

Applications of Tissue Engineering in Joint Arthroplasty

Current Concepts Update



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KEYWORDS

• Tissue engineering • Articular cartilage • Stem cells • Arthroplasty

KEY POINTS

- The technology of tissue engineering has witnessed substantial advancements and innovations in the recent years and carries significant potential for treating cartilaginous disorders.
- Although a variety of techniques in articular cartilage are available, preliminary data for almost all are encouraging.
- Several cell sources exist for tissue engineering; however, many parameters need further optimization, including the best-suited use of each cell source.
- Tissue engineering is already impacting clinical practice and will surely play an essential role in the daily practice in the foreseeable future.

INTRODUCTION

Cartilage is a highly specialized connective tissue maintained by chondrocytes. Articular cartilage is a highly organized tissue that is prone to undergo many alterations resulting from aging, trauma, or inflammatory processes, the end result of which is tissue deterioration, functional impairment, and pain.^{1,2} Limited by the lack of vascularization and ability of migration of healthy chondrocytes to the damaged area, articular cartilage has a very limited ability to repair, making the management of the disease processes rather challenging.³⁻⁵ Currently, total hip and

total knee replacement are the preferred surgical interventions for end-stage arthritis.⁶⁻⁸ More recently, tissue engineering and regenerative medicine have witnessed substantial advances, particularly with the introduction of new articular cartilage repair techniques.

Tissue engineering is a discipline aimed at restoring the functional role of various organs through the regeneration and formation of new tissues. It is being studied and applied in most organ systems, restoring the function of various tissues and organs, such as heart valves, blood vessels, the trachea, and bladder, among many others.⁹⁻¹² In general, tissue-engineering

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application follows a general principle, albeit the presence of variances that occur within each step. The first step in tissue engineering is the proper choice of cells.^{13–15} After being harvested, cells are cultured in vitro by placing them into a biomaterial scaffold that allows for cell differentiation or proliferation. The system is then placed in a bioreactor, which provides the necessary signals for proper development.¹⁶ The tissue construct is finally implanted into the host (Fig. 1). The aforementioned protocol simplification serves as a model, and it should be reiterated that multiple variations of this general protocol exist, such as cell-free techniques, among others.^{17,18} The purpose of this review is to present a current-concepts update on cell-based articular cartilage tissue engineering and briefly assess clinical trials using each cell source.

Chondrocyte-dependent Tissue Engineering

Various cell sources can be used in tissue engineering. A summary of the characteristics, main advantages, and disadvantages of each are presented in Tables 1 and 2. Chondrocytes, being the cells responsible for cartilage synthesis, have long been studied and used in articular tissue engineering.

Autologous chondrocyte implantation

Autologous chondrocyte implantation (ACI) was introduced in 1989¹⁹ and was applied in the clinical setting in 1994 for treatment of deep cartilage defects of the knee.²⁰ Since its introduction, various clinical trials have been conducted to

assess the outcome and validity of the intervention. ACI is a 2-stage process:

1. First step, harvest and growth: arthroscopic excision of a biopsy from a healthy non-load- or low-load-bearing articular cartilage.
 - a. Cartilage is then treated with enzymes in order to release chondrocytes.
 - b. Followed by in vitro expansion to up to 48 million cells.
2. Second step, debridement and implantation: following the surgical debridement of the damaged cartilage, the chondrocytes are implanted into the injured area to healthy articular tissue and covered by a membrane, usually a periosteal flap or collagen sheet to void cell leakage.^{2,21,22}

Various studies and trials reported positive short- and long-term follow-up outcomes with ACI technique.^{23–27} However, with the current studies at hand,^{28–30} the best use of ACI is still not well formulated. More work is needed to define the settings where ACI provides the best functional and/or financial outcome compared with the current standard treatments. The challenges that exist for ACI include prevention of cell leakage from the repair site and a high reoperation rate.

Chondrocyte-seeded scaffolds and matrix-induced autologous chondrocyte implantation

Similar to ACI, matrix-induced autologous chondrocyte implantation (MACI) is a 2-step procedure involving donor-site chondrocyte extraction

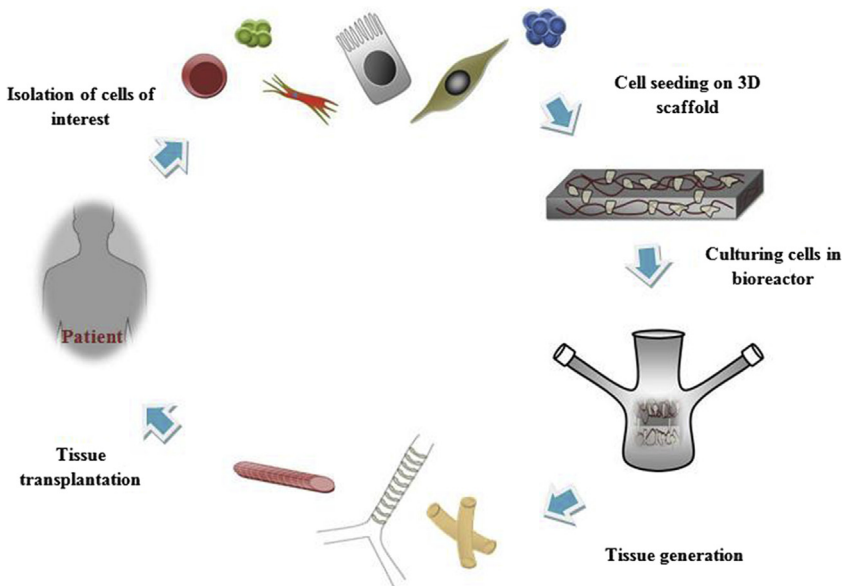

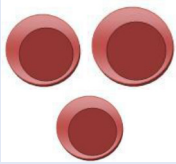
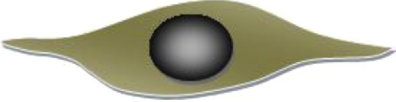

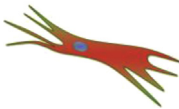


Fig. 1. General scheme for the process of tissue engineering.

Table 1
The characteristics of various cell sources that can be used in tissue engineering

Cell Source	Origin	Differentiation Capacity
Embryonic stem cells (ESC)	Blastocyst's inner cell mass	Cells of all 3 germ layers
		
iPS	Fibroblasts, hair follicle dermal papilla cells, umbilical vein endothelial cells, hepatocytes, melanocytes	Cells of all 3 germ layers
		
MSCs	Bone marrow, muscle, liver, umbilical cord blood, placenta and amnion, peripheral blood, pancreas, Wharton's jelly, brain, dental tissue, adipose tissue	Bone, cartilage, adipose tissue, muscle, neural, endothelial, insulin-producing cells
		
Very small embryonic-like stem cells	Bone marrow, cord blood, peripheral blood	Cells of all 3 germ layers
		
Direct conversion	Fibroblasts	Neurons, hepatocyte-like cells, multilineage blood progenitors, cardiomyocytes, macrophage-like cells
		
Terminally differentiated cells	Tissue of interest	—

followed by implantation. However, MACI uses an extra step in which the expanded chondrocytes are seeded into a 3-dimensional (3D) matrix made of porcine-derived mixed collagen (type I and III).³¹ Chondrocyte-seeded scaffolds are numerous and include hyaluronan-based scaffolds,³² bioresorbable poly(lactic coglycolic acid) polymers,³³ and agarose-alginate hydrogel,³⁴ among many others.³⁵ In general, the use of scaffold aims at replicating the in vivo conditions in which the cells survive. This approach allows for the following:

1. Proper cellular growth and differentiation
2. Maintenance of the chondrogenic phenotype of the cells
3. Balanced and homogeneous distribution of chondrocytes and cartilage formation ensuring mechanical stability^{36,37}

The tissue construct is thus more robust and capable of mimicking the crucial characteristics of the articular cartilage.^{38,39} Although ACI requires cells to be injected, in scaffold-based

Table 2
The main advantages and disadvantages of various cell sources that can be used in tissue engineering

Cell Source	Advantages	Main Disadvantages and Challenges
Embryonic stem cells	Give rise to any cell type, unlimited proliferation	Scarce supply, ethical restrictions, immune compatibility
iPS	Give rise to any cell type, avoid host/donor incompatibility, production of patient-specific cell types, no ethical restrictions	Avoiding accumulation of environmental DNA damage, avoiding genetic modifications when using viral integration, target cell purification, efficiency of reprogramming, time consumption and costs, optimizing cell source for reprogramming, incomplete overlap with ESCs
MSCs	Give rise to a wide variety of cells, widely distributed and found, certain sources accessible with minimal invasive procedures, no ethical concerns, immune-compatible	Differentiation potential differs depending on origin, MSC lineage commitment dependent on various parameters to be resolved, phenotypic changes by prolonged passaging
Direct conversion	Direct generation of cells from fibroblasts with no need to revert to pluripotency	Limited cell types can be produced, time consuming, require further studies for optimization
Terminally differentiated cells	No need to induce differentiation, cells of interest already present	Scarce supply, limited proliferation capacity, cannot act as cell sources for tissues damaged by tumors

techniques, the cell-based scaffold is sutured or glued to the damaged cartilage. Although MACI has shown beneficial outcomes,³¹ independent of the scaffold material used,^{24,31,40,41} the procedure has not yet been proven superior to ACI or other standard interventions.^{21,42–45} A recent systematic review asserted the need of more large-scale studies to dictate the optimal clinical application of MACI.⁴⁶

ACI's most reported adverse effect is hypertrophy of the flap used in sealing the implanted cells.² Other adverse effects include postoperative pain as well as scar formation and limited mobility and fibroarthrosis secondary to the arthrotomy.^{22,36,37} In addition, the need for a perifocal solid cartilage onto which the periosteal flap or collagen sheet would be fixed narrows the applicability of ACI to focal cartilage lesions.²² In contrast, scaffold-based MACI allows a better filling of the defect, is less technically challenging, has greater graft stability resulting in shorter recovery period, and can be used

in diffuse defects when grafts can be fixed directly into subchondral bone.^{2,22} Disadvantages of both techniques include cost, procedure complexity, and potential of chondrocyte dedifferentiation in culture into fibroblast-like cells.⁴⁷

More recently, tissue engineering has been applying more prolonged forms of 3D seeding. In MACI, chondrocytes are seeded for 3 days, after which the tissue is implanted. This seeding technique might constitute an insufficient time for tissue organization, extracellular matrix (ECM) deposition, and achievement of biochemical integrity, rendering the tissue fragile and incompetent. To that end, new methods are implementing longer culturing periods, extending up to 6 weeks. The longer duration permits ample time for chondrocytes to proliferate, mature, deposit their own ECM, and achieve functional standards of mechanical robustness.^{35,48} Aside from maintaining cells in their regular micro-environment of ECM, multiple confounding variables can impact the development and growth

of cells, especially in terms of maintaining and inducing cellular differentiation. As chondrocytes expand in culture to achieve an adequate number of cells, the cells lose their chondrogenic phenotype with each passage. Minimizing dedifferentiation can be attained by decreasing the number of passages, optimizing expansion medium components (ie, growth factors), 3D culturing,^{35,49–51} and exogenous mechanical stress.⁵² The use of growth factors for chondrocyte expansion is an ongoing field of research. FGF-2 has been shown to maintain chondrogenic phenotype, induce proliferation, and promote neocartilage with higher matrix content.^{53–55} Many other factors have been reported to play a pivotal role in chondrocyte proliferation and differentiation, including EGF, TGF- β 1, and BMPs, among others.^{56–60} Scaffolds used in cartilage tissue engineering are numerous and beyond the scope of this review. However, such scaffolds are generally divided into microporous (hydrogels) and macroporous scaffolds, each with its own advantages and disadvantages.³⁵ Biomimetic stimuli are also known to play integral roles in chondrocyte differentiation and development. A main exogenous stimulus in 3D culture is mechanical stimulation. Cartilage endures mechanical stress and continuous load bearing, and thus, the designed neotissue must be able to mirror this capacity and withhold regular joint loads. Chondrocytes are known to proliferate and produce more ECM in response to mechanical loads, such as hydrostatic pressure and dynamic compression, among others.^{52,60–65} However, applying mechanical stimuli in a consistent manner and in large scale remains a technical challenge.³⁵ Other relevant exogenous stimuli include hypoxia, which increases ECM deposition and improves the biochemical properties of collagen,^{66,67} pH,⁶⁸ direct perfusion,⁶⁹ the use of chemicals and enzymes,^{35,70} and coculturing with mesenchymal stem cells (MSCs).^{71,72}

Scaffold-free technologies rely on culturing chondrocytes at high densities. Over a couple of weeks, cells secrete ECM while adhering together,^{73,74} which results in forming the final robust neotissue. Stimulation of these constructs with exogenous stimuli has been shown to result in tissue with similar properties and qualities of normal *in vivo* cartilage.^{2,67,70,75} Clinical trials are being conducted on both Chondrosphere (Teltow, Germany) and RevaFle (St. Louis, MO, USA), the 2 main scaffold-free constructs.

Stem Cell-based Tissue Engineering

Chondrocyte-dependent cartilage regeneration remains costly and invasive and carries the risk

of dedifferentiation into a fibroblast-like stage. Thus, stem cells have been explored as an alternative source of cells.

Mesenchymal stem cells

MSCs hold a true promise for tissue engineering. MSCs are capable of differentiating into bone, cartilage, adipose tissue, muscle, neural, endothelial, and insulin-producing cells.^{76–80} MSCs retain their multilineage differentiation potential in culture with an extensive proliferative ability in an uncommitted state.⁸¹ “Mesenchymal stem cells” is a terminology used to refer to stromal cells with specific properties. The International Society for Cellular Therapy proposed a standard set of rules to define the identity of these cells⁸²:

1. MSCs should be plastic adherent, forming fibroblast-like colonies
2. MSCs should be able to differentiate into various specialized cell lineages
3. Ability to express defined cell surface marker profiles

Although there is no definite set of markers, the agreed upon markers of MSCs include specific immunophenotypic marker combinations (CD73, CD90, and CD105) and lack both hematopoietic markers (CD11b, CD19, CD34, and CD45) and class II major histocompatibility complex (MHC) molecules (HLA-DR).⁸² MSCs have various sources such as bone marrow (BM-MSCs), muscle, liver, synovium, umbilical cord blood (UC-MSCs), placenta and amnion, peripheral blood, pancreas, dental tissue, adipose tissue (ASCs), and urine.^{79,83–88} The wide variety and large number of sources, capability of differentiating into various types of specific-cell lineages, minimal ethical concerns, and immune-compatibility make MSCs a robust viable option in tissue engineering and regenerative medicine.

Bone marrow mesenchymal stem cells

BM-MSCs are the most studied MSCs for cartilage tissue engineering. BM-MSCs from a diseased individual have been shown to produce cartilage similar to that of healthy MSCs donors and maintain the chondrogenic phenotype in the presence of TGF- β .^{37,89} As well, BM-MSCs have been shown to maintain an anti-inflammatory state in diseased organs.⁹⁰ In general, these cells have been implemented in the clinical setting in 2 ways:

1. Intra-articular injection of the cells
2. Using an MACI-like approach

The beneficial outcomes of intra-articular injection have been reported in preclinical studies, case series, as well as randomized studies.^{91–97} The MACI-like technique has also shown promising results, albeit less evidence and support in the literature. Culturing BM-MSCs on scaffolds before implantation has shown good functional outcomes in several studies.^{98–102} However, some studies also noted no benefit of BM-MSC's administration per se when used as an add-on to the current standard procedure of microfracture. Nevertheless, the beneficial effect stems from the minimal invasive technique used in the BM-MSC group.¹⁰³

In summary, the use of BM-MSCs has been showing substantial promise. Direct injection of BM-MSCs into diseased cartilage has shown beneficial outcomes comparable to ACI, with the added benefit of being less costly and avoiding the risk of an additional surgery and donor site morbidity. However, many parameters still need to be optimized, including dosing regimens, and results of current and further trials must be analyzed to ensure safety of MSCs, effectiveness over the long-term and comparative efficacy to other available treatments.

Umbilical cord derived mesenchymal stem cells

Umbilical cord blood has been shown to contain stem cells with mesenchymal properties^{104,105} capable of differentiating into various cell types including chondrocytes.^{106,107} Collection of umbilical cord derived MSCs (UC-MSCs) is noninvasive and relatively easy, with not much of an ethical debate generated.¹⁰⁸ To date, no human clinical trial was conducted to assess the efficacy of cartilage generated using UC-MSCs. However, results of a limited number of preclinical studies seem encouraging. In one study, using UC-MSCs with a hyaluronic acid hydrogel composite in minipigs resulted in a superior and more complete hyaline cartilage regeneration than the control group.¹⁰⁹ Another study using rat models also showed significant improvement in the knee receiving UC-MSCs compared with the contralateral one.¹¹⁰ Although UC-MSCs are showing positive results in preclinical trials, it is still too early to draw a conclusion, especially with the lack of human clinical trials.

Adipose tissue-derived mesenchymal stem cells

ASCs have been regarded as a desirable cell choice for various reasons:

1. Readily accessible
2. Availability in large quantities

3. Capability of differentiation similar to BM-MSCs
4. Lack of immunogenicity
5. Anti-inflammatory properties
6. Minimal ethical considerations^{111–113}

In a study of 18 patients, intra-articular injection of ASCs resulted in improved function and pain of the knee joint with documented regeneration of hyaline-like articular cartilage.¹¹⁴ The beneficial effects of ASCs on cartilage regeneration were also evident in 3 other trials, with a total of 133 patients.^{115–117} One of the studies found improved results of scaffold-based ASCs compared with ASCs injection alone.¹¹⁵ Other early studies have shown improvement in validated outcomes scores and pain scores but have not shown evidence of cartilage regeneration, one of the primary goals of stem cell technology. The feasibility and positive outcomes of ASCs injection were also documented in a study of an elderly population with cartilage healing, functional improvement, and pain reduction.¹¹⁸ Similar to BM-MSCs, although initial results are encouraging, more research and trials should be invested in this promising technology.

Peripheral blood-derived mesenchymal stem cells

Peripheral blood has been found to be a source of MSCs capable of differentiating into chondrocytes.¹¹⁹ Even though limited in number, the effect of PB-MSCs on cartilage repair has been largely positive in all clinical trials conducted so far. The earliest study was conducted in 2011 on 5 patients, showing the proof of concept of using PB-MSCs for cartilage repair.¹²⁰ Following that, 4 more clinical trials were conducted,^{121–124} demonstrating beneficial effects with clinical improvement and histologic evidence of substantial deposition of chondrogenic ECM.

Synovial-derived mesenchymal stem cells

In vitro and preclinical studies had shown the differentiation capacity as well as the beneficial effect of synovial-derived MSCs on cartilage repair.^{125–128} Human trials however had been limited. In one study, clinical outcome was improved, and documented healing was observed on MRI and second-look arthroscopy.¹²⁹ Interestingly, the second trial showed a significant improvement using synovial-derived MSCs compared with MACI.¹³⁰ However, this trial had a relatively small sample size of only 14 participants.

Other mesenchymal stem cells

Other tissue sources have been reported to harbor cells with chondrogenic differentiation potential.¹³¹ These other tissue sources include dermal stem cells,^{132,133} muscle-derived MSCs,¹³⁴ placenta-derived MSCs,¹³⁵ ear elastic cartilage,¹³⁶ and periosteum.^{137,138}

Induced Pluripotent Stem Cells

Induced pluripotent stem cells (iPS) are autologous, somatic cells that undergo nuclear reprogramming into a primordial, embryonic stem cell-like state.¹³⁹ iPS cells have the hallmarks of ES cell, including the following:

1. Morphology
2. Unlimited self-renewal
3. Expression of key pluripotency genes
4. Normal karyotype

In addition, human iPS cells have been proven to undergo functional differentiation into specialized cell lineages of all 3 embryonic germ layers. Reprogramming aims to induce differentiated cells to reverting to pluripotency. Once pluripotency is achieved, differentiation into almost any cell type can be achieved.¹⁴⁰ The initial description of generating iPS was from Yamanaka in which introducing only 4 transcription factors (Oct3/4, c-Myc, Sox2, and Klf4) reprogrammed mouse adult fibroblasts into a pluripotent state.^{141–143} Following that, a variety of cells were used to induce pluripotency using different methods, including hair follicle dermal papillae,¹⁴⁴ umbilical vein endothelial cells,¹⁴⁵ hepatocytes,¹⁴⁶ melanocytes,¹⁴⁷ adipose tissue,¹⁴⁸ peripheral blood cell,^{149,150} and many others.¹⁵¹ iPS were shown to differentiate into cartilage in vitro and actually had proven beneficial effect in preclinical studies.^{152–154} Although promising, evidence supporting iPS is still in an early stage compared with other cell sources. Many issues need to be resolved, including the differentiation capacity and chondrogenic phenotype in the long run, the potential for teratogenesis, resolving any carry-over undesired “epigenetic memory”¹⁵⁵ and further in vivo testing.

DIRECT LINEAGE CONVERSION

More recently, scientists were able to induce cell-to-cell differentiation directly, bypassing the need to induce a pluripotent state. Direct conversion currently uses fibroblasts as the cell source and has been shown to be able to produce macrophages,¹⁵⁶ neuronal cells,^{157–160} hepatocytes,¹⁶¹ multilineage blood cells,¹⁶²

and cardiomyocytes.^{163,164} Fibroblasts have also been directly converted into chondrocytes with documented chondrogenic ECM deposition.^{165,166} In one pioneering study implementing direct conversion using cell sources other than fibroblasts, placental-derived cells were used for direct conversion into chondrocytes.¹⁶⁷ The advent of transdifferentiation is certainly a critical step in the advances of tissue engineering; however, further research and investigation are required before being able to take it from the bench side to rigorous in vivo studies.

SUMMARY

This review focused on tissue engineering techniques for cartilage repair that uses cell sources. However, other cell-free techniques are already being applied for cartilage repair. The technology of tissue engineering has witnessed substantial advancements and innovations in recent years and carries significant potential for treating cartilaginous disorders. Although much work is still required to truly develop and mimic the native human cartilage with its various aspects, this goal is much closer to reality with each day.

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