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# New Horizons in Spine Research: Intervertebral Disc Repair and Regeneration

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Low back pain and neck pain are the first and fourth leading causes, respectively, of years lived with disability.[1] The widespread prevalence of back pain makes it among the most costly heathcare conditions, yet, it is surprisingly not among the top ten health conditions receiving research funding.[2] This funding discrepancy was noted by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) with a Roundtable on the Role of Disc Degeneration in Neck and Back Pain highlighting the need for novel research and partnerships to overcome some of these challenges.[3] To advance novel spine science and collaborations, the 3rd International Spine Research Symposium, co-sponsored by the Philadelphia Spine Research Society (PSRS), NIAMS/NIH, and the Orthopaedic Research Society (ORS), was held to enhance understanding of the clinical problems associated with degenerative disc disease, and to highlight cutting-edge scientific research in areas of basic biology, epidemiology, disease mechanisms, biomechanics, tissue engineering, and imaging of the intervertebral disc (IVD).[4] Two special issues on "New Horizons in Spine Research" are outcomes from that meeting, with articles selected from the strong response to the "call for papers." This second issue focuses on fundamental topics of intervertebral disc repair and regeneration, and supports the important objective of the Orthopaedic Research Society Spine Section (http://www.ors.org/spinesection) to accelerate translational of advanced research to improved spine patient care through enhanced communication and collaboration.

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## REGENERATIVE MEDICINE STRATEGIES

Vedicheria and Buckley, review cell-based therapies for intervertebral disc and cartilage regeneration,[5] and note that there is little guidance for translating IVD repair strategies due to the heterogeneity of preclinical approaches and paucity of clinical studies. Therefore, the authors review and make important parallels with cartilage repair studies to provide useful models to help accelerate translation of IVD repair techniques. Total IVD replacement is among the most ambitious and exciting research areas in IVD tissue engineering. Martin et al. evaluated the in vivo performance of an acellular disc-like angle ply structure that mimics the structure of the native IVD in a rat tail model and identified that native cells can infiltrate between layers to promote tissue formation and restore some biomechanical behaviors.[6]

Mesenchymal stem cell injections are another way to induce disc regeneration. Maidoff et al. showed that timing was important for in vivo delivery of mesenchymal stem cells into injured rat IVDs since early delivery resulted in greater amounts of glycosaminoglycan accumulation than late delivery, and results suggested that early treatments may have more beneficial effects.[7]

An alternative approach would be to stimulate cells in early degeneration to regenerate their extracellular matrix. Gawri et al. demonstrated inorganic polyphosphates can promote proteoglycan accumulation in nucleus pulposus cell culture even under hypoxic conditions.[8] Growth factors can also induce repair. Li et al. demonstrated that bone morphogenetic protein 2 (BMP-2) and BMP-7 heterodimer delivered in a fibrinhyaluronan hydrogel stimulated nucleus pulposus cells to produce aggrecan and collagen II using in vitro studies as well as organ culture models which better simulate in vivo conditions.[9]

IVD degeneration is known to induce a catabolic shift, commonly associated with pro-inflammatory cytokine production. When cultured in hypoxic and proinflammatory media, micropellets of mesenchymal stem cells co-cultured with nucleus pulposus cells demonstrated reduced MMP-13 and ADAMTS-5, suggesting an immunomodulary effect, since nucleus pulposus cells alone had a greater up-regulation of both anabolic and catabolic genes.[10] One of the cytokines involved in degeneration is IL-1β. Daniels et al. showed that this pro-inflammatory cytokine upregulated three key signalling pathways in human nucleus pulposus cells, p38 MAPK, c-jun, and NFκB. Interestingly these pathways were not affected by the pro-anabolic factor, GDF-5, whereas ERK 1/2 was activated by both.[11] Furthermore, NFκB inhibition resulted in the largest reduction in IL-1β induced catabolism. Cell loss is another feature of degeneration. Li et al. showed that alterations in osmolarity are capable of inducing nucleus pulposus cell apoptosis in organ culture and this was mediated by activation of the ERK 1/2 signalling pathway.[12]

Rapamycin treatment in the acute stage following spinal cord injury suppressed microglial activation in the lumbar spinal cord, reduced neural tissue damage and attenuated neuropathic pain.[13] This may be a new treatment for the repair of damaged cords or at least suggests a signalling pathway that contributes to the pathology of cord injury.

## BIOMECHANICAL FACTORS IN IVD DEGENERATION AND REPAIR

Internal disc disruption and annular tears are some of the causes of back and leg pain, yet IVD defects seen on standard imaging techniques are also common in healthy controls. Chun et al. used phase-contrast magnetic resonance imaging methods to show that cerebrospinal fluid flow in the lumbosacral spine had slower flow velocities in patients with lumbar spinal stenosis than controls, suggesting that altered cerebrospinal fluid dynamics might explain some neurological manifestations of lumbar spinal stenosis.[14] Yet, IVD disruptions on imaging are commonly not associated with pain so that improved functional knowledge of IVD injury propagation is required. Shahraki et al., used finite element modelling with Tsai-Wu damage criteria to predict annulus fibrosus damage initiation and propagation under different loading conditions.[15]

Poro-elastic finite element modelling showed similar patterns of increased motion due to IVD degeneration as spinal fusion, suggesting that IVD degeneration is a risk factor for increased adjacent segment degeneration in addition to fusion.[16] Adjacent segment intervertebral joint loads were calculated to be sensitive to sagittal alignment and degree of lordosis that is surgically imposed during fusion with a loss of lordosis increasing shear forces at the upper adjacent level.[17] A human cadaveric study showed that degree of IVD degeneration and height were similar for Diffuse Idiopathic Skeletal Hyperostosis patients as for controls, suggesting a limited role for IVD degeneration in its pathogenesis.[18]

Zhu et al. developed a cell-activity-coupled mechano-electrochemical finite element model of the IVD with simulated degenerative changes and biological treatments. IVD spatial water content patterns were found to be very sensitive to degenerative state and to biological treatments that increased cell density, increased glycosaminoglycan synthesis rate, and decreased glycosaminoglycan degradation rate.[19]

## SURGICAL REPAIR, SCOLIOSIS, AND INFECTION

A prospective trial found that the creation of a small cavity in the vertebral body during vertebraplasty reduced the rate of cement leakage.[20] Attenuation of signal on computed tomography scans in sacral regions strongly correlated with lumbar attenuation values, suggesting opportunistic computed tomography scans can be used to assess sacral bone mineral density.[21] When evaluating bone-implant interfaces, pedicle screw behaviour was better represented with a cadaveric compectomy model than pure pull-out testing.[22]

Retrospective correlation analyses between thoracic volume modelling from planar x-rays and pulmonary function tests found that scoliosis correction increased thoracic volume and improved total lung capacities in cases where pre-operative lung capacity was severely restrictive.[23] Tethering procedures have received increasing interest for fusionless treatment of adolescent idiopathic scoliosis. A posterior allograft tendon tether was effective at controlling spinal deformities in growing pigs, suggesting this method shows promise as a potential method for scoliosis correction.[24]

Although relatively uncommon, post-operative spinal infections can be a devastating complication after spinal surgery, and a mouse model of spine implant infection was

developed using in vivo bioluminescence and fluorescence imaging to non-invasively quantify bacterial burden and host inflammation longitudinally.[25] A composite biomaterial strategy used to treat a rabbit in vivo spinal tuberculosis model found that anti-tuberculosis drugs had better penetration using hydroxyapatite microspheres but poly (lactic-co-glycolic acid) carriers were better for distribution.[26]

## CONCLUSIONS

This issue includes papers that improve understanding of IVD repair and regeneration, biomechanical factors and cytokines in IVD injury and degeneration, and spinal cord injury repair. The benefits of surgical repair in scoliosis, and a new animal model for disc infection are also described. It is our hope that these studies will stimulate further research that results in the development of safe, novel treatments that will help improve the lives of patients with spine pathologies.

## References


1. Murray CJ, Atkinson C, Bhalla K, et al. The state of US health, 1990–2010: burden of diseases, injuries, and risk factors. JAMA. 2013; 310:591–608. [PubMed: 23842577]
2. The burden of musculoskeletal diseases in the united states: prevalence, societal, and economic cost. American Academy of Orthopaedic Surgery; 2008. http://www.boneandjointburden.org/
3. NIAMS/NIH roundtable on the role of disc degeneration in neck and back pain. National Institute of Arthritis and Musculoskeletal and Skin Diseases; Oct 27. 2014 http://www.niams.nih.gov/News_and_Events/Meetings_and_Events/Roundtables/2014/disc_degeneration.asp#cit3
4. Orthopaedic Research Society Philadelphia Spine Research Society. ORS PSRS 3rd International Philadelphia Spine Research Symposium. Thomas Jefferson University; Philadelphia, PA: Nov 9–12. 2015 http://www.ors.org/philaspinemeeting/
5. Vedicherla S, Buckley CT. Cell-based therapies for intervertebral disc and cartilage regeneration—current concepts, parallels, and perspectives. J Orthop Res. 2016; 35:8–22. [PubMed: 27104885]
6. Martin JT, Kim DH, Milby AH, et al. In vivo performance of an acellular disc-like angle ply structure (DAPS) for total disc replacement in a small animal model. J Orthop Res. 2016; 35:23–31. [PubMed: 27227357]
7. Maidhof R, Rafiuddin A, Chowdhury F, et al. Timing of mesenchymal stem cell delivery impacts the fate and therapeutic potential in intervertebral disc repair. J Orthop Res. 2016; 35:32–40.
8. Gawri R, Shiba T, Pilliar R, et al. Inorganic polyphosphates enhances nucleus pulposus tissue formation in vitro. J Orthop Res. 2016; 35:41–50. [PubMed: 27164002]
9. Li Z, Lang G, Karfeld-Sulzer LS, et al. Heterodimeric BMP-2/7 for nucleus pulposus regeneration—in vitro and ex vivo studies. J Orthop Res. 2016; 35:51–60. [PubMed: 27340938]
10. Ouyang A, Cerchiari AE, Tang X, et al. Effects of cell type and configuration on anabolic and catabolic activity in 3D co-culture of mesenchymal stem cells and nucleus pulposus cells. J Orthop Res. 2016; 35:61–73. [PubMed: 27699833]
11. Daniels J, Binch AA, Le Maitre CL. Inhibiting IL-1 signaling pathways to inhibit catabolic processes in disc degeneration. J Orthop Res. 2016; 35:74–85. [PubMed: 27391542]
12. Li P, Gan Y, Wang H, et al. Role of the ERK1/2 pathway in osmolarity effects on nucleus pulposus cell apoptosis in a disc perfusion culture. J Orthop Res. 2016; 35:86–92. [PubMed: 27035885]
13. Tateda S, Kanno H, Ozawa H, et al. Rapamycin suppresses microglial activation and reduces the development of neuropathic pain after spinal cord injury. J Orthop Res. 2016; 35:93–103. [PubMed: 27279283]
14. Chun SW, Lee HJ, Nam KH, et al. Cerebrospinal fluid dynamics at the lumbosacral level in patients with spinal stenosis: a pilot study. J Orthop Res. 2016; 35:104–112. [PubMed: 27664416]

15. Shahraki NM, Fatemi A, Agarwal A, et al. Prediction of clinically relevant initiation and progression of tears within annulus fibrosus. J Orthop Res. 2016; 35:113–122. [PubMed: 27325391]
16. Natarajan RN, Andersson GB. Lumbar disc degeneration is an equally important risk factor as lumbar fusion for causing adjacent segment disc disease. J Orthop Res. 2016; 35:123–130. [PubMed: 27152925]
17. Senteler M, Weisse B, Rothenfluh DA, et al. Fusion angle affects intervertebral adjacent spinal segment joint forces-model-based analysis of patient specific alignment. J Orthop Res. 2016; 35:131–139. [PubMed: 27364167]
18. Kuperus JS, Westerveld LA, Rutges JA, et al. Histological characteristics of diffuse idiopathic skeletal hyperostosis. J Orthop Res. 2016; 35:140–146. [PubMed: 27101345]
19. Zhu Q, Gao X, Brown MD, et al. Simulation of water content distributions in degenerated human intervertebral discs. J Orthop Res. 2016; 35:147–153. [PubMed: 27153106]
20. Arabmotlagh M, Rickert M, Lukas A, et al. Small cavity creation in the vertebral body reduces the rate of cement leakage during vertebroplasty. J Orthop Res. 2016; 35:154–159. [PubMed: 26919407]
21. Hoel RJ, Ledonio CG, Takahashi T, et al. Sacral bone mineral density (BMD) assessment using opportunistic CT scans. J Orthop Res. 2016; 35:160–166. [PubMed: 27391403]
22. Schulze M, Gehweiler D, Riesenbeck O, et al. Biomechanical characteristics of pedicle screws in osteoporotic vertebrae—comparing a new cadaver corpectomy model and pure pull-out testing. J Orthop Res. 2016; 35:167–174. [PubMed: 27003836]
23. Ledonio CG, Rosenstein BE, Polly DW Jr, et al. Pulmonary function tests correlated with thoracic volumes in adolescent idiopathic scoliosis. J Orthop Res. 2016; 35:175–182. [PubMed: 27208463]
24. Sun D, McCarthy M, Dooley AC, et al. The utility of an allograft tendon for scoliosis correction via the costotransverse foramen. J Orthop Res. 2016; 35:183–192. [PubMed: 26990453]
25. Dworsky E, Hegde V, Loftin A, et al. A novel in vivo mouse model of implant related spine infection. J Orthop Res. 2016; 35:193–199. [PubMed: 27116085]
26. Liu P, Jiang H, Li S, et al. Determination of anti-tuberculosis drug concentration and distribution from sustained release microspheres in the vertebrae of a spinal tuberculosis rabbit model. J Orthop Res. 2016; 35:200–208. [PubMed: 26996958]