Potential Biologic Therapies for the Intervertebral Disc

Christopher Evans

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Biology offers several strategies for restoring the degenerating disc, including the use of recombinant or natural proteins that increase matrix accumulation and assembly, enhance the number of disc cells, or in other ways lead to restoration of the native healthy disc. Recombinant bone morphogenetic protein-7 (osteogenic protein-1) shows promise in this regard. Other growth factors, as well as cytokine antagonists such as the interleukin-1 receptor antagonist, are also good candidates. Because disc degeneration is a chronic, progressive disorder occurring over many years, it is likely that growth factors and other therapeutic proteins will need to be present in the disc for extended periods of time. The intradiscal injection of recombinant or natural proteins is unlikely to fulfill this requirement. In this scenario, the delivery of genes that encode the protein in question may provide a better delivery system. Kang and associates have pioneered this strategy, demonstrating the responsiveness of disc cells to in situ genetic modification.

The success of protein and gene therapy requires the presence of an adequate number of responding cells. Disc degeneration is accompanied by a decline in cellularity. Restoring cell numbers could be achieved by either stimulating the division and inhibiting the death of endogenous cells or by introducing new cells into the disc. The latter strategy may be more successful, especially if the endogenous cells of a degenerating disc are unresponsive or otherwise abnormal. When pursuing this strategy, there are several important reasons why it is better to introduce progenitor cells than to attempt to harvest and reintroduce mature disc cells. Progenitor cells of the mesenchymal lineage, available from bone marrow, fat, and other convenient sources, could be useful. However, although the presumption exists that these types of cells can differentiate into disc cells, this has never been demonstrated. One impediment to confirming differentiation into a disc cell is our inability to identify these cells; there are no robust molecular, biochemical, or biologic markers. The serious study of disc-cell biology at this level would be most rewarding.
to regulate matrix turnover at the level of gene expression, particularly transcription, given that a number of key transcription factors (such as Sox-4, 5, and 9; NF-κB; and AP-1) have been identified.

Because intervertebral disc degeneration is associated with reduced cellularity, restoration may be aided by treatments that protect against cell death or promote mitosis. Several of the growth factors that promote matrix accumulation also serve as survival factors, and many are mitogenic. Whether cell death primarily reflects environmental stresses, responses to radicals, or other stimuli is not known.

Also unknown is whether restoration of the disc would also eliminate the pain that is associated with intervertebral disc degeneration. Pain might have to be considered a separate, albeit related, therapeutic target (Table I).

**Protein Therapy**

Cells of the anulus fibrosus and nucleus pulposus respond to a number of different cytokines. Several growth factors, including bone morphogenetic protein-2 (BMP-2), BMP-7 (also known as osteogenic protein-1 [OP-1; Stryker, Kalamazoo, Michigan]), growth and differentiation factor-5, transforming growth factor-β (TGF-β), and insulin-like growth factor-1 (IGF-1) stimulate matrix production, while interleukin-1 (IL-1) and tumor necrosis factor (TNF) inhibit the synthesis of matrix and enhance its catabolism. Thus, a rationale exists for administering growth factors or cytokine antagonists to the degenerating disc.

Several recombinant growth factors and cytokine antagonists are already in clinical use for the treatment of musculoskeletal conditions (Table II); a few of them, such as BMP-2, BMP-7, and parathyroid hormone, have a direct application in the orthopaedic arena. Although none are yet approved for the treatment of intervertebral disc degeneration, an application has been filed with the United States Food and Drug Administration for the intradiscal injection of recombinant human BMP-7. This filing is based on preclinical data demonstrating that nuclear and anular cells respond to BMP-7 by dividing and also by increasing their synthesis of aggrecan and collagen. Moreover, intradiscal injection of BMP-7 increases disc height in normal rabbits and slows loss of disc height in a lapine model of intervertebral disc degeneration.

The effectiveness of growth factors such as BMP-7 might be enhanced by the coadministration of additional proteins with synergistic actions. For example, as discussed by Sobajima et al., combinations of TGF-β, BMP-2, and IGF-1 act collaboratively to stimulate proteoglycan synthesis in the disc. The addition of molecules with antioxidant properties or the ability to inhibit matrix degradation might provide further benefit. In the latter context, an obvious candidate is the interleukin-1 receptor antagonist (IL-1Ra), the recombinant form of which is already in clinical use as the drug Kineret (anakinra) for the treatment of rheumatoid arthritis.

Although recombinant proteins are often effective clinically, they are very expensive. The TNF antagonists used to treat rheumatoid arthritis, for instance, cost well over $10,000 per year; BMPs used to promote bone growth cost approximately $5,000 per application. If the effective treatment of intervertebral disc degeneration were to require the administration of several different recombinant growth factors, antioxidants, and cytokine antagonists, the cost and complexity would become prohibitive. One solution is to inject cocktails of native, rather than recombinant, proteins obtained from a convenient, autologous source such as blood. This is the basis for administering autologous conditioned serum.

When peripheral blood is withdrawn and incubated with etched glass beads, leukocytes within the aspirate enrich the plasma with anti-inflammatory cytokines, such as IL-1Ra, IL-4, and IL-10, as well as growth factors, including fibroblast growth factor-2, TGF-β, and hepatocyte growth factor. After clotting, centrifuging, and filtering, the autologous conditioned serum, which is marketed in Europe as Orthokine, is returned to the body. It has been used successfully, by way of local injection, for the treatment of muscle injuries, human and equine osteoarthritis, and radiculopathy. The use of Orthokine in the intervertebral disc has not been reported, but is worthy of consideration given its impressive safety record and rich mixture of growth factors, cytokine antagonists, and, possibly, additional helpful agents.

**Gene Therapy**

Rapid biologic clearance is one limitation of protein therapy, whether administered by injection of purified, recombinant proteins or autologous conditioned serum. This is an important consideration for a chronic condition such as intervertebral disc degeneration. Gene transfer has the ability to pro-

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**TABLE I Issues for Biologic Treatment of Intervertebral Disc Degeneration**

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<td><strong>Type of therapeutic?</strong></td>
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<tr>
<td>Anabolic (e.g., BMP, FGF, IGF, PDGF)</td>
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<td>Cytokine antagonist (e.g., IL-1Ra, TNFαR)</td>
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<td>Proteinase inhibitor (e.g., TIMPs, Serpins, PAlS)</td>
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<td>Transcription factor (e.g., NF-κB, AP-1, Sox)</td>
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<td>Antioxidant</td>
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<td>Analgesic</td>
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<tr>
<td>Other</td>
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<td><strong>Mode of delivery?</strong></td>
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*BMP = bone morphogenetic protein, FGF = fibroblast growth factor, IGF = insulin-like growth factor, PDGF = platelet-derived growth factor, IL-1Ra = interleukin-1 receptor antagonist, TNFαR = tumor necrosis factor soluble receptor, TIMPs = tissue inhibitors of metalloproteinases, Serpins = inhibitors of serine endopeptidase (serine protease), and PAlS = plasminogen activator inhibitors.*
TABLE II Recombinant Proteins in Clinical Use for the Treatment of Musculoskeletal Conditions*

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Protein Used</th>
<th>Mode of Administration</th>
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<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>Enbrel (etanercept) (bivalent TNFsR: IgG Fc)</td>
<td>Subcutaneous</td>
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<td>Remicade (infliximab) (partially humanized anti-TNF antibody)</td>
<td>Intravenous</td>
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<td>Humira (adalimumab) (fully humanized anti-TNF antibody)</td>
<td>Subcutaneous</td>
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<tr>
<td></td>
<td>Kineret (anakinra) (interleukin-1 receptor antagonist)</td>
<td>Subcutaneous</td>
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<td>Delayed bone-healing</td>
<td>Infuse bone graft (BMP-2) (Medtronic Sofamor Danek, Memphis, Tennessee)</td>
<td>Surgically implanted</td>
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<td></td>
<td>OP-1 (BMP-7) (Stryker, Kalamazoo, Michigan)</td>
<td>Surgically implanted</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Forteo (teriparatide) (PTH 1-34)</td>
<td>Intramuscular</td>
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</table>

*TNFsR = tumor necrosis factor soluble receptor, IgG Fc = the constant fragment of immunoglobulin G, BMP = bone morphogenetic protein, OP-1 = osteogenic protein-1, and PTH = parathyroid hormone.

Noncoding sequences of nucleic acids also hold therapeutic potential. For instance, it is possible to administer oligonucleotides that contain the response elements within the promoter regions of genes. These decoys bind their cognate transcription factors, thus making them unavailable to drive expression of the genes in question. They are widely and successfully used experimentally both in vitro and in vivo, and a phase-I clinical trial is under way in which oligonucleotide decoys for the transcription factor NF-κB are injected into the joints of subjects with rheumatoid arthritis.

Several types of ribonucleic acid (RNA) molecules may also be used to regulate gene expression for therapeutic purposes. Antisense RNA, for example, contains sequences that are complementary to the target messenger RNA molecules to which they bind and thereby inactivate. One antisense RNA drug, Vitravene (fomivirsen), is on the market for the treatment of cytomegalovirus infections of the eye.

Lack of specificity has restricted the development of other promising antisense strategies. An alternative RNA-based approach makes use of ribozymes. These are RNA molecules with the ability to catalyze the degradation of target RNA molecules in a sequence-specific manner; a number of them are in preclinical development for various indications. The recent discovery of RNA interference, however, has provided a powerful new avenue for drug development that has displaced much of the enthusiasm for antisense molecules and ribozymes. Small, interfering RNA (siRNA) molecules are produced from larger double-stranded precursors through the action of an enzyme known as Dicer. In a precise, sequence-specific, and highly efficient manner, the siRNA molecule binds to and cleaves its target mRNA molecules.

The relatively short biologic lifetimes of RNA molecules limit their use in the treatment of chronic conditions such as intervertebral disc degeneration. However, sequences that encode these molecules may be incorporated into viral vectors and expressed for extended periods of time by the gene-transfer methods indicated above.
Cell Therapy

Given that intervertebral disc degeneration is associated with loss of cells, there is the potential to reverse degenerative processes by the introduction of cells with the ability to regenerate disc tissue. In one embodiment of this approach, the cells would be genetically modified to improve their regenerative capabilities, thereby implementing a form of ex vivo gene therapy. The development of cell therapies is impeded by poor knowledge of disc-cell biology.

Of the potential sources of cells for cell-based therapies, autologous disc cells seem the least promising. These cells would presumably be harvested from the patient’s own degenerating disc and, in addition to the need for an intrusive recovery procedure, the cells may be abnormal and poorly suited for repair. Mesenchymal stem cells, which can be readily obtained from autologous sources such as bone marrow, are better candidates. Although the presumption exists that these cells can differentiate into disc cells, this has not been demonstrated. Because both the various cell types found within the human intervertebral disc and mesenchymal stem cells lack robust phenotypic markers, it is difficult to study the differentiation of disc cells from their presumptive progenitors. Serious study of disc-cell biology at this level would be most rewarding.

The clinical use of either adult disc cells or progenitor cells will require the ex vivo expansion of the cells. Although this is feasible, it is expensive—a matter of considerable importance in the present health-care environment. The use of allogeneic progenitor cells would offer a more cost-effective approach. This possibility arises because of claims that mesenchymal stem cells can be successfully allografted. If so, a universal donor line of these cells, genetically modified or not, could be established and used directly in all suitable patients. The first human clinical trial involving allografted mesenchymal stem cells is about to begin, so preliminary data on the success of allografting should become available soon.

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Regardless of their origin, the survival of the transplanted cells could be a limiting factor. The interior of the degenerating disc provides a harsh environment that is acidic, hypoxic, and poor in nutrients. The transplants may have to be preconditioned, possibly by genetic manipulation, if they are to survive and restore matrix under these unfavorable conditions.

Conclusions

Biology has much to offer orthopaedics in general and the treatment of intervertebral disc degeneration in particular. Protein, gene, and cell therapies for a variety of indications are being developed and might be used singly or in combination for the treatment of intervertebral disc degeneration. To be clinically useful, such modalities need to be not only effective, but also safe and affordable. Within these constraints, there is room for considerable optimism about their eventual clinical use.

References