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## **Cell-Based Therapy for Human Osteoarthritis**

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## 1. Introduction

Articular cartilage has a function to smooth the movement of the joints and to decrease the coefficient of friction. Recently, it has been reported that "lubricin," a mucinous glycoprotein encoded by the *PRG4* gene, provides boundary lubrication in the articular joints [1]. Also, the articular cartilage has a role of shock absorber against an external force. The articular cartilage is hyaline cartilage composed of water (approximately 70%), cell (less than 3%), and abundant extracellular matrix (approximately 20%) such as type II collagen and proteoglycan. The articular cartilage is highly differentiated avascular tissue, and blood vessels, nerves, and lymphatic vessels are not present in the articular cartilage of adults. Based on the above, it is well known that damaged articular cartilage has a very limited capacity for self-repair. Even minor injuries may lead to progressive damage and result in osteoarthritic joint with significant pain and disability.

In 1989, it was reported that cartilage defect could be repaired with cultured chondrocytes in animal experiments in rabbits [2]. Based on this result, Brittberg et al. [3] performed clinical application for humans of autologous chondrocyte transplantation in 1994. However, some problems have been pointed out in this surgery. One was the possibility of dedifferentiated of cultured cells, which decreased matrix production ability because of monolayer culture. Another was the uneven distribution of injected chondrocytes caused in part by leak of the cell suspension from the periosteum covering the cartilage defect. To solve these problems, Ochi et al. [4] devised the use of atelocollagen as a scaffold: implantation of three-dimensional cartilage-like tissues using cultured autologous chondrocytes embedded in atelocollagen gel. This method has been currently used as a clinical application for osteochondritis dissecans since 2012 [5]. However, there is yet no clinically approved cell-based strategy for treatment of osteoarthritis (OA)-based cartilage lesions. Basic researchers and clinicians are focusing on alternative methods for cartilage repair, aiming to regenerate OA cartilage tissues. Cell-based



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therapy is an attractive biological method, and its studies have progressed in accordance with the development of tissue engineering.

## 2. Cell-based therapy for OA

Cell-based therapies using various cell types such as the chondrocytes or the bone marrow have been researched conventionally. Autologous chondrocytes are actually in clinical application for cartilage defects, and the surgical procedures such as marrow stimulation have also been performed for the purpose of cartilage repair. Although short-term results of these methods are good, there remains in doubt about long-term results. Mesenchymal stem cells (MSCs) are harvested from different sources such as the bone marrow, synovial tissue, and adipose tissue and have multilineage potentials. Recently, research in cartilage tissue engineering focuses on the use of MSCs as an alternative to autologous chondrocytes. Furthermore, induced pluripotent stem (iPS) cells or Muse cells might overcome the disadvantages of MSCs: insufficient number of cells, cell harvesting procedures with pain, and unstable differentiation potential of cells.

The regeneration of hyaline cartilage provides to improve the symptoms and ultimately prevent or delay progression to osteoarthritic joints. Cell-based therapies have been increasingly applied because they have the potential to regenerate the cartilage tissues.

## 2.1. Chondrocyte

## 2.1.1. Autologous chondrocyte implantation

Autologous chondrocyte implantation (ACI) was first reported in 1994 for treatment of focal cartilage defects in the tibiofemoral and patellofemoral compartments [3]. Since this report, chondrocyte-based therapy has become to be expected; a periosteal cover (first-generation ACI), a collagen-membrane cover (second -generation ACI), and a variety of three-dimensional scaffolds (third-generation ACI) are used for the methods of fixation. In these methods, arthrotomy and a two-stage surgical procedure are used. Long-term durability and success as long as 11 years of follow-up periods have been reported [6–13]. ACI is the first articular cartilage repair method using tissue engineering, but there is a problem that a sufficient number of cells cannot be secured by the case. Its usefulness is still under discussion.

## 2.1.2. Matrix-induced autologous chondrocyte implantation

A variation of the original periosteum membrane technique is matrix-induced autologous chondrocyte implantation (MACI). MACI membrane consists of a porcine type I/III collagen bilayer seeded with chondrocytes and MACI can promote hyaline-like cartilage repair. The technique of MACI procedure can eliminate many problems of first- or second-generation ACI, and the cell-seeded membrane can be implanted over a less inaccessible area or at osteochondral junctions because of its adhesive property [14]. Meyerkort et al. reported that both MACI and tibial tubercle transfer (TTT) using the Fulkerson technique were used to treat cartilage

defects in the patellofemoral joints and provided a durable graft on 5-years resultant with clinical improvement [15–17].

## 2.2. Bone marrow

Marrow stimulation techniques such as abrasion arthroplasty, drilling, and microfracture penetrate the subchondral bone and induce the formation of fibrocartilage repair tissues [18]. Although these methods were performed traditionally, it has been shown recently that bleeding from the bone marrow resulted in the supply of cytokines, osteoprogenitor cells, and chondroprogenitor cells. Also, there have been many reports related to induction of MSCs by bone marrow stimulation techniques. Clinically, although excellent short-term outcomes have been reported after bone marrow stimulation, the durability of marrow-stimulated repair tissues has shown the tendency to functional decline with further follow-up.

## 2.2.1. Abrasion arthroplasty

In 1986, Johnson [19] reported about achievement of abrasion arthroplasty, removing dead bone superficially and providing vascularity tissues for blood clot attachment. According to this method, subsequent fibrocartilage formation was maintained integrity for up to 6 years. Sansone et al. [20] reported a 20-year follow-up of abrasion arthroplasty, with a positive functional outcome of 67.9%.

### 2.2.2. Multiple perforation (drilling)

In 1959, Pridie [21] reported about a method for multiple perforation to subchondral bone using a drill with a 6-mm diameter. After partial weight bearing for 6 weeks, holes drilled were filled with fibrocartilage. However, recent reports related to medial opening-wedge high tibial osteotomy suggest that subchondral drilling is not necessary because there is no significant difference in the formation of fibrocartilage with or without subchondral drilling [22].

## 2.2.3. Microfracture

Microfracture is common procedure for cartilage repair, which produces a small fracture of the subchondral bone using awls to penetrate eburnated bone to promote blood flow to the bony surface. There is a report that short-term results were good, but 38.1% proceeded to total knee arthroplasty (TKA) in a 6.8-year follow-up [23]. In other papers, the survival rate was 88.8% at a 5-year follow-up and decreased 67.9% at a 10-year follow-up [24, 25].

#### 2.3. Mesenchymal stem cell

Nucleated cells in the bone marrow are mostly hematological cells, which float when they are cultured. However, some of the cells in the bone marrow adhere to culture dishes *in vitro*, proliferate itself, and form colonies. Thus, adherent cells are regarded as bone marrow mesenchymal cells (BMMCs). In 1974, Friedenstein et al. [26] reported that osteochondral progenitor cells were present in BMMCs, and in 1999, Pittenger et al. [27] reported about the

pluripotency of BMMCs, named MSCs. Currently, it is well known that MSCs are adult stem cells and have the possibility of differentiating into multiple cell types, including adipocytes, chondrocytes, osteocytes, and cardiomyocytes [28].

#### 2.3.1. Bone marrow MSC

Articular cartilage is insufficient for the capacity of cartilage repair, and the damaged cartilage tissues are not restored in complete hyaline cartilage in adults. We reasoned that the chondroprogenitor cells supplied to the cartilage defects are not sufficient. Then we have focused on the BMMCs, which might include MSCs, to supply sufficient chondroprogenitor cells to cartilage defects [29]. In our study in rabbits, BMMCs, which had a fibroblastic morphology and pluripotency for differentiation, were isolated from the bone marrow of the tibiae of rabbits, grown in monolayer culture. The autologous cells were then implanted into fullthickness articular cartilage defects in the knee joints of each rabbit. Advantages of this method included the use of autologous cells and absence of immunoreactivity. Furthermore, we investigated the efficiency of cartilage-derived morphogenetic protein 1 (CDMP1) genetransfected autologous BMMCs for cartilage repair in a rabbit cartilage defect model [30]. CDMP1, a member of the transforming growth factor- $\beta$  superfamily, is an essential molecule for the aggregation of mesenchymal cells and acceleration of chondrogenic differentiation. BMMCs were isolated from the bone marrow of the tibiae of rabbits, grown in monolayer culture, and transfected with the CDMP1 gene or a control gene (GFP) by a lipofection method. During in vivo repair of full-thickness articular cartilage defects, cartilage regeneration was enhanced by the implantation of CDMP1-transfected autologous BMMCs (Figure 1). The defects were filled with hyaline cartilage, and the deeper zone showed remodeling to subchondral bone over time. The repair and the reconstitution of zones of hyaline articular cartilage were superior to simple BMMC implantation. The histological score of the CDMP1transfected BMMC group was significantly better than those of both control BMMC group and empty control group (Tables 1 and 2). Our studies suggest that the modulation of BMMCs by factors such as CDMP1 allows enhanced repair and remodeling compatible with hyaline articular cartilage.

## 2.3.2. Synovial MSC

Sekiya et al. [31] previously reported that MSCs in synovial fluid from anterior cruciate ligament injury, meniscus injury, or patients with OA were much more than those from healthy volunteers and increased according to postinjury period or severity. The MSCs in synovial fluid are considered to be derived from synovial tissue and are positive for CD44, CD73, and CD90, which are markers of MSCs, and negative for CD34 and CD45, which is a marker of hematopoietic stem cells and leukocyte progenitor cells, respectively. Intra-articular injection of the synovial MSCs promoted meniscus regeneration and protected articular cartilage by arthroscopic and histological observations in pig [32], rat [33], or porcine [34] massive meniscal defect models. We research for synovial fluid cells that are not accompanied by pain in the cell harvest and describe about its advantage in the latter part of this manuscript.



**Figure 1.** Representative histological appearance of the defects after 4 weeks. (A–J) Safranin-O/fast green staining. (A–C) Empty control group. (D–F) Left knees of GFP-transfected BMMC group. (G–I) Right knees of CDMP1-transfected BMMC group. (D and G, E and H, F and I) Bilateral knee specimens from the same rabbits. (J) Higher magnification of I. (K) Immunohistochemical staining specific for type II collagen. (L) Immunohistochemical staining specific for type I collagen. (A–L) Scale bar is 500 µm.

#### 2.3.3. Adipose-derived MSC

Adipose tissues contain various cells such as blood cells, endothelial cells, and smooth muscle cells, in addition to adipocytes. Adipose tissues are also rich in microvasculature which adjoins with MSCs. Adipose-derived MSCs (ASCs) can be established by following method. Subcutaneous or visceral adipose tissues are minced and treated with type I collagenase. Then infranatant cells are centrifuged at low speed, and the cell pellet is placed in a flask. ASCs propagate themselves rapidly. Currently, two clinical trials for humans, which are the intra-articular injection for OA in France and the intravenous administration to rheumatoid arthritis in Spain, have been undergoing.

## 2.4. Induced pluripotent stem cells

iPS cells have pluripotency and the potential for self-renewal similar to ES cells. Recent study has made it possible to generate integration-free iPS cells and to differentiate iPS cells toward chondrocytes [35]. As an alternative approach, chondrocytic cells can be induced directly from dermal fibroblasts without going through the iPS cell stage. In 2011, Hiramatsu et al. [35] generated *in vitro* polygonal chondrogenic cells from adult dermal fibroblast cultures by ectopic expression of reprogramming factors (c-Myc and Klf4) and one chondrogenic factor

(SOX9). Namely, this approach could lead to the preparation of hyaline cartilage directly from skin without generating iPS cells. Recently, Yamashita et al. [36] reported that hyaline cartilage was generated from human iPS cells in immunodeficiency rats and immunosuppressed minipigs.



\*Modified from the scale described by Pineda et al. [46] and Wakitani et al. [47].

<sup>+</sup>Total smooth area of the reparative cartilage compared with the entire area of the cartilage defect.

Table 1. Histological grading scale for cartilage defect\*

Interval until animals were killed (weeks)	No	Grade (points)							
	Cell and r	A. morphology natrix staining	B. Surface regularity	C. Integrati	on Subtotal (A–C)	D. Filling of defect a	E. Reconstitution of subchondral bone nd osseous connecti	Subtotal on (D–E)	Total
CDMP1 transfected	BMMCs	;							
2	10	6.2	0.7#	1.2	8.1#	0.8	2.6#	3.4#	11.5#
4	10	4.4	0.1#	0.7	5.2#	0.7	1.5	2.2	7.4#
8	10	4.6	0.3*,#	1.0	6.0*,#	0.7	1.1	1.8#	7.8*,#
GFP transfected BM	<b>/MCs</b>								
2	10	7.0	1.2	1.4	9.6	1.2	2.6	3.8	13.4
4	10	6.2	0.9	0.9	8.0	1.1	1.6	2.7	10.7
8	10	6.8	1.5	1.0	9.3	1.5	1.9	3.4	12.7
Empty control									
2	2	8.0	3.0	2.0	13.0	2.5	3.0	5.5	18.5
4	7	6.6	1.1	1.6	9.3	1.6	1.9	3.4	12.7
8	7	7.4	1.6	1.0	10.0	1.6	2.0	3.6	13.6

\*P < 0.05, when compared to the GFP group at corresponding time (Mann–Whitney U-test).

\*P < 0.05, when compared to the empty control at corresponding time (Scheffe test for multiple comparison).

**Table 2.** Results of the histological grading scale

#### 2.5. Multilineage-differentiating stress enduring (Muse) cell

As a novel type of pluripotent stem cells, Muse cells were recently reported as adult human MSCs without introducing exogenous genes, and they are present in mesenchymal tissues such as the bone marrow, adipose tissue, dermis, and connective tissue of organs [37–40]. In particular, Muse cells have been detected more abundant in adipose tissues than in other organizations [41]. Also, Muse cells have a low tumor-forming ability compared with embry-onic stem (ES) cells and a high efficiency of change to iPS cells by Yamanaka gene introduction [42]. They can migrate to damaged tissues by intravenous injection *in vivo*, spontaneously differentiate into cells compatible with the targeted tissue, and contribute to tissue repair. Thus, Muse cells will be expected to play important role in regenerative therapy by further studies.

## 3. MSCs in synovial fluid of human OA

In 2004, Jones et al. [43, 44] reported that the MSCs in synovial fluid in the inflammatory and degenerative arthritis, including OA, possessed high proliferative potential and could differentiate into several mesenchymal lineages. Aspiration of synovial fluid in the cases of hydrarthrosis caused by OA has the following great advantages: extremely simple technique, feasible during routine practice in outpatients, no need for local or general anesthesia for cell harvest, and effective usage of synovial fluid supposed to be discarded in the cases of hydrarthrosis.

#### 3.1. Potential of chondrogenic differentiation of synovial fluid cells

We investigated the possibility of chondrogenic differentiation of the cells derived from synovial fluid and compared with the BMMCs previously performed in human OA [45]. Synovial fluid was aspirated from 26 knee joints of outpatients with OA and those of six patients just before skin incision at TKA. Bone marrow was obtained from the femur before the insertion of the femur rod at the time of TKA. Each aspirated fluid was diluted in  $\alpha$ -modified Eagle's minimum essential medium ( $\alpha$ MEM), and mononuclear cells using Ficoll-Paque PLUS (GE Healthcare) were harvested and cultured. Primary passage cells were used for flow cytometry assay and for chondrogenic assay, total RNA was prepared from each pellet of cultured cells, and pellets were used for immunohistochemical staining.



**Figure 2.** A, B) Phase-contrast photomicrographs of cultured synovial fluid cells on day 6 (A) and day 28 (B) showing fibroblast-like morphology. On day 28, the culture dish in subconfluency. (C–E) Multipotency of the cultured synovial fluid cells. (C) Osteogenesis was shown by alkaline phosphatase staining and the expression of osteopontin messenger (m) RNA (*OPN*). (D) Chondrogenesis was shown by toluidine blue staining and the expression of type II collagen mRNA (*Col2a1*). (E) Adipogenesis was shown by oil red-O staining and the expression of PPAR<sub>γ</sub> mRNA (*PPAR*<sub>γ</sub>).

In the results, the morphology of the cultured synovial fluid cells was fibroblastic, similar to that of BMMCs. Also, the synovial fluid cells had an ability to differentiate into osteoblasts, chondrocytes and adipocytes (Figure 2). The cultured synovial fluid cells strongly expressed

CD13, CD44, and CD105 but lacked CD10, CD14, and CD45 in flow cytometry analysis. Both mRNA expression of aggrecan and type II collagen had an increasing tendency at day 21 compared with day 7. Also, the cell pellets derived from synovial fluid showed intense toluidine blue staining, indicating chondrogenic differentiation.

## 3.2. Potential of cartilage regeneration of synovial fluid cells

Synovial fluid was aspirated from the OA knees before 1 month of TKA and cultured *in vitro*. Degenerative OA cartilage was obtained at the time of TKA. Approximately  $5 \times 10^5$  autologous synovial fluid cells were labeled with Cell Tracker Green (CTG) (Invitrogen) in 200-µL αMEM and were transplanted gently on macroscopic degenerative tissues of OA cartilage. After10 min, medium was removed and changed into chondrogenic medium. One week later, the tissues were observed under a fluorescent microscope.



**Figure 3.** *Ex vivo* study using synovial fluid cells. (A) The formation of repaired tissue was shown by hematoxylin and eosin (HE) staining (Black arrows). (B) Magnified feature of A. (C) Repaired tissues and the surroundings of CTG-stained cells were weakly positive by safranin-O staining. (D) Fluorescent microscopy showed that CTG-labeled synovial fluid cells existed in repaired cartilage. (E) Magnified feature of D. (F) CTG-positive cells had a tendency to infiltrate into the original degenerative cartilage (White arrows). N.C.: Negative Control without CTG-labeled cells.

Histopathologically, degenerative tissues with transplanted CTG-labeled cells were weakly positive by safranin-O staining, which indicated that they were toward cartilage tissues (Figure 3). Fluorescent microscopy showed that CTG-labeled synovial fluid cells existed in the repaired

tissues, which indicated that the tissues were constructed of autologous transplanted cells and the synovial fluid cells had a tendency to adhere to the degenerative cartilage. Furthermore, they seemed to infiltrate into the original degenerative cartilage of OA.

#### 3.3. Cell-based therapy using synovial fluid cells

From previous and our current study, it has been recognized that synovial fluid in OA knee joints contain the adherent cells, and these cells have a potential of cell proliferation and chondrogenic differentiation *in vitro*. The primary culture of the human synovial fluid cells showed the formation of colonies of fibroblast-like cells, similar to those of BMMCs in both flow cytometry and real-time PCR analysis [34]. The infiltration of synovial fluid cells into the degenerative cartilage indicates that the possibility of attachment to OA cartilage in humans may promote the production of extracellular matrix and regeneration of hyaline cartilage. Further studies are need, but we expect the benefits of synovial fluid cells on OA cartilage tissues.

## 4. Conclusions

Many studies using various cell types for OA treatment are being performed. These short-term results appear mostly satisfactory, but there remains a problem that repaired tissues become fibrocartilage thereafter. Fibrocartilage leads to different biomechanical characteristics compared with hyaline cartilage and progresses to OA. MSCs based on self-repair and multilineage potentials provide to hyaline cartilage regeneration. In particular, bone marrow-derived MSCs are the most commonly used cell type for cartilage regeneration, but harvesting of the bone marrow is a painful procedure and has the risk of wound infection and sepsis. Alternatively, synovial fluid cells have great advantages and cartilage regeneration potential similar to bone marrow-derived MSCs. Naturally, long-term studies are needed whether repaired tissues are durable within the joint, but the use of synovial fluid cells may be expected to cartilage regeneration for OA therapy.

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