Link N as a Therapeutic Agent to Treat Early Intervertebral Disc Degeneration

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Abstract—Degenerative disc disease begins in the central nucleus pulposus region of the IVD and has been implicated as a major component of spine pathology. Currently, the two major clinical procedures for treating disc degeneration are disc excision and spinal fusion. Although these procedures offer relatively good short-term clinical results in relief of pain, in many instances they have been disappointing because of altered spinal mechanics leading to subsequent degeneration at adjacent disc levels. Biological intervention to repair the early degenerate disc or prevent future degeneration would be the ideal treatment, and recent advances in tissue engineering offer the unique opportunity to repair or at least retard further degeneration of nucleus pulposus using growth factor supplementation. Being a synthetic peptide, Link N has considerable benefits for clinical use over recombinant growth factors because it can be chemically produced, rather than biologically, making quantity manufacturing and quality control more manageable at lower cost.

Keywords—Back pain, intervertebral disc, Link N, Tissue engineering.

I. INTRODUCTION

Intervertebral disc degeneration is an insidious disorder that begins early in adult life and may progress slowly for decades until becoming symptomatic and requiring medical intervention. There are currently no proven treatments to prevent, stop or even retard disc degeneration, and surgery is often the ultimate outcome. Surgery commonly involves excision of the degenerate disc and fusion of the adjacent vertebrae, but this is not a benign procedure as it can result in adjacent segment disc degeneration due to altered spine biomechanics. A biological means to treat disc degeneration is therefore desirable. Supplementation with growth factors to promote matrix synthesis, with or without concurrent supplementation by disc cells or stem cells, represents the most common biological approach (1). However, growth factor therapy is expensive and side effects are likely with systemic administration. Link N represents a possible means of circumventing these difficulties.

II. STRUCTURE OF LINK N

Link-N represents the N-terminal 16 amino acids of the human link protein that stabilizes the interaction of aggregan with hyaluronan in proteoglycan aggregates in both articular cartilage and intervertebral disc. It is generated in vivo by the action of matrix metalloproteinases and has been shown to promote aggregan and collagen synthesis by chondrocytes. As aggregan degradation and loss is the hallmark of early cartilage degeneration, its replacement is a prerequisite for cartilage repair, leading to the suggestion that Link N may provide a feedback mechanism designed to stimulate repair during cartilage degeneration. Link N is also able to stimulate matrix synthesis by cells of both the annulus fibrosus and nucleus pulposus (2), suggesting that it may exert a similar beneficial role during intervertebral disc degeneration.

III. TREATMENT OF DISC DEGENERATION BY LINK N

In the face of prolonged ongoing degeneration the natural Link-N mediated repair mechanism may be inadequate as the supply of endogenous link protein is limited. However, it may be possible to supplement with exogenous Link N to achieve the desired effect. The benefit of Link-N supplementation is supported by in vivo studies in the rabbit lumbar disc annular needle puncture model of intervertebral disc degeneration (3). Following needle puncture, disc degeneration rapidly proceeds, associated with aggregan loss in the disc and a reduction in disc height. Upon Link N administration by a second intradiscal injection, aggregan synthesis is stimulated and the loss of disc height is partially restored, suggesting a reparative process (Figure 1). Aggregan message levels were examined following Link N treatment because it is the major contributor to the GAG content of the tissue and hence is responsible for tissue swelling and function (Figure 2). Furthermore, aggregan loss is a feature of disc degeneration, and its replacement is essential for repair. Link N injection led to a significant increase (p < 0.001) in aggregan gene expression in both the AF and NP, when compared to saline alone. Collagen message levels were examined following Link N treatment because the collagen fibrils allow the IVD to entrap the proteoglycan aggregates as well as provide tensile strength to the tissue. Link N injection led to a significant increase (p < 0.001) in type II collagen (COL2A1) gene expression in the NP, when compared to saline alone (Figure 2). However, although there was a slight increase in COL2A1 message in the AF, this was not significant (p = 0.36). In contrast, Link N injection led to a significant increase (p < 0.001) in type I collagen (COL1A1) gene expression in the AF, but a significant decrease in the NP (p < 0.01) (Figure 2). However, one must bear in mind that the structure of the rabbit disc is quite different to large
mammals, and such a study does not guarantee success in the human.

IV. Stimulation by Link N

Stimulation of aggrecan synthesis by Link-N can be achieved within the intact adult human disc in organ culture following intradiscal injection (4). The beneficial effect of Link-N is maintained for at least 1 week following administration, suggesting retention within the disc, which is therapeutically desirable to avoid frequent repeated injection. Link-N can also exert its beneficial effect even in the presence of inflammatory cytokines (5), indicating that ongoing inflammation associated with degeneration would not be an impediment to repair. In addition, the beneficial effects of Link-N are not confined to the stimulation of aggrecan, but also include down-regulating the production of several metalloproteinases known to be involved in matrix degradation. Thus Link N has the potential to not only stimulate repair but also retard degeneration (3, 5-8). Each of these features enhances the value of Link N as a therapeutic agent for treating disc degeneration. Furthermore, Link-N does not possess the osteoconductive properties associated with growth factors such as BMP7 that also stimulate matrix production, and is therefore not likely to produce undesired ossification (7).

V. Therapeutic Potential of Link N

One obstacle to clinical treatment using Link-N is the route of administration and avoiding the need for repetitive intradiscal injection, which carries the risk of promoting further degeneration. Recent studies have shown that Link N can diffuse within the disc and slowly pass through the cartilage endplate but not the outer annulus fibrosus (4). Such permeability of the endplate raises the question of whether systemic administration of Link N could be a viable therapeutic option. Diffusion into the disc may be achievable by conjugating the Link N to a molecule that can target the disc, such as an MRI contrast agent. Only time will tell whether such a dream will become reality, but if so the low cost associated with Link N production will make it an economically attractive therapeutic option with no known adverse side effects.

VI. Conclusions

When administered to the degenerate disc in vivo, Link N stimulated aggrecan gene expression and down-regulated metalloproteinase expression, and there was a trend towards increased proteoglycan content of the disc, in both the NP and AF (3). These are features needed for any agent designed to stimulate disc repair. Therefore in principle, Link N supplementation could be an option for treating disc degeneration.

REFERENCES


