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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.<sup>1</sup> The widespread prevalence of back pain makes it among the most costly healthcare conditions, yet, it is surprisingly not among the top ten health conditions receiving research funding.<sup>2</sup> 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.<sup>3</sup> 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).<sup>4</sup> 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.

## REGENERATIVE MEDICINE STRATEGIES

Vedicheria and Buckley, review cell-based therapies for intervertebral disc and cartilage regeneration,<sup>5</sup> 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.<sup>6</sup>

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.<sup>7</sup>

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.<sup>8</sup> 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.<sup>9</sup>

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 immunomodulatory effect, since nucleus pulposus cells alone had a greater up-regulation of both anabolic and catabolic genes.<sup>10</sup> One of the cytokines involved in degeneration is IL-1 $\beta$ . Daniels et al. showed that this pro-inflammatory cytokine upregulated three key signalling pathways in human nucleus pulposus cells, p38 MAPK, c-jun, and NF $\kappa$ B. Interestingly these pathways were not affected by the pro-anabolic factor, GDF-5, whereas ERK 1/2 was activated by both.<sup>11</sup> Furthermore, NF $\kappa$ B inhibition resulted in the largest reduction in IL-1 $\beta$  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.<sup>12</sup>

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.<sup>13</sup> 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.<sup>14</sup> 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.<sup>15</sup>

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.<sup>16</sup> 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.<sup>17</sup> 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.<sup>18</sup>

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.<sup>19</sup>

## SURGICAL REPAIR, SCOLIOSIS, AND INFECTION

A prospective trial found that the creation of a small cavity in the vertebral body during vertebroplasty reduced the rate of cement leakage.<sup>20</sup> 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.<sup>21</sup> When evaluating bone-implant interfaces, pedicle screw behaviour was better represented with a cadaveric compectomy model than pure pull-out testing.<sup>22</sup>

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.<sup>23</sup> 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.<sup>24</sup>

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.<sup>25</sup> 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.<sup>26</sup>

## 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.

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