Chapter

Current Tissue Engineering Approaches for Cartilage Regeneration

He Huang, Hongyao Xu and Jianying Zhang

Abstract

Cartilage is one of the critical tissues existed in human and animal bodies. Unlike most tissues, cartilage does not have blood vessels, nerves, and lymphatics. Most cartilage tissues *in vivo* are subjected to large mechanical loads, and its principal function is to provide a smooth and lubricated surface to facilitate the transmission of mechanical loads with a low frictional coefficient. As a result, cartilage tissues are easily injured. Cartilage defects are frequently caused by trauma, aging, congenital diseases (osteochondritis), and many more factors such as endocrine pathologies and cancer. The damaged cartilage has a limited capacity for healing and repairing. Thus, restoration of normal structure and function to damaged cartilage is one of the most challenging areas in orthopedic research and sports medicine. Tissue engineering provides a prospective alternative strategy by seeding chondrogenic cells into or onto biocompatible scaffolds to produce engineer cartilage for damaged cartilage repair. This book chapter has summarized recent progress in cartilage tissue engineering including stem cells, growth factors, bioactive molecules, and biomaterial scaffolds used for cartilage regeneration. The procedures for some new approaches have also been described.

Keywords: chondrogenesis, cartilage tissue engineering, stem cells, growth factors, platelet-rich plasma, bioactive molecules, biomaterial scaffold

1. Introduction

Cartilage is one of the critical tissues existed in human and animal bodies, such as rib cage, ear, nose, bronchial tubes, intervertebral discs, meniscus, and the joints between bones [1]. Cartilage injuries are the most common diseases. According to National Health Interview Survey (NHIS), in 2010–2012, about 52.5 million adults in the USA had doctor-diagnosed arthritis, and by 2040, the number of US adults with doctor-diagnosed arthritis is projected to increase 49% to 78.4 million. That means about 25.9% of all adults have arthritis [2, 3]. Degeneration of the intervertebral disc, a fibrocartilaginous joint residing between adjacent vertebrae in the vertebral column, is the most frequent cause of low back pain and another significant cartilage-related disease [4]. The overall cost of chronic low back pain exceeds the combined costs of stroke, respiratory infection, diabetes, coronary artery disease, and rheumatoid disease [5]. However, the damaged cartilage has little ability for repairing itself due to the lack of blood supply, nerves, and lymphangion [1], and the effective therapeutic treatments for cartilage regeneration are very few.

Tissue engineering is an interdisciplinary field that applies the principles of engineering and the life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function [6]. Stem cells, scaffold, and biologic active molecules are three key components in tissue engineering [7]. Successful tissue engineering relies on multiple factors including obtaining appropriate cells for implantation, directing the development of those cells on an appropriate differentiated pathway using growth factors and/or cytokines, supporting the growing cells on a three-dimensional matrix, and having that matrix remains in the injured tissue area, at least until healing is completed [6, 8]. This book chapter highlights the recent developments of tissue engineering approaches including stem cells, biomaterials, bioactive compounds, and reagents used for cartilage regeneration and repair.

2. Stem cells used for cartilage regeneration

Stem cells have multidifferentiation potential, which can differentiate into distinctive end-stage cell types including bone, cartilage, muscle, bone marrow stroma, tendon/ligament, fat, dermis, and other connective tissues [9]. There are many cell types that have been manipulated *in vitro* and subsequently implanted to repopulate a cartilage defect. It must be ensured that the implanted cells are immunoprivileged or provide immunosuppressive agents to avoid rejection by the host immune system.

2.1 Autologous chondrocytes

Autologous chondrocytes were first used for the treatment of cartilage defects of the patients by a Swedish group in 1994 [10]. This approach needs a slice of healthy articular cartilage obtained arthroscopically from proximal part of the medical femoral condyle of the affected knee joint during the first operation [11]. The chondrocytes were isolated from this healthy articular cartilage and cultured for 2–3 weeks to prepare enough cells (about 5×10^6) for damaged cartilage repair [11]. The clinical studies have shown that the treatment of autologous chondrocytes prompts pain reduction, improves quality of life, and delays the need of joint replacement in many cases [12–14]. Despite the encouraging clinical results, there are still limitations to the use of autologous chondrocyte transplantation. The conventional technique is accompanied with periosteum harvest and fixation over the cartilage defects via large skin incisions. Autologous chondrocytes were injected underneath the periosteal flap. Hypertrophy of the periosteum with high rate of revision arthroscopies and the risk of transplant failure of up to 20% are major drawbacks of the conventional autologous chondrocyte transplantation [14]. Moreover, the complexity and the cost of the two surgical procedures, the biological response of the periosteal flap, and the de-differentiation and consequent capacity loss associated with *in vitro* expansion of isolated chondrocytes are also the limitations [15].

2.2 Bone marrow-derived mesenchymal stem cells (BMSCs)

Mesenchymal stem cells (MSCs) are multipotent stromal cells first identified and described in 1966 by Alexander Fridenstein [16, 17]. Adult MSCs were originally isolated from bone marrow in 1999 by Pittenger and his colleagues [18]. Subsequent studies have demonstrated that MSCs present in various parts of the body including bone marrow (BM), peripheral blood, umbilical cord blood, fatty tissues, skeletal and cardiac muscles, Wharton's Jelly of umbilical cord, facet joints, interspinous ligaments, and ligamentum flavum [19–23]. Many studies have shown that MSCs can migrate to injury sites, induce peripheral tolerance, and inhibit the release of

proinflammatory cytokines. It has been demonstrated that MSCs can also promote tissue repair and survival of damaged cells [24]. However, it is not clear which adult tissue-derived MSCs should be used as a good source for cartilage repair.

Autologous bone marrow mesenchymal stem cell (BMSCs) transplantation was first used for the repair of full-thickness articular cartilage defects in human patellae by a Japanese group [25]. BMSCs were aspirated from iliac crest and the nucleated cells were cultured. Adherent cells were subsequently collected, embedded in a collagen gel, transplanted into the articular cartilage defect in patellae, and covered with autologous periosteum. Six months after transplantation, clinical symptoms (pain and walking disability) were improved and the improvement was persisted for 9 years post-transplantation [26]. Sixteen years after transplantation, no clinical problem has been reported. Human autologous BMSCs have been used successfully to treat articular cartilage defects. Twelve months after BMSC transplantation, magnetic resonance imaging (MRI) revealed complete defect fill and complete surface congruity with native cartilage [27]. Currently, autologous BMSC transplantation has been widely used for cartilage repair [26, 28, 29]. Although BMSC treatment did not require any cell expansion or manipulation, reducing costs, and risks involved, the quantity of bone marrow cells was somewhat unsatisfactory [16].

2.3 Adipose-derived stem cells (ADSCs)

Among MSCs, adipose-derived stem cells (ADSCs) have been recognized as an appropriate cell type with chondrogenic potential and high proliferation capacity [30, 31]. Approximately 400,000 liposuction surgeries are performed in the USA each year, and these procedures yield anywhere from 100 ml to 3 liters of lipoaspirate tissue [32]. This material is routinely discarded. It is well known that adipocytes are developed from mesenchymal cells via a complex cascade of transcriptional and non-transcriptional events that occur throughout the human life. Thus, adipose tissue is a good stem cell source.

The initial methods to isolate cells from adipose tissue were developed by Rodbell and colleagues [33]. They isolated adipose-derived stromal cells from rat fat pads by four steps. Step 1: Adipose tissue was minced into small pieces. Step 2: The adipose tissue pieces were digested with collagenase. Step 3: The cell pellet was obtained by centrifuge. Step 4: The cell pellet was cultured for future use. This protocol has been widely used for the isolation of adipose-derived stem cells (ADSCs) from human adipose tissues with some modifications [34, 35].

The adipose tissue can be collected by needle biopsy or liposuction aspiration. The collected adipose tissues should be washed with 5% penicillin/streptomycin (P/S)-containing phosphate-buffered saline (PBS) twice, and then the tissue samples should be put in a sterile tissue culture plate and cut into small pieces. The minced tissues are digested with 0.075% collagenase at 37°C for 30 min; the collagenase is removed by centrifuging the digested solution (adipose tissue and collagenase mixture) at 1200 g for 10 min; the adipose-derived stem cells-containing pellet is then resuspended with culture medium (alpha-MEM, Mediatech, Herndon, VA) supplemented with 20% of fetal bovine serum (FBS), 1% L-glutamine (Mediatech, Herndon, VA), and 1% penicillin/streptomycin (Mediatech, Herndon, VA). The cell suspension is filtered through 70-μm cell strainer and cultured in a humidified tissue culture incubator at 37°C with 5% CO_2. The medium is changed every second day until the cells reach 80–90% confluence. It is important that the adipose tissue should be treated within 24 hours, and the cells isolated from about 500 mg of adipose tissue should be added into one well of 12-well plates.

Adipose-derived stem cells (ADSCs) are readily accessible with no morbidity and display the capability to differentiate into several cell lineages, including the

spontaneous chondrogenic differentiation [30]. Compared with bone marrow-derived MSCs, adipose-derived MSCs from lipoaspirates are acquired using a less invasive procedure and are in large amounts [36]. ADSCs have been used for the repair of articular cartilage defect in nonweight-bearing areas [37].

2.4 Synovial-derived stem cells (SDSCs)

Synovial-derived MSCs have been isolated from human synovial fluid and synovium of the knee and the hip using the following protocols [38, 39]. The synovial tissue samples (wet weight 10–50 mg) were obtained aseptically from the joints and rinsed twice with Hanks' balanced salt solution (HBSS; Life Technologies, Carlsbad, CA) supplemented with antibiotic-antimycotic solution (100 units/ml penicillin, 100 μg/ml streptomycin, and 0.25 μg/ml amphotericin B; Life Technologies; Carlsbad, CA). The washed tissues were minced into small pieces and digested with 0.5 ml of 0.2% collagenase (Life Technologies, Carlsbad, CA) in high-glucose Dulbecco's Modified Eagle's Medium (DMEM; Life Technologies, Carlsbad, CA) at 37°C for 1 hour. The digested solution were removed by centrifugation at 1500 g for 10 min; the SDSCs-containing pellet was resuspended in growth medium (high-glucose DMEM supplemented with 10% FBS and 100 units/ml penicillin, 100 μg/ml streptomycin) and cultured in a humidified tissue culture incubator at 37°C with 5% CO_2. The medium was first changed at day 7 and changed every 3 days until the cells reach 80–90% confluence. It is important that the synovial tissue should be treated within 24 hours.

SDSCs obtained by above procedures have a higher proliferative capacity and chondrogenic potential than the MSCs derived from other sources [39, 40]. A small synovial tissue biopsy is an easily accessible source of autologous MSCs in the context of an explorative or therapeutic arthroscopy. These cells can be subsequently used for the regeneration of damaged cartilage. Autologous chondrocyte transplantation used for cartilage defect repair is limited by the availability of cells, particularly in elderly individuals, and by the well-known dedifferentiation events associated with chondrocyte expansion [39, 41]. Furthermore, SDSCs can be harvested relatively in a minimally invasive manner from synovial fluid and retain a particularly high capacity for chondrogenic differentiation and proliferation compared with MSCs obtained from other tissues, such as bone marrow or cartilage, those have second injury on healthy tissues. SDSCs may be an optimal alternative source of chondrogenic cells for cartilage defect repair.

A recent research has shown that xenogenic implantation of equine SDSCs into rat cartilage defect area leads to articular cartilage regeneration [42]. Horse joints are anatomically equivalent to the human knee and ankle; as a result, horses are widely used as large animal preclinical models for cartilage repair studies. However, large animal studies pose logistical and financial challenges, and small animal rodent models are cost-effective and have proven to be useful for proof-of-concept studies. There was no any immune response to the equine cells in the treated rat knees [42]. This result was also confirmed by a xenogenic transplantation of human MSCs in a critical size defect of the sheep tibia for bone regeneration [43]. Another xenogenic transplantation study has shown that human MSCs can enhance damaged pig intervertebral disc regeneration [44].

3. Growth factors used for cartilage regeneration

Growth factors play an important role in cartilage regeneration. Although some growth factors used in cartilage repair have been well documented [45], it is

necessary to summarize the most important chondrogenic differentiation-related growth factors in this chapter.

3.1 Transforming growth factor-beta family (TGF-β)

In cartilage repair, the four most thoroughly investigated members of TGF-β superfamily are TGF-β1, TGF-β3, bone morphogenetic protein-2 (BMP-2), and bone morphogenetic protein-7 (BMP-7) [45, 46]. It has been reported that TGF-beta 1 stimulates chondrocyte synthetic activity and decreases the catabolic activity of IL-1 [47]. TGF-β3 has been used to simulate extracellular matrix (ECM) synthesis in rabbit cartilage injury [48]. Bone morphogenetic proteins (BMPs) play an important role in the development of bone and cartilage. They are involved in the hedgehog pathway, TGF beta signaling pathway, and in cytokine-cytokine receptor interaction. Animal studies have shown that BMP-2 enhanced cartilage matrix production and blocked the IL-1-induced cartilage degeneration [49].

BMP-7 is another gold standard growth factor for cartilage repair [50]. It has been reported that BMP-7 inhibits cell proliferation but stimulates ECM synthesis in both SDSCs and BMSCs [51, 52].

3.2 Insulin-like growth factor-I (IGF-I)

IGF-1 is a multifunctional growth factor. The studies have found that IGF-1 play an important role in maintaining articular cartilage integrity. IGF-I deficiency has led to the development of articular lesions [53]. IGF-1 can not only enhance the synthesis of proteoglycans and upregulate the gene expression of collagen II but also can reduce the degradation of extracellular matrixes by decreasing the production of matrix metallopetidase-13 (MMP-13) [54–56]. The research has shown that IGF-1 exerts these functions in a dose-dependent manner [57]. Low dose of IGF-1 has a beneficial effect on bone remodeling by increasing bone formation markers in serum [58]. Higher IGF-1 levels in osteoarthritis (OA) osteoblasts could be correlated with bone sclerosis [59].

3.3 Fibroblast growth factor (FGF)

There are two FGF members used in cartilage regeneration. One of them is called as basic FGF (bFGF) or FGF-2, and the other one is called as FGF-18. FGF-2 increases anabolic material levels and decreases aggrecanase levels in cartilage. In vivo study has indicated that bFGF can promote cartilage repair [60]. However, some study indicated that the concentration of FGF-2 in synovial fluid samples of OA patients is approximately twice that of normal healthy knee joints [61]. Further studies found that FGF-2 promoted the repair of partial thickness defects of articular cartilage in immature rabbits but not in mature rabbits [62].

A rat model study has shown that FGF-18 stimulates chondrogenesis and cartilage repair in a concentration-dependent manner [63]. More studies have demonstrated that FGF-18 may present a therapeutic agent for osteoarthritis [64, 65]. A recombinant form of human FGF-18 has been used for cartilage injury treatment [66].

3.4 Platelet-rich plasma (PRP)

Platelets play a fundamental role in hemostasis and are a natural source of growth factors. More than 30 growth factors have been identified in PRP; among them, the following six growth factors play an important role in cartilage

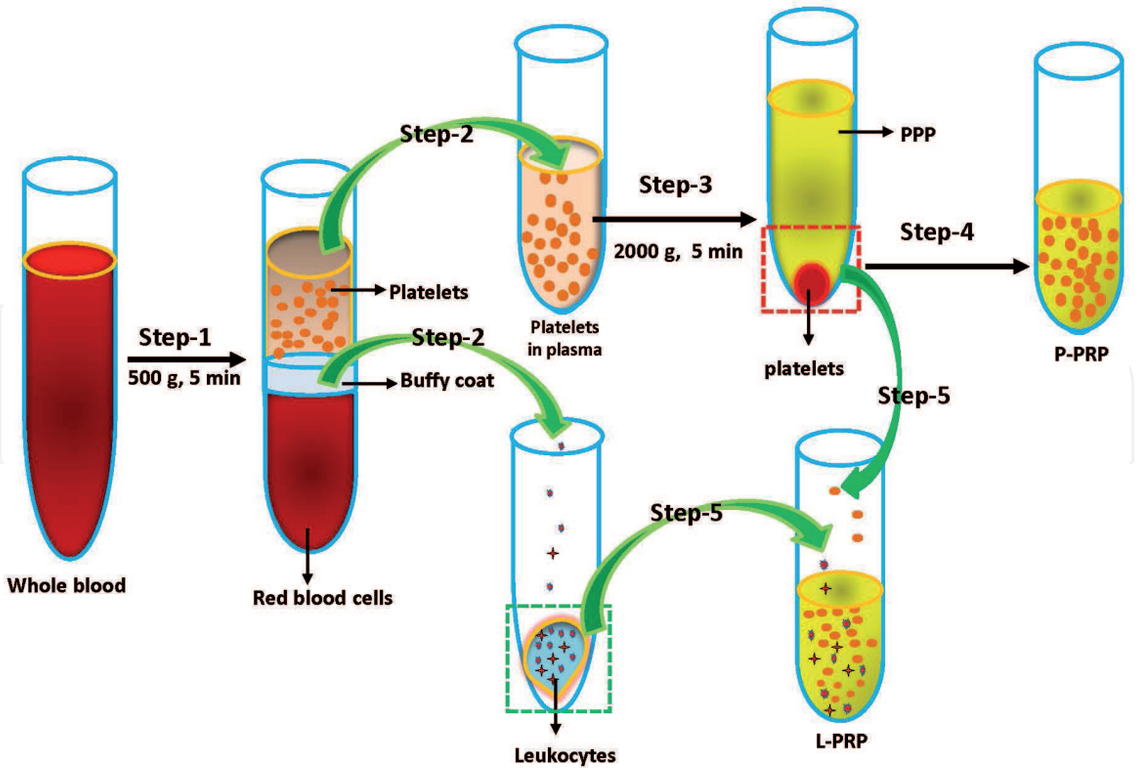

Figure 1.
Scheme of preparation of P-PRP and L-PRP from whole blood using five steps.

regeneration. They are TGF-β1, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), insulin-like growth factor 1 (IGF-1), epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF) [67, 68].

The concentration of platelet in PRP used for cartilage repair should be two to three times higher than that of baseline [69]. PRP can be prepared by the following five procedures (**Figure 1**). **Step 1:** blood (9 parts) is added into 3.8% sodium citrate solution (1 part) in a centrifuge tube and centrifuged at 500 g for 5 min to obtain three layers. **Step 2:** The supernatant at the top layer is transferred into a new tube, which is called as platelets-containing plasma, and the middle layer is transferred into another new tube, which is called leukocytes-containing plasma. **Step 3:** The platelets-containing plasma is centrifuged at 2000 g for 5 min to separate platelet-poor plasma (PPP) from the platelet pellet. **Step 4:** The platelet pellet is resuspended with appropriate amount of PPP to make pure PRP (P-PRP). **Step 5:** The leukocytes-containing plasma is mixed with platelet pellet and resuspended with appropriate amount of PPP to make leukocytes-containing PRP (L-PRP). Both P-PRP and L-PRP can be used for cartilage tissue engineering [70].

4. Bioactive molecules used for cartilage tissue engineering

Bioactive molecules used in cartilage tissue engineering include two kinds of materials: one is small molecular weight bioactive compound and the other one is high molecular weight materials including some nature biomaterials and synthetic polymers. Both of them play critical role in cartilage tissue engineering.

4.1 Kartogenin (KGN)

Kartogenin (KGN), a small heterocyclic molecule, has been discovered to enhance chondrogenic differentiation of human MSCs by regulating the

CBFbeta-RUNX1 transcriptional program [71, 72]. Animal studies have shown that KGN can promote rabbit meniscus regeneration [73] and wounded rat enthesis repair [70, 74]. *In vitro* and *ex vivo* experiments showed that KGN can reduce nucleus pulposus cell degeneration induced by interleukin-1beta (IL-1β) and tumor necrosis factor-alpha [75]. More recent studies indicated that KGN inhibited pain behavior, chondrocyte inflammation, and attenuated osteoarthritis progression in mice [76]; enhanced collagen organization and mechanical strength of the repaired enthesis of mouse rotator cuff [77]; and induced chondrogenic differentiation of dental pulp stem cells [78].

These findings invigorate research into small-molecule therapy and regenerative medicine for cartilage diseases. It also provides new insights into the control of chondrogenesis that may ultimately lead to a stem cell-based therapy for osteoarthritis (OA). KGN and other structurally related small molecules that can promote selective differentiation of MSCs into chondrocytes may prove to be extremely useful for improving the outcome of cell-based therapy by stimulating endogenous mechanisms for repair of damaged cartilage, thus enhancing the joint's intrinsic capacity for cartilage regeneration [79].

4.2 Simvastatin

Simvastatin is a kind of HMG-CoA reductase inhibitor, which is widely used therapeutically to reduce morbidity and mortality in patients with hyperlipidemic cardiovascular disease [80]. In addition to lowing low-density lipoprotein (LDL) cholesterol, statins have broad-range pleiotropic effects, including anti-inflammatory effects, which could exert an effect on synovium and cartilage [81]. Animal studies found that simvastatin markedly inhibited not only developing but also established collagen-induced arthritis [82]. Simvastatin inhibited the IL-6 and TNF-α production of human chondrocytes and cartilage explants in a concentration-dependent manner. Higher concentrations of simvastatin decreased nitric oxide (NO) production in both of human chondrocytes and cartilage explants [83]. Statin treatment has also been shown to positively regulate components of the extracellular matrix in a rabbit OA model [84]. More studies have shown that local application of simvastatin enhanced tendon-bone interface healing in rabbits [85]. These studies have shown that the effect of simvastatin on articular chondrocytes may provide novel insight regarding the role of cholesterol homeostasis and signaling during cartilage development.

4.3 Biomaterial scaffolds for cartilage tissue engineering

Biomaterial scaffolds play an important role in cartilage tissue engineering, which act as a carrier to deliver the cells and bioactive molecules to the damaged tissue areas and also work as a template for tissue regeneration, to guide the growth of new tissue.

There are two groups of biomaterial scaffolds used for cartilage tissue engineering. They are synthetic polymers and natural polymers. Commonly used natural materials in cartilage repair are agarose, alginate, chitosan, collagen, fibrin, and hyaluronan.

Agarose is a galactose polymer, which is suitable for cell encapsulation, especially for chondrocytes. When the ADSCs were cultured in agarose, they were differentiated into chondrocytes as evidenced by upregulation of the production of glycosaminoglycan (GAG) [86]. Moreover, dynamically loaded cell-seeded agarose hydrogel provided better graft tissues in a repair model of full thickness defects in rabbit joint cartilage [87]. PRP combined with agarose as a bioactive scaffold has shown to enhance cartilage repair [88].

Another extensively studied natural scaffold used for cartilage tissue engineering is alginate, which is a polysaccharide extracted from brown algae. Generally, alginate is hydrophilic and water-soluble, thickening in neutral conditions, which is of great importance for *in situ* hydrogel formation [89]. The good gelling properties of alginate-based scaffolds allowed them to be used as an injectable scaffold for the damaged cartilage repair. Human dental pulp stem cells were cultured in 3% alginate hydrogel and implanted in a rabbit damaged cartilage area. Three months after surgery, significant cartilage regeneration was observed [90]. More studies have been done by mixing the cells or/and growth factors with alginate solution to form gel microspheres in an isotonic $CaCl_2$ solution (**Figure 2**). The findings have shown that the cells are distributed homogeneously inside the gel microspheres. Those cell-containing alginate beads can be used as chondrogenesis-promoting scaffolds for cartilage regeneration [91, 92].

Chitosan is another natural polysaccharide extracted from crustacean shells, particularly from shrimps and crabs. Chitosan contains glucosamine and hyaluronic acid (HA), which are basic components of the native cartilage. Therefore, chitosan is widely used for cartilage tissue engineering. The recent studies have shown that chitosan-hyaluronic acid hydrogel promoted wounded cartilage healing in a rabbit model [93, 94].

Collagen is a main component of the extracellular matrix (ECM) of chondrocytes. Collagen gel has been widely used as substrates for articular cartilage substitutes [95, 96]. Injectable type II collagen gel has been used to treat full-thickness articular cartilage defects [97]. Clinical study has demonstrated that collagen gel can be used to replace cartilage and subchondral bone [98].

Fibrin hydrogels used for articular cartilage repair has been well documented by a review paper [99]. It has been reported that chondrocytes survived in the fibrin gel and enhanced their synthetic activity as evidenced by the increase of the production of GAG and collagen type II [100]. Human fibrin hydrogels have been approved by the Food and Drug Administration (FDA) for cartilage tissue engineering [101].

Hyaluronan is a main component of native cartilage. Similarly to the other native biomaterial scaffold, hyaluronan is the most widely used scaffold for cartilage tissue engineering. The studies have shown that hyaluronan upregulated collagen II expression and downregulated collagen I expression in human MSCs when they were cultured in hyaluronan gel [102].

Although bioactive natural scaffolds have very good biocompatibilities, their mechanical properties still need to be improved. In addition to natural bioactive scaffolds, synthetic materials provide good mechanical properties suitable for cartilage tissue engineering. These synthetic polymers are either used alone or combined with natural biomaterials for cartilage research.

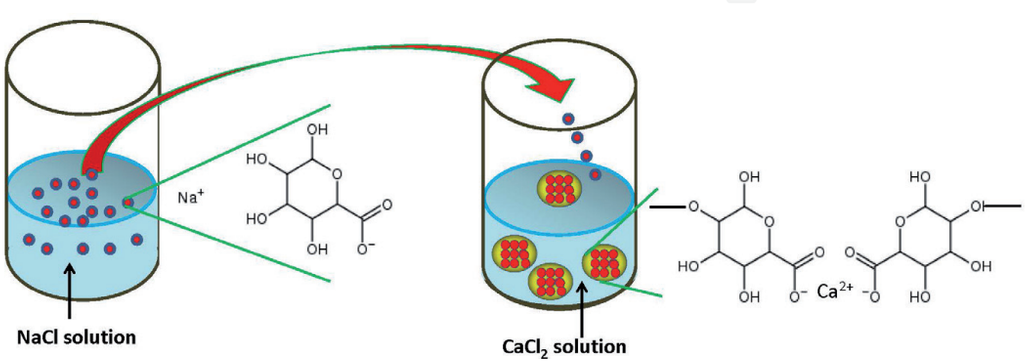

Figure 2.
The intermolecular network of alginate molecules is formed in calcium chloride solution. Alginate can be dissolved with sodium chloride (left image), but cross-linked each other in calcium ions-containing solution to form hydrogel (right image).

The most famous synthetic polymers for cartilage regeneration are polylactic acid (PLA), polyglycolic acid (PGA), and their copolymer polylactic-co-glycolic acid (PLGA). These polymers have a beneficial range of mechanical characteristics and high biocompatibility. Owing to the fact that PLA-PGA polymers have been successfully used in the clinics including sutures, screws, and pins [103–105], they are also used for articular cartilage defect repair in rabbits [106] and meniscal lesion repair in dogs [107]. Currently, two PLA-based scaffolds have been clinically used for cartilage repair: one is BioSeed ®-C and the other one is TRUFIT CB™. The PLA-based polymer scaffolds have shown significant improvement in patient outcomes for the treatment of post-traumatic OA and focal degenerative cartilage defects [108, 109].

Polyethylene glycol (PEG), a nontoxic synthetic polymer, is widely used with other natural materials to enhance their mechanical strength for cartilage tissue engineering. The studies have indicated that PEG-based hydrogel can promote chondrogenic differentiation of MSCs *in vitro* and *in vivo* [110, 111]. Injectable hydrogels used for cartilage tissue engineering have been well summarized by several review papers [112]. PEG-HA scaffold-treated patients achieved significantly higher levels of tissue fill in cartilage defects [113].

5. New surgical techniques for cartilage regeneration

Surgical techniques are more important for cartilage repair. In any cartilage repair techniques, the preparation of the defect bed to receive the implant is essential [114]. In order to promote cartilage regeneration, several new surgical techniques have been developed.

5.1 Arthroscopic surgery

Arthroscopic surgery is a common orthopedic procedure that is used in the diagnosis and treatment of problems inside a joint. Generally, the cartilage defect is measured with an arthroscopic graded probe, and the size and the shape of the defect are templated using sterile paper or aluminum that is subsequently used to prepare the graft if it is not an injectable gel form [114]. Besides the defect preparation and measurement, most operations can be done under an arthroscopy. Currently, arthroscopic surgery has been widely used for various damaged cartilage treatments such as degenerative meniscal tear [115] and osteoarthritis of the knee [116].

5.2 Open surgery

Open surgery is used for some arthroscopically inaccessible cartilage defects such as patella, trochlea, posterior femoral condyle, and some scaffolds that cannot be implanted arthroscopically [114]. This technique has been widely used in cartilage tissue engineering for animal surgery and clinical practice.

5.3 Microfracture surgery

Microfracture surgery is a surgical technique used to repair damaged cartilage by making multiple small holes in the surface of the joint to stimulate a healing response. This technique was developed in the early 1980s by Steadman and his colleagues. The technical details of microfracture have been well summarized [117]. Several animal studies have been completed to assess the microfracture technique [118, 119]. The functional outcomes of patients treated with microfracture for traumatic chondral defects have shown significant improvement [120]. Currently, microfracture surgical

technique is considered to be an effective arthroscopic treatment for full-thickness cartilage defect [121]. However, some studies have shown that the younger patients have better clinical outcomes and quality cartilage repair than older patients [122].

5.4 Mosaicplasty surgery

Mosaicplasty surgery is another common cartilage restoration technique in standard clinical practice. This technique was introduced into clinical application in 1992 [123]. Mosaicplasty surgical technique is based on the mosaic-like transplantation of several small, cylindrical plugs of bone and cartilage to provide an even resurfaced area. The long-term clinical follow-up results have shown that the mosaicplasty-treated patients can regain their pre-injury activity level [124].

The studies have demonstrated that the treatment of mosaicplasty in a single cartilage defect size one to five square centimeters of the femoral condyle resulted in clinically relevant better outcome than microfracture [125, 126].

6. Conclusions and future research on cartilage tissue engineering

Cartilage tissue engineering is to use a biomaterial scaffold, bioactive molecules, and cells to produce new cartilage under special conditions. The rapid progress in material science, life science, and engineering has resulted in advancements in the treatment options for various illnesses and diseases, especially for cartilage defects. However, the field of cartilage tissue engineering is still in developing stage. The number of potential variables in cartilage tissue engineering strategy is vast, and the key challenges remain to be addressed. As cartilage tissue engineering incorporates the fields of cell biology, nuclear transfer, and material science, personnel who have mastered the techniques of cell harvest, culture, expansion, transplantation, and polymer design is essential for the successful application of these technologies to build new cartilage and extend human life. The future research on cartilage tissue engineering should thus be aimed at investigating and evaluating tissue engineering approaches, as well as surgical techniques for cartilage repair in disease-compromised animal models to gain a better understanding of clinically feasible design. It is necessary to develop a model system for the study of normal and pathological cartilage tissues.

Conflict of interest

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