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Novel Cell-Based Techniques in Management of Osteoarthritis

Mihovil Plečko[1], Damir Hudetz[1,2,3] and Dragan Primorac[1,3,4,5,6,7]

[1]*St. Catherine Specialty Hospital, Croatia*

[2]*Clinical Hospital Sveti Duh, Croatia*

[3]*School of Medicine, JJ Strossmayer University of Osijek, Croatia*

[4]*Children's Hospital Srebrnjak, Croatia*

[5]*Eberly College of Science, The Pennsylvania State University, University Park, State College, USA*

[6]*The Henry C. Lee College of Criminal Justice and Forensic Sciences, University of New Haven, West Haven, USA*

[7]*School of Medicine, University of Split, Croatia*

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***Corresponding author:** Mihovil Plečko, St. Catherine Specialty Hospital, Croatia, USA, Tel: +385 1 2867 400; Email: mihovil.plecko@gmail.com

Abstract

Articular cartilage is a hyaline cartilage 2-4 mm thick. It has a unique role to resist physical loads and to lower the friction between opposing articular surfaces, providing the possibility of movement in joints. Cartilage lesions can be a result of trauma or degeneration. Regeneration of the cartilage is a process starting from perichondrium, a layer of extra-articular connective tissue that surrounds hyaline cartilage and contains undifferentiated cells with the capacity to differentiate into chondrocytes. In physiological conditions, chondrocyte's synthetic activity is in balance with proteolytic enzymes that moderate processes of degeneration of the ECM. When this homeostasis is compromised, disease called osteoarthritis (OA) starts to arise. OA is currently the leading cause of physical disability in the modern world. Pathogenesis of OA is still being broadly investigated. Current conventional biological treatment options are often unsatisfying and patients have to undergo total joint replacement operations. For these reasons, novel techniques are being developed. One of the most promising group of this techniques is one based on cells being implanted into joints, which includes autologous chondrocyte implantation and matrix-associated chondrocyte implantation, bone marrow mesenchymal stem cells and autologous microfragmented fat tissue with adipose tissue-derived mesenchymal stem cells. This mini-review shows current data available from preclinical and clinical trials considering this three-novel cell-based techniques in management of OA.

Keywords: Articular Cartilage; Osteoarthritis; Autologous Chondrocyte Implantation; Bone Marrow Mesenchymal Stem Cells; Autologous Microfragmented Fat; Adipose Tissue Derived Mesenchymal Stem Cells.

Abbrevations: OA : OsteoArthritis; ECM: Extra-Cellular Matrix; PG: Proteoglycans; GAG glycosAminoGlycans; ACI: Autologous Chondrocyte Implantation; MACI: Matrix Assisted Autologous Chondrocyte Implantation; CaReS: Cartilage Regeneration System; MSCs: Mesenchymal Stem Cells; BMSCs: Bone Marrow Mesenchymal Stem Cells; AdMSCs: Adipose Tissue-Derived Mesenchymal Stem Cells; SVF: Stromal Vascular Fraction.

Introduction

Articular cartilage is a hyaline cartilage 2-4 mm thick. It has a unique role to resist physical loads and to lower the friction between opposing articular surfaces, providing in that manner the possibility of movement in joints. Cartilage consists of chondrocytes located in lacunas, surrounded by extra-cellular matrix (ECM). This type of tissue has no blood vessels, lymph vessels or nerves, hence obtaining nutrients by diffusion from synovial fluid inside of the joint capsule and through capillaries in the surrounding connective tissue (perichondrium) [1]. Chondrocytes, which take up to 5% of total cartilage tissue, produce and maintain ECM which is formed from collagen, proteoglycans, hyaluronic acid, water, calcium salts and other glycoproteins [2] Proteoglycans (PGs) are molecules formed by covalent bonding of centrally positioned protein called aggrecan and glycosaminoglycans (GAGs) (except hyaluronic acid), long unbranched polysaccharides made of repeating disaccharide units. Proteoglycans bond with chain of hyaluronic acid forming structures called proteoglycan aggregates [3].

Due to their characteristics they can bind a large number of cations, mostly Na+, through ionic bonds, thus making them extremely hydrated. Firmness of the cartilage depends on this bondage of water to GAGs and on electrostatic bonds between collagen fibers and GAGs. Cartilage lesions can be a result of trauma or degeneration. They can be described as full-thickness or partial, focal or generalized. Regeneration of the cartilage is a

process starting from perichondrium, a layer of extra-articular connective tissue that surrounds hyaline cartilage and contains undifferentiated cells with the capacity to differentiate into chondrocytes [4]. In physiological conditions, chondrocyte's synthetic activity is in balance with proteolytic enzymes that moderate processes of degeneration of the ECM. When this homeostasis is compromised, disease called osteoarthritis (OA) starts to arise [5]. OA is currently the leading cause of physical disability in the modern world. It is a heterogeneous condition with many risk factors (ie. obesity, overuse, previous trauma) that cause or promote progression of the disease [6].

It is divided into four grades by the International Cartilage Repair Society [7]. Pathogenesis of OA is still being broadly investigated. Studies indicate the importance of macro/microtrauma, destruction of ECM, inflammatory cytokines, TGF-β1, subchondral bone, bone marrow lesions etc. [8-13] Still, current conventional biological treatment options are often unsatisfying and patients have to undergo total joint replacement operations. For this reasons, novel techniques are being developed. One of the most promising group of this techniques is one based on cells being implanted into joints.

Autologous Chondrocyte Implantation and Matrix-Associated Chondrocyte Implantation

Autologous chondrocyte implantation (ACI) is hyaline-like cartilage restorative cell therapy, used to treat medium to large full-thickness cartilage lesions in the knee [14]. Initially, it was performed as a two-stage procedure. Firstly, a small biopsy of autologous articular cartilage is taken from a minimal weight-bearing area or from the damaged tissue of cartilage defect itself. Release of chondrocytes by enzymatic digestion in laboratory follows. After being cultured, chondrocytes are returned to the surgeon for a second surgical procedure in which they are implanted into the defect, under periosteum, which is harvested from the proximal tibia and sutured to the surrounding cartilage of the defect, thus creating a sealed space. This technique is referred as first generation of ACI. ACI is indicated for younger patients (15 to 50 years of age), with moderate symptoms and well-contained full-thickness chondral lesions measuring between 2 and 10 cm2 with an intact bone bed [14].

Advantage of this technique is that it uses autologous cells which do not cause tissue rejection due to immune response. Disadvantages are that it is a two-stage procedure, thus lasting for several weeks, that it requires an open incision and full-thickness cartilage around the defect. Furthermore, periosteum is often hard to suture, leading to significant possibility of cell leakage, and is prone to hypertrophy, calcification and delamination [15,16]. Nevertheless, ACI demonstrates good long term outcomes with over 70% of success [17]. The next generation eliminated the necessity of harvesting periosteal flaps, introducing collagen membrane to cover and seal chondrocytes in the defects. Collagen membrane is sutured to cartilage surrounding the defect and covers and seals the defect. Implantation of chondrocytes follows. As well as in first generation, suturing of collagen membrane is extensive and cell leakage is a possible complication of the surgery. This led to development of the third generation of ACI, called matrix assisted autologous chondrocyte implantation (MACI).

It introduced matrices or 3D scaffolds that are precultured with chondrocytes, following implantation to the affected cartilage lesion site. The biocompatible scaffolds secure the delivery of chondrocytes to the location of the lesion. Materials used as matrix are collagen hydrogels or membranes, copolymer of polyglycolic/polylactic acid, polydioxanone and hyaluronic acid, where chondrocytes are placed into the matrix and then fixed to the chondral defect with fibrin glue [18]. Benefit of MACI is the ability to perform surgery without having to suture the periosteum/collagen membrane to the surrounding cartilage, thus avoiding all the complications associated with it. A representative of MACI is a 3D hydrogel called Cartilage Regeneration System (CaReS), based on colagen type I prepared from rat tail tendons.

Autologous chondrocytes are derived from a cartilage biopsy specimen and are embedded into matrix without any additional processing. This implants are manufactured custom made in height and size to fit precisely into the chondral defect. Recent study [15] showed that CaReS is clinically effective and leads to significant functional improvement and reduction of pain. All in all, patients undergoing ACI/MACI treatment have favorable mid to long-term results.

Bone Marrow Mesenchymal Stem Cells

Regenerative medicine has a role to support and stimulate natural mechanisms of reparation within the body in order to help them heal defects that they could not repair on their own. Various cell types have been studied to find those with the potential to enhance regeneration processes in the body. One of those cell types are adult mesenchymal stem cells (MSCs) [19]. MSCs are undifferentiated cells with the capacity for self-renewal and capability of proliferation and differentiation into various cell lineages. They were first isolated from the bone marrow [20]. Bone marrow mesenchymal stem cells (BMSCs) have the potential to differentiate into a variety of cells, including chondrocytes [21]. Because of their specific characteristics, both autologous and allogenic BMSCs are being used in different conditions. Preclinical studies showed the potential of BMSCs to promote regeneration of cartilage tissue in goats when injected into joint which had prior surgical induction of OA [22].

Furthermore, BMSCs embedded into hyaluronan-based scaffold had positive outcome when used in rabbit OA models [23]. A clinical study was conducted to compare outcomes of the first ACI generation therapy and BMSCs therapy, concluding that BMSCs are as effective as ACI therapy. Advantages of using BMSCs over ACI are that it requires one less surgery, it is cheaper and donor-site morbidity is lower [24]. One clinical trial showed that

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patients with OA who underwent intra-articular administration of allogenic BMSCs have significantly lower level of pain than the placebo group [25]. Another study was conducted on 30 patients with chronic knee pain which was unresponsive to conservative treatments. All patients had radiological evidence of OA. They were randomized and divided into two groups. The test group was treated with allogenic BMSCs by intra-articular injection, while the control group received intra-articular injections of hyaluronic acid. Results showed significant improvement in pain and function levels over a period of 1 year as well as a significant decrease in poor cartilage areas with cartilage quality improvements measured by MRI T2 relaxation [26]. Mechanisms how BMSCs induce or promote cartilage regeneration and/or patient's quality of life still have to be clarified, but currently available data is encouraging.

Autologous Microfragmented Fat Tissue With Adipose Tissue-Derived Mesenchymal Stem Cells

Mesenchymal stem cells have the ability to differentiate into a variety of cell lineages as well as the ability to secrete many bioactive molecules. Paracrine secretion of cytokines, chemokines, growth factors etc. leads to trophic, immunomodulatory and anti-microbial effects [27]. Because of this features MSCs are often referred to as "mini-drugstores" or "medicinal signaling cells" [28]. As importance of MSCs started to rise in recent years, researchers often focused on searching for a source of MSCs that would be easier to harvest and would have sufficient quantity of this cells. Studies showed that MSCs reside in perivascular niches, therefore most of the tissues contain a certain amount of MSCs [29]. Moreover, perivascular cells named pericytes possess qualities similar to MSCs and could be precursors of MSCs [30]. As well as this two cell types, perivascular niches also contain endothelial progenitor cells, which were just recently presented to have regenerative potential in several conditions related to musculoskeletal system pathology [31]. Because of its sufficient level of vascularization and its abundance, human adipose tissue was introduced as a new source of MSCs [32]. Adipose tissue-derived mesenchymal stem cells (AdMSCs) are considered to be ideal for application in regenerative therapy. Fat tissue that contains AdMSCs can be easily harvested by minimally invasive techniques (ie. lipoaspiration) with a low percentage of complications and without leaving any true deficit on the harvesting site. Lipoaspirate contains derivate called stromal vascular fraction (SVF). SVF contains adipocytes, preadipocytes, MSCs, pericytes, endothelial progenitor cells, mastocytes, macrophages etc [33]. Lipoaspirate can be processed enzymatically or mechanically, releasing these cells and giving the ability to implant them directly to joints or to undergo prolonged ex vivo expansion. Enzymatic processing and/or ex vivo expansion lead to decrease in multipotency of this cells, as well as this type of procedures have complex regulatory issues [34]. Different approach is mechanical processing of the lipoaspirate which gives a product named autologous microfragmented fat tissue with AdMSCs. It contains preserved adipose structural niches of optimal size and allows transplantation of patients own AdMSCs by injection into joints, following clinical point of care principles, thus avoiding additional manipulation of this cells [34].

Conclusion

Recent studies show that the use of autologous microfragmented adipose tissue with AdMSCs in patients with knee OA significantly reduces level of pain, improves cartilage GAG content and slows down expected GAG decrease over time, suggesting that this therapy is slowing down progression of OA [35,36]. This procedure is simple, minimally invasive and quick with low percentage of complications. It is also important to underline that no malignant behavior of AdMSCs was reported in clinical studies so far [37]. Because AdMSCs are easily obtained and have a significant regenerative potential, this procedure could play an important role in future OA management.

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