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A combinatorial relative mass value evaluation of bioactive factors in degenerative cervical and lumbar discs: New indications for gene therapeutic approaches of spinal disc degeneration

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Degenerative intervertebral disc disease is common after middle age and can cause loss of disc height with painful nerve impingement, bone and joint inflammation. Despite the clinical importance of these problems, the pathology of cervical disc degeneration were studied merely from a morphologic view point using magnetic resonance imaging (MRI), without addressing the issue of biological treatment approaches. Moreover, a wide range of endogenously expressed bioactive factors in degenerative cervical and lumbar discs were not investigated. Nucleus pulposus (NP) cells play a central role in intervertebral disc maintenance by organizing the expression of anabolic, catabolic, anti-catabolic and inflammatory cytokines that affect the extracellular matrix. Intervertebral disc degeneration is associated with imbalances of these factors, resulting in a catabolic inflammatory metabolism. Although degenerative lumbar discs have been targeted by different biological treatment approaches, the quantities of disc cells and the concentrations of gene therapeutic factors used in animal models fluctuate extremely. These indicate lack of experimentally acquired data regarding disc cell proliferation and levels of therapeutic targets, which are vital for rational gene therapeutic approaches. Therefore, we analyzed proliferation rates of degenerative NP cells and their endogenous expression levels of anabolic, catabolic, anti-catabolic and inflammatory matrix proteins.

Grades of intervertebral disc degeneration were determined by preoperative MRI. Then grade III, IV and V disc tissues were isolated from 78 patients operated due to spinal disc herniation (63 lumbar, 15 cervical, mean age 56 / range 29 - 84 years). NP cells were cultured for four weeks with low-glucose in collagen I scaffold. Their proliferation rates were analyzed using 3-(4, 5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide. The protein expression levels of 28 therapeutic targets were analyzed using enzyme-linked immunosorbent assay.

During progressive grades of degeneration NP cell proliferation rates remained similar in all groups, independent of gender, age and grades of degeneration. Significantly decreased aggrecan and collagen II expressions ($P < 0.0001$) were accompanied by accumulations of selective catabolic and inflammatory cytokines ADAMTS-4, ADAMTS-5, MMP-3, IL-1β and IL-1R combined with low expression level of the anti-catabolic factor TIMP-3 ($P < 0.0001$). However, the concentration of the anabolic factors BMP-2, BMP-4, BMP-6, BMP-7, IGF-1, TGF-β1 and TGF-β3 remained below the minimal detectable quantities.

Hence, gene therapeutic interventions regulating relevant bioactive factors identified in this work might contribute to the development of regenerative treatment approaches and inhibit inflammatory catabolism of intervertebral discs.

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