cycle and decrease in the cellular number resulting in the reducing in the loss of water absorption capacity are the prominent cellular findings. The existing surgical methods are not intended for the curing of the patient; they restrict motion in the postoperative period and the fusion created transmits the extra stress to the adjacent spinal structures. The disc function is not restored even if the pain is eliminated. Several alternative methods have been developed for intervertebral disc fusion, including synthetic intervertebral discs and fresh-frozen allograft transplantation.[17] Use of artificial materials is limited since they do not have self-repair and forming capacities.

Treatments intending the repair and regeneration of the intervertebral disc tissue however, allow the restoration of the function together with the restoration of the anatomic morphology.

Disc Structure

Intervertebral disc is histologically classified as fibrocartilage. The normal intervertebral disc includes at least seven different collagen types (Tip I, II, III, V, VI, IX, XI). Types I and II are most frequently seen types.[4] While annulus fibrosus (AF) mostly includes Types Tip I and Tip II collagen, nucleus pulposus (NP) mostly include Type II collagen. Collagen plays and important role in the load-lifting task of the disc. Elements of the extracellular matrix changes with ageing and degeneration.[2] Intervertebral disc is the most avascular tissue in the human body and regeneration of this tissue is as low as the articular cartilage.[16] Therefore, almost no regeneration occurs in the nucleus pulposus and annulus fibrosus after the surgical treatments performed because of disc herniation, and degeneration of the intervertebral disc is unavoidable.[11]

AF cells are cells with fibrochondrocyte characteristics within dense and mechanically strong matrix. NP cells, however, are located within mechanically weaker matrix and contain larger amounts of water.[19]

According to the studies, the chondrocyte-like cells in the area forming the border between the medial face of the AF, NP and the endplate also called in the junction point assume a critical role in the tissue repair mechanism.[21]

The most prominent cellular and biochemical change related to degeneration is the decrease in the cellular density within the disc. Reducing of the

cartilage-specific extracellular matrix elements including type II collagen accompanies this.[9] The matrix proteoglycan binds water and creates a large inflation pressure. This pressure decreases with the decreasing NP cell number and the lamellar structure in the internal side of AF will be impaired.[2] The increasing biomechanical pressure causes annular tears.

Transplantation Types and Related Studies

The idea of supporting the cellular number through cell transplantation had originated from the decreasing of NP cellular loss or increasing the regeneration. In the rat model that was developed initially by Nishimura et al. in 1998, the fresh autologous or frost-preserved NP cells were restituted to the disc that degeneration was created through nuclear aspiration, and slowing down of degeneration was shown.[15] The regenerative therapies developed after this include the cell therapy, gen therapy and tissue engineering.[8]

Cell Therapy

The cells used for tissue engineering on annulus fibrosus are harvested from humans or other species. It was found in the studies performed on naturally herniated discs contained larger numbers of aged cells, which makes the use of these for regeneration more difficult.[7] Since the external and internal AF cells cultured in vitro are found in artificial gel and lack the normal matrix tissue, they loose their original phenotypes and become identical. The reducing of the cellular diversity also reduces the similarity with the normal tissue. With the purpose of eliminating this negative effect, specialized 3-dimensional environmental factors are being studied.[1,5,6] Use of the mesenchymal stem cells to avoid the problems like cellular ageing or insufficient cell number can be an alternative method.[3] However, there are no studies showing the transformation of stem cells into AF cells.

In their study on dogs, Hohaus *et al.*, they harvested autologous disc cells from the lumbar region lomber and multiplied them in the culture, and then cultured these cells again in the discs of the subjects 12 weeks later; and found in this study that, disc cells survived after the transplantation, maintained their reproduction capacity and secreted normal-like extracellular matrix.[9] Significant correlations were found between the cell transplantation and the preservation of the height in the disc space in the long-term follow-up.

In the Euro Disc Randomized Trial that followed this study, the disc materials harvested from 120 patients with lumbar disc hernia and surgical indication with minimal interventional open sequestrectomy were cultured and the cells required for transplantation were obtained. According to the 2-year results of the trial, it was found that in patients that autologous disc transplantation was performed, the relief of pain was more prominent, the fluid contents of the disc cells was greater, and the fluid levels in the adjacent vertebral discs were significantly higher.

Gen Therapy

Genetic studies on the disc regeneration have shown that the osteogenic protein-1 (OP-1) is effective on the NP cells and increases the total DNA production, collagen content and proteoglycan production.[13,20] On the other hand, Zhang et al. found that the bone morphogenetic protein-13 and transcription factor Sox9 increase the collagen production in AF cells.[23] Despite these promising studies, there are no animal or human genetic studies performed in vivo.

Tissue Engineering

The final purpose in AF tissue engineering is to ensure the mechanical stability and formation of live tissue in the long-term. The scaffolds used in tissue engineering must meet the AF deficit in the basis, must be capable of adhering to the surrounding tissues, must provide the environment for the stem cells to survive, must be biocompatible and must meet the mechanical characteristics of the spinal motion segment.[10] In vivo studies on tissue engineering are few in number.

Mizuno et al. cultured the cells they harvested from sheep NP and AF in the intervertebral disc alloy (bio-artificial disc) containing calcium alginate surrounded with polyglycolic acid they obtained using

tissue engineering techniques, and implanted these cells on the backs of athymic mice.[14] Although the AF cells of these composite have similarities with the normal tissue, further studies on cellular arrangement, cellular reproduction, implantation of the disc material, compliance with the surrounding tissues and mechanical properties are required.

Sato et al. cultured the annulus fibrosus cells in rabbits using the tissue engineering methods, and then injected this allograft containing the transplant cells to the damaged annulus fibrosus and nucleus pulposus lacunas in the rabbit intervertebral discs.[19] As a result of this study, the postoperative narrowing was markedly prevented in the intervertebral disc space in the group of tissue transplants including regenerative cells, and it was shown that allograft AF cells were live and displayed reproductive cells.

Ruan et al. performed intervertebral disc transplantation in humans for the first time.[18] In this preliminary clinical study, five allograft discs were implanted to five patients with cervical disc hernia without using fixation, and positive results were found at the year 5. Minimal height loss was observed radiologically in the disc space. In this study, it was reported that although there was degeneration in the early period, this was reversed in the late period. However, since the histological data could not be obtained with obvious reasons and since the benefits of the transplantation outweighing the risks is controversial, indicates that more comprehensive clinical studies are required.

As an alternative to these studies, gel foam, platine coil, bone cement and tissue adhesives were injected into the herniated disc model in swine, and it was found that gel foam only was not weaker as compared to the intact disc.[22] However, in cases where the annulus defect is greater, this study has weaknesses.

In conclusion, researches on AF and NP are still in the beginning stage. Regeneration studies are insufficient particularly in the areas of implantation and fixation. It is currently not known which patient groups will benefit more from autologous disc cell transplantation. However, if the future results of the studies on stem cells and regenerative cells meet the expectations, disc transplantation with safe an easy techniques is seen possible.

References

1. Alini M, Li W, Markovic P, Aebi M, Spiro RC, Roughley PJ. The potential and limitations of a cell-seeded collagen/hyaluronan scaffold to engineer an intervertebral disc-like matrix. Spine 28:446-54, 2003
2. Antoniou J, Steffen T, Nelson F, Winterbottom N, Hollander AP, Poole RA, Aebi M, Alini M. The human lumbar intervertebral disc: evidence for changes in the biosynthesis and denaturation of the extracellular matrix with growth, maturation, ageing, and degeneration. J Clin Invest. 98:996-1003, 1996
3. Evans C. Potential biologic therapies for the intervertebral disc. J Bone Joint Surg Am 88 (Suppl 2):95-8, 2006
4. Eyre DR. Collagens of the disc. Ghosh P (ed), The biology of the intervertebral disc. Boca Raton: CRC Press, 1988:171-188
5. Gruber HE, Fisher EC Jr, Desai B, Stasky AA, Hoelscher G, Hanley EN Jr. Human intervertebral disc cells from the annulus: three-dimensional culture in agarose or alginate and responsiveness to TGF-beta1. Exp Cell Res 235:13-21, 1997
6. Gruber HE, Leslie K, Ingram J, Norton HJ, Hanley EN. Cell-based tissue engineering for the intervertebral disc: in vitro studies of human disc cell gene expression and matrix production within selected cell carriers. Spine J 4:44-55, 2004
7. Gruber HE, Ingram JA, Norton HJ, Hanley EN Jr: Senescence in cells of the aging and degenerating intervertebral disc: immunolocalization of senescence-associated beta-galactosidase in human and sand rat discs. Spine 32:321-7, 2007
8. Hegewald AA, Ringe J, Sittinger M, Thome C. Regenerative treatment strategies in spinal surgery. Front Biosci 13:1507-25, 2008
9. Hohaus C, Ganey TM, Minkus Y, Meisel HJ. Cell transplantation in lumbar spine disc degeneration disease. Eur Spine J 17 (Suppl 4):492-503, 2008
10. Leung VY, Chan D, Cheung KM. Regeneration of intervertebral disc by mesenchymal stem cells: potentials, limitations, and future direction. Eur Spine J 15 (Suppl 3):406-13, 2006
11. Lipson SJ, Muir H. Experimental intervertebral disc degeneration: morphologic and proteoglycan changes over time. Arthritis Rheum 24:12-21,1981
12. Luk KD, Ruan DK. Intervertebral disc transplantation: a biological approach to motion preservation. Eur Spine J 17 (Suppl 4):504-10, 2008

13. Masuda K, Takegami K, An H, Kumano F, Chiba K, Andersson GB, Schmid T, Thonar E. Recombinant osteogenic protein-1 upregulates extracellular matrix metabolism by rabbit annulus fibrosus and nucleus pulposus cells cultured in alginate beads. J Orthop Res 2003 21:922-30, 2003

14. Mizuno H, Roy AK, Vacanti CA, Kojima K, Ueda M, Bonassar LJ. Tissue-engineered composites of anulus fibrosus and nucleus pulposus for intervertebral disc replacement. Spine 29:1290-8, 2004

15. Nishimura K, Mochida J. Percutaneous reinsertion of the nucleus pulposus. An experimental study. Spine 23:1531-8, 1998

16. Ochi M, Uchio Y, Tobita M, Kuriwaka M. Current concepts in tissue engineering technique for repair of cartilage defect. Artif Organs 25:172-9, 2001

17. Olson EJ, Hanley EN Jr, Rudert MJ, Baratz ME. Vertebral column allografts for the treatment of segmental spine defects. An experimental investigation in dogs. 16:1081-8, 1991

18. Ruan D, He Q, Ding Y, Hou L, Li J, Luk KD. Intervertebral disc transplantation in the treatment of degenerative spine disease: a preliminary study. Lancet 369:993-9, 2007

19. Sato M, Asazuma T, Ishihara M, Ishihara M, Kikuchi T, Kikuchi M, Fujikawa K. An experimental study of the regeneration of the intervertebral disc with an allograft of cultured annulus fibrosus cells using a tissue-engineering method. Spine 28:548-53, 2003

20. Takegami K, An HS, Kumano F, Chiba K, Thonar EJ, Singh K, Masuda K: Osteogenic protein-1 is most effective in stimulating nucleus pulposus and annulus fibrosus cells to repair their matrix after chondroitinase ABC-induced in vitro chemonucleolysis. Spine J 5:231-8, 2005

21. Tsuchida T: A pathological study of experimental chemonucleolysis with collagenase. Nihon Seikeigeka Gakkai Zasshi 61:1237-49, 1987

22. Wang YH, Kuo TF, Wang JL: The implantation of non-cell-based materials to prevent the recurrent disc herniation: an in vivo porcine model using quantitative discomanometry examination. Eur Spine J 16:1021-7, 2007

23. Zhang Y, Anderson DG, Phillips FM, Thonar EJ, He TC, Pietryla D, An HS: Comparative effects of bone morphogenetic proteins and Sox9 overexpression on matrix accumulation by bovine anulus fibrosus cells: implications for anular repair. Spine 32:2515-20, 2007