Intervertebral Disc Degeneration Etiology

Both iron overload and lipid peroxide accumulation contribute to the occurrence, development, and treatment of musculoskeletal diseases, such as osteoporosis, osteoarthritis, osteosarcoma, intervertebral disc degeneration, and spinal cord injury. see ferroptosis

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Intervertebral disc degeneration (IDD) is an age-dependent progressive spinal disease that causes chronic back or neck pain. Although aging has long been presented as the main risk factor, the exact cause is not fully known. DNA methylation is associated with chronic pain, suggesting that epigenetic modulation may ameliorate disc degeneration. We examined histological changes in the DNA methylation within the discs and their association with pain-related transient receptor potential vanilloid subtype 1 (TrpV1) expression in rats subjected to IDD. Epigenetic markers (5-hydroxymethylcytosine (5hmC), 5-methylcytosine (5Mc)), DNA methyltransferases (DNMTs), and Ten-eleven translocations (Tets) were analyzed using immunohistochemistry, real-time PCR, and DNA dot-blot following IDD. Results revealed high 5mC levels in the annulus fibrosus (AF) region within the disc after IDD and an association with TrpV1 expression. DNMT1 is mainly involved in 5mC conversion in degenerated discs. However, 5hmC levels did not differ between groups. A degenerated disc can lead to locomotor defects as assessed by ladder and tail suspension tests, no pain signals in the von Frey test, upregulated matrix metalloproteinase-3, and downregulated aggrecan levels within the disc. Thus, we found that the DNA methylation status in the AF region of the disc was mainly changed after IDD and associated with aberrant TrpV1 expression in degenerated discs.

The potential relationship between disc infection and disc degeneration-related symptoms remain controversial, with contradictory evidence available in the literature. Several studies have demonstrated the presence of infected extruded nucleus tissue from first-time disc herniation, implicating the role of disc microbial infection in disc degeneration. The current study is a pilot study evaluating if high infection rates are prevalent in Australian degenerate disc cohort.

Institutional ethics approval was obtained (HREC 13/218). The pilot project was a single spine centre prospective cohort of patients undergoing spine surgery for degenerate disc disease. In each case, disc material was obtained and prolonged aerobic and anaerobic cultures performed as per methods used by Stirling et al.

To date, a total of 168 patients have been enrolled, with male: female=1:1. Surgical caseload includes: 17.9% anterior cervical fusion, 35.0% anterior lumbar fusion, 40.7% lumbar discectomy and 5.7% posterior lumbar fusions. 34.1% patients presented with neck pain, 31.6% with arm pain, 59.3% with leg pain and 64.2% with back pain. 20.2% of the patients received transforaminal or epidural or facet joint injections prior to surgery. In this pilot study, 19.6% were culture positive, with P. acnes predominant in 50%. Disc-only cultures were positive in 27.8% of lumbar cases and 18.5% of cervical cases, with predominant organisms being P. acnes.

Similar to the infection rates from previous studies, this Australian cohort had 19.6% infection rates when disc only cultures are performed. P. acnes is the predominant organism followed by streptococcus sp. It is imperative to perform contaminant controls as such high infection with skin bugs is a significant finding [1)].

Molecular basis

Pro-inflammatory mediators modulate catabolic reactions, resulting in changes in extracellular matrix (ECM) homeostasis and, finally, neural/vascular ingrowth-related chronic intractable discogenic pain. In ECM homeostasis, anabolic protein-regulating genes show reduced expression and changes in ECM production, while matrix metalloproteinase gene expression increases and results in aggressive ECM degradation. The resultant loss of normal IVD viscoelasticity and a concomitant change in ECM composition are key mechanisms in DDDs. During inflammation, a macrophage-related cascade is represented by the secretion of high levels of pro-inflammatory cytokines, which induce inflammation. Aberrant angiogenesis is considered a key initiative pathologic step in symptomatic DDD. In reflection of angiogenesis, vascular endothelial growth factor expression is regulated by hypoxia-inducible factor-1 in the hypoxic conditions of IVDs. Furthermore, IVD cells undergoing degeneration potentially enhance neovascularization by secreting large amounts of angiogenic cytokines, which penetrate the IVD from the outer annulus fibrosus, extending deep into the outer part of the nucleus pulposus. Based on current knowledge, a multi-disciplinary approach is needed in all aspects of spinal research, starting from basic research to clinical applications, as this will provide information regarding treatments for DDDs and discogenic pain [2].

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2)
Kim JH, Ham CH, Kwon WK. Current Knowledge and Future Therapeutic Prospects in Symptomatic Intervertebral Disc Degeneration. Yonsei Med J. 2022 Mar;63(3):199-210. doi: 10.3349/ymj.2022.63.3.199. PMID: 35184422.