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Cartilage repair: Generations of autologous chondrocyte transplantation

Stefan Marlovits *, Philip Zeller, Philipp Singer, Christoph Resinger, Vilmos Vécsei

Department of Traumatology, Center for Joint and Cartilage, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria

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Abstract

Articular cartilage in adults has a limited capacity for self-repair after a substantial injury. Surgical therapeutic efforts to treat cartilage defects have focused on delivering new cells capable of chondrogenesis into the lesions. Autologous chondrocyte transplantation (ACT) is an advanced cell-based orthobiologic technology used for the treatment of chondral defects of the knee that has been in clinical use since 1987 and has been performed on 12,000 patients internationally. With ACT, good to excellent clinical results are seen in isolated post-traumatic lesions of the knee joint in the younger patient, with the formation of hyaline or hyaline-like repair tissue. In the classic ACT technique, chondrocytes are isolated from small slices of cartilage harvested arthroscopically from a minor weight-bearing area of the injured knee. The extracellular matrix is removed by enzymatic digestion, and the cells are then expanded in monolayer culture. Once a sufficient number of cells has been obtained, the chondrocytes are implanted into the cartilage defect, using a periosteal patch over the defect as a method of cell containment. The major complications are periosteal hypertrophy, delamination of the transplant, arthrofibrosis and transplant failure. Further improvements in tissue engineering have contributed to the next generation of ACT techniques, where cells are combined with resorbable biomaterials, as in matrix-associated autologous chondrocyte transplantation (MACT). These biomaterials secure the cells in the defect area and enhance their proliferation and differentiation.

Keywords: Autologous chondrocyte transplantation (ACT); Matrix-associated autologous chondrocyte transplantation (MACT); Cartilage defect; Surgical cartilage repair; Tissue engineering

1. Introduction

Articular cartilage is a narrow layer of specialized connective tissue that permits smooth, frictionless movement of diarthrodial joints. It is comprised of a relatively small number of cells (chondrocytes) embedded in an abundant extracellular matrix. The latter consists predominantly of type-II collagen, proteoglycans and water, along with smaller amounts of other collagen types and non-collagenous proteins [1]. Damaged articular cartilage has a limited capacity for self-repair. Joint surface defects that exceed a critical size heal poorly and usually lead to osteoarthritis. Several therapeutic strategies have been developed to repair damaged articular cartilage. The most popular of these strategies are microfracture, mosaicplasty and autologous chondrocyte transplantation (ACT) [2].

ACT is a biological approach to the treatment of large full-thickness chondral defects of the knee, based on the implantation of a suspension of cultured autologous chondrocytes beneath a tightly sealed periosteal flap. This procedure has been in clinical use since 1987 and has been performed on more than 12,000 patients worldwide. ACT has demonstrated significant and durable benefits for patients in terms of diminished pain and improved function [3–5].

However, despite the promising clinical results, the use of ACT carries a number of limitations, essentially related to the complexity of the surgical procedure and the biological response of the periosteum [2,6,7]. Recently, the use of three-dimensional scaffolds has been shown to favor the maintenance of a chondrocyte-differentiated phenotype [8–11]. Thus, efforts are now focused toward a tissue-engineered approach, which combines laboratory-grown cells with appropriate three-dimensional biocompatible scaffolds for the purpose of generating new tissues or tissue equivalents.

* Corresponding author. Tel.: +43 1 40400 5964; fax: +43 1 40400 5947.
E-mail address: stefan.marlovits@meduniwien.ac.at (S. Marlovits).

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These efforts have modified the technique of classical ACT and led to the formation of new generations of cell-based cartilage repair procedures. An overview of the different developments, the modification of the surgical technique, and the published results is presented in this paper.

2. Procedure and variations of ACT

The concept of ACT is based on a three-step procedure: from a small biopsy of hyaline cartilage, chondrocytes are isolated and expanded in an in vitro process. The primary goal of the initial in vitro chondrocyte cell culture is to increase the number of cells in order to provide a sufficient number to fill a focal defect of articular cartilage. To accomplish this, chondrocytes are isolated from small slices of cartilage harvested arthroscopically from a minor weight-bearing area of the injured knee. The extracellular matrix is removed by enzymatic digestion, and the cells are then expanded in monolayer culture. Once a sufficient number of cells has been obtained, the chondrocytes are implanted into the cartilage defect (Fig. 1). After implantation, the cells begin production of a cartilage matrix that gradually fills out the cartilage defect in the defect area, which is similar to the mesenchymal condensation that occurs during limb formation [6].

2.1. First step: Cartilage biopsy

In the initial intervention, an arthroscopy of the involved joint is performed. The cartilage defect is inspected and the decision is made about whether a cell transplantation is possible or indicated. Next, healthy hyaline cartilage is taken from an unloaded joint area (150–300 mg) and the biopsy is transferred in a special nutrient solution to a sterile transportation vessel.

2.2. Second step: Chondrocyte cultivation

The in vitro process is carried out under laminar air flow conditions in certified laboratories. Chondrocytes are released form the biopsies with enzymatic digestion of the extracellular matrix and expanded using standardized cell culture techniques. After reaching a defined cell number, either a cell suspension is produced or the cells are transferred on a three-dimensional biomaterial used as a cell carrier.

2.3. Third step: Cell implantation

The implantation of the cultivated cells usually requires an arthrotomy of the joint followed by careful preparation of the cartilage defect up to the intact adjacent cartilage without violation of the subchondral bone plate. The chondrocytes are implanted as a cell suspension beneath a sealed cover or as a cell-carrier construct.

The various modifications of the classical ACT technique led to the formulation of different generations of chondrocyte-based cartilage repair.

3. Generations of ACT

3.1. First generation of ACT

The classic ACT was described by Brittberg et al. as the first generation of a cell transplantation technique for cartilage repair, based on the implantation of a suspension of cultured autologous chondrocytes beneath a sealed periosteal cover [3]. The steps in open ACT include arthrotomy, preparation of the defect, periosteal harvest, suturing the periosteum over the defect, water-tightness testing, application of

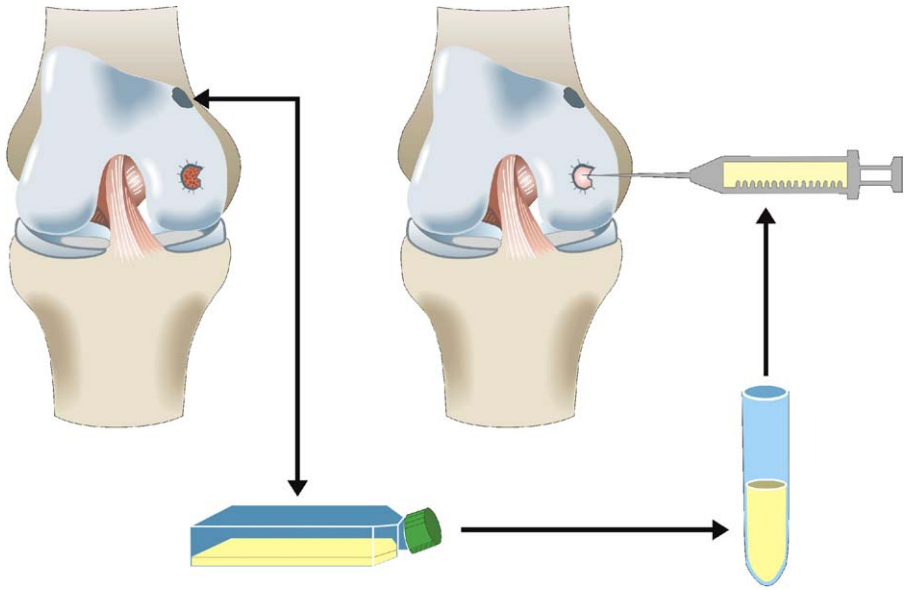

Fig. 1. Basic concept of autologous chondrocyte transplantation (ACT) with cell harvesting, expansion in monolayer cell-culture and implantation.