Symptomatic Intervertebral Disc Degeneration

Degenerated intervertebral discs (d-IVDs) contribute to low back pain (LBP) and are highly common. While some Intervertebral Disc Degenerations cause discogenic LBP, others are pain-free. Understanding the differences in pathophysiology between painful and pain-free intervertebral disc degeneration (IDD), especially the pathogenic signaling involved in the regulation of painful d-IVDs, is vital for achieving satisfactory effects in clinical treatment.

Peng et al. revisited findings on the detection of inflammatory factors in d-IVDs and summarized the differences between d-IVDs that are painful and those that are pain-free. They postulated that persistent inflammation and innervation are the key factors distinguishing those that are symptomatic and those that are not. This highlights the necessity to use painful, rather than pain-free, degenerated discs in the mechanistic study of disc degeneration and in the development of regenerative approaches, to avoid false positive/negative outcomes. Based on previous molecular d-IVD studies, they also postulated the signaling events from disc overload/ injury to discogenic pain. Although these proposed events are supported by experimental findings, many details about how they are interconnected are not addressed and therefore require experimental investigation [1)].

This phenomenon is caused by several processes, including matrix degradation in IVD tissues, which is mediated by matrix metalloproteinases (MMPs) and inflammatory responses, which can be mediated by interactions among immune cells, such as macrophages and IVD cells. In particular, interleukin (IL)-1 beta (β), which is a master regulator secreted by macrophages, mediates the inflammatory response in nucleus pulposus cells (NP) and plays a significant role in the development or progression of diseases.

Kim et al. developed a custom Electrostimulation (ES) platform that can apply low-constant-current stimulation (LCCS) signals to microfluidic chips. Using this platform, they examined the effects of LCCS on IL-1β-mediated inflammatory NP cells, administered at various currents (5, 10, 20, 50, and 100 μA at 200 Hz). The results showed that the inflammatory response, induced by IL-1β in human NP cells, was successfully established. Furthermore, 5, 10, 20, and 100 μA LCCS positively modulated inflamed human NP cells' morphological phenotype and kinetic properties. LCCS could affect the treatment of degenerative diseases, revealing the applicability of the LCCS platform for basic research of electroceuticals [2)].

Molecular basis

Proinflammatory 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 [3].

1)

Peng Y, Lv FJ. Symptomatic versus Asymptomatic Intervertebral Disc Degeneration: Is Inflammation the Key? Crit Rev Eukaryot Gene Expr. 2015;25(1):13-21. doi: 10.1615/critreveukaryotgeneexpr.2015012369. PMID: 25955814.

2)

Kim AG, Kim TW, Kwon WK, Lee KH, Jeong S, Hwang MH, Choi H. Microfluidic Chip with Low Constant-Current Stimulation (LCCS) Platform: Human Nucleus Pulposus Degeneration In Vitro Model for Symptomatic Intervertebral Disc. Micromachines (Basel). 2021 Oct 21;12(11):1291. doi: 10.3390/mi12111291. PMID: 34832700; PMCID: PMC8621874.

3)

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.