Research Statement Hwang

Low back pain affects over 80% of the United States population [1]. According to the Agency for Healthcare Research and Quality, back-related ailments account for over 660,000 hospital visits and over 325,000 surgeries annually in the USA [2]. Low back pain, which arises from aging and disc degeneration, is believed to be a cell-driven process that originates in the nucleus pulposus (NP) region of the intervertebral disc (IVD). With aging and disc degeneration, healthy, large, vacuolated, immature NP cells that are normally arranged in cell clusters transition to a sparse population of smaller, isolated chondrocyte-like cells [3, 4], resulting in decreased NP cell matrix production, and loss of NP-phenotype and NP-related matrix proteins that are essential for maintenance of healthy and functional extracellular matrix (ECM) [5-9]. All of these biological changes result in significant loss of water, proteoglycans and collagen content in the IVD ECM, which causes morphological and structural changes such as formation of fissures, instability of the spine/spinal segment and decreased disc height [10, 11].

Current methods for treatment of disc degeneration, such as discectomy or spinal fusion aim to treat the symptoms associated with back pain, but these procedures are extremely invasive, result in decreased range of motion in the spine, and oftentimes lead to accelerated disc degeneration in adjacent discs [5, 11-14]. Therefore, there is significant interest in developing new strategies for disc degeneration that address the underlying biological causes of the disease to stop or reverse the degenerative changes that occur during disc degeneration rather than just addressing the symptoms [11, 15, 16].

In order to successfully develop biological strategies for treatment of disc degeneration, it is necessary to understand the biological mechanisms that regulate healthy NP cell survival. Healthy, juvenile NP cells naturally reside in NP tissue in cell clusters, and there is significant evidence indicating cell clustering is necessary for NP cells to remain functional [5, 17]. Some work has been done to understand the microenvironmental cues that NP cells use to remain as cell clusters, however, not much is known regarding the actual role of cell clusters in regulating NP cell phenotype and morphology. The goal of my thesis is to elucidate a mechanism by which NP cells are able to form cell clusters and maintain the juvenile phenotype when cultured on soft, laminin-rich hydrogels. Specifically, my thesis aims to understand the role of the cell adhesion molecule, N-cadherin, in regulating NP cell clustering, and maintaining juvenile NP cell phenotype and morphology. A secondary goal is to elucidate the potential to promote degenerate, adult NP cells towards a juvenile NP cell phenotype using soft, laminin-rich hydrogels to promote N-cadherin mediated cell-cell adhesions.

The results of this work may be used in tissue engineering or cell delivery strategies by which degenerate, adult NP cells can be reverted back to a juvenile NP cell phenotype to treat disc degeneration.

References


