The Role of BMP9 in Regulating the Proliferation and Survival of the Intervertebral Nucleus Pulposus Cells (NPCs)

Tong-Chuan He, MD, PhD
Department of Orthopaedic Surgery and Rehabilitation Medicine
The University of Chicago Medical Center

ABSTRACT
The intervertebral disc (IVD) cells are fibrocartilaginous cushions functioning as the spine’s shock absorbing system, and are composed of an annulus fibrosus (AF) and a nucleus pulposus (NP). With ageing or injuries, the disc changes in morphology and becomes more disorganized, ultimately leading to degeneration of intervertebral discs and back pain. We previously demonstrated that BMP9 is one of the most potent regulators of mesenchymal stem cell (MSC) differentiation. We further found that BMP9 is highly expressed in NP cells at as early as E12.5 and postnatally. Moreover, our recently established BMP9 knockout mice exhibit the features of disc degeneration. Here, we investigate the functional role of BMP9 in regulating the proliferation and survival of NP cells (NPCs) of IVDs. Using the reversibly immortalized mouse NP cells (iNPCs), we found that BMP9 stimulation of iNPCs significantly promotes the cells progressing into S phase. The removal of immortalizing gene SV40 T antigen in iNPCs reduces their proliferative activity, which can be effectively enhanced by BMP9 stimulation. Furthermore, BMP9 stimulation significantly increases the expression of chondrogenic markers in iNPCs. Conversely, in vivo BrdU labeling and PCNA immunohistochemical staining indicate that NP cell's proliferative activity is significantly decreased in the IVDs derived from BMP9 knockout mice. Using the in vivo cell implantation assay, we found that BMP9-transduced iNPCs can form masses that exhibit varied degrees of cell proliferation and chondrogenic differentiation, as demonstrated by H & E staining, alcian blue staining, and immunohistochemistry. Using our recently established mouse IVD organ culture system, we found that intervertebral disc injection of the adenovirus expressing BMP9 significantly prolongs the NP cell survival in culture for up to two weeks. Taken together, our results accumulated thus far strongly suggest BMP9 may play an important role in regulating the proliferation and survival of NP cells of the IVDs. These findings should expand our understanding of pathogenesis of degenerative disc diseases.