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Autologous costal chondral transplantation and costa-derived chondrocyte implantation: emerging surgical techniques

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***Abstract*:** It is a great challenge to cure symptomatic lesions and considerable defects of hyaline cartilage due to its complex structure and poor self-repair capacity. If left untreated, unmatured degeneration will cause significant complications. Surgical intervention to repair cartilage may prevent progressive joint degeneration. A series of surgical techniques, including biological augmentation, microfracture and bone marrow stimulation, autologous chondrocyte implantation (ACI), and allogenic and autogenic chondral/osteochondral transplantation, have been used for various indications. However, the limited repairing capacity and the potential pitfalls of these techniques cannot be ignored. Increasing evidence has shown promising outcomes from ACI and cartilage transplantation. Nevertheless, the morbidity of autologous donor sites and limited resource of allogeneic bone have considerably restricted the wide application of these surgical techniques. Costal cartilage, which preserves permanent chondrocytes and the natural osteochondral junction, is an ideal candidate for the restoration of cartilage defects. Several *in vitro* and *in vivo* studies have shown good performance of costal cartilage transplantation. Although costal cartilage is a classic donor in plastic and cosmetic surgery, it is rarely used in skeletal cartilage restoration. In this review, we introduce the fundamental properties of costal cartilage and summarize costa-derived chondrocyte implantation and costal chondral/osteochondral transplantation. We will also discuss the pitfalls and pearls of costal cartilage transplantation. Costal chondral/osteochondral transplantation and costa-based chondrocytotherapy might be up-and-coming surgical techniques for recalcitrant cartilage lesions.

***Keywords*:** cartilage defect, chondrocyte, costal cartilage, cytotherapy, tissue engineering

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Introduction

Symptomatic osteochondral lesions of the diarthrosis, such as the hip, tibiofemoral, patellofemoral and tibiotalar joints, are clinically challenging due to the poor self-repair capacity of cartilage and the accelerated deterioration under a weight-bearing environment.[1,2] If a considerable cartilage defect is left untreated, degenerative changes and unmatured osteoarthritis inevitably arise.[3,4] Advancing diagnostic techniques[5] revealed that recalcitrant arthropathies in young people become notable diseases. Surgical interventions to repair cartilage could prevent the progression of joint degeneration.[6]

A series of surgical techniques are used for cartilage repair, with varied indications and surgical outcomes.[7,8] Biological augmentation, including platelet-rich plasma (PRP),[9] bone marrow aspirate concentrate (BMAC) and mesenchymal stem cells are used solely or synergistically for cartilage repair.[2] Microfracture is a traditional method for obtaining functional recovery and pain relief at short- and mid-term follow up.[10–12] However,

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many factors affect bone marrow stimulation techniques, which yield heterogeneous outcomes.[10,13,14] Allografting immediately restores the contour of a large osteochondral defect and shows promising functional and radiographic outcomes.[15,16] Mosaicplasty, in combination with fresh osteochondral allografting, regains frictionless articular cartilage with the superiority of a one-stage process and fast rehabilitation.[17] Fresh and juvenile allograft cartilage is beneficial for osteochondral defects of large loading articulations and the small joints of the hands and feet.[18–21] Autologous chondrocyte implantation (ACI) consists of a cartilage biopsy from a nonweight-bearing area, *in vitro* chondrocyte culture and expansion, and surgical implantation of the collected chondrocytes.[22] Long-term follow up of ACI has confirmed clinical improvement for osteochondritis dissecans.[23] Although there is no randomized controlled study comparing the abovementioned surgical techniques, increasing evidence shows more promising outcomes from allograft transplantation. Osteochondral allograft might be the most suitable protocol for prior failed cartilage repair.[24–26] Histological methods are helpful in evaluating the microscopic appearance of the regenerated tissue following various techniques.[27] Microscopic observation of failed repair following abrasion, periosteal flap grafting and ACI revealed a mixed composition of collagen (Col) I, II and X. Fibrous proliferation was also obvious, but hyaline cartilage regeneration was limited.[28] A more recent study found that specimens from failed ACI, microfracture and periosteal transplantation were mainly composed of fibrous connective tissue and fibrocartilage. However, no Col X was found, and hyaline cartilage formation was scarce.[29] The distinct shortcomings of allogeneic osteochondral grafting stem from the imbalance between the large clinical demand and limited resources. Although autologous osteochondral plugs and chondrocytes are obtained from nonweight-bearing areas of diarthrosis, the total volume is restricted, and the potential long-term side effects should be noted.

Costal cartilage, which preserves permanent chondrocytes, is an ideal candidate for the repair of cartilage defects. The harvesting of costal cartilage does not interfere with the articular structure, and potential complications are avoidable and minimal. Autologous costal cartilage transplantation is widely used in the plastic and cosmetic surgery due to craniofacial microsomia,[30] auricles of congenital microtia,[31] tracheal reconstruction[32] and congenital tracheal stenosis.[33] Meanwhile, overgrowth or undergrowth of the costal cartilage might lead to deformity of the thoracic cavity.[34–36] Therefore, the use of costal cartilage as the attracting donor and underlying pathology was examined in clinical and translational studies.

In this review, we first introduce the fundamental properties of costal cartilage, which contribute to the basis of its experimental and clinical applications (Figure 1). Second, the pre-clinical and clinical uses of costal cartilage and costa-derived chondrocyte implantation are summarized. Third, we also discuss the pitfalls and pearls of costal cartilage transplantation and lessons from its use in plastic surgery. Finally, the existing challenges and potential strategies are highlighted.

The properties of costal cartilage

Human articular cartilage is a multilayered structure containing chondrocytes in different stages of maturation and an ossification microenvironment (Figure 2). The extracellular matrix (ECM), which is mainly composed of Col II for hyaline cartilage, also contains Col III/IX/XI/VI/X, glycosaminoglycans (GAGs), proteoglycans and glycoproteins.[4] The ECM is the residential microenvironment of chondrocytes, and it plays an important role in the regulation of chondrogenesis and pathological processes.

Similarly, but differently, the growth plates of foetal bovine ribs are divisible into five different zones: the hypertrophic, lower proliferative, upper proliferative, intermediate and resting zones.[37] The deposition of perlecan increases during proliferation and might be sulphated. Costal cartilage undergoes a natural mineralization, which is not considered a degenerative change. For example, mineralization of the first rib begins at the end of puberty, and large cartilage canals with vascular invasion and perivascular connective tissue present in the middle of the second decade. This kind of osteogenesis should not be simply categorized as intramembranous or endochondral ossification.[38] Human ribs have two separate cartilaginous regions: one region forms the joint with the sternum, and the other region is for longitudinal growth. The cartilage of the rib becomes vascularized immediately after birth, but mineralization is arrested only after differentiation of the costal chondrocyte has advanced to the late

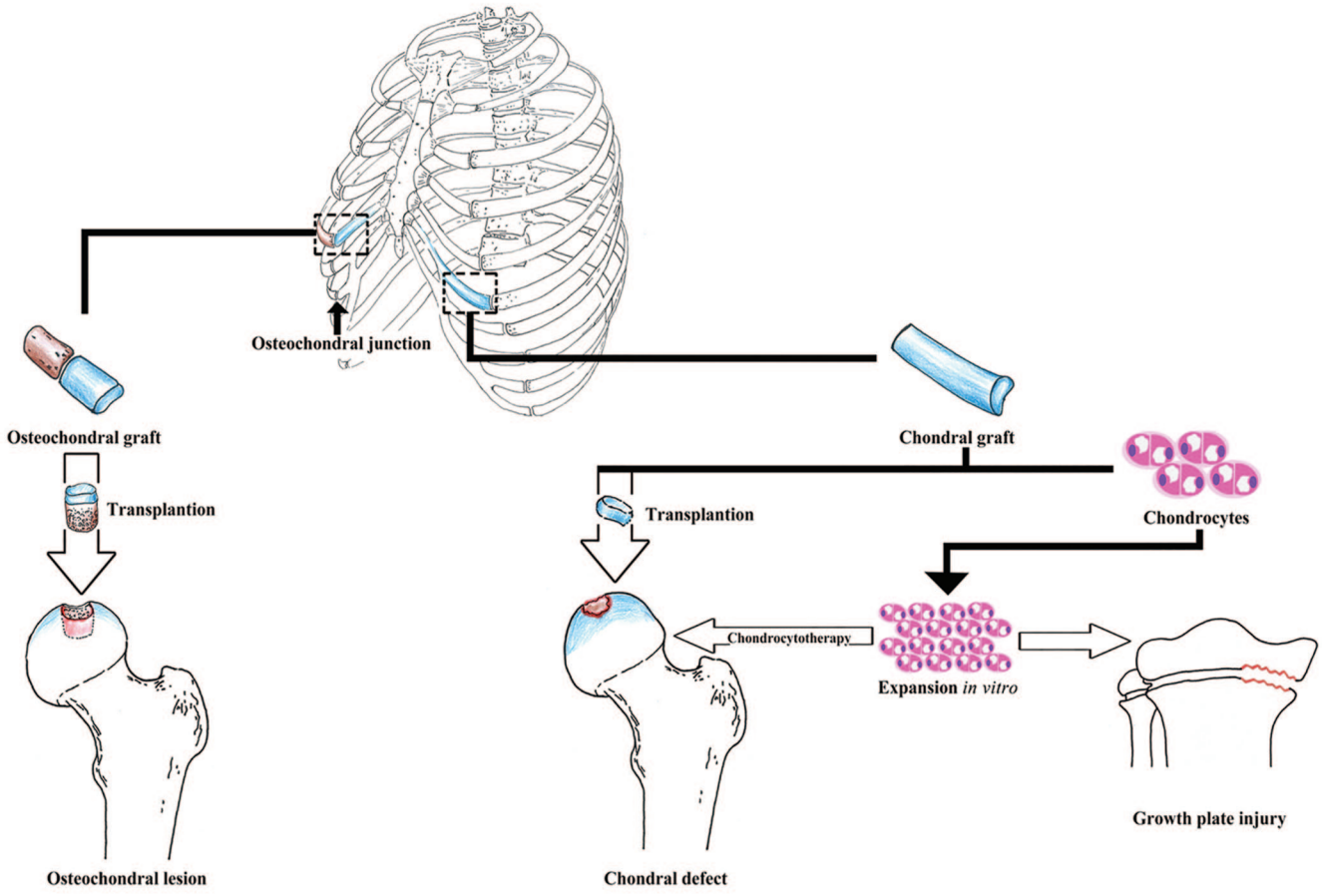

Figure 1. Schematic of costal chondral/osteochondral transplantation and costa-derived chondrocytotherapy.
The costal junction may indicate a deep osteochondral lesion, and the costal cartilage may be used for full-thickness cartilage defects. Alternatively, costal cartilage may be cut into small pieces, and digested and expanded *in vitro* to obtain sufficient chondrocytes. The costa-derived chondrocytes are functional seed cells to cure cartilage defects and growth plate injury.

stage. *In vitro* findings indicated that parathyroid hormone (PTH) stimulates costal chondrocytes to exhibit the phenotype of fully differentiated hypertrophy.[39] Therefore, PTH is essential for the late differentiation of costal cartilage. The costal cartilage is surrounded by a perichondrium, which is a kind of dense connective tissue that contains a special niche of housing chondrogenic pioneering cells, and it critically contributes to the costal cartilage regeneration.[40] Samples of ribs six to eight were collected from patients with pectus carinatum for microscopic morphological study. Scanning electron microscopy and atomic force microscopy showed collagen fibres approximately 600 nm in diameter that assembled into a large complex running parallel to the cartilage, with a unique straw-like structure. Chondrocytes likely occur singly or as doublets, and centrally located chondrocytes produce more aggrecan. The expression of decorin, Col2A1, aggrecan and tissue inhibitor of metalloproteinase 1 (TIMP1) is high, which indicates the underdifferentiated nature of costal cartilage.[41]

Biological properties

Investigators are enthusiastic about comparing the biological properties of chondrocytes from different origins. Chondrocytes derived from rib, ear and nose were isolated separately in one study and expanded in a cocktail composed of transforming growth factor beta-1 (TGF-β1), fibroblast growth factor 2 (FGF-2) and alpha- and beta-receptor ligand of platelet-derived growth factor (PDGF-bb),[42] altogether, TFP. The capacity and quality of the induced chondrogenesis were compared thereafter. A significant increase in glycosaminoglycan and messenger ribonucleic acid (mRNA) expression of Col II was found in costa-derived chondrocytes but the quality of

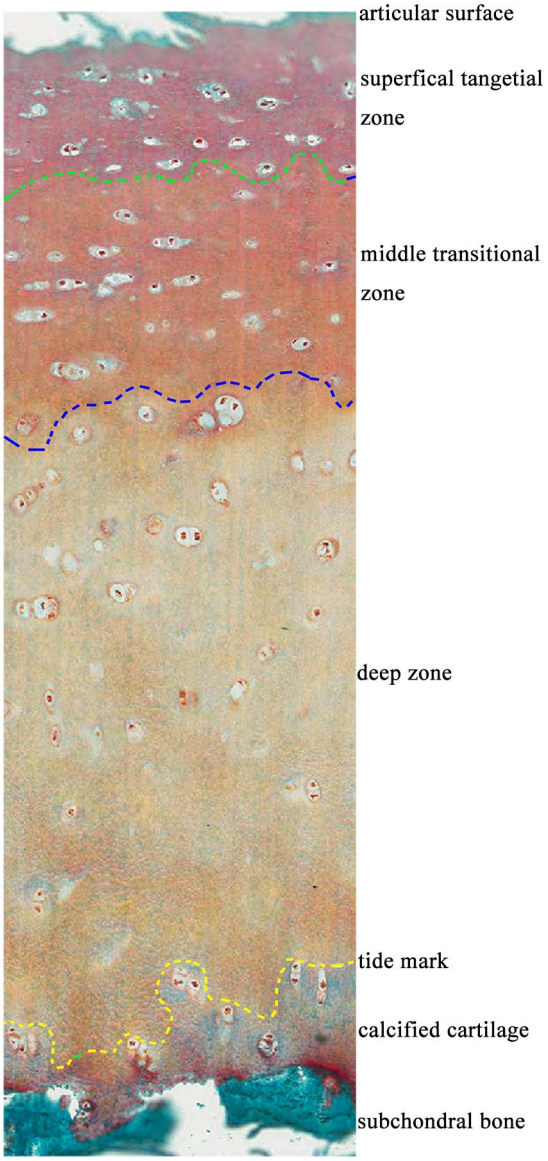

Figure 2. Multilayered structure of the cartilage from the femoral head.
Chondrocytes in different stages of maturation are buried in the extracellular matrix with varied ossification (Goldner Trichome staining).

generated cartilage pellets was inferior.[42] A recent similar study also used chondrocytes from ear, nasoseptal and costal cartilage to compare the cell yield, proliferation, chondrogenesis and capacity of cartilage formation.[43] Three different kinds of cartilage were sensitive to basic fibroblast growth factor (bFGF) within eight passages and showed the strongest capacity of chondrogenesis at the fifth passage. Although minor matrix changes existed, the formed cartilaginous product had mature cartilage features, like the original native tissue.[43] The authors of another study compared cell yield, expansion, and chondrocyte dedifferentiation and redifferentiation capacity between costal and articular cartilage of rabbit.[44] These authors found that costal chondrocytes were advantageous in cell yield and expansion. Chondrocytes from both origins became dedifferentiated with serial cultures, but the capacity of redifferentiation improved when these chondrocytes were cocultured with a high density of collagen gel.[44] The contraction of collagen gel can reflect the degree of fibroblastic dedifferentiation during chondrocyte expansion. They observed the surface area of the reconstructed cartilage being reduced to 11.11% for articular chondrocytes and 4.34% for the costal chondrocytes at 14 days. When costal chondrocytes from passage four were subjected to high-density three-dimensional (3D) culture, they could regain the hyaline cartilage phenotypes, similar to chondrocytes from passage two.[44]

Kitaoka and colleagues established a chondrocyte cell line from the costal cartilage of SV40 large T-antigen transgenic mice.[45] Costa-derived chondrocytes had similar phenotypes as articular cartilage and embryonic limbs, which suggests that costal cartilage is a competent alternative as a donor site for the repair of articular cartilage defect. Taken together, although inconsistencies might exist due to heterogeneity in cell passages and culture media, increasing evidence shows that costal chondrocytes maintain an underlying biological property to exhibit the desired phenotypes of chondrocytes derived from articular cartilage.

Biochemical and biophysical properties

Numerous biochemical and biophysical factors affect the biological behaviour of cultured chondrocytes. Growth factors, chemokines and many other stimulators are used for the promotion of proliferation and prevention of chondrocyte dedifferentiation.[46,47] Biophysical factors, including cell density, oxygen concentration and ECM, also impact the characteristics of chondrocytes cultured *in vitro*.

The components of the culture medium and seeding density affect the postexpansion chondrogenic potential of costa-derived chondrocytes.[48] Supplementation of 1 ng/ml TGF-β1, 5 ng/ml bFGF and 10 ng/ml PDGF increased glycosaminoglycan, decreased the ratio of Col I/Col

II and strengthened the compressive property.[48] A density of 2 million cells/5 mm diameter construct was beneficial in enhancing the matrix synthesis and tensile/compressive properties compared with 3, 4 or 5 million cells/construct,[48] which is inconsistent with previous studies that demonstrated the priority of higher chondrocyte density. We believe that the most efficacious seeding density and cocktail of growth factors must be investigated further in self-assembled cartilage formation. The oxygen concentration regulates the expansion and differentiation properties of costa-derived chondrocytes. Low oxygen (5%) in combination with serum-free medium and FGF2 improved cell expansion, reduced dedifferentiation, enhanced redifferentiation capacity into cartilage and ameliorated the proteomic profile.[49] The electrical cell membrane of costal chondrocytes is close to that of cardiomyoblast cells, and gadolinium (Gd) blocks ion channels, which results in a significant reduction in membrane capacitance and conductance.[50]

The ECM constitutes the microenvironment of chondrocytes, and it dramatically regulates expansion and dedifferentiation in an *in vitro* culture system.[51] The ECM derived from articular chondrocytes was superior to that from bone marrow and yielded a better ratio of Col 2A1/Col 1A1 and a more cartilage-like ECM.[51] An appropriate artificial matrix also plays a beneficial role in the maintenance of chondrocytes. An artificial matrix of poly(L-lactic-acid) maintained chondrocyte phenotype during *in vitro* expansion, which might be associated with cellular adhesion *via* the $\alpha_5\beta_1$ integrin.[52]

Biomechanical properties

One of the most important characteristics of hyaline cartilage lies in its superior biomechanical properties. Physiologically, articular cartilage transfers load between bones and facilitates the frictionless motion of diarthrosis.[53] Mechanical stimulation is also a critical biophysical factor that may be used to induce changes in the gene expression of chondrocytes and ECM deposition.[54] *In vitro* studies using cyclic tensile strain and compressive stimulation directed the ossification mode of mesenchymal stem cells.[54,55]

Mechanical loading induces costa-derived chondrocytes towards articular cartilage regeneration. Compressive stimuli at the phase of matrix synthesis and maturation increase instantaneous moduli by 92% and 87%, respectively. However, combined compression at both phases did not further strengthen the property beyond a one-time stimulation. In terms of magnitude, passive axial compression of 3.3 kPa and 5.5 kPa increased neocartilage compressive properties by 42% and 48%, respectively. When a further bioactive regimen was supplemented, the tensile properties of formed cartilage was increased 2.6-fold compared with an untreated control.[56] Murphy and colleagues found that TGF-β1, chondroitinase ABC (C-ABC) and hydrostatic pressure separately or synergistically improved the hyaline cartilage regeneration of costal chondrocytes.[57] The optimum combination yielded robust hyaline cartilage with a property of tensile modulus of 2 MPa and a compressive instantaneous modulus of 650 kPa.

Costal cartilage from mutant mice lacking β1 integrins in their chondrocytes showed round chondrocytes and a loss of polarity. Although the levels of Col II and aggrecan were similar, the absence of β1 integrins increased the stiffness and modified the diffusion properties of costal cartilage.[58] Therefore, β1 integrins might play a critical role in the biomechanical function of costal cartilage.

Costal chondral/osteochondral grafting in animal models

Preclinical animal models are essential to reveal the cellular mechanisms and the histological and morphological results of costal cartilage transplantation.[59] Several studies reported convincing outcomes of costal chondral/osteochondral grafting for the treatment of cartilage and osteochondral defects. Histological and radiographical evaluations show that the transplanted costal chondral/osteochondral graft is capable of fusing with the receipt site, and it restores complex cartilage lesions in multiple animal models. A costal osteochondral plug was transplanted to a full-thickness articular defect of the knee in a rabbit model. Histological union was achieved in all animals. Chondrocyte viability was confirmed microscopically in the 48-week grafts. The general appearance of chondrocytes in the transplanted costa was similar to the host cartilage. The expression of Col II and aggrecan was consistent with normal articular cartilage.[60] For large osteochondral defects, multiple sliced costal cartilage could be synergistically used to repair the defect. Histological findings revealed that the

intergraft gap between separated costal cartilage was filled by fibrous tissue, and the cleft between transplanted cartilage and host bone was interlinked by newly formed woven bone.[61] The junction and union between transplanted cartilage and recipient tissue is very important for functional recovery.[62] Alternatively, a cancellous iliac bone block could be isolated and implanted onto the surface of costal cartilage to yield an osteochondral complex. The hybrid structure repaired the large full-thickness cartilage defect.[63] However, autologous sternal cartilage transplantation did not yield satisfactory outcomes for articular defects of the radial carpal bone in athletic horses.[64]

With the accumulated data from animal studies, many striking issues have emerged that deepened our understanding of cartilage pathology and accelerated the translational research. First, the local microenvironment plays a crucial role in the regeneration following costal cartilage transplantation.[65] To overcome the unfavourable microenvironment of a cartilage defect, Mao and colleagues used ECM derived from allogeneic human articular chondrocytes, which promoted the expansion of human primary chondrocytes *in vitro* with reduced dedifferentiation.[51] Second, products from platelets promote cartilage repair following costal cartilage grafting. A hybrid technique involving the implantation of hyaline cartilage chips, platelet-poor plasma and intra-articular injection of growth-factor-rich plasma, enhanced chondrogenesis and yielded hyaline cartilage in a sheep model.[66] Next, the potential of self-repair is closely associated with the position of the cartilage defect and might be site specific. For instance, a 4×4 mm^2 defect at the load-bearing area of the femoral head achieved a better histological score compared with the head–neck junction area.[67] *In situ* tissue engineering for cartilage regeneration also showed an encouraging pilot outcome and potential clinical application. A kind of decellularized cartilage matrix-derived scaffold with a functionalized self-assembly peptide homed endogenous reparative cells and yielded superior hyaline-like cartilage.[68]

The anatomical characteristics of costal cartilage in many animals are well described.[69] Cartilage defects and reparative protocols in different animal models should not be simply compared, but the research data provide us a beneficial reference to initiate breakthrough studies in human beings.

Autologous cartilage/costa-derived chondrocyte implantation

Ribs have become a potential donor site of chondrocytes for ACI. ACI with seeding chondrocytes from nonarticular heterotopic cartilage has advantages of lesser donor-site morbidity with a comparable ECM synthesis profile to the articular cartilage.[70] Chondrocytotherapy with seeding cells from the rib or nonweight-bearing areas of diarthrotic joints showed a prospective outcome for recalcitrant cartilage lesions. Cell-free scaffolds demonstrated several advantages; however, a recent study indicated an increased 5-year failure rate following implantation of a Col I scaffold, which suggests the clinical importance of seeding cells in cartilage repair.[71] ACI may also be used as a salvage protocol for failed prior cartilage-repairing operation. Ellender and Minas used salvage ACI to treat a 10 cm^2 full-thickness chondral defect of the femoral head.[72] The patient had a previous autologous osteochondral mosaicplasty. Chondrocytes were obtained from nonweight-bearing areas of the knee, with a size of 0.5×1 cm^2, which yielded approximately $2 \times 10^5 - 3 \times 10^5$ cells. A total of 48 million cells were produced after *in vitro* expansion. Notably, the authors used a special collagen to secure the implanted chondrocytes. The patient was free of pain at a 2-year follow up. Images of contrast-enhanced magnetic resonance imaging (MRI) demonstrated repair tissue fill and radiographs showed a normal joint space. The surgical technique was used in another, more difficult case of post-traumatic osteonecrosis of the femoral head.[73] Histological staining of the biopsy tissue 15 months postoperatively showed viable chondrocytes, which were profoundly integrated with the subchondral bone. At 18 months postoperatively, computed tomography (CT) scanning demonstrated that the joint space exhibited good congruity. However, there are no case reports using autologous costa-derived chondrocytes for articular repair. On the one hand, a thin cartilage biopsy does not significantly influence the normal structure of the donor joint. On the other hand, *in vitro* studies show that the density of chondrocytes is higher in articular hyaline cartilage than in costal cartilage. Nevertheless, costa-derived chondrocytes are competitive candidates for chondrocytotherapy. For juvenile patients, long-term complications induced by the loss of articular cartilage must be clarified.

The adjuvant effects of platelet-derived products show inconsistent outcomes of chondrogenesis and cartilage repair during ACI. Platelet-derived

fibrin demonstrated positive effects on cartilage repair, and the experimental outcome was better when autologous chondrocytes were used jointly.[74] PRP was also beneficial for cartilage regeneration at the donor site following costal cartilage harvesting.[75] A commercially available platelet lysate enhanced chondrocyte proliferation, but the chondrogenic capacity was inferior to the control.[76]

Chondrocytes from the proliferating layer of the growth plate showed more chondrogenic phenotypes, a higher proliferation rate, increased expression of chondrogenic-related genes, higher content of glycosaminoglycan and more chondrogenic extracellular matrix.[77] Chondrocytes from the growth plate may be isolated, cultured and expanded *in vitro* and used to prevent bone bridge formation.[78,79] However, no report has used autologous chondrocytes from the growth plate for cartilage repair, primarily due to potential severe complications.

Clinical autologous costal chondral/osteochondral transplantation

Historically, costal chondral/osteochondral transplantation was largely used in plastic and cosmetic surgery. However, with the accumulated experience in the care of hand, wrist and elbow cartilage disease, costal chondral and osteochondral grafts broadened their indication for weight-bearing joints, such as hip, knee and foot.

Costal osteochondral transplantation is an effective method to restore metacarpophalangeal and proximal interphalangeal joints to avoid arthrodesis and arthroplasty.[80,81] Costal osteochondral grafting was also used to reconstruct proximal scaphoid due to fracture or necrosis.[82] For finger joints reconstructed with costal osteochondral graft, Sato and colleagues harvested the fifth or sixth costo-osteochondral junction, which was shaped to fit the defect in metacarpophalangeal joint in three cases, proximal interphalangeal joint in nine, distal interphalangeal joint in three and thumb interphalangeal joint in two. The average time to bone union of the graft was 58 days. The biopsy histology showed that scattered chondrocytes were viable within the ECM and exhibited the same appearance as normal hyaline cartilage.[83] Costal cartilage transplantation is indicated to cure trapeziometacarpal osteoarthritis. In a retrospective study including 100 cases, the surgical technique restored thumb stability and strength.[84]

Costal cartilage transplantation shows encouraging effects for the treatment of intra-articular malunion following distal radius fractures. In a series of seven patients, costal cartilage from the eighth rib was harvested and implanted in a trough created at the epiphysis metaphysis junction of the distal radius. Union was achieved in all cases without complications, and the functional and radiographic outcomes were satisfactory.[85] For advanced traumatic arthritis of the radiocarpal joint, costal osteochondral transplantation is a convincing alternative to preserve wrist motion. In a study enrolling 29 cases (7 due to malunited intra-articular distal radius fractures; 18 due to scaphoid osteopathy; and 4 due to Kienböck disease), costal cartilage from the ninth rib showed satisfactory radiographic and histological results. The graft was vital, and no signs of resorption or necrosis were observed.[86]

The clinical transplantation of autologous costal osteochondral graft was used for osteochondritis dissecans of the *capitulum humeri* secondary to elbow trauma and yielded satisfactory results in two patients.[87] In a more recent cohort study of 26 patients, cylindrical costal osteochondral graft was used to cure large defects ($\geqslant$15 mm in diameter) of the capitellum due to osteochondritis dissecans. All patients were satisfied with the functional improvement. Osseous union and revascularization of the graft were achieved successfully.[88] Sato and colleagues demonstrated that the favourable indication was advanced osteochondritis dissecans of the capitulum in teenagers with significant symptoms.[89] Costal osteochondral graft was also successfully used to cure fracture-induced osteonecrosis of the radial head in an adolescent boy.[90]

Although costal chondral/osteochondral transplantation demonstrated remarkable benefits for cartilage defects of nonweight-bearing joints, it is rarely used in the lower limbs. We reported a 20-year-old man with traumatic osteonecrosis of the femoral head.[91] Through the Smith-Petersen approach, the affected hip was dislocated to expose the femoral head, and another surgical team harvested the costal osteochondral graft. The degenerated cartilage and subchondral bone were removed using an 8 mm trephine. The costal chondral graft was trimmed into pieces to match the cylindrical defect. Essential internal fixation with absorbable screws was adopted to enhance the stability of costal grafts. The short-term follow up showed that pain was completely relieved, and ambulation was dramatically improved. We

accumulated more successful cases of costal chondral grafting for cartilage defects of the hip, knee, ankle and the first metatarsophalangeal joint.

Pitfalls and pearls

Costal cartilage transplantation is widely used in clinical practice,[30,31,92–98] but multiple factors might influence the prognosis. With the increasing evidence of costal cartilage, pitfalls of this emerging surgical technique must also be highlighted. Pitfalls and pearls from autologous costal cartilage grafting in plastic surgery and allogeneic cartilage transplantation are instructive to improve the quality of skeletal reconstruction with costal cartilage.

Warping and overgrowth of the cartilage

Warping of the costal cartilage is a serious complication in plastic surgery.[93,99] For costal cartilage transplantation, preoperative evaluation is very important, and the size of harvested cartilage should be sufficient.[100] The surgical technique of transverse slicing of the sixth–seventh costal cartilaginous junction may yield adequate cartilage and was reported as an effective method to prevent warping. Warping of the cartilage may cause the loss of press-fit stability, which suggests that cartilage fixation is an essential procedure. Growth of the transplanted free costochondral grafts was observed in children with hemifacial microsomia. Overgrowth might occur, but the underlying mechanism of costochondral growth has not been definitely elucidated.[98]

Morphological matching

The demand of the frictionless motion of non-weight-bearing joints demonstrated that morphological matching was not a critical issue for upper limbs. However, the role of contour matching must be addressed in biological restorations of weight-bearing joints. An absolute match never exists, but it must be approximated. Autologous osteochondral graft from the ipsilateral non-weight-bearing area of the femoral head could be harvested to repair the cartilage defects in the weight-bearing surface, and very similar curvatures showed satisfactory clinical and radiographic outcomes at mid-term follow up.[101] Although the sphericity of femoral head was not restored to normal, care should be taken to harvest osteochondral plugs with a similar spherity.[102] In rare conditions, autologous osteochondral grafts from the femoral head due to hemiarthroplasty are used to repair cartilage defects of the lateral femoral condyle in multiple osteonecrosis.[103] We hypothesize that a remodelling mechanism likely includes the plasticity and elasticity of the costal cartilage.

Age and defect size

Cartilage repair is critical for adolescents to avoid unmatured degenerative joint. However, we do not know the exact effect of increasing age on the outcome of cartilage transplantation. One study revealed that arthroscopic matrix-assisted autologous chondrocytotherapy was beneficial for patients older than 40 years with International Cartilage Regeneration and Joint Preservation Society (ICRS) grade 3–4 lesions. Age is not a strict contraindication of cartilage reparative surgery.[104] In our experience, costal chondral grafting relieved pain and improved range of motion at short-term follow up.

ICRS grade, defect size, and symptom duration did not affect the baseline Knee Injury and Osteoarthritis Outcome Score, but the size of the defect was a considerable factor of surgical protocol.[105] The absolute and relative size of the cartilage lesion did not influence postoperative outcomes after osteochondral allograft transplantation for isolated femoral condyle lesions.[106] Large defect size is not a contraindication of costal cartilage transplantation, especially for young patients.

Complications

Postoperative complications are minimal, and cosmetic concerns are acceptable using the advanced techniques of costal harvesting.[107,108] For patients younger than 10-years old, the risks of the chest-wall deformities and thoracic scoliosis should be noted following harvesting of costal cartilage. The incidence of deformity might be higher for upper ribs. An intact costochondral junction was critical in minimizing these severe complications.[109]

Calcification of the costal cartilage is a natural progress that should be carefully evaluated preoperatively using ultrasonography[110] or dual-energy CT imaging.[111] Generally, ossification initiates from the first rib cartilage and progresses up to

the twelfth rib.[100] Costal cartilage calcification is closely associated with ageing.[112–114] Severe calcification of the costal cartilage might increase the incidence of pneumothorax due to perichondrium adhesion. It is difficult to trim calcified cartilage, which might also become a new predisposition to induce cartilage erosion.

The microenvironment of the cartilage defect is also vital to the healing of transplanted cartilage. Inflammatory responses following cartilage damage might involve neutrophil infiltration and cytokine release, which are closely associated with the consequent repair process.[115] Therefore, an exact understanding of the spatiotemporal distribution of the inflammation cascade plays a fundamental role in reconstructive surgery.

Challenges and strategies

The challenges of cartilage degeneration and surgical restoration are great. Although we have a considerable understanding of the biology of chondrocytes and physiology of cartilage, little is known about the natural history of self-repair modulation and specific function of this multilayered structure (Figure 2). The concept of the osteochondral unit must be highlighted in the pathogenesis of cartilage degeneration.[116] Cartilage damage is rarely an independent event of chondrocytes, and it intimately involves the whole joint. The uncertainty of the relationship between intra-articular joint disease on imaging and complaints of pain must be further investigated to deepen our understanding of the mechanism of articular pathology.[117] Surgical techniques of arthroscopy, although less invasive in facilitating enhanced recovery,[118] cannot resolve fundamental problems of the arthropathy.

Costal chondral transplantation and costa-derived chondrocytotherapy are promising surgical techniques in caring for challenging cartilage lesions. For patients with inherent or secondary joint disease, healthy hyaline cartilage is inherently limited. In these scenarios, costa should be considered as the origin of chondrocytes. However, the costa is just a donor site of chondrocytes and hyaline cartilage, which might yield optimal outcomes in combination with other advanced surgical techniques or biotechniques. In terms of basic research, the optimal protocol to preserve phenotypes of chondrocytes and increase extracellular matrix production is still at the stage of exploration.[119,120] Although chondrocytes are more resistant to hypoxia and ischaemia, the effect of microenvironment with irritated inflammation on cellular senescence and death is not fully elucidated currently.[121,122] In terms of clinical investigations, observational studies are indispensable in revealing the natural history of arthropathies in young adults, and high-standard clinical trials are desired to reflect the therapeutic effect of costal chondral transplantation and costa-derived chondrocytotherapy.[123] *In vitro* expansion is currently used to yield sufficient chondrocytes;[124] however, we do not know whether preculture is necessary for a small lesion. The quantity and quality of transplanted chondrocytes are everlasting topics in cytotherapy.[119] The density (number of chondrocytes per defect size) of chondrocyte implantation is multifactorial and might be personalized.[22] Tissue engineering might shed light on future methods to strengthen costal chondral transplantation and costa-derived ACI.[125] Tissue-engineering approaches are based on a strategic liaison between cells, scaffolds and signalling molecules to inspire intrinsic repair capacity or rely on extrinsic materials for regeneration.[59,126,127] The spatial complexity of cell types and tissue organization demonstrate that routine biomaterials for bone engineering cannot restore a totally biomimetic structure. It is possible to use novel 3D bioprinting technology to biofabricate skeletal architecture, layer by layer, which is especially significant for cartilage engineering due to its complex nature.[128,129] Pilot studies indicated that a 3D matrix might yield beneficial effects on the phenotypes and vitality of chondrocytes.[51,130,131] However, the optimum formulation of synthetic matrix is to be determined.[52,132] Biomaterial-guided gene therapy is also an attractive strategy for augmenting the intrinsic mechanisms of cartilage repair and suppressing the detrimental inflammatory response, simultaneously.[133,134] Stem cells play a fundamental role in cartilage repair.[119,127] *In situ* biofabrication using adipose-derived mesenchymal stem cells is reportedly feasible for cartilage repair.[124] It is interesting to discern the shift from cartilage- and bone marrow- to adipose-derived cells in clinical translational research, but more phase III trials were based on seed cells from cartilage.[135] Strategies for *in situ* cartilage repair may be initiated through endogenous reparative cell-homing techniques[68] to yield so-called *in vivo* tissue engineering to repair the cartilage defect.[136] Cytokines and chemokines, including bone morphogenetic

proteins, are beneficial for articular cartilage regeneration.[137] Detrimental factors suppressing chondrogenesis might be targeted to repair cartilage.[138] CRISPR-Cas9 may be used to target matrix metallopeptidase 13 in human chondrocytes, resulting in decreased metalloproteinase and increased Col II deposition.[139] Finally, products of tissue engineering cartilage derived from autologous chondrocytes were used in human trials.[140,141] Although tissue engineering is currently used for alar lobule restoration and articular defects, we believe more sophisticated commercially available products could challenge defects of cartilage.[140–142]

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