

Stem Cell and Cartilage in Orthopaedics

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In the past decade, much has been learnt about the regeneration and repair of skeletal tissues. Regeneration involves slow replacement of tissues with identical tissue. It occurs readily in the embryo, hardly at all in neonates, and is never observed in adults. In 1743 Hunter¹ stated, "From Hippocrates to the present age it is universally allowed that ulcerated cartilage is a troublesome thing and that, once destroyed, is not repaired." A now extensive knowledge base of both repair and regeneration in orthopaedics tissues has enabled the development of new and innovative treatment modalities.

Articular cartilage is unique avascular, aneural and alymphatic load-bearing live tissue which is supported by the underlying subchondral bone plate. It is unique in that the extra cellular matrix is composed of a complex combination of type II collagen fibrils which are specifically arranged and have bonded to them very large water-retaining molecules called aggrecan molecules. This combination of molecules gives articular cartilage its unique ability to resist the repetitive compressive load-bearing necessary for the activities of daily life without undergoing premature repair.

Articular cartilage injuries have a limited potential to heal, which, over time, may lead to osteoarthritis.^{2,3} Cartilage defects in the knee may cause pain, swelling and catching. There are several different surgical procedures available to treat cartilage injuries, but no method has been judged superior. The ultimate aim of treatment is restoration of normal knee function by regenerating hyaline cartilage in the defect and complete integration of the regenerated cartilage with the surrounding cartilage and underlying bone. Chondrocytes are responsible for the unique features of articular cartilage; it seems rational to use truly committed chondrocytes to repair an articular cartilage defect.

Autologous chondrocytes cells expanded *in vitro* and combined with periosteum were first implanted in articular cartilage defects of patients in 1978.⁴ This first generation of chondrocytes transplantation procedures was initially termed autologous chondrocytes transplantation. Today, the technique is called autologous chondrocytes transplantation or autologous chondrocytes implantation (ACI). Implantation consists of an arthrotomy, preparation of the defect, (Fig. 1) harvest of a periosteal flap, fixation of the periosteal flap to the defect, (Fig. 2) securing a watertight seal with fibrin glue, implanting the chondrocytes, (Fig. 3) and wound closure.

ACI resulted in the formation of new cartilage that was similar to normal cartilage in that it had an abundance of type II collagen and metachromatically stained matrix. The chondrogenic cells in the transplant may be able to repair cartilage more efficiently than the chondrocytes at the margin of the injured cartilage. The culturing procedure increased the number of chondrocytes initially isolated by 10 to 20 times. A fraction of the cultured cells were able to re-express their chondrogenic phenotype, after the use of culturing procedures known to facilitate the production of cartilage matrix.⁴ The tissue that results from reparative techniques such as drilling and abrasion is disorganised fibro cartilaginous tissue with type I collagen fibres^{5,6}

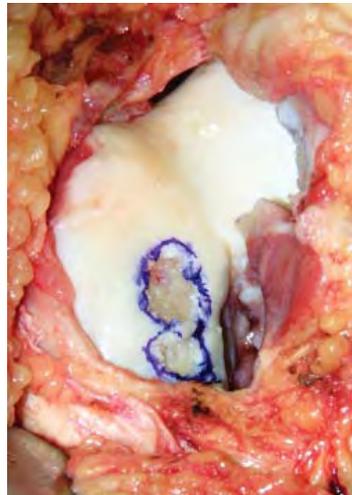


Fig. 1. Intraoperative photograph of a left medial femoral condyle chondral ulcer in 43-year-old female.



Fig. 2. Intraoperative photograph demonstrating a periosteal flap stitched over patella ulcer.



Fig. 3. Intraoperative photograph demonstrating a chondrocytes injected under periosteal flap on patella.

that is unable to restore the biomechanical properties of normal articular cartilage.⁷

Initially, ACI was limited to relatively small or medium-sized focal chondral and osteochondral defects of the weight-bearing surfaces of the femoral condyles and the patellofemoral joint. As notable success was obtained in these joints, the indications were extended to other diarthrodial surfaces, including talar, tibial, humeral capitular, and recently, femoral head lesions. Theoretical and practical considerations suggest that the ideal diameter of the defect is between 1 and 4 cm². Usually, both of the patellofemoral peripheries allow graft harvest for defects of 3 to 4 cm². Under certain conditions the ACI can be used as a salvage procedure for defects as large as 8 to 9 cm², but such extension of the indication can result in a higher rate of donor-site morbidity.⁸

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In treating patients, it is important that ACI is recognised as only 1 element. In every case, it is necessary to treat any additional joint abnormalities that would contribute to the failure of the joint. Accordingly, the treatment of instability, malalignment and meniscal and ligament tears must be incorporated in the operative and postoperative rehabilitation algorithms. ACI permits an immediate full range of motion, but requires 2 weeks of non-weight-bearing and an additional 2 to 3 weeks of partial weight-bearing after the operation.

However, there are some concerns about the procedure as it is currently performed. For example, it is 2-step procedure (with 1 step being an open arthrotomy), and the technique of suturing the periosteum is tedious and cumbersome. In addition it is expensive and somewhat technique-dependant.⁹ The question of chondrocytes phenotype and stability has not been effectively quantitated with use of this technique. Nonetheless, it has changed our view of the biological potential for the repair of articular cartilage. The success of this procedure has spawned a number of new protocols involving various cell-based therapy systems to elicit cartilage repair.

Many adult tissues contain populations of stem cells that have the capacity for renewing themselves after trauma, disease or aging. The cells may be found within the tissues or in other tissues that serve as stem cell reservoirs. For example, bone marrow not only is the major source of adult hematopoietic stem cells (HSCs) that renew circulating blood cells, but also contains mesenchymal stem cells, now referred as bone marrow stromal stem cells (MSCs), which contribute to the regeneration of mesenchymal tissues such as bone, cartilage, fat, tendon, muscle and stroma. MSCs can be isolated from other cells in bone marrow by their tendency to adhere to tissue culture flasks and density gradient centrifugation, which presents an intriguing model for examining the differentiation of stem cells.

Presently researchers focused on the use of periosteal-derived stem cells for repair of osteochondral defects for a number of reasons. The first reason is that these cells are easily expanded in culture and can be phenotypically stable. Also, they are ideal for the delivery of various genes promoting the repair, maintenance, and anabolic

metabolism of cartilage in lesions. Candidate genes for this application include bone morphogenic protein-7 (BMP-7), insulin-like growth factor-1 (IGF-1), and possibly transforming growth factor-beta (TGF-beta).⁹

Today tissue engineering is a field of biomedicine that is growing rapidly, and cell biologists, engineers and surgeons have to work closely together to reduce the gap between where the cartilage repair technology is today and where we want it to be. This interdisciplinary repair technology may be named biomedical surgery, and its novel instruments include embryonic stem cells, pluripotent mesenchymal stem cells, morphogens, smart biomaterials and gene transfers, which the different researchers should try to make into a biological well-tuned orchestra.

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