An overview of various treatment strategies, especially tissue engineering for damaged articular cartilage

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ABSTRACT

Many traditional procedures, including surgical methods such as microfracture of subchondral bone and soft tissue transplantation, have been widely used to treat damaged cartilage. However, there is still no definitive cure for cartilage defects. In recent decades, tissue engineering has raised hopes for the repair of defective cartilage. Different approaches are used for cartilage engineering, in which cells, scaffolds, and biological signals or growth factors may be used alone or in combination. Additionally, the imitation of the mechanical properties of the natural cartilage tissue by bioreactors is also helpful in this regard. It should be noted that in the transplantation of engineered cartilage tissue, there are challenges such as poor integration, inflammation and phenotypic instability that may lead to failure of neo-cartilage transplantation. Therefore, a comprehensive understanding of the multiple therapeutic approaches, including surgical procedures, cell-based methods and tissue engineering, should be obtained. The present review article provides this information, along with a variety of factors, including cells, materials, and biological/biomechanical factors required for the engineering of cartilage tissue, as well as the challenges ahead and their solutions.

Introduction

In the orthopaedic field, cartilage damage is often created due to congenital, trauma, cancer, or ageing diseases [1–4]. After the injury, cartilage tissue has a minimal ability to repair [5,6]. Traditional methods of cartilage repair include autograft transplantation of periosteum/perichondrium [7], allograft/cartilage transplantation of osteochondral [8,9], microfracturing [10] and autologous chondrocyte implantation (ACI) [11]. Major limitations of these methods are morbidity of donor-site and lack of integration of transplanted tissue [12–14]. The treatment used to overcome these limitations is particulated juvenile articular cartilage (PJAC) method, which is an autograft articular cartilage graft in which 1-mm cartilage cubes are taken from 13 years old donors [15]. Also, Autologous matrix-induced chondrogenesis (AMIC), which combines the microfracture method with matrix-based techniques, is another procedure that has been used for repair of cartilage defects [16]. As an alternative strategy, tissue engineering using stem cells and biodegradable scaffolds has raised many hopes [17] (Figure 1).

Cartilage engineered in tissue engineering has many uses in orthopaedic fields to repair damaged cartilage tissue [14]. In cartilage tissue engineering, various three-dimensional (3 D) scaffolds have been developed to mimic native ECM. The 3 D neo-cartilage tissues are then produced by the cultivation of the chondrogenic cells on the artificial scaffolds in a medium containing biochemical and biomechanical stimuli. Besides, sometimes, scaffold-free engineered products are used to avoid the side effects of the products resulting from the destruction of scaffolds [18,19]. Different natural or synthetic materials [20–23], various types of cells, including stem cells and primary cells [24,25], biochemical factors, including bone morphogenetic proteins (BMPs), Transforming growth factor-β (TGF-β) [26,27], fibroblast growth factors (FGFs) [28,29], insulin-like growth factors (IGFs) [30], SRY (sex determining region Y)-box (SOX) [31,32], Cartilage-Derived Morphogenetic Protein I and II (CDMP I and II) [33,34], and biomechanical stimuli, including shear, compressive and tensile stresses [35,36] have been investigated for the cartilage tissue engineering.

Despite the great efforts in cartilage tissue engineering, there are several challenges, including inflammation, poor integration and phenotypic instability that need to be addressed [37,38]. In summary, various methods such as enzymatic treatment and therapies based on growth factors, platelet-rich plasma (PRP), glycosaminoglycan (GAG)
combinations, caspase inhibitors, antioxidants and P188 surfactants have been evaluated to address these problems [39–41].

The present paper provides a comprehensive understanding of the issues related to cartilage tissue engineering, cartilage damage mechanisms, cartilage response to injury and traditional methods of repairing damaged cartilage, including subchondral bone microfracture, soft tissue grafts and cell therapy. It also mentioned some of the most effective factors, including antioxidants, caspase inhibitors, and anti-inflammatory drugs that protect chondrocytes from mechanical damage. Also, the present paper focuses on recent advances in the use of scaffolds, growth factors, and stem cells in improving cartilage repair.

**Articular cartilage injury and response of damaged tissue**

Common causes of joint degeneration are ligament/meniscal/joint capsule tears, intra-articular fractures and joint dislocations [42,43]. Understanding the mechanical aspects and loading forces on the articular cartilage is necessary to understanding the mechanisms of injury [44].

The extracellular matrix of articular cartilage is composed of water and macromolecules such as proteoglycans and collagens. Proteoglycans are the main cause of tissue stiffness, resilience and durability, and collagens are the main cause of tissue tensile strength and its shape. Therefore, slowly or suddenly applied loads have different effects on articular cartilage [45]. When the forces are applied slowly, fluid motion deforms the cartilage and reduces the force applied to the matrix framework. On the contrary, when the forces are suddenly and rapidly applied, the matrix framework must withstand a lot of force. Following high force, damage to the matrix network, cells, and subchondral bone occurs [45]. The severity and type of injury, as well as the repair and remodeling of the damaged surfaces, determine the risk of developing post-traumatic osteoarthritis [46,47]. Joint injuries are divided into three groups:

I. Chondral damage without visible disruption of articular cartilage
II. Chondral damage with visible mechanical disruption of cartilage
III. Osteochondral damage with visible mechanical disruption of cartilage and bone [48–52]

In cases where there is no mechanical disruption to the articular surface, chondrocytes can repair the damage. This is if they are safe from further injury [53]. While in the presence of mechanical disruption in the cartilage surface, activated chondrocytes are unable to repair the damage [54,55]. Also, in the presence of mechanical disruption in the subchondral bone and cartilage, the bone repair is performed, but complete cartilage repair is not done [54].

Blunt trauma and its repetition over a period of time can cause changes in the cartilage matrix, including a reduction in the matrix proteoglycan and collagen disruptions [56,57]. In these cases, if the complication is not severe and chronic, the matrix is regenerated by chondrocytes [58,59]. For example, a study of the effect of blunt trauma on articular cartilage demonstrated that articular cartilage could endure impact loads of up to 25 newtons per square millimetre (25 MPa) without being damage [60]. They showed that the impact loads above this level killed the chondrocyte and cleaved the cartilage. Besides, many of these acute or repetitive blunt traumas cause mechanical damage to the calcified cartilage zone-subchondral bone area, while the joint surface remains intact [61–62]. Many experimental studies have also shown that repetitive impact loads split the cartilage matrix lead to progressive destruction of the cartilage [63]. In this regard, the cartilage tissue after being injured and the body’s response to it, is damaged and destroyed in three phases [64,65]. The initial phase leads to apoptosis of chondrocyte (Figure 1).
and an increase in proinflammatory cytokines such as tumour necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), matrix metalloproteinases (MMPs), nitric oxide, and free radicals [66,67]. An example of a treatment that can target this phase is intra-articular injection of agents that inhibit proinflammatory cytokines [68]. Therapeutic procedures that target the second phase focus on the downstream effects of immediate response. Finally, the third stage involves events related to joint injury care. In general, the main goal of treatment in these cases is to reduce the inflammatory response, decrease the apoptosis of cartilage cells, reduce the destruction of the cartilage matrix and increase the construction of the new matrix [69–71].

In severe mechanical injuries, in addition to articular surface cartilage damage, the subchondral is also damaged, causing haemorrhage, fibrin clot formation, and inflammatory responses [51,52,72]. In this case, releasing various growth factors from collagen-associated platelets, including platelet-derived growth factor (PDGF), bone morphogenic protein (BMP), transforming growth factor-beta (TGF-β) and insulin-like growth factor (IGF-I and II), may improve the repair of osteochondral damages [73]. Also, by using biological interactions, cartilage damage caused by mechanical stress is reduced. For example, D’Lima and Haut showed respectively that caspase inhibitor reduces chondrocyte apoptosis [74–76], and P188 surfactant decreases the chondrocyte necrosis [77–79]. In addition, antioxidants also reduce the chondrocyte damage caused by mechanical stress [80,81].

**Major procedures for repairing articular cartilage**

In addition to traditional techniques such as subchondral bone microfracture, periosteum/perichondrium transplantation, and autologous chondrocyte implantation, scientists have used various techniques in recent years to repair damaged cartilage, including osteochondral allograft/autograft transplantation (OATS), autologous matrix-induced chondrogenesis (AMIC), particulated juvenile allograft chondrocytes (PJAC), and tissue engineering [82–85].

**Subchondral bone microfracture**

Throughout the history of damaged cartilage repair, many methods have been used to stimulate the bone marrow, such as subchondral drilling and microfracturing. The method of microfracturing was developed by Steadman [10,86]. In marrow-stimulating procedures, penetration of the subchondral bone leads to fill of defect by marrow-derived cells and blood, and eventually, a blood clot is formed. Wound repair cascade then occurs, including acute inflammatory response and cell chemotaxis. Finally, it leads to the creation of vascularised granulation tissue and the proliferation of high-potency mesenchymal precursor cells with the capacity to differentiate into different mesenchymal cell types. In the first few days after subchondral perforations, fibrous arcs are made at the surface of the defect that direct the growth of the mesenchymal cell along the long axes. After that, undifferentiated mesenchymal cells gradually differentiate into osteoblasts, fibroblasts, chondroblasts, and chondrocytes, which eventually lead to the formation of new bone in deeper zones and fibrocartilage in more superficial zones of the defect [87–90]. Therefore, full-thickness articular cartilage defects could be improved through the subchondral bone penetration, so that after about 6 to 8 weeks, bone and fibrocartilaginous tissues are formed by MSCs in the bone and cartilage defect sites [91–94]. Currently, surgeons use different methods to stimulate the formation of cartilaginous surfaces. These methods include abrasion of the articular surface, arthroscopic drilling, and making small fractures with tools such as awls [95–100]. The clinical effect of treating cartilage damage with microstructure has been described in a recent case-control study [101]. However, fibrocartilage is not mechanically comparable to hyaline cartilage and is easily degraded [102,103]. Achieving the formation of hyaline cartilage without ossified or fibrous tissue in cartilage defects is still challenging, which has ultimately led to extensive scientific efforts and researchs to find adjuvant therapies to improve repair with microfracture procedure [90].

**Autologous chondrocyte implantation (ACI)**

Method of cell transplantation, as an alternative surgical procedure, is used for providing cell populations to the defected areas of the chondral and osteochondral. Through this method, both undifferentiated cells and chondrocytes can be used for transplantation, which ultimately leads to the production of new cartilage matrix [104]. Also, autologous cell transplantation is used to treat cartilage defects [105,106]. Autologous chondrocyte implantation (ACI), introduced by Brittberg, is a two-step technique in which the chondrocytes are first harvested from a non-weight bearing part of the body, and then expanded in the laboratory. In the second stage, the chondrocytes are implanted at the site of the defect and protected by a periosteal flap (ACI-P) [11,107]. Because ACI is a two-step procedure and has a long recovery rate, it may not be ideal for the elderly population [108,109]. In many studies, the periosteum has been used as a cover for ACI (ACI-P) due to its chondrogenic properties. Subsequent studies in this area led to the development of absorbable covers such as porcine-derived type I/type III collagen (ACI-C) [110–112].

**Soft tissue grafts**

Providing a new cell source with a natural and organic matrix, as well as protecting host cells and grafts from over-load, are important benefits of the soft tissue grafts. Based on animal experiments and clinical studies, the researchers concluded that new cartilage could be created by transplanting soft tissues such as the periosteum or perichondrium [95,113,114]. An important factor in soft tissue transplantation is the patient’s age, which has a negative impact on the outcome [115–117]. Studies have shown that patients over 40 years old did not have a good results after arthroplasty [118,119]. Therefore, soft tissue grafts have a favourable outcome in young patients. Besides, transplant hypertrophy is
another limitation that can be caused by the use of periosteum as a covering material [120]. Also, the harvesting of periosteum prolongs the time of operation and needs greater surgical exposure [110]. Therefore, periosteotomy causes a lot of pain and arthrofibrosis. Later, to overcome these limitations, the use of matrix-induced autologous chondrocyte implantation (MACI) using a collagen bilayer seeded with chondrocytes, and porcine-derived type I/type III collagen as a cover (ACI-C) were developed, which are variations of the original periosteum-cover method [121].

**Osteochondral allograft/autograft transplantation (OATS)**

Transplantation of osteochondral grafts from a non-weight bearing donor site is a different method, performed in a one-step procedure [109,122]. Hangody and Karpati first introduced this procedure in the 1990s, which is still a popular technique [123,124]. This procedure can be done both in the form of autograft and allograft [125]. There is no risk of graft rejection and disease transmission in osteochondral autograft transplantation (OAT). However, since there are potential complications associated with autograft resection, resection is limited to smaller lesions [126]. On the other hand, osteochondral allograft transplantation (OCA) circumvents the size limitation and complications associated with autograft resection, which is an advantage of allograft transplantation. However, allografts have the potential to transmit disease, and their availability is limited [127].

**Autologous matrix-induced chondrogenesis (AMIC)**

Autologous matrix chondrogenesis (AMIC) was first introduced by Behrens, and its role in stimulating marrow was later confirmed by Steinwachs et al. [103,128]. AMIC is a one-step procedure that combines standard procedure of microfracturing with the collagen I/III matrix. This matrix covers the blood clot and mesenchymal stem cells (MSCs) in it, while allowing MSCs to differentiate into chondrocytes [129]. The major advantages of the AMIC method are that it is a single-step procedure and does not require cartilage removal leading to donor site complications, and is also a cost-effective method in which the cells do not need to expand in vitro [130]. On the other hand, the limitations of this procedure are that it should not be performed when there are inflammatory diseases (e.g. rheumatoid arthritis), kissing lesions (2 defects on opposite sides), tumours, associated fractures, and osteoporosis [130].

**Particulated juvenile allograft chondrocytes (PJAC)**

In recent years, there have been many advances in cartilage repair techniques that have led to the use of particulated juvenile allograft chondrocytes at the lesion site to produce the native cartilaginous surfaces [131]. The DeNovo NT Natural Tissue Graft (Zimmer, Warsaw, IN, USA) is the graft material accessible for this procedure (133). This method is based on the ability of juvenile cartilage cells to migrate from cartilage graft after fixation at the site of injury [132]. This allograft substance is composed of immature live chondrocytes in their native extracellular matrix. Donors in this treatment are usually younger than 13 years old, and any of the packages taken from them can be used to cover a 2.0 cm² defect as a one-step method for focal defects [133,134]. Fibrin glue is also used to fix these cartilaginous fragments at the site of the lesion [135,136].

**ECM analog and tissue engineering**

One way to deliver and protect cells in the treatment of chondral defects is to use an artificial matrix. These synthetic matrices also allow and stimulate the growth of host cells, increase the formation of new matrix, and improve the attachment of new cells and fresh matrix to each other and the host tissue [137,138]. Tissue engineering has proven to be very useful and promising in this regard. The primary purpose of cartilage tissue engineering is to repair diseased and damaged cartilage to restore its normal function. Tissue engineering has three main components, including cells, bio-functional factors and biomaterials, which are known as the tissue engineering triad (Figure 2). Much progress has been made in the use of various cells, factors and materials in cartilage tissue engineering, which are discussed below.

**Biomaterial engineering for construction of scaffolds**

In cartilage tissue engineering, synthetic and natural materials are used to make scaffolds that mimic the natural environment of chondrocytes [22,139–141]. Biomaterials used must be biocompatible and do not cause immune and inflammatory reactions [23]. They should be able to create a three dimensional (3-D) environment for binding, growth and differentiation of cells [142,143]. The final 3-D structure must also allow the transfer of nutrients, growth factors, gases, ions, etc. and be able to be transmitted to the body with minimal invasive properties [144,145]. In addition, biodegradability is also an important factor in tissue engineering that should be consistent with tissue remodelling [142]. The various techniques that have previously been used to build multi-material scaffolds for articular cartilage tissue engineering are as follows:

I. **Embedded solid structures** [146]: composite scaffolds are obtained by combining hydrogels containing multiple cells with rigid polymers. The purpose of using hydrogels in this method is to strengthen cell seeding in hard scaffolds [147–150].

II. **Embedded textiles and fibres for reinforcement** [146]: composite scaffolds are obtained by embedding the non-woven fibres in the hydrogel. The main advantage of this method is the good mechanical properties of the final scaffold [140,151–153].

III. **Multilayered designs include multilayered cartilage constructs, layered osteochondral constructs and multi-layered constructs from homogenous scaffolds. These composite scaffolds can create adhesions between the**
cartilage layer and its underlying bone layer [146,154–156].

IV. 3-D woven composite materials [146]: composite scaffolds are obtained by combining the 3D woven porous fibres with the hydrogel. Scaffolds made in this way show mechanical properties, including compressive, shear and tensile forces, similar to native cartilage [157].

Some researchers have used solid scaffolds for cartilage tissue engineering for large defects [158]. Among the solid scaffolds, collagen sponge was widely used to the cartilage engineering [159,160]. On the other hand, among the various types of 3D scaffolds, hydrogels, three dimensional and hydrophilic polymeric networks, have found more application in cartilage tissue engineering due to their ability to absorb water and biological fluids [161]. For example, hydrogels made from polyethylene glycol were used in cartilage tissue engineering due to their high water absorption, biocompatibility, biodegradability, elasticity, and nutrient transport [162–164]. In recent years, various types of hydrogels, including thermos-responsive hydrogels [165,166], photosensitive hydrogels [19,167,168] and hydrogels loaded with the chondroinductive [171] or chondroprotective factors [170,171], have been studied. It should be noted that in the design of hydrogels, there must be a balance between different characteristics, including chondroinductive properties, electrical conductivity, mechanical properties, biocompatibility and degradation rate [158,172].

Among the various types of hydrogels, Cell-laden hydrogels were widely used as bioink in 3D bioprinting approach for cartilage tissue engineering [21,173–175]. In recent years, 3D bioprinting technology in the field of tissue engineering, especially cartilage, has developed rapidly [140,176,177]. The purpose of 3D bioprinting is to provide structures using automated systems and the characteristics of cells/tissues to deliver living cells, scaffold materials, growth factors and nutrients among other substances [140]. In this system, cells and bioactive agents are usually deposited by hydrogels in layers, causing biopaper or bioink [178]. In recent years, many advances have been made in this field, which has led to the introduction of new methods in the field of cartilage tissue engineering. Robotic-assisted 3D bioprinting is one of these methods that has had promising results in the reconstruction of damaged cartilage tissue in vivo [179]. These types of robotic devices are minimally invasive surgical techniques that offer many additional benefits, including better safety, faster healing, and shorter hospital stays – the result of less traumatic surgery [177,180].

Various materials are used to make different scaffolds in cartilage tissue engineering. The most common biomaterials used in cartilage tissue engineering are as follows:

I. Proteins, including collagen (Maix®, MACI®, MaioRege®, Atelocollagen®), fibrin (Tissucol kit®), silk and gelatine [20,181–184].

II. Polysaccharides, including Chitosan (BST-CarGel®), Hyaluronic acid (HYAFF-11®), Cellulose, Alginate [185–187].

III. Synthetic materials such as Polyethylene glycol, Polylactic acid, Poly(lactic-co-glycolic acid) (Bio-Seed®-C) [188]
IV. Different combinations of natural materials and synthetic polymers (composite materials) such as MaioRegen\textsuperscript{V}, Chondro-Gide\textsuperscript{V}, and Maix\textsuperscript{V} are the protein-based products that are clinically used to transplant autologous chondrocytes [181,182]. Also, Atelocollagen\textsuperscript{V} is a type I collagen gel used for three-dimensional culture and \textit{in vivo} transplantation of autologous chondrocytes [183] or mesenchymal stem cells (MSCs) [184].

Hyalograft\textsuperscript{V} (HYAFF-11\textsuperscript{V}) is a hyaluronic acid matrix with autologous chondrocytes [185], which has led to clinical success in human articular cartilage [186]. These highly porous sponges can enhance chondrogenic differentiation [191]. Also, BST-CarGel\textsuperscript{V} scaffold is another polysaccharide-based matrix, which is made of β-glycerophosphate and chitosan, and has been clinically successful [187].

Bio-Seede\textsuperscript{V}-C is a porous structure matrix based on synthetic materials including polylactic acid (PLA), polyglycolic acid (PGA), and polydioxanone, and is clinically capable of forming hyaline cartilage [188]. Besides, the combination of the ceramics with natural and synthetic polymers was used as a scaffold in cartilage tissue engineering [189]. For example, MaioRegen\textsuperscript{V}, which was made of type I collagen and hydroxyapatite, presented promising results [190]. The chondrogenic differentiation of mesenchymal stem cells and phenotypic stability of chondrocytes on these materials have been demonstrated in various experiments.

In addition to the materials mentioned earlier, the decellularized matrix, as a natural material, has been used in many cartilage tissue engineering studies and has yielded promising results [192,193]. Because the structural and mechanical properties of these types of biocompatible scaffolds are similar to native tissue, cellular responses are well performed on them [22,196]. In a study, decellularized cartilage particles (DCC) were chemically constructed, and then cartilage-forming was investigated [195]. In this study, it was found that DCC significantly increased the chondroinduction of rat bone marrow-derived mesenchymal stem cells (rBMSCs). On the other hand, another advantage of this type of material is that it can be used as a xenograft to regenerate cartilage tissue [196].

Another item used in cartilage reconstruction is sheet technologies, including cell sheet, electro-spun sheet, and the previously described acellular matrix sheet. Because the use of synthetic materials causes complications such as inflammation and other immune responses, the researchers created a cell sheet method that is often developed at temperature-sensitive cultivation dishes coated with Poly N-isopropyl acrylamide (PIPAAm) [197,198]. However, because it is difficult to manipulate stacked cell sheets, the researchers created acellular matrix sheet technology [199]. With a better understanding of native extracellular matrix nanostructures, electro-spun sheet technologies have also been developed that are more manipulative and controllable than acellular matrix sheets [200]. In a study conducted by Xue, electro-spun fibrous sheets made of gelatine/polycaprolactone (GT/PCL) were used to reconstitute cartilage [201]. They used the electro-spun fibres for 3D cartilage engineering with chondrocytes through a sandwich model. Finally, they achieved promising results. They found that these types of electro-spun sheets could provide a biomimetic microenvironment, while also having little degradation and inflammation [201].

\textbf{Chondrogenic cells}

One of the main components of cartilage tissue engineering is cells [202]. In cartilage injuries, to produce the hyaline tissue, appropriate cells that can produce hyaline or hyaline-like tissue should be used [20,203]. In general, chondrocytes, stem cells, genetically modified cells and fibroblasts have been tested in cartilage tissue engineering. However, stem cells and chondrocytes are the main chondrogenic cells in cartilage regeneration and engineering. Chondrocytes can be obtained from a variety of sources, such as nasal septum, auricular cartilage, costal cartilage, and articular cartilage [204]. Each of these chondrocytes with different sources is
tissue-specific and creates tissue with the original characteristics [204]. Carticel® and Celect® are procedures containing articular autologous chondrocytes that have been marketed [205]. In order to autologous chondrocyte implantation for the repair of femoral condyle cartilage defects, Carticel® is used, which is a method for extraction and in vitro expansion of autologous chondrocytes [206]. Another method used for transplantation of the autologous chondrocytes is Celect®, which is used only for the isolation and proliferation of chondrocytes containing a specific marker [207].

On the other hand, MSCs as multipotent cells, can be differentiated into various cell types, including osteoblasts, adipocytes, chondrocytes, as well as neuronal and myogenic cells [208]. MSCs were isolated from muscles, adipose tissue, bone marrow, perichondrium and periosteum [209]. Among them, MSCs separated from fat, bone marrow, synovium and muscle were considered as the chondrogenic cells [210]. MSCs are very promising in tissue engineering because they modulate the immune system and do not express the major histocompatibility complex (MHC) class II, which is responsible for the immune rejection of the transplant [211]. Therefore, it is suggested that these cells be used as allogeneic cells. For example, Cartistem® , recently approved by Korean Food and Drug Administration, is made of allogeneic stem cells isolated from umbilical cord blood and used to treat osteoarthritis (OA) [212]. Human induced pluripotent stem cells (hiPSCs) are another type of cells for cartilage tissue regeneration that are obtained from somatic cells by reprogramming transcription factors (Sox2, Oct4, Myc and Klf4) [213]. Recently, the development of efficient chondrocytes from hiPSCs has been reported [214]. Because these cells are patient-specific cells and are unlikely to be rejected by the immune system, they are very promising in cartilage tissue engineering and regenerative medicine. Another type of pluripotent cells that can be useful in cartilage tissue engineering is embryonic stem cells (ESCs), which first form the embryoid bodies that ultimately differentiate into chondrocytes [215]. Embryonic stem cells (ESCs) have a great advantage due to their pluripotency and unlimited self-renewal, and are widely used [216]. Because these cells are immortal, they can potentially provide an unlimited supply of chondrogenic cells, which is why they are important in regenerating or replacing damaged cartilage tissue [215,217]. Despite their usefulness in cartilage tissue engineering, the extraction of these cells is associated with ethical and political issues that limit their use [218]. Also, undifferentiated ESCs can cause tumours and increase the risk of developing teratomas in the body, which is another limitation of the use of these potent cells [219].

Bio-functional factors and chondrogenic differentiation

In addition to scaffolds and suitable cells, appropriate stimuli should be used to differentiate the cells into the desired chondrocytes and form an extracellular matrix [220]. Numerous studies have shown that multiple factors, such as Transforming Growth Factor β (TGFβ) [209,221], Bone Morphogenic Proteins (BMPs) [222,223], Cartilage-Derived Morphogenetic Protein I and II (CDMP I and II) [224,225], Insulin-Like Growth Factor (IGF-1) [221], SRY (Sex determining Region Y)-box (SOX) [218,226] and Fibroblastic Growth Factor (FGF) [218,227,228] are effective in achieving this goal (Table 1). Treatments based on combining growth factors with other approaches such as transplantation of cell and scaffold have been developed in recent years.

Moreover, various aspects of the environment, including mechanical stimuli (shear, compressive and tensile stresses) [229], low oxygen tension [230–233] and 3D culture (Table 2) [234,235], are also effective in the chondrogenic differentiation of MSCs.

The main function of cartilage tissue is mechanical resistance to mechanical stresses including compressive, shear and tensile forces, and creating an environment with a minimum coefficient of friction (0.03–0.06) [247]. Compression, shear and tensile modulus for cartilage tissues are estimated to be from 0.08 to 2 MPa, 0.05 to 0.25 MPa and 5 to 25 MPa, respectively [248]. These unique mechanical properties of cartilage tissue are due to the presence of abundant water, collagen, glycosaminoglycans and their specific organisation. Therefore, the creation of neo-cartilages with acceptable mechanical properties that have mechanical resistance in the environment inside the body is one of the main criteria in the engineering of cartilage tissue. Various studies have shown that imitation of the mechanical conditions of cartilage tissue by bioreactors increases the chondrogenic differentiation [249,250]. Bioreactors create different physicochemical conditions of native cartilage tissue in the laboratory and can control environmental factors such as temperature, pH, O2 stress, nutrient supply, and waste disposal [251]. Various bioreactors have been used in this regard, such as rotating bioreactors [252], wavy-walled bioreactors [253] and perfused vessels [254], all of which, along with growth factors, affect cell proliferation, morphology, and ECM deposition [255,256].

Challenges in cartilage tissue engineering

Despite many advances in engineering cartilage tissue in vitro, challenges remain in the successful clinical transfer of engineered cartilage tissue. These problems, which often arise after transplantation of engineered tissue into the body, include phenotypic instability, poor integration, and inflammation (Figure 4). A basic problem in cartilage tissue engineering is the poor integration of engineered tissue with the surrounding environment. Factors influencing tissue integration include cell phenotype in transplanted tissue, donor age, cell death at the edge of the wound, and the maturity degree of engineered structures [37,257]. The extracellular matrix components of native cartilage tissue, which include collagen and glycosaminoglycans (GAGs), can interfere with integration [258]. Native tissue matrix can impede the integration of engineered tissue by preventing adhesion and diffusion of matrix proteins and cells [258]. Interestingly, traditionally in tissue engineering, researchers are also looking to stimulate increased production of these components at levels similar to native tissue, which could be an intervening factor for
integration. Enzymatic treatment is one of the ways to deal with this problem, which enhances the integration by disrupting specific molecules of the matrix [259]. Hyaluronidase and collagenase improve integration with implanted cartilage by increasing cell density at the wound site [259]. It has also been shown that temporary reduction of GAG at the cartilage surface by chondroitinase-ABC (c-ABC) and trypsin, respectively, improves coverage by repair cells and integration of restored tissue [218]. In order to better integrate the implanted tissue, in addition to enzymes, a series of factors that disrupt the formation of cartilage matrices, such as β-aminopropionitrile (BAPN), Insulin-like Growth Factor 1 (IGF-1) and para-nitrophenyl-β-D-xyloside, are used, which disrupt the formation of proteoglycans and lead to better integration [260]. Although the temporary absence of matrix components such as GAG and collagen in engineered cartilage provides a strong integration, their presence is also essential for stress resistance in the body. Therefore, bioactive agents such as c-ABC and lysyl oxidase-like 2 (LOXL2), which play a dual role and are effective in improving integration as well as increasing collagen production and traction, should be used in tissue engineering to address this challenge.

Another challenge that may arise in cartilage tissue engineering is inflammation at the transplant site. Although the exact mechanisms of action of inflammatory cytokines in cartilage problems, especially osteoarthritis, need further clarification, inflammation is now recognised as a major factor in the development and progression of osteoarthritis [38]. Severe inflammatory reactions are observed in joint injuries that cause post-traumatic osteoarthritis [261]. Joint injuries increase the inflammatory cytokines in the articular cavity, which ultimately increase the cartilage destruction. Inflammatory cytokines in arthritic joints include Interleukin-1β (IL-1β) and tumour factor necrosis factor-α (TNF-α), which are involved in the progression of cartilage destruction [38]. Also, several in vitro studies have shown that the destructive effects of an inflammatory environment can affect the engineered cartilage tissue inside the body. For example, it has

### Table 1. Principal growth factors used in cartilage tissue engineering.

| Growth factor Type | Mechanism | Reference |
|--------------------|-----------|-----------|
| Transforming Growth Factor β (TGFβ) | TGFβ facilitates the repair of damaged cartilage tissue so that it is completely integrated into the surrounding tissue. | [200,221] |
| Bone Morphogenic Proteins (BMPs) | BMPs act as chemotaxis factors for mesenchymal stem cells. | [222] |
| Cartilage-Derived Morphogenetic Protein I and II (CDMP I and II) | CDMPs are essential for joint and cartilage morphogenesis. | [224,225] |
| Insulin-Like Growth Factor (IGF-1) | IGF-1 is an essential factor for the proliferation, differentiation and production of matrix in articular chondrocytes. | [218,221] |
| SRY (sex-determining region Y)-box (SOX) | SOX-9 transcription factor, as an essential molecule, regulates cartilage formation through chondrogenic differentiation. | [218,226] |
| Fibroblastic Growth Factors (FGFs) | FGFs increase the expression of SOX-9. | [218,227,228] |

### Table 2. Effective environmental factors in chondrogenic differentiation of MSCs.

| Environmental chondrogenic factors | Effects | Reference |
|-----------------------------------|---------|-----------|
| Mechanical stimuli                | Stimulation of chondrogenic differentiation of MSCs | [236–239] |
| Low oxygen tension                | Upregulation of chondrocyte phenotype by hypoxia-inducible factors (HIFs) | [231,240–243] |
| 3D culture                        | Increase in matrix fabrication | [244–246] |
been shown that both the use of an osteoarthritic synovium-derived medium and the activation of the nuclear factor kappa B (NF-κB) pathway using IL-1β and TNF-α inhibit chondrogenesis of MSCs [262,263]. In addition, inflammation in the arthritic joint can prevent the integration of neo-cartilage tissue into the joint [37]. Therefore, for better cartilage repair, an environment should be provided to control the inflammation. For this purpose, growth factors that suppress IL-1β such as IGF-1, platelet-derived growth factor (PDGF)-bb and bone morphogenetic proteins (BMP-2 and BMP-9 [40,41]), GAG compounds such as glucosamine, hyaluronic acid and chondroitin sulphate, which have anti-inflammatory properties [264,265], and platelet-rich plasma (PRP) [39,266], are used. PRP includes various levels of chemokines/cytokines, adhesive proteins, and growth factors that restore tissue function and reduce pain in osteoarthritic joints [266,267].

Another common challenge for the cartilage tissue is **phenotypic instability**, which creates fibrous cartilage that does not have the function of hyaline cartilage [268]. Stem cells chondrogenesis is mostly associated with increased collagen expression (type X) and hypertrophic differentiation. These complications are especially common in osteoarthritis and are stimulated by some growth factors, ECM degradation products, and cytokines [269,270]. Therefore, the osteoarthritis environment is likely to cause hypertrophic differentiation of transplanted cells in cartilage tissue engineering. On the other hand, the development of hypertrophic phenotype in engineered tissue increases mineralisation [268]. To overcome the challenge of phenotypic instability in engineered tissue, much information needs to be obtained about signalling pathways and molecules associated with hypertrophy processes. For example, a combination of SOX-5/-6/-9 is able to suppress hypertrophic markers and osteogenic markers in human MSCs [271,272]. Also, Nkx3.2, which is involved in the development of cartilage as a transcription factor, demonstrates the potential to prevent hypertrophy by inhibiting runt-related transcription factor-2 (RUNX-2) function [273,274]. Besides, studies have shown that parathyroid hormone (PTH), parathyroid hormone-related peptide (PTHrP), and BMP-7 molecules, while inducing chondrogenic differentiation, inhibit type X collagen in MSCs, thereby inhibiting hypertrophic differentiation [275–277].

**Conclusions**

Tissue engineering, which is continually evolving as an interdisciplinary field of research, could be a permanent solution to many incurable diseases, especially cartilage damage, which is often complicated and not completely curable. Previously, surgical procedures such as subchondral bone microfracture and soft tissue transplantation were the main methods of treating damaged cartilage. Later, cell therapy and now tissue engineering became more suitable options for this purpose. Therefore, it seems that the engineering of cartilage tissue and the production of neo-cartilages from natural or synthetic biomaterials that have the ability to release effective factors in the treatment of cartilage damage is a more effective therapeutic approach for cartilage diseases, especially OA. However, before using this new treatment strategy, it is necessary to evaluate a large number of compounds of biological substances, cells, biomaterials and various agents such as antioxidants, anti-inflammatory agents, etc.

**Authors’ contributions**

Azizeh Rahmani Del Bakhshayesh conceived the study and participated in its design and coordination. All authors helped in drafting the manuscript. All authors read and approved the final manuscript.
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