Mechanisms of Age-Related Decline in Insulin-Like Growth Factor-I (IGF-I) Dependent Proteoglycan Synthesis in Rat Intervertebral Disc Cells

Shin'ya Okuda, MD (Suita, Japan), Akira Myoui, MD, Kenta Ariga, MD, Takanobu Nakase, MD (Osaka, Japan), Kazuo Yonenobu, MD, Hideki Yoshikawa, MD (Ashiya, Japan)

INTRODUCTION: Age-related fluctuations in insulin-like growth factor-I (IGF-I) dependent proteoglycan synthesis in rat intervertebral disc cells were investigated.

METHODS: Nucleus pulposus tissue and cells were harvested from the coccygeal vertebrae of 8-, 40-, and 120-week-old rats. Age-related change in the expression of IGF-I and its receptor (IGFR) were assessed together with IGF-I-dependent proteoglycan synthesis by the cultured nucleus pulposus cells. We also carried out western blot analysis of IGFBP-1 and further examined IGF-I signal transduction through tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1), which is a signal transducer of IGF-I.

RESULTS: Semi-quantitative RT-PCR analysis indicated that the expression of IGFR in 120w cells decreased clearly in comparison with the cells of younger animals. On the other hand, IGF-I-dependent proteoglycan synthesis decreased with age, and the sharpest decline of synthesis was found between cells from 8- and 40-weeks of age, although the level of IGF-I/IGFR gene expression was maintained in 40-week-old animals. Consistent with the results of proteoglycan synthesis, the expression of phosphorylated IRS-1 decreased with age. Thus, we investigated the expression of IGFBP-1 and proteoglycan synthesis using Long R3 IGF-I, which was not influenced by IGFBPs. IGFBP-1 was strongly expressed in 40w cells when compared with the expression in 8w cells. Furthermore, proteoglycan synthesis in 40w cells supplemented with Long R3 IGF-I was up-regulated in comparison with that in 40w cells supplemented with IGF-I.

CONCLUSIONS: The present findings indicated that the age-related decline in IGF-I-dependent proteoglycan synthesis in nucleus pulposus is due at least in part to the increase in IGFBPs at the early stages of aging, and further suggests that a loss of proteoglycan synthesis during the late stages of aging is due to the down regulation of IGFR in addition to an increase in IGFBPs.