Marko Pecina · Mislav Jelic · Alan Ivkovic ·
Damir Hudetz

Gene therapy applications in orthopaedics

Received: 7 October 2005 / Accepted: 12 November 2005 / Published online: 18 March 2006
© Springer-Verlag 2006

Dear Editor,

With great interest and enthusiasm, we read the article “Orthopaedic applications of gene therapy” [1]. The authors should be congratulated for their concise yet very thorough and excellent coverage of the gene therapy applications in orthopaedics. However, it is our opinion that articular cartilage deserved more of their attention. Primarily, we think that the subsection heading “Cartilage repair” should be expanded to “Cartilage repair and regeneration”, particularly since the authors did mention “stimulation of cartilage regeneration” which implies the possibility of inducing intrinsic healing of the damaged cartilage by hyaline cartilage formation. When treating localised cartilage defects we should ask ourselves: What kind of new tissue formation inside the defect do we want to induce? Ideally we aim for articular cartilage regeneration, not repair, which would mean formation of hyaline cartilage, not fibrocartilage. Treatment options published in the literature can be roughly divided into two concepts—reparative and restorative. The end result of the first concept is fibrocartilage, and the microfracture technique is the most popular representative. In contrast, the restorative concept aims for hyaline cartilage implantation/formation and includes implantation of osteochondral plugs with perfectly organised cartilage and matrix and/or cell therapy,

namely autologous chondrocyte transplantation. Anabolic factors including members of the TGF-beta superfamily, such as BMPs, have proven their potential to stimulate chondrogenesis and synthesis of cartilage-specific matrix components in animal models [2, 3]. However, those proteins have short half-lives and it is difficult to maintain adequate in situ concentrations necessary for their proper functioning. Furthermore, many proteins act intracellularly and because cells cannot normally import these proteins, they cannot be used in soluble forms. These problems are the reason why gene therapy has attracted so much attention lately. The transfer of the respective genes into the joint, possibly in combination with the supply of chondroprogenitor cells, might be an elegant method to achieve a sustained delivery of such therapeutic factors at the required location in vivo [4]. Pascher et al. [5] developed a novel ex vivo method by using coagulated bone marrow aspirate as a mean of gene delivery to cartilage. Vector-seeded and cell-seeded bone marrow clots (“gene plugs”) were found to maintain their structural integrity following extensive culture and maintained transgenic expression for several weeks.

Therefore, we conclude that there is a huge potential for new tissue formation by gene therapy transduction of cells of different origin. Cells originating subchondrally, in combination with gene therapy, may form tissue of higher quality than is achieved with the classical microfracture technique. On the other hand, hyaline cartilage formation by gene therapy induction in combination with cell implantation (possibly on biodegradable scaffolds) might be the answer to the current limitations of cartilage treatment modalities, and may provide permanent solution for the patients. Many animal studies are currently underway to investigate gene therapy-induced cartilage regeneration of chondral and osteochondral defects, and some of these investigations can be expected to lead to clinical trials and yield answers to these open questions.

M. Pecina · M. Jelic · A. Ivkovic (✉)
University of Zagreb, Orthopaedic Surgery,
Salata 7, 10000 Zagreb, Croatia
e-mail: aivkovic@inet.hr
Tel.: +385-1-481911
Fax: +385-1-4818810

D. Hudetz
University of Zagreb, Clinical Hospital for Traumatology,
Zagreb, Croatia

References

1. Lind M, Bunger C (2005) Orthopaedic applications of gene therapy. *Int Orthop* 29:205–209
2. Jelic M, Pecina M, Haspl M, Kos J, Taylor K, Maticic D, McCartney J, Yin S, Rueger D, Vukicevic S (2001) Regeneration of articular cartilage chondral defects by osteogenic protein-1 (bone morphogenetic protein-7) in sheep. *Growth Factors* 19:101–113
3. Pecina M, Jelic M, Martinovic S, Haspl M, Vukicevic S (2002) Articular cartilage repair: the role of bone morphogenetic proteins. *Int Orthop* 26:131–136
4. Yokoo N, Saito T, Uesugi M, Kobayashi N, Xin KQ, Okuda K, Mizukami H, Ozawa K, Koshino T (2005) Repair of articular cartilage defect by autologous transplantation of basic fibroblast growth factor gene-transduced chondrocytes with adeno-associated virus vector. *Arthritis Rheum* 52:164–170
5. Pascher A, Palmer GD, Steinert A, Oligino T, Gouze E, Gouze JN, Betz O, Spector M, Robbins PD, Evans CH, Ghivizzani SC (2004) Gene delivery to cartilage defects using coagulated bone marrow aspirate. *Gene Ther* 11:133–141