Future management of osteoarthritis arthroplasty or gene therapy

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Introduction

The last few years have seen a total transformation of attitudes toward articular cartilage lesions and diseases. Previously, the physicians preferred not to discuss osteoarthritis (OA) because there was a sense of hopeless inevitability about the disease for which little could be done. Orthopedic surgeons became more interested in OA when joint replacement surgery was developed, but joint replacement cannot duplicate the durability and function of the normal cartilage.

At present, articular cartilage is an exciting area for research and investigation. There is widespread belief that the course of OA can be modified.

Gene therapy for osteoarthritis

The clinical goal in the treatment of OA is to decrease or prevent the inflammatory process and restore a healthy articular surface. Thus, gene therapy strategies for this disease can be roughly divided into two approaches. The first is the delivery of genes that counteract the inflammatory process and the second is delivery of cells and genes that can promote chondrogenesis and new cartilage formation.

A number of cytokines show promise as antiarthritic agents, but their use is hindered by inefficient delivery methods. The proteins cannot be administered orally and hence require either systemic or intra-articular delivery. The short half-life of these molecules, however, requires the administration of high doses or multiple doses. As an alternative approach, gene therapy has the potential to circumvent the existing limitations associated with protein delivery by inducing a sustained release of the biological agent at therapeutic levels. For cartilage tissue, this is achieved by the direct transfer of the gene, which encodes the therapeutic agent, to the cells at the afflicted joint(s) or by implanting cells that have been first genetically modified *in vitro*. Using these methods, numerous proof-of-principle experiments have demonstrated the ability to deliver genes *in vitro* and *in vivo* to chondrocytes, synoviocytes, chondroprogenitor cells, and mesenchymal stem cells with the goal of cartilage regeneration or inhibition of arthritic disease progression. Insulin-like growth factors (IGFs), bone morphogenetic proteins (BMPs), fibroblast growth factors, hepatocyte growth factors, and transforming growth factor-β (TGF-β) have been shown to affect chondrocyte metabolism and proliferation [1]. Growth factors with selective specificity for cartilage have not been identified yet [2].

IGF-1 plays an important role in cartilage homeostasis, has a stimulatory effect on normal chondrocyte matrix synthesis and degradation at concentrations as low as 10 ng/ml, and is upregulated ~8 weeks after cartilage injury [3,4]. To investigate cartilage repair using a gene therapy approach, rat perichondral cells, transfected *ex vivo* through an adenovirus to express IGF-1, were implanted in a rodent partial-thickness cartilage defect model [5]. Examination of cartilage repair at 8 weeks after implantation indicated that the cells had retained their chondrocyte morphology and had formed a structure that resembled hyaline cartilage and stained positive for collagen type II.

The delivery of a gene to overexpress TGF-β is particularly attractive for osteoarthritic patients because TGF-β has a greater stimulatory effect on osteoarthritic chondrocytes than on normal chondrocytes [6]. TGF-β1 has anti-inflammatory properties and stimulates new matrix synthesis by chondrocytes [7]. However, the direct injection of large doses of TGF-β to the joint can stimulate fibrosis of the synovial lining and osteophyte formation, whereas systemic injection is immunosuppressive and may lead to fibrosis of tissues, in particular the kidney and liver [2,6,8]. Thus, recent evidence strongly suggests that a gene therapy approach using TGF-β1 to treat an arthritic condition is inappropriate.

At therapeutic levels, several BMPs will stimulate cell proliferation, stimulate the deposition of extracellular matrix by chondrocyte, and inhibit chondrocyte dedifferentiation. Although naturally expressed by chondrocytes, BMPs must be used cautiously to enhance cartilage repair, as they are potent stimulators of ossification.

To date, research in the application of gene therapy for cartilage repair has mainly focused on combating the symptoms, namely, inflammation and irritation, of arthritic cartilage. Interleukin 1 (IL-1) and tumor necrosis factor-α are the two principal mediators in rheumatoid arthritis. Many cells demonstrated the ability to deliver

genes *in vitro* and *in vivo*, including chondrocytes, synoviocytes, chondroprogenitor cells, and mesenchymal stem cells. The primary cell target for in-vivo gene transfer with the goal of cartilage regeneration is synoviocytes. These cells are found throughout the synovial membranes, which line the intra-articular surfaces of the joints. The synovium is an attractive target because it is easily accessible, has a large surface area, and is in direct contact with the joint space. The use of autologous synoviocytes, transfected *ex vivo* using retrovirus encoding human IL-1Ra indicated a chondroprotective effect and a mild anti-inflammatory effect. Implantation of the synoviocyte cells in an arthritic rat model showed that cells expressed the cDNA for 9 days after implantation, and IL-1Ra overexpression suppressed joint inflammation and the erosion of cartilage and subchondral bone [9]. Potential disadvantages that may limit the effectiveness of in-vivo gene transfer to synoviocytes are the transient expression associated with DNA delivered using an adenovirus and the naturally rapid turnover rate of these cells during inflammatory conditions [3].

Chondrocytes may be the preferred cells for the treatment of cartilage surface defects as they naturally synthesize type II collagen and aggrecan. Furthermore, chondrocytes may be harvested as a homogenous cell population and readily transfected. Although ideal from an immunological prospective, the use of autologous chondrocytes is limited by the required surgical intervention, the limited quantity of cartilage available for harvest, and the tendency of chondrocytes to dedifferentiate *in vitro* to a fibroblast-like cell [10,11].

Stem cells are a distinct population of cells that form the source of tissues. Two main features characterize stem cells of all types: self-renewal ability, and the ability to give rise to differentiating cells. Stem cells can be further divided into two major groups. The first group constitutes embryonic stem (ES) cells, which together with the totipotent zygote present a cell population able to give rise to a multitude of cell types and tissues [12]. The second group constitutes adult stem cells, which reside in adult tissues and give rise to differentiated, tissue-specialized cells. These cells are responsible for the regenerative capacities of tissues. Generally, adult stem cells present a more limited range of differentiation lineages compared with ES cells. Adult cells are preferable for therapeutic purposes as they are considered safer for transplantation with lesser proliferation capacity and tumorigenicity compared with ES cells. Adult mesenchymal stem cells (MSCs) are stem cells residing in a variety of adult mesenchymal tissues. Readily isolated from the bone marrow and expanded in culture, they were shown to differentiate into various mesenchymal lineages including bone, cartilage, adipose, muscle, and tendon [13]. Their accessibility and ease of manipulation *in vitro* has made bone-marrow-derived adult MSCs natural candidates for orthopedic gene therapy studies and the focus for the development of therapeutic approaches in orthopedic therapy. However, bone-marrow-derived adult MSCs are not the only stem cells found to differentiate into various skeletal tissues. Stem cells from other tissues, such as muscle and fat, were also found to have similar properties. The emergence of cell-based clinical therapies using MSCs were at three different approaches: first, tissue-engineering approaches in which MSCs are seeded into three-dimensional scaffolds to generate functional tissues for replacement of defective tissues; second, we see the use of MSC transplantation to replace defective host cells; and third, harnessing the properties of MSCs to act as cytokine/growth factor producers to stimulate repair or inhibit degenerative processes.

The scientific and clinical challenge remains: to perfect cell-based tissue-engineering protocols to utilize the body's own rejuvenation capabilities by managing surgical implantations of scaffolds, bioactive factors, and reparative cells to regenerate damaged or diseased skeletal tissues.

The future for joint arthroplasty

To date, joint arthroplasty is the most applicable and effective method for treating OA. Successful high-performance arthroplasty is dependent on durability, efficient return to high activity, and patient satisfaction from a 'normal'-feeling joint. Critical elements of arthroplasty procedures include patient factors, surgical approach, instrumentation, and prosthesis design. New techniques and technologies such as arthroscopic and minimally invasive surgery, navigation and computer-assisted surgery, and new bearing surfaces and implant designs must be evaluated and improved to make arthroplasty procedures more sophisticated and effective. A proper balance needs to be reached between high performance and survivorship, so that one does not compromise the other.

Computer-based navigation and planning, for example, although not yet standard of care, is gradually making its way into more and more knee and hip arthroplasty procedures, and there have been recent developments in robotic computer-assisted surgery and other high-tech enabling tools that could lead to wider acceptance of these devices by surgeons. This new generation of enabling tools is designed to provide a more precise, and in some cases customized, implant procedure, and some of these devices could potentially make difficult surgeries easier and faster to perform.

Minimally invasive surgery addresses the demands of the patients and the economic needs of social security systems to reduce costs (and therefore hospital stay). There is no reason why the long-term implant survival rate should be shorter than in a conventional procedure, and, even if long-term survival time is shorter, the cause can be addressed without sacrificing the goal of minimal invasiveness. The concept of resurfacing, invented by Wagner more than 20 years ago, has attracted the attention of McMinn. Resurfacing is used frequently, especially in the UK. There has been no dislocation reported, and the disadvantage of an extensive approach is now addressed by smaller incisions for this implant.

A major concern is the considerable increase in metal ions and whether there will be any harmful results from this, such as synovitis, causing loosening.

The concept of very short stems will perhaps show only marginal benefit to the patient. The idea is that proximal press fit of a femoral component does not require a long stem but only contact points to the cortical bone. Loosening of such a very short femoral component would destroy less bone. There are no long-term data available and no reports as to whether the expected effects of bone preservation will occur when revision is performed.

Despite orthopedic surgeons' conservative reputation when it comes to adoption of new technology, high-tech devices and gene therapy technology are increasingly finding a place in treatment of this disease. However, the dark horse of OA therapy has not been identified yet.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Smith P, Shuler FD, Georgescu HI, Ghivizzani SC, Johnstone B, Niyibizi C, *et al*. Genetic enhancement of matrix synthesis by articular chondrocytes: comparison of different growth factor genes in the presence and absence of interleukin-1. Arthritis Rheum 2000; 43:1156–1164.

2 Van den Berg WB, Van der Kraan PM, Scharstuhl A, Van Beuningen HM. Growth factors and cartilage repair. Clin Orthop Relat Res 2001; 391 (Suppl): S244–S250.

3 Nixon AJ, Brower-Toland BD, Bent SJ, Saxer RA, Wilke MJ, Robbins PD, Evans CH. Insulinlike growth factor-I gene therapy applications for cartilage repair. Clin Orthop Relat Res 2000; 379 (Suppl): S201–S213.

4 Saxer RA, Bent SJ, Brower-Toland BD, Mi Z, Robbins PD, Evans CH, Nixon AJ. Gene mediated insulin-like growth factor-I delivery to the synovium. J Orthop Res 2001; 19:759–767.

5 Gelse K, Von der Mark K, Aigner T, Park J, Schneider H. Articular cartilage repair by gene therapy using growth factor-producing mesenchymal cells. Arthritis Rheum 2003; 48:430–441.

6 Evans CH, Robbins PD. Potential treatment of osteoarthritis by gene therapy. Rheum Dis Clin North Am 1999; 25:333–344.

7 Shuler FD, Georgescu HI, Niyibizi C, Studer RK, Mi Z, Johnstone B, *et al*. Increased matrix synthesis following adenoviral transfer of a transforming growth factor β1 gene into articular chondrocytes. J Orthop Res 2000; 18:585–592.

8 Arai Y, Kubo T, Kobayashi K, Ikeda T, Takahashi K, Takigawa M, *et al*. Control of delivered gene expression in chondrocytes using heat shock protein 70B promoter. J Rheumatol 1999; 26:1769–1774.

9 Otani K, Nita I, Macaulay W, Georgescu HI, Robbins PD, Evans CH. Suppression of antigen-induced arthritis in rabbits by ex vivo gene therapy. J Immunol 1996; 156:3558–3562.

10 Fernandes JC, Martel-Pelletier J, Pelletier J-P. Gene therapy for osteoarthritis: new perspectives for the twenty-first century. Clin Orthop Relat Res 2000; 379 (Suppl): S262–S272.

11 Yoo JU, Mandell I, Angele P, Johnstone B. Chondrogenitor cells and gene therapy. Clin Orthop Relat Res 2000; 379 (Suppl): S164–S170.

12 Adachi N, Sato K, Usas A, Fu FH, Ochi M, Han C-W, *et al*. Muscle derived, cell based ex vivo gene therapy for treatment of full thickness articular cartilage defects. J Rheumatol 2002; 29:1920–1930.

13 Gelse K, Jiang Q-J, Aigner T, Ritter T, Wagner K, Pöschl E, *et al*. Fibroblast-mediated delivery of growth factor complementary DNA into mouse joints induces chondrogenesis but avoids the disadvantages of direct viral gene transfer. Arthritis Rheum 2001; 44:1943–1953.