

## Biological Repair and a Preventive Approach for Disc Degeneration

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**ANABOLIC PATHWAY:** The effect of growth factors on the regulation of matrix metabolism and cell proliferation has been extensively studied in articular cartilage, whose cells are phenotypically closely related to some cells in the intervertebral disc (IVD). The clinical application of growth factors has been proposed as a method of enhancing cartilage repair in osteoarthritis and after traumatic cartilage injury. On the other hand, studies of growth factors using IVD cells are limited. Recently, the difficulties in culturing IVD cells *in vitro* were partially overcome by three-dimensional culture techniques using alginate gels or a pellet culture system. Studies on the effects of the bone morphogenetic protein (BMP) family, such as osteogenic protein-1 (OP-1, otherwise known as BMP-7) (1) and growth differentiation factor-5 (GDF-5, otherwise known as CDMP-1 or BMP-14) (2) in our laboratory and others (3) showed that it is possible to stimulate the biological activity of IVD cells.

For *in vivo* studies, the availability of recombinant protein and the use of gene transfer techniques accelerated progress in this field of research. The development of a reproducible animal model for quantitative studies in a reasonably sized animal, such as the rabbit, makes it possible to analyze the effects of growth factors *in vivo* (4). Recently, using the rabbit annular puncture model, our laboratory has shown that a single injection of the growth factor, OP-1, induced a significant restoration of disc height and an improvement in the histological and biochemical parameters of disc degeneration (5).

The results from these *in vitro* and *in vivo* studies clearly suggest the potential usefulness of recombinant growth factors as therapeutic drugs or as medical devices.

**Catabolic Pathway:** In addition to efforts to stimulate the anabolic pathway, further efforts have been made to inhibit the catabolic cascade, which causes disc degeneration, by the oral administration of a drug or an intradiscal signaling pathway modification technique.

In order to inhibit the degradation of the IVD by matrix degrading enzymes, such as

metallo-proteinases and aggrecanase, the effects of the coumarin derivative, Esculetin, was assessed in both an *in vitro* and an *in vivo* setting. The oral administration of an esculetin prodrug showed a significant suppression of disc height loss and histological changes in the rabbit annular puncture model (6-8).

The nuclear factor, kappa B (NF- $\kappa$ B) transcription factor, plays an important role in the regulation of cytokines and metalloproteinases. An *in vitro* study, using the alginate culture system, showed a very high transfection rate with a naked decoy oligonucleotide (ODN) containing the NF- $\kappa$ B cis element with a resulting inhibition of the activity of IL-1 and TNF measured by several biological parameters (9). The intradiscal injection of the NF- $\kappa$ B ODN resulted in a significant recovery of the disc height loss induced by an annulus needle puncture (10).

An intradiscal injection therapy has a pharmacokinetic advantage over an intra-articular injection for a joint disease. This is because of the structural uniqueness of the IVD as an avascular and alymphatic structure, which is also isolated in a confined space where a single injection can be effective with a longer half-life as indicated by Thompson, Oegema et al. (11). In summary, therapies combining growth factors and anti-cytokine or enzyme agents will be optimal approaches to provide both structural and symptom modification for degenerative disc diseases.

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