Clinical Orthobiological Approach to Acute Cartilage Injury: Pros and Cons

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Contents

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40.1 Introduction

Articular cartilage has the ability to absorb stress, create low friction and high resistance to wear, which provide smooth joint movement and weight-bearing capabilities. To enable these special properties, cartilage has a peculiar structure. Articular cartilage is composed of a small number of chondrocytes and extracellular matrix (ECM). Chondrocytes constitute approximately 1% of the cartilage tissue and play a vital role in maintaining a healthy ECM. The ECM consists of a network of collagen fibrils with proteoglycan. Type 2 collagen is the main component, with Type 9 and 11 constituting minor components. The structure of the articular cartilage is divided into four zones: the superficial, transition, deep, and calcified zone. Each zone has a different cell size, shape, number, and content, comprising different properties of ECM. The tidemark anchors cartilage tissue to the subchondral bone plate. Notably, cartilage has neither vascularity nor nerves, which make spontaneous repair difficult [1]. Thus, untreated cartilage defects, especially those greater than 1.5 cm in diameter, will eventually progress to osteoarthritis (OA). To prevent the progression of OA after cartilage injury, the diagnosis and choice of appropriate treatment in the acute phase of OA is crucial to the achievement of biological healing.

Acute cartilage injury occurs in association with joint trauma including sprain, dislocation, and fracture. In fact, not only cartilage defects

A. Gobbi et al. (eds.), *Bio-orthopaedics*, DOI 10.1007/978-3-662-54181-4_40

but also osteochondral fractures occur frequently, which means that both cartilage and subchondral bone conditions should be taken into consideration. The subchondral bone plate plays an important role in cartilage metabolism, and a damaged subchondral bone plate no longer maintains cartilage homeostasis, which subsequently leads to loss of cartilage proteoglycan and glycoprotein. The management of subchondral bone should be the focus of any cartilage repair strategy. Accurate diagnosis of acute cartilage injury is important, in order to avoid further cartilage damage and loss of biological healing. However, acute cartilage lesions are difficult to diagnose because symptoms are not specific and often masked by injuries to surrounding tissues, for example, ligamentous injury or other intra-articular pathologies [2, 3]. In addition, symptoms are often masked by more obvious and significant injuries like fractures. To diagnose acute cartilage injury, it is important to know its incidence, pathomechanism, and imaging features. Various therapeutic trials have been carried out to achieve better results than with conventional treatments.

40.2 Incidence of Cartilage Injury

Acute cartilage injury is often associated with joint injury including fracture, ligament injury, and dislocation. To be able to assess the extent of the cartilage injury, the incidence of joint-related cartilage injury should be understood. The incidence and location of the chondral/osteochondral injury in various types of fractures have been reported. Cadaveric studies have revealed that osteochondral fractures in the knee occur in the medial femoral condyle, in the position of both knee extension and lateral rotation, or in knee flexion with medial rotation. Tibial plateau lesions occur in knee extension and medial rotation at the medial plateau or in knee flexion and lateral rotation at the lateral plateau [4]. The incidence of isolated osteochondral fractures in acute knee injuries is reported to be approximately 4%, all as full-thickness lesions which generally occur with hyperflexion injury [5]. The incidence of articular cartilage lesions as identified on arthroscopy is up to 20% in patients with hemarthroses of the knee [6, 7]. The incidence of cartilage injury associated with ankle fracture is reported to be high. The incidence of lateral talar dome lesions in 50 patients undergoing surgical fixation of malleolar ankle fracture is approximately 38% [8]. Cartilage injury assessed by arthroscopy at open reduction internal fixation is up to 79% [9, 10]. Cartilage injury can be often seen in joint sprain, subluxation, and dislocation, including ligament injuries. In an ACL injury, bone bruising and cartilaginous damage to the lateral femoral condyle occur by valgus stress, causing a shearing force across the joint, and the incidence of osteochondral fractures with ACL injuries is reported to be as high as 80% [11, 12]. Patellar dislocation is also common with the occurrence of osteochondral fractures, with its incidence being approximately 70% [13, 14].

Articular cartilage injury in acute joint injury has been shown to occur frequently, so the existence of cartilage injury should be taken into consideration during the management of acute joint injury.

40.3 Diagnosis/Imaging

Diagnostic imaging plays an important role in the assessment of the extent, instability, and progression of the lesion [15]. Cartilage injury is poorly visualized by standard radiograph. Even an osteochondral fracture is not easily identified due to a small bone fragment associated with an articular cartilage fragment [16]. Standard arthroscopic radiography of the knee detected osteochondral lesions in only 32% of cases [14]. It is reported that up to 60% of lesions are missed on initial presentation after patella dislocation [17]. Osteochondral lesions in the talus are reportedly detected on radiograph in 69% of cases [18].

MRI and CT are superior to radiography for the detection of chondral/osteochondral lesions [19]. CT can detect small osteochondral fragments with high resolution images, but it is not able to depict bone marrow edema. On the other hand, MRI, especially short tau inversion

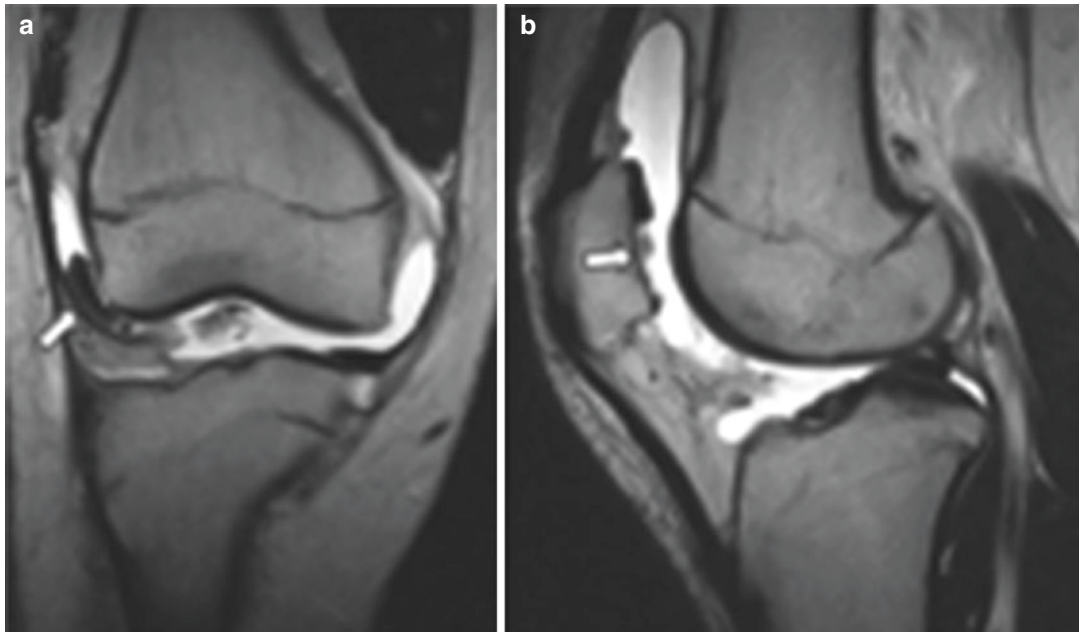

Fig. 40.1 Magnetic resonance imaging (MRI) of acute cartilage injury in patella. (**a**) Osteochondral fragment can be seen (*arrow*). (**b**) Cartilage defect on the patella (*arrow*)

recovery (STIR) sequence, can detect bone edema with highly sensitivity [20]. MRI can detect articular cartilage defects in the knee with 86% sensitivity and 97% specificity [21]. MRI can detect a femoral condyle lesion with the sensitivity and specificity of 86–93% and 72–88%, respectively [22]. Regarding osteochondral lesion of the talar dome, the MRI is able to detect them with 95% sensitivity and 100% specificity [23]. In addition to high sensitivity and specificity for the detection of chondral/osteochondral lesions, MRI has the advantage of detecting other soft tissue abnormalities that are often associated with chondral/osteochondal injuries. Moreover, MRI can evaluate the stability of a chondral/osteochondral fragment (Fig. 40.1). The sign of instability on MRI is the presence of a fluid signal interposed between the chondral/osteochondral fragment and the underlying bone, and extensive bone marrow edema at the donor bone and irregularity of the articular surface [24]. However, MRI might overdiagnose or overestimate the extent of a chondral/osteochondral lesion or the size of a fragment due to bone edema, which may be more difficult to treat [25, 26].

40.4 Treatment

Although it has been reported that smaller lesions do not develop into advanced arthritis, chondral defects tend to progress extensively, leading to early-stage osteoarthritis. Chondral/osteochondral defects are treated surgically in many cases. However, the time frame for surgical treatment for an osteochondral fragment in the acute phase is tight because a loose osteochondral fragment swells, causing further cartilage degeneration. Moreover, a loose osteochondral fragment can damage the other cartilage surfaces in the joint. The most ideal treatment is the reattachment of the osteochondral fragment to the donor site, which can anatomically restore the cartilage surface. In the case of the fragment being unsalvageable, it should be removed and the donor site resurfaced by several techniques including microfracture, osteochondral graft, and the tissue-engineering technique. However, such repaired tissue covering the donor site differs from native cartilage in terms of its histological and mechanical properties. Each procedure has the pros and cons, and appropriate procedure should be chosen (Table 40.1).

Table 40.1 Pros and cons of cartilage repair procedures

Cartilage repair procedure for acute cartilage injury	Pros	Cons
Fixation of osteochondral fragment	• Anatomical restoration by original cartilage surface	• Complications by fixation devices
Microfracture	• Quick, minimally invasive and short recovery time	• Replacement by non-hyaline cartilage tissue • Poor long term results
Cartilage Autograft Implantation System (CAIS)	• Replacement by chondrocytes and cartilage matrix without cell culture	• Harvesting normal cartilage
Juvenile particulated cartilage allografts	• Replacement by chondrocytes and cartilage matrix without cell culture and harvesting normal cartilage • One step procedure	• Potential risk of disease transmission • High cost • Inability to put the product back on the shelf once open
Autologous matrix-induced chondrogenesis (AMIC)	• No donor site morbidity • Possibility of all-transarthroscopic cartilage repair • Low cost compared to ACI	• Replacement by non-hyaline cartilage tissue • Influence of age-related MSC in donor site

40.4.1 Fixation of Chondral/Osteochondral Fragment

The large osteochondral fragment should be reattached whenever possible. It is reported that a mean fragment size of 436 mm^2 no longer responds to conservative treatment and that the prognosis of larger lesions is worse than that of smaller lesions [27, 28]. Fixation of osteochondal fragment can anatomically restore the articular cartilage surface. In a previous report about osteochondritis dissecans, it was revealed that the articular cartilage regenerated after fixation of an unstable lesion by histological analysis [29]. The osteochondral fragment can be fixed with metallic screws with countersunk heads, a bone peg, and bioabsorbable pins. Metallic screws may damage the opposite side of articular cartilage surface and the removal of these screws may also damage the articular cartilage [30]. Therefore, using a bioabsorbable implant to fix the osteochondral fragment has been popular [31, 32] (Fig. 40.2). Bioabsorbable implants are degraded and replaced by surrounding tissue, which leads to the biological healing of the lesions. However, several complications such as aseptic synovitis due to biological reactivity and back-out have been reported [33, 34].

When fixing the osteochondral fragment, healing of the lesion is expected to occur via the bone-to-bone healing. However, a purely cartilaginous fragment, without bone attached, rarely exists. In this case, the fixation of a large chondral fragment is quite challenging but worthwhile since it has the potential to achieve the biological healing. Several reports have described the successful repair of an isolated chondral fragment involving acute trauma and stress reaction, using bioabsorbable pins, autograft bone pegs, and suture anchors [35–37]. With or without bone attached, fixation of the chondral/osteochondral fragment should be the main method of treatment when reconstructing the native cartilage surface.

40.4.2 Microfracture

Microfracture is a common procedure to produce a fibrocartilage repair surface in small chondral/osteochondral fragments (Fig. 40.3). The subchondral bone in the defect is perforated to allow bleeding and to form a clot which contains mesenchymal stem cells. These cells differentiate into chondrocytes and fibrochondrocytes and then form a fibrocartilage to fill the defects. A matrix of fibrocartilage mainly consists of Type 1 collagen and other non-collagenous proteins, which means inferior mechanical properties compared to normal articular cartilage [38]. Due to these properties, repaired tissue in the defect gradually deteriorates and long-term results of microfracture have been reported to be poor [39].

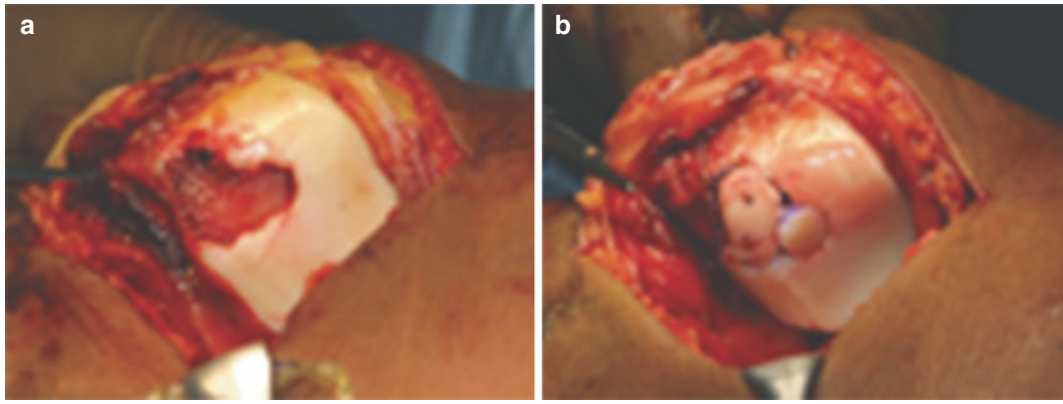

Fig. 40.2 Articular cartilage injury of patella in accordance with patella dislocation. (**a**) Osteochondral defect on the patella. (**b**) Osteochondral fragment was reattached using bioabsorbable pins, and osteochondral graft was implanted into the severe damaged area

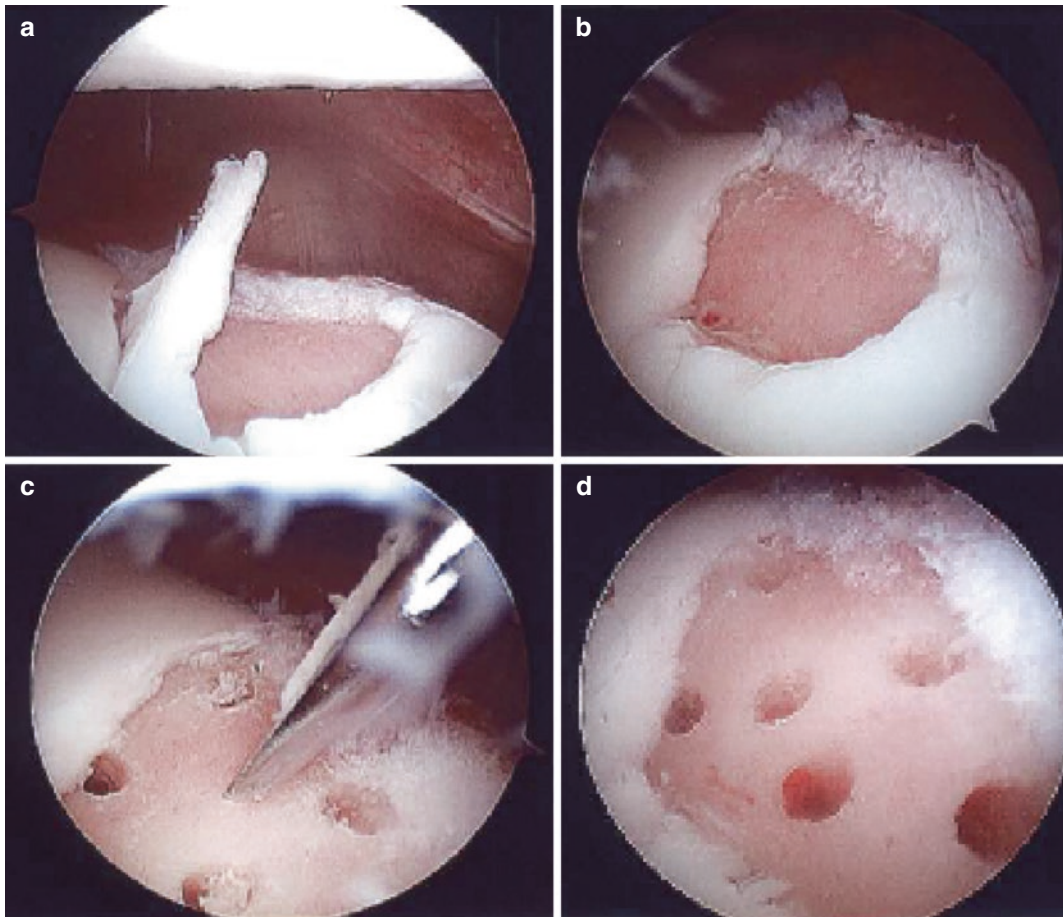

Fig. 40.3 Microfracture for small cartilage defect at lateral femoral condyle. (**a**) Cartilage defect. (**b**) After the removal of cartilage fragment. (**c**) Drilling using K-wire. (**d**) After the drilling

Recently, the procedure of microfracture has been changed to improve the clinical outcome regarding the depth and diameter of the channel for marrow access, called second-generation microfracture. The penetration depth ranges from 2 to 4 mm, being deeper than that of conventional microfracture, which hardly reaches the marrow-rich subchondral spogiosa below the sclerotic subchondral bone plate [40]. However, a new microfracture procedure, which is able to create repaired tissue with the native cartilage properties, is also required.

Only if the chondral/osteochondral fragment is severely damaged an alternative procedure is used, such as osteochondral autograft or allograft, or autologous chondral implantation (ACI) for large cartilage defects [41]. For the treatment of cartilage defects, cell therapies using chondrocytes, MSCs, and other cell sources have been used [42, 43]. However, in the acute phase of cartilage injury, a point-of-care approach including the use of an "off-the-shelf" product is desirable. In addition to the conventional methods, cartilage fragment implantation without culture, a combination of various materials, as well as biological factors are applicable to accelerate and improve the repair process.

40.4.3 Minced Cartilage

Autologous chondrocytes may result in good repair tissue for the cartilage defect. However, the procedure with cell culture such as ACI is not appropriate for an acute cartilage defect. Using a cartilage fragment is an alternative procedure to repair a cartilage defect using chondrocytes without cell culture. It is reported that coverage with minced cartilage from a large cartilage fragment for an acute cartilage defect achieves good clinical results [44]. In this report, a large chondral fragment was retrieved and minced into multiple small fragments (<1 × 1 × 1 mm) using a scalpel. The cartilage defect was debrided and drilled into the subchondral bone using a 1.4 K-wire. Then, minced cartilage fragments were placed into the cartilage defect and fixed using fibrin glue. This concept was already proposed in the 1980s, and the procedure using minced cartilage has been modified and developed in combination with various materials to become CAIS (Cartilage Autograft Implantation System) [45, 46]. Moreover, the juvenile allograft cartilage fragment has become available recently as an "off-the-shelf" product. In an in vitro study, chondrocytes have been proven to grow from cartilage fragments and the cartilage matrix [47, 48]. As for the size of cartilage fragment, a comparative study with fish scales (diameter 8 mm, thickness 0.3 mm), cubes with 2 mm side, cubes with 1 mm side, and cartilage paste (<0.3 mm) revealed that cartilage paste exhibits good ECM production compared to other groups [49]. The optimum degree of chondral fragmentation for ECM production should be considered when mincing the cartilage fragment.

A clinical randomized control trial showed that at 2 years follow-up, the CAIS group showed significantly better results in the International Knee Documentation Committee (IKDC) score and Knee injury and Osteoarthritis Outcome Score (KOOS) when compared to the microfracture group [50]. In this study, the surgical procedure of CAIS is as follows. The articular cartilage is arthroscopically harvested from a minimal load-bearing area. Then, the harvested cartilage is minced into 1–2 mm pieces. The minced cartilage is dispersed onto the biodegradable scaffold and fixed by fibrin glue. The scaffold is trimmed to adjust to the debrided cartilage defect and is implanted with the fixation using bioabsorbable staples.

Juvenile particulated cartilage allografts have been available for clinical use since 2007. Numerous clinical results of their use for cartilage defects of the knee and ankle joint have shown good outcomes at the short-term follow-up [51–53]. Although this procedure could successfully restore cartilage defects, there are several disadvantages including the potential risk of disease transmission, high cost, and the inability to preserve the product for any length of time once open [52]. Cartilage repair using minced cartilage, CAIS, and Juvenile-particulated cartilage allografts is a relatively novel procedure, so clinical data to support this procedure is limited.

Table 40.2 Pros and cons of biological alternatives

Biological alternatives	Pros	Cons
Bone marrow aspirate concentration (BMAC)	• Easy harvesting and processing • Anabolic effects on chondrocytes by growth factors • Anti-inflammatory effects • Possibility of arthroscopic implantation with scaffold	• Amount of the aspirate not yet unclear • Need of scaffold not yet clear • Influence of host condition not yet clear
Platelet rich plasma (PRP)	• Easy preparation and delivery technique • Stimulation chondrocytes proliferation and synthesis of collagen and proteoglycans • Anti-inflammatory effects • Nociceptive effect	• Optimal platelet concentration, leukocyte content, growth factor and cytokines profile and yet clear • No standardized dosing protocol • Influence of host condition not yet clear

However, this procedure has the potential to be a good option to repair acute cartilage defects.

40.4.4 Microfracture with Biological Augmentations

Microfracture is widely recognized as a first-line procedure for cartilage repair although it has limitations regarding lesion size and long-term functional improvements. To enhance the results of microfracture, several procedures in combination with the collagen scaffold and biological alternatives, such as platelet-rich plasma (PRP) and bone marrow aspirate concentration (BMAC) have been developed and their clinical results are displayed in Table 40.2. These one-step procedures may also be applied for acute cartilage injuries.

40.4.5 Autologous Matrix-Induced Chondrogenesis (AMIC)

Autologous matrix-induced chondrogenesis (AMIC) has emerged as a relatively new technique modification of microfracture with a porcine collagen scaffold [54, 55]. The indications of AMIC are basically as follows: focal chondral or osteochondral defect with outerbridge classification grade 3–4 with a defect size of approximately 1.0–8.0 cm^2 and patient age of 18–55 years old. The microfractured cartilage defect is covered with collagen scaffold to allow for the ingrowth of MSCs from the subchondral bone into the scaffold, which induces differentiation into the chondrogenic lineage. AMIC has several advantages such as no donor-site morbidity, the possibility of all-transarthroscopic cartilage repair, and low cost compared to ACI. New trials using polyglycolic acid-hydroxyapatite (PGA-HA) scaffolds instead of porcine collagen scaffold have been conducted [56, 57]. Good clinical results of AMIC in mid-term follow-ups have been reported [58, 59].

40.4.6 Bone Marrow Aspirate Concentration (BMAC)

MSC has been well recognized as an attractive cell source to regenerate repaired tissue due to its ability to multi-differentiate [60]. However, MSC only represents 0.0001–0.01% of mononuclear cells in bone marrow aspirates [61]. BMAC is commonly produced by the concentration of the bone aspirates. BMAC has plenty of growth factors including the platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), and bone morphogenetic proteins (BMP)-2 and BMP-7, which have anabolic and anti-inflammatory effects [62]. Good clinical outcomes using BMAC for focal cartilage defect (>3 cm^2) have been reported [63]. BMAC is used in combination with microfracture and scaffold including collagen I/III membrane although some cases omit the microfracture technique [64, 65]. Although BMAC is one of the most attractive sources for cartilage defect repair, several aspects such as safety, amount of aspirate, and scaffold requirement need further exploration.

40.4.7 Platelet-Rich Plasma (PRP)

Autologous platelet-rich plasma (PRP) has been reported as having plenty of cytokines, growth factors, and inflammatory mediators, which can stimulate the healing of cartilage, bone, and other soft tissues. Due to these properties and their easy administration, PRP has been widely used for the treatment of musculoskeletal disorders [66]. Since several studies revealed that PRP is able to stimulate chondrocyte proliferation and increase their synthesis of collagen and proteoglycans, the application of PRP for osteochondral pathologies (including osteochondral lesion and osteoarthritis) has increased [67, 68]. In addition, PRP has anti-inflammatory and nociceptive effects for OA.

Although a range of PRP preparation methods have been reported, all methods are relatively easy and growing interest in PRP enables us to use the several commercially available PRP preparation kits. With this availability of PRP preparation, simple-and-easy delivery techniques, such as an intra-articular injection of PRP for osteochondral pathologies, is a notable advantage in clinical use. Indeed, the majority of studies using PRP for osteochondal pathology is for osteoarthritis. Overall, clinical scores improved in short-term although it remains unclear whether these clinical benefits can be maintained. Some previous reports on focal cartilage lesions of the knee and talus using PRP showed short-term benefits [69]. In the management of acute cartilage injury, administration of PRP as an adjunct to surgical treatment may provide a better clinical outcome. However, several problems still remain. Optimal platelet concentration, leukocyte content, growth factor, and cytokines profile, as well as influence of the host condition require elucidation. Moreover, a standardized dosing protocol should be established. Further investigation to accumulate evidence on PRP rationale is required.

40.5 Future Perspective

To improve the conventional methods or to develop a more efficient treatment for acute cartilage injury, several animal studies have been conducted. For acute cartilage injury, "point-of-care" procedures are desirable so that growth factors and gene therapy can be focused on.

Growth factors have potent roles with the stimulation of cell proliferation and differentiation through the specific binding of transmembrane receptors with target cells [70]. The effects of growth factors on cartilage repair have been investigated due to their strong anabolic effects. Among the growth factors, the transforming growth factor-β (TGF-β) super family, the fibroblast growth factor (FGF) family, and the insulin-like growth factor (IGF) have been well investigated. In the TGF-β family, TGF-β1, 2, and 3 and bone morphologic proteins (BMP) 2, 4, and 7 play an important role in chondrogenesis and cartilage homeostasis regarding cartilage repair. TGF-β1, 2, and 3 are recognized as a potent stimulators of chondrogenesis [71]. An in vivo study demonstrated that using TGF-β1 in conjunction with a calcium alginate bead scaffold was more successful in repairing the osteochondral defect than the scaffold alone [72]. However, it has been reported that an intra-articular injection of TGF-β may cause synovial fibrosis and endochondral ossification [73]. It should not be forgotten that TGF-β has a multifunctional role in various cells, thus efficient cartilage defect application systems are needed.

The BMP family also has similar chondrogenic effects to TGF-β. Therefore, application of BMPs for cartilage repair has been examined. Administration of BMPs into the cartilage defect, when combined with a scaffold such as alginate gel and collagen sponge, promotes an effective cartilage repair [74–77].

IGF-1 is an anabolic cartilage factor, which plays an important role in cartilage homeostasis [77]. In vivo studies have shown that administration of IGF-1 can result in good repair tissue in the cartilage defect but that its beneficial effect is increased when combined with other growth factors such as TGF-β and BMPs [78, 79]. To improve cartilage repair, further investigation into the combination of IGF-1 with other growth factors is needed.

The FGF family also plays an important role in cartilage homeostasis. Among the FGF family,

several in vivo studies have shown that FGF-2 has the potential to promote good cartilage repair due to its potent mitogenic effect on MSCs and chondrocytes [80]. Notably, administration of FGF-2 has been found to improve not only cartilage repair but also the subchondral bone condition [81, 82]. However, several in vivo studies reported that FGF-2 has the potential to induce OA-like features in chondrocytes [83]. The development of a proper growth factor delivery system to the cartilage defect site is required to preclude any potential adverse effects on clinical cartilage repair.

Gene therapy has great potential as a therapeutic strategy for various diseases including cartilage injury. Transgenes are delivered by viral or nonviral vectors, generating nascent proteins which are synthesized locally with post-translational modification. Several animal studies using gene therapy have been conducted through two approaches. One approach is via direct gene transfer into the cartilage defect, whereby the recombinant adeno-associated virus is loaded with FGF-2, and IGF-1 and SOX9 are applied directly to the osteochondral lesion [84–86]. Another approach involves the bone marrow clot being mixed with adenovirus vectors to become what is known as a "gene plug," and is then transferred into the cartilage defect. Promising results of cartilage defect in vivo studies using a gene plug containing cDNA encoding anabolic factors such as BMP-2, Indian hedgehog protein, and TGFB1 have been reported [87–89]. The efficacy of genetically modified allogeneic chondrocytes in a large animal model has also been reported. Implantation of allogeneic chondrocytes following adenoviral transduction with IGF-1 into full-thickness chondral defects can achieve successful repair [90]. Clinical trials using allograft chondrocytes modified genetically have been already undertaken [91]. Human chondrocytes from a newborn with polydactyly transduced with a retrovirus encoding *TGFB1*, and cDNA were introduced into cartilage lesions with a fibrin scaffold. Transduced cells were irradiated prior to implantation due to the carcinogenic potential of the retrovirus. The effectiveness and safety of gene therapy for cartilage lesions should be carefully examined.

Recently, microRNAs (miRNAs) have been attracting attention due to their important role in the pathogenesis of diseases and their potential as therapeutic targets. MiRNAs are short (around 22 nt) non-coding RNA which regulate gene expression at the post-transcriptional level. MiRNAs are conserved across the phyla and exhibit a tissue-specific or developmental stage-specific expression pattern [92, 93]. Aberrant expressions of miRNAs causing several diseases have been explored, including those which cause cancer and systemic diseases such as rheumatoid arthritis [94, 95]. Regarding the development and disease pathogenesis of cartilage, evidence of the importance of miRNAs has drastically increased [96, 97]. MiRNAs can serve as a novel therapeutic target molecule because the up- or downregulation of endogenous miRNAs is possible. Using miRNA mimics can increase the function of endogenous miRNAs and synthetic complementary oligonucleotides of miRNA, miRNAs sponges, and small molecules for repression of transcription can be used to silence endogenous miRNAs. Many in vivo studies have been conducted into the administration of miRNA mimics or antisense for several disease models except for cartilage defects. Clinical trials targeting miRNAs in human diseases such as hepatitis C have been already conducted [98]. The identification of cartilage-specific miRNAs and the clarification of their function will be accompanied by the anticipation of miRNA-based drug cartilage repair. Therapeutic trials using miRNA mimics in rat models have reported on ACL and meniscus injuries which accompany cartilage injury. An intra-articular injection of a miR-210 mimic, which is a potent inducer of angiogenesis, can promote the healing of the ACL and meniscus tear in a rat model [99, 100]. If these specific hurdles of miRNA-based drugs such as off-target-effect are overcome, an effective therapeutic strategy to target miRNAs for acute cartilage injury will be realized in the near future.

At present, multiple procedures for acute cartilage injury are present, but fixation of the chondral/osteochondral fragment is the only procedure capable of regenerating articular cartilage. The biology of the articular cartilage must be fully

elucidated before cartilage repair technologies can advance. Accumulating evidence of experimental studies on cartilage repair will enable us to develop a clinical application of novel procedures for biological healing.

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