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Current Advances in Regenerative Medicine for Articular Cartilage Injury: Progress and Market Trends

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Abstract

Today, treatments of cartilage and osteochondral lesions are routine clinical procedures. Treatment of large Articular Cartilage (AC) defects is technically difficult and complex, often accompanied by failure. Articular cartilage is a highly specialized connective tissue with limited ability to repair itself after injury due to a lack of blood vessels, lymph, and nerves. Therefore, without sufficient and potent intervention, cartilage lesions can easily lead to progressive tissue degeneration, disabling joint pain, and eventually the degenerative disease, Osteoarthritis (OA). Various treatments for cartilage regeneration have shown encouraging results, but unfortunately, none of them have been the perfect solution. New minimally invasive and effective techniques are being developed. The development of tissue engineering technology has created strong promise to engineer or regenerate functional and healthy articular cartilage. In this technology, potential stem cell sources are mainly supplied with pluripotent stem cells and mesenchymal stem cells from various sources. In the meantime, some such as BioSeed®-C and NOVOCART® have been marketed. In this review, the common techniques of articular cartilage reconstruction and the clinical application of articular cartilage tissue engineering are described in detail.

Keywords: Articular cartilage; Cartilage gene therapy; Cartilage product; Regenerative medicine; Tissue engineering; Transplantation methods

Introduction

Articular cartilage is a complex organ with connective tissue that has a limited repair capacity [1]. Usually, small lesions that penetrate the subcutaneous bone layer are repaired by creating a fibrous scar, but extensive injuries require medical intervention. In recent years, a variety of surgical and non-surgical treatments have been developed to repair cartilage, but the complete treatment of lesions larger than 2-4 mm of the articular cartilage remains a therapeutic challenge [2].

Recently, tissue engineering and regenerative medicine using stem cells and biomaterials were able to revolutionize tissue and organ regeneration [3]. This method allows custom design for tissue regeneration and offers tissue replacement that mimics native tissue without adverse effects such as suppression of the immune system or contamination of the donor disease [4]. One of the major challenges in this method is designing appropriate scaffolds with the structure of native tissues [5]. Tissue-engineered cartilage must be highly compatible to prevent acute immune response after transplantation, also it must have special properties such as the ability to combine with subcutaneous bone and adjacent cartilage, mimic the mechanical properties of natural cartilage to maintain function, and withstand long-term loads [6].

In this study, new methods of repairing extensive joint cartilage injuries using different cellular sources and synthesis techniques are reviewed and a list of commercial products used in the treatment of cartilage injuries is presented.

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Tissue Engineering Strategies for Articular Cartilage Regeneration

Current strategies for repairing articular cartilage, including surgical and non-surgical treatments, have not yet provided long-term solutions for repairing large articular cartilage lesions [2]. Tissue engineering and regenerative medicine can provide alternative treatment strategies using appropriate scaffolding, cells, and biochemical and biomechanical stimuli [3]. This method allows a custom design to regenerate native tissue without side effects such as infection transmission or the use of immunosuppressive drugs [5]. Tissue-engineered cartilage must be biocompatible and can connect with the subcutaneous bone and adjacent cartilage. In addition, it should be able to mimic the physical and mechanical properties of native tissue [6].

Scaffold for Articular Cartilage Tissue Engineering

In recent years, various scaffolds including synthetic or natural materials such as polylactides, polyglycolide, hyaluronic acid, collagen, and silk have been studied for articular cartilage tissue engineering [7]. In previous studies, a matrix derived from decellularized cartilage was used as a natural source for scaffolding in cartilage regeneration. This substrate was able to synthesize the extracellular matrix of cartilage by inhibiting the hypertrophic differentiation of embedded Mesenchymal Stem Cells (MSCs). The results also showed that the synthesized extracellular matrix could support the differentiation of mesenchymal stem cells into fibroblast and fibrochondrocyte phenotypes [8]. Hydrogels are another class of materials used as scaffolds in articular cartilage tissue engineering. These materials have received a lot of attention due to their injectability and ductility compatible with irregular defects of articular cartilage. On the other hand, due to the advent of 3D printing technology, achieving the right hydrogel can be a big step in the design and customization of graft implants in the repair of cartilage defects. In addition, in this technology, cells and growth factors can be included in the scaffold structure during synthesis [9]. In previous research has used synthetic polymers such as polycaprolactone and polylactic acid, as well as natural sources such as alginate and hyaluronan to create custom anatomical scaffolds for articular cartilage in 3D printers [10]. Stimuli-responsive hydrogels or smart hydrogels are a group of hydrogels in which a specific transition occurs due to small changes in the environment [11]. This group of hydrogels in response to various external physicochemical factors such as chemical stimuli [12], temperature changes [13], solvent type [14], pH [15], ionic strength [16], wavelength or light intensity [17] or electric fields and magnetically are sensitive [18].

The use of smart hydrogels in actuators, sensors, scaffolds, and drug delivery has received considerable attention because of their rapid response to environmental stimuli, which can cause significant changes. Designing scaffolds based on intelligent injection hydrogels with nanostructured properties and rapid response to stimuli can be an appropriate option to meet all the essential needs of cartilage regeneration [11]. One of the necessities of transferring the functional properties of native tissue to the product of tissue engineering is the design and production of scaffolds that can mimic the mechanical properties of native tissue. For example, studies have shown that polyethylene glycol and chondroitin sulfate-derived hydrogels produce structures with stiffness gradients (0.005-0.06 MPa) that can mimic the glycosaminoglycan gradient in articular cartilage [19].

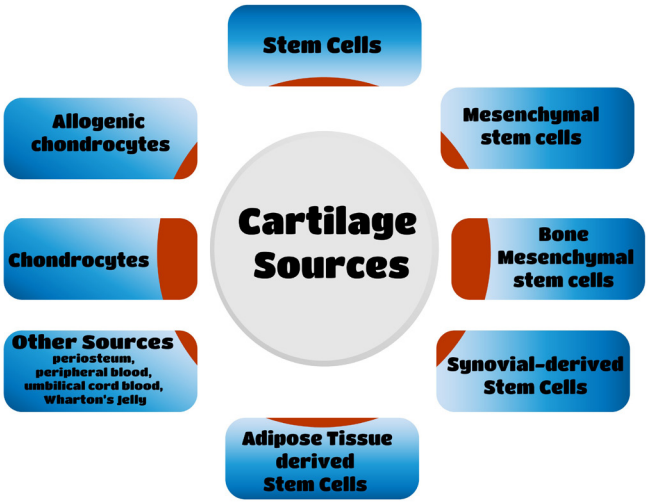

Figure 1: Viable cell sources for cartilage tissue engineering and validated in animal models.

Current Cell Sources for Articular Cartilage Damage

The ultimate goal of cartilage repair is to find an ideal cell source that can be easily isolated, expanded, and cultured to express and synthesize cartilage-specific Extracellular Matrices (ECM), such as type II collagen and aggrecan. Stem cells and chondrocytes have been investigated for their potential as viable cell sources for cartilage tissue engineering and validated in animal models (Figure 1) [20].

Figure 1: viable cell sources for cartilage tissue engineering and validated in animal models

Chondrocytes

Chondrocytes are resident cells of articular cartilage that produce ECM components. As such, they are regarded as the logical choice for cartilage tissue engineering. Indeed, chondrocytes isolated from various tissues, including ribs, nasal septum, ear, or articular cartilage, have been utilized for cartilage tissue engineering [20]. Recently, various studies have focused on articular chondrocytes as a viable cell source for cartilage repair. Autologous Chondrocyte Implantation (ACI) has been regarded as a preferable, long-term treatment prescription. When compared to multipotent marrow cells, passaged articular chondrocytes have the greater innate potential to form hyaline-like cartilage [20]. Nowadays, Matrix-induced Autologous Chondrocyte Implantation (MACI) is used as one of the most extensive methods for the clinical treatment of articular cartilage defects. One major limitation of using chondrocytes is their instability in monolayer culture, which results in their loss of phenotype [21].

As previously mentioned, most efforts to regenerate cartilage have focused primarily on chondrocytes from immature animals. Neonatal and young chondrocytes exhibit faster growth rates, better capacity for rapid expansion in vitro, and greater chondrogenic potential compared with chondrocytes isolated from older donors.

However, these limitations can be eliminated by the addition of growth factors such as platelet-derived growth factor (PDGF), Transforming Growth Factor beta 1 (TGFβ-1), TGFβ-2, fibroblast growth factor 2 (FGF-2), and/or Insulin Growth Factor 1 (IGF-1). Nevertheless, research is still necessary to optimize culture techniques for aged chondrocytes and define their potential clinical uses and limitations [20].

Allogeneic Chondrocytes

Allogeneic chondrocytes have been used with some success in animal models involving rabbits. Although antigens are strongly expressed on chondrocytes, they have been revealed to be non-immunogenic and exert immunomodulatory effects, which make allogeneic chondrocytes an ideal alternative source. The advantages of the allogeneic approach are single surgery, high seeding density with early culture, and decreased dedifferentiated cell use [22]. The isolation of chondrocytes from cartilage ECM in culture causes a loss of the chondrocyte property and results in the conversion of the chondrocytes to fibroblastic cells [23].

Stem Cells

Stem cells are self-renewing cells that can produce more stem cells through mitosis because of their undifferentiated biological character or can differentiate into specialized cells. Stem cells lay a foundation for organ systems and tissues and play various roles in tissue repair, development, and disease progression. They can produce a substantial number of cells, facilitating the restoration of larger defects to help overcome critical challenges in tissue engineering and regenerative medicine [20]. In cartilage regeneration, stem cells are obtained from the patient or other donors and then cultured in vitro in a certain microenvironment. Cells are then proliferated and differentiated towards a chondrogenic lineage under a controlled environment, including hypoxia, high-density microenvironment, co-culturing, and specific growth factors. Subsequently, along with bioactive factors and scaffold materials, these cells may be implanted into cartilage defect sites and finally, cartilage regeneration may be achieved [24]. In recent years, the application of MSCs and mesenchymal progenitor cells, including Adipose-Derived Stem Cells (ADSCs), Bone Marrow-Derived Stem Cells (BMSCs), and Embryonic Stem Cells (ESCs) and Induced Pluripotent Stem Cells (iPSCs), has emerged as an attractive strategy to improve the reparative processes of cartilage lesions compared with implantation of other cell types, such as articular chondrocytes. They are regarded as the most suitable or promising cell sources for cartilage tissue engineering and regeneration [20].

Mesenchymal Stem Cells (MSCs)

Mesenchymal Stem Cells (MSCs) are alternative cell sources for cartilage repair. They possess a high proliferation capacity and can be obtained from a variety of tissues, including adipose tissue, bone marrow, periosteum, synovium, umbilical cord vein and placenta [20,23]. MSCs exhibit multilineage potential, such that these cells can differentiate in to chondrogenic, osteogenic, and adipogenic lineages in vitro. MSCs can undergo chondrogenic differentiation when cultured as micro-pellets in the presence of a defined medium containing TGFβ and dexamethasone. Despite MSCs' ability to differentiate into chondrocytes, expansion seems to reduce such ability in these cells. More evidence is needed to observe the efficiency of transplanted MSC-derived chondrocytes in cartilage repair in vivo. The transplanted cells induce tissue repair through their secreted soluble factors [23]. MSCs secrete a wide variety of matrix molecules, bioactive factors, growth factors, colony-stimulating factors, cytokines, and chemokines. These secretions can modulate the microenvironment and affect cell migration, proliferation, and differentiation. Furthermore, MSCs are considered "immune privileged" cells, indicating that they may be safer than other cells types for use in cartilage tissue engineering [24]. The preclinical data with regards to allogeneic cells is conflicting. Allogeneic MSCs in rabbit model have displayed promising potential in comparison with autologous cells. However, autologous chondro-progenitor cells in horse models have been reported to facilitate repair compared with allogeneic cells [25].

Several studies have shown that MSCs are promising cell sources for cartilage regeneration. However, there are some limitations to the use of MSCs. First, the decreasing ability of MSCs for self-renewal with age limits their potential for differentiation. Second, they are associated with a tendency to exhibit tumorigenesis and malignant transformation. Finally, even under controlled conditions, neither the structure nor the function of the restored tissue is similar to that of articular cartilage [24].

BMSCs

With characteristic multipotency, rapid proliferative capacity and ease of isolation, BMSCs are another promising candidate for cartilage regeneration [20]. BMSCs were assessed with respect to cartilage repair in a rabbit model in 1994. In this experiment, a mixture of BMSCs and type I collagen was implanted into the cartilage defects. Twenty-four months later, the histological scores were found to be slightly improved compared with the control group. Since then, increased data from animal models presented optimistic outcomes and confirmed the potential for BMSC applications in cartilage tissue engineering [24]. BMSCs can be differentiated into chondrocytes under different culture conditions. Regardless of culture methods or scaffolds, in terms of in vitro culture, TGFβ generally enhances chondrogenesis; nevertheless, the degree of chondrogenesis is dependent on the scaffolds [20]. To date, a variety of scaffolds have been used in combination with chondrogenic media supplementation and TGFβ to drive chondrogenesis of BMSCs, including agarose, alginate, Polyethylene Glycol (PEG), silk, gelatin/chondroitin/HA tri-copolymer, polyglycolic acid/polylactic acid (PGA/PLA), PLGA-Collagen meshes, electrospunpolycapro-Lactone (PCL), poly (L-lactic acid)-co-poly (ε-caprolactone) P(LLACL)/ type I collagen nanofiber yarn mesh, and others [24]. Some reports have shown increased sulfated GAG production by BMSCs cultured in alginate compared with agarose gels [26]. Chondrogenesis was indicated by increased aggrecan and type II collagen accumulation and expression. In addition to TGFβ1, the cycling of GFs (e.g., BMP-6 and IGF-1) also affects chondrogenesis during in vitro culture. BMP-2 and TGFβ1 have been proved that they promote the differentiation of MSC into hyaline-like cartilage tissue [24]. BMSC chondrogenesis capacity could be enhanced through hypoxic isolation/expansion. Additionally, the co-culture of BMSCs and chondrocytes is a promising strategy to generate tissue-engineered cartilage yielding increased cell proliferation and cartilaginous ECM deposition with positive type II collagen expression. This may result from cell-cell interactions and GF secretion, or a chondrogenic microenvironment provided by endogenous chondrocytes that increases chondrogenesis of BMSCs [27]. Although comparative trials have shown that BMSC therapy is comparable to ACI and superior to other traditional treatments, Haleem et al. [28] suggested that BMSC application shows better short-to-long-term clinical outcomes as well as fewer complications than ACI. In addition, histological analyses revealed that the defect sites were primarily comprised of hyaline-like cartilage after BMSC implantation. Taken together, these data supported the application of BMSCs in cartilage tissue engineering and regenerative medicine [24]. While BMSCs have been widely used for chondrogenesis, the mechanical integrity of the produced matrix re-

mains a limitation. In long-term MSC-laden agarose gel culture, chondrogenesis was observed, but the mechanical properties and amount of matrix produced were inferior compared with that produced by chondrocytes isolated from the same donor [20]. Animal experiments have utilized allogeneic BMSCs to repair defects in cartilage and bone tissue. Chinese investigators have proved that BMSCs are able to survive, proliferate and differentiate after allo-transplantation, which provides evidence for the application of BMSCs in the tissue engineering for the repair of cartilage defects. Another aim of this study was to prove allogeneic BMSCs potential in clinical settings. Qi et al transfected retroviruses carrying human telomerase reverse transcriptase into BMSCs to prepare the immortalized human BMSCs. Chondrogenic differentiation was induced in the BMSCs in vitro. Therefore, these immortalized BMSCs will be applied in allo-transplantation. The results proved that allogeneic BMSCs survived after allo-transplantation in BMSCs group and differentiated into chondral cells to repair cartilage defects [29].

Unfortunately, the application of BMSCs is limited by several disadvantages. The first is complications involved in harvesting bone marrow from the donor site, including pain, morbidity of the donor site, infection, and even sepsis. Additionally, the limited number of BMSCs and issues related to aging are also factors that should be considered when considering the use of BMSCs in cartilage tissue engineering [30].

Adipose Tissue-Derived Stem Cells (ADSCs)

The adipose tissue is as another source with great promise for multipotent progenitor cells. Similar to the bone marrow, the adipose tissue also originates from the embryonic mesoderm [31]. Adipose tissue is not only easily accessible, also contains a large proportion of MSCs (about 5% of all stromal cells), with a density approximately 100 times more than found in bone marrow [20]. ADSCs, first reported in 2001, exist in all types of white adipose tissues, such as internal and subcutaneous fat, and can be isolated through collagenase digestion [32]. Among the different cell sources, ADSCs have been described an ideal cell source for tissue engineering with the following advantages: the ability to be isolated from tissues in comparatively large quantities, better anti-aging ability in both differentiation and proliferation, excellent anti-inflammatory and non-immunogenic properties, and few ethical concerns in association with application of ADSCs. ADSCs, like BMSCs, can be induced for chondrogenic differentiation in a controlled microenvironment, including a 3D culture environment with a defined medium containing growth factors, such as ascorbic acid, TGFβ, and dexamethasone [24]. Recently, ADSC-derived chondrocytes have been achieved in high density micro mass cultures, agarose, alginate, fibrin gel, collagen-based scaffolds, and other substrates [20]. In addition, it has been shown that a novel Elastin Like Polypeptide (ELP) can promote chondrogenic differentiation of ADSCs without media supplements. In monolayer culture, dynamic compression combined with exogenous SRY-related HMG box 9 (SOX9) demonstrated positive effects on chondrogenesis of ADSCs in a 3-D porous poly (lactic-co-glycolic acid) (PLGA) scaffold. The use of GFs, such as Bone Morphogenetic Protein 2 (BMP-2), BMP-4, BMP-6 and FGF-2, also affects the chondrogenesis of ADSCs 2 [33]. Collectively, these results demonstrate the important role of GFs in ADSC-based chondrogenesis. Notably, comparative studies suggest that ADSCs exhibit lower chondrogenic potential compared with stem cells isolated from other sources, such as umbilical cord tissue and bone marrow. As these cells exhibit lower type II collagen gene expression and reduced accumulation of cartilage-specific matrix proteins compared with other cell types, research is still necessary to optimize the chondrocytic differentiation potential of ADSCs 2 [34]. Furthermore, hypoxia treatment and coculturing can help promote chondrogenic differentiation as well. Previous in vivo studies have reported that applications of ADSCs in cartilage tissue engineering can obtain reliable outcomes. Nonetheless, most of the experiments using ADSCs are from case reports or phase I clinical trials, and only a few control studies have been performed. One multicenter study reported that ADSC injection results in 75% symptom improvement in 63% of patients and about 50% symptom improvement in 91% of patients after 1 year. Nevertheless, additional studies of the use of ADSCs are required to reach definitive conclusions [24].

Synovial-Derived Stem Cells (SDSCs)

The synovial membrane (SM) was recently found to be an attractive source for cartilage tissue engineering owing to its proximity to the articular cartilage. SDSCs were identified as MSCs that could be isolated from the SM while exhibiting multilineage differentiation potential in culture.

Many studies have reported the outstanding potential of SDSCs for chondrogenesis, as well as their applications in cartilage tissue engineering both in vitro and in vivo [35]. By controlling the microenvironment, SDSCs can be induced to form hyaline-like cartilage. Additionally, Koga and coworkers suggested that new cartilage was formed in a rabbit model with transplantation of undifferentiated SDSCs into full-thickness defects of the cartilage. Moreover, ample cartilage matrix secretion was confirmed on the basis of immune-histological scores and transmission electron microscopy. SDSCs and chondrocytes have also been shown to have similar secretion activities. In particular, both may secrete type II collagen without increasing the accumulation of type X collagen and express the gene for proteoglycan [23]. Positive results have also been reported in clinical studies. For example, Sekiya et al. claimed that cartilage regeneration and symptom improvement could be achieved in most patients 3 years after SDSC transplantation through arthroscopy in defected cartilage [35].

Other Sources of MSCs

In addition to above-mentioned tissues, MSCs can also be derived from other connective tissues, such as the skeletal muscle, periosteum, peripheral blood, umbilical cord blood, Wharton's Jelly, and dental pulp. As the largest organ in the human body, skeletal muscle is an attractive cell source for cartilage tissue engineering. Moreover, via muscle biopsy, harvesting of the muscle can be minimally invasive [24]. In 2007, Usas et al. showed that in vivo cartilage healing could be improved by transplanting Muscle-Derived Stem Cells (MDSCs). MSCs can be isolated from the periosteum as well using TGFβ, which has the potential to induce the cells towards the chondrogenic lineage. Nevertheless, periosteum-derived MSCs are quite rare and difficult to obtain, contributing to their limited application. Peripheral Blood-Derived Mesenchymal Stem Cells (PBMSCs), which were first isolated in 2000, show comparable chondrogenic potential to BMSCs. Moreover, the quality of cartilage restoration was improved with the use of PBMSC injection in clinical studies [36].

Additionally, extra-embryonic cells, such as Wharton's Jelly Stem Cells (WJSCs), placenta-derived mesenchymal stem cells, and Umbilical Cord Blood Stem Cells (UMSCs) are invaluable

sources for cartilage tissue engineering. For example, Wharton's jelly has been reported as a probable source of chondrogenic potentialized stem cells. The existence of UMSCs was first reported by Erices et al. in 2000; these cells were found to be naiver than BMSCs with greater potential for use in cartilage tissue engineering. Nonetheless, the storage of umbilical cord tissues is challenging, limiting the applications of these cells [37].

Comparison of the Applications of Different MSCs in Cartilage Tissue Engineering

As described above, many MSCs display potential for chondrogenesis; nevertheless, the ideal cell source for MSCs for applications in cartilage tissue engineering is still controversial. Although Bone Marrow-Derived Mesenchymal Stem Cells (BMSCs) are the most widely studied MSCs, synovium- derived MSCs (SDSCs) have superior potential for chondrogenic differentiation. Studies have shown that higher percentages of hyaline cartilage are observed in SDSCs-repaired cartilage tissue [38].

Furthermore, with the use of autologous human serum, SDSCs can be expanded faster than any other cell source. Moreover, pellets derived from the SM show greater secretion of cartilage matrix components, which makes them heavier. ADSCs have better histological appearance and biomechanical properties than periosteum-derived MSCs, but with lower chondrogenic potential than BMSCs. nonetheless, ADSCs are present in adipose tissues at a proportion of 1 in 100 cells, which is approximately 500-fold higher than that of BMSCS in the bone marrow. In contrast, UMSCs show 2 times higher population doubling numbers than BMSCS as well as 1.7 times higher numbers than ADSCs have similar chondrogenic capacity. Unfortunately, the application of UMSCs is limited by difficulties in the storage of umbilical cords [24].

Induced Pluripotent Stem Cells (iPSCs)

As iPSCs possess unlimited self-renewal capacity, they can be used as an infinite cell source for cartilage tissue engineering. The iPSCs, which can be produced from skin fibroblasts by introducing a few key transcription factors, can be used to generate differentiated cells exhibiting young properties, such as healthier production, faster proliferation, and longer-lasting activities. Therefore, they may be a good source of cells to repair articular cartilage defects [20]. Several reports have demonstrated the ability of iPSCs to differentiate into various lineages by overexpression of transgenes or induction with cytokines and small molecules [20,24]. iPSCs can also be combined with 3-D nanofibrous scaffolds for cartilage regeneration. Nam Y et al. had proved that chondrogenic pellets could be generated from the outgrowth cells derived from blood mononuclear cell-derived hiPSCs (CBMC-hiPSCs), and revealed that CBMC-hiPSCs might be regarded as a promising candidate for articular cartilage regeneration. In addition, studies have shown that use of human iPSCs (hiPSCs) can be regarded as a clinically translatable and efficient approach to repair rat osteoarthritic cartilage, with differentiated hiPSCs forming hyaline cartilage tissues 8 weeks after transplantation into the articular cartilage of NOD/SCID mouse knee joints. Chondroinducedh iPSCs were also implanted in osteochondral defects of immunosuppressed rats, showing a great quality of cartilage repair [20]. The preparation of patient-iPSCs and subsequent differentiation under Good Manufacturing Practice (GMP) guidelines is costly. A library of allogeneic clinical GMP grade hiPSCs is under development to lower costs and enable large scale treatment. This iPSC bank is comprised of cells from homozygous donors for major HLA types in order to minimize immune rejection risk when the generated tissues are transplanted. It is much easier to prepare homozygous HLA hiPSCs than hESCs, because it is easier to find individuals who bear homozygous HLA types and are willing to donate their somatic cells to generate iPSCs in comparison with embryos to generate ESCs. hiPSC - derived chondrocytes tend to resemble chondrocytes of juveniles rather than adults, meaning they possess more anabolic and less antigenic activity. Such findings indicate that a single allogeneic iPSC can be utilized for all recipients, which not only would standardize production quality but prevent excessive costs [23]. Nonetheless, before utilizing iPSCs as a candidate for cartilage tissue engineering, further studies are needed to overcome the drawbacks associated with their use, such as teratoma formation and the possibility of genetic disorders. Nevertheless, due to the tumorigenicity of hiPSCs, their clinial applications are also limited. Although these protocols represent important steps for expanding the use of iPSCs for articular cartilage tissue repair, they still have many limitations. These include use of either feeder or embryoid body stage cells that can abate reproducibility or cause cell heterogeneity. It has been confirmed that the chondrogenically differentiated human iPSCs can form articular cartilage[20].

ESCs

ESCs exhibit the best differentiation potential and may supply an unlimited cell population for cartilage tissue engineering [32]. ESCs can be divided into Wharton's jelly stem cells, umbilical cord blood stem cells, amniotic fluid-derived stem cells and placenta-derived mesenchymal stem cells. Before ESCs differentiate into chondrocytes, these cells must pass through an aggregation stage of embryoid bodies [20]. Transplanted hESCs-derived chondrogenic cells maintain long-term viability with no evidence of tumorigenicity, and provide a highly-efficient, practical and safe strategy of applying hESCs for cartilage tissue engineering. The effects of TGFβ and BMP-2 on early stages of chondrogenic differentiation and commitment by hESCs was also evaluated, and found significant chondrogenic induction of hESCs. Mouse ESCs undergo chondrogenesis with BMP-2 and BMP-4, as confirmed by type II collagen and alcian blue staining. Chondrogenesis of ESCs is also upregulated by increased production of endogenous TGFβ and BMP signaling activity. Furthermore, co-culture of hESCs with primary chondrocytes was shown to induce chondrogenesis, whereby co-cultured cells expressed type II collagen and SOX9, while cultures of hESCs alone did not. Even though, in clinical, there are many new methods for maintaining hESCs, including serum-free, feeder-free methods, and coculture with other cells. But their applications are extremely limited because of their tumorigenicity [20]. Although the vast proliferation capabilities of ESCs make them an appealing cell source, many limitations continue to hinder their clinical use including difficulties in ESC purity and selection, ethical issues, possibility of teratoma formation and antigenicity [20,24]. Additionally, research using ESCs for cartilage tissue engineering is still relatively new. As such, more information about ESCs, as well as new strategies for differentiation and purification, are required to characterize their potential as a viable cell source for cartilage tissue engineering [39].

Cartilage Progenitor Cells (CPCs)

CPCs are potential alternatives as cell sources for cartilage tissue engineering. Convincing evidence has shown that numerous CPCs can be separated from the surface of the articular cartilage and can be induced to differentiate into cartilage under

a high-density microenvironment using specific growth factors [40]. Moreover, a comparative study indicated that CPCs are superior to MSCs for use in cartilage tissue engineering owing to their lower expression of collagen type X, a sign of hypertrophy of cartilage, however, in cartilage tissue engineering, the major concern associated with the use of CPCs is the difficulty involved in obtaining the cells [24].

Chondrocyte Different Expansion Procedure In Vitro

In the process of articular cartilage tissue engineering, two main phases can be identified. A first phase where few isolated cells need to be expanded in order to provide sufficient cells and a second phase where a cartilage is engineered either inside the body (in vivo) or in a cell culture (in vitro) using an appropriate scaffold. Expanded cells are seeded onto three dimensional scaffolds to form cell-polymer constructs, which are cultured in vitro and then used either as implants or for in vitro research [41].

Retention of phenotypic function in the cell population is critical in cartilage tissue engineering. Articular cartilage derived chondrocytes display minimal proliferative capacity. They dedifferentiate upon repeated passaging and the numbers of cell divisions chondrocytes undergo in vitro decreases with age. The limitations of adult chondrocytes to maintain their phenotype expression and differentiation ability after extensive expansion in vitro has led to the investigation of the potential use of pluripotent stem cells and progenitor cells as a source for tissue engineering [42].

Extensive chondrocyte expansion is required to obtain the number of cells needed for tissue engineering applications. To utilize such cells differentiation would be required to restore their functional phenotype after expansion. Human chondrocytes differentiation has been previously shown to be improved by human serum and growth factors. Because 3 dimensional structures improve phenotype retention in articular chondrocytes as well as encouraging matrix molecules formation, Alginate bead was used for encapsulation as the differentiation method. The differentiation of expanded chondrocytes and chondrogenesis of stem cells is stimulated by the factors including insulin-transferrin-selenium-linoleic acid-bovine serum albumin (ITS + 1) dexamethasone (dex), TGF-β1, Insulin-like Growth Factor I (IGF-I), and Bone Morphogenic Protein 14 (BMP-14) [43]. Serum may provide chondrogenic factors in a manner dependent on maturation, so that human serum, FBS, and adult bovine serum (ABS) may have different effects on chondrogenesis [44].

Currently Available Culture Systems for Chondrocytes Expansion

Despite the improvements introduced by the use of large scale operation units, monolayer systems which largely rely on simple monolayer culture flasks (i.e., T Flasks, Petri dishes or tissue culture well plates) present very low ratios of surface to volume, which inevitably make them inefficient in term of scalability [45]. If production of articular chondrocytes is to be significantly increased, the number of culture units has to be remarkably increased, making the process time consuming and laborious. The result is that the expansion process may not be cost effective. The introduction of three-dimensional alternative systems including Pellet culture, Encapsulation inside hydrogel beads and microcarriers could potentially provide the improved ratio of surface to volume necessary to cope with the scale of cell expansion required for allogeneic tissue engineering applications [46]. One of these alternatives is the use of cell-seeded microcarriers for cell expansion. In microcarrier cells culture technology anchorage-dependent animal cells are grown on the surface of small spheres which are maintained in stirred suspension culture. Cells attach and spread on the surface provided by the microcarriers and gradually grow into confluent layers. Finally, the microcarrier expanded cell population has been also proven to maintain the ability to undergo chondrogenesis in vitro, an essential requisite for any proposed expansion method. As a result, due to both its desirable expansion capacity and more critically its operational advantages compared to conventional single layer cultures, micro-carrier cultures are potential alternatives for large scale expansion [47].

Stem Cell Derived ECM for Cartilage Repair

Natural biomaterials such as MSC-ECM have been examined as scaffolds for tissue engineering because of their substantial bioactivity and high biocompatibility [48]. There are new cell-based therapies for cartilage tissue regeneration, including such chondrocyte or stem cell treatment. More than 90% of patients with Autologous Chondrocyte Implantation (ACI) for treating OA had satisfactory function five years after the implantation, according to long-term analysis of clinical trials [49]. In contrast of this, undifferentiated stem cell injections increase the likelihood of cell migration towards the inappropriate cite, and they may develop into ectopic tissue [50]. Increased autoimmune responses may raise the risk of malignancy or other harmful impacts of cell treatment following cartilage regeneration when using modified or allogeneic cells [51]. EVs (Extracellular Vesicles) and soluble substances generated through Mesenchymal Stem Cells (MSC) have a role in stem cell therapeutic efficacy [52]. mRNAs, proteins, microRNAs, and liposomes are all included inside the membrane of endosomal EVs, which have a diameter of 30–150 nm. These characteristics might be useful in the creation of therapeutic biomarkers for medication delivery [53]. As a result of their enhanced physicochemical strength and biocompatibility, EVs such as exosomes have recently emerged as powerful cell-free transfer mechanisms [54]. Apoptosis bodies, Micro Vesicles (MVs), and exosomes are the three primary EV groups released by cells. In addition to miRNA, DNA, RNA, and proteins, several different forms of vesicles can be secreted by MSCs [55].These vesicle groups are supposed to be homogenous in size and density, although the subtypes are indeed diverse [56]. EVs-MSCs have been shown in preclinical research to be effective in treating a variety of disorders, but clinical trials must still address issues of safety. Human articular chondrocytes or bone marrow stromal cells were used to generate cell type-specific Extracellular Matrix (ECM), which replicates a native milieu, to reduce chondrocyte dedifferentiation during in vitro growth. Spectrometry and atomic microscopy have shown that AC-ECM and BM-ECM have distinct ECM compositions and physical features, respectively. Accumulation of HAC (Human Articular Chondrocytes) cells on AC-ECM were significantly faster than on BM-ECM or the conventional culture surface [57].

Small Molecules (Exosomes)

It has been a long time since Vacanti first introduced the term "tissue engineering" [58], but since then, researchers have used it to develop a new method of regenerating cartilage and bone tissue using a mix of synthetic substrates, cells, and bioactive chemicals with the goal of providing a potential option for improving cartilage and bone regeneration by speeding up the

healing process [59]. In recent years, exosomes, one form of Extracellular Vesicles (EVs) released by cells and that vary in diameter between 50 to 130 nm, have been investigated into it for their wide variety and shedding processes. They were shown to play emerging roles in various cellular mechanisms, such as cell signaling, immune response modulation, and natural cycles of biological colonies [60,61]. Cell-to-cell communication is expected to have a significant impact on the course of healing due to the interconnectedness of chondrocyte regeneration processes. Exosomes, which may deliver bioactive hydrocarbons, nucleic acids, and proteins, are now a hot topic in the regeneration area because of their role in intercellular communication [62]. Coculture of Stem cells with harmed chondrocytes has long been known to promote regeneration through the secretion of numerous factors by SCs, including Proinflammatory cytokines such as IL-6, FGF 2, and insulin-like growth factor, all of which have been shown to promote chondrocyte proliferation and matrix synthesis [63]. In light of the fact that the success of MSC-based joint disease treatments is attributed to paracrine signaling, exosomes, as being one of the components of MSC release, have also been recommended as a successful therapy to restore osteochondral abnormalities [64]. Exosomes from MSCs have been shown to have chondroprotective benefits in joint disorders by Cosenza et al [65]. Chondrocyte indicators (type II collagen and proteoglycans such as aggrecan) and inflammatory markers (such as iNOS) were dramatically increased by intra-articular injection of exosomes from MSCs into a collagenase-induced Osteoarthritis (OA) model. Chondrocyte apoptosis and inflammation worsening by activation of monocytes are two possible outcomes of these substances [66].

Gene therapy: Introducing foreign genetic material or gene patterns into various cell types is known as gene transfer. Gene therapy is use of gene transfer methods to treat illness [67]. Non - viral gene transfer is known as transfection, while viral gene transfer is known as transduction [68]. The initial experiments used ex vivo retroviral gene transduction to modify synoviocytes of patients with terminal rheumatoid arthritis, followed by reinjection of the transformed cells into the Metacarpophalangeal (MCP) joint [69,70]. Concerning OA, a phase I procedure is presently underway, employing an ex vivo method utilizing retroviral TGF- β [71]. There is a growing amount of evidence from a variety of transgenic and somatic genetic manipulation research suggesting gene transfer may be used to increase athletic capacity. Numerous genes have previously been cloned into functional vectors, and others are being examined for clinical trials in order to disease therapy [72]. The difficulty for antidoping authorities will be detecting these endogenously created gene products because to the similarities between the transferred cDNA and the endogenously manufactured protein, as well as the low specificity of indirect testing technologies [73]. The reports have concentrated on membrane healing proteins, transposable elements, and growth factors delivery. Much of the research has been on IGF1 expression. Regardless of the vector utilized, the primary limiting factor in the efficiency of cartilage regeneration following GT has been temporary transcription of the gene product. A second reason limiting GT's effects in cartilage healing has been the achievement of inadequate amounts of target proteins such as growth pathway. But at the other hand, in the initial few days following GT, supra-therapeutic or hazardous doses are typically reported in an attempt to boost the target protein's expression. Despite the advances, the length of expression is still inadequate to induce cartilage regeneration [74].

Transplantation Methods in Cartilage Tissue Engineering

Tissue engineering involving cells seeded on scaffolds made of synthetic and natural biodegradable polymers can be a promising for the future treatment of diseases including cartilage defects. These polymers can be injected as a minimally invasive procedure or as a pre-made graft to treat large irreparable defect, including osteoarthritis. Scaffolding as a mechanical substrate for cells and bioactive factors could help guide and organize cells to regeneration process [75]. Today, various surgical and non-surgical methods are used to cartilage regeneration. In any method of cartilage regeneration, preparation of a suitable substrate for replacing the implants is very important [2]. Several new surgical procedures have been developed to promote cartilage regeneration.

Injection method: Minimally invasive surgery can reduce connective tissue damage and wound size, resulting in faster healing, so we have tried to design injectable structures that replace surgical techniques to repair cartilage tissue [76]. There are several cross linking manner for in situ polymerization of injectable structures, such as thermal, chemical and photo-cross linking [77]. Photo-cross linker has more considered than other polymerization methods due to possibility of spatial and temporal control of the polymerization method by adjusting the light intensity and duration of light exposure [78]. These cross-linking methods have also been used for cell encapsulation and synthesis of bioactive molecules [79,80]. In addition to being less invasive, these structures may fill gaps, especially for the treatment of irregular form or difficult to reach defects [80].

Hydrogels are common and injectable scaffolds in cartilage tissue engineering [81]. The production of new tissue with this method is enhanced by implanting cells in a 3-D matrix. Hyaluronic Acid (HA) and collagen based materials are widely used as biodegradable and biocompatible material for cartilage regeneration [82]. In addition, several natural, synthetic materials and copolymers have been shown to mimic the mechanical environment of cartilage tissue and its properties [83]. In recent study, the role of advanced manufactured methods in cartilage regeneration was evaluated in cartilage defects of rabbit model. They used methacrylate hyaluronic acid as a photo cross linker hydrogel containing Kartogen in with PLGA nanoparticle. The results of this study showed that in comparison with the untreated group, this single-step surgery without cells, after 3 months was able to show the formation of hyaline cartilage with a high content of type II collagen [84]. Microspheres have been considered as an efficient transport system for the controlled release of drugs and biological agents. In tissue engineering, microspheres are widely used as cell-carrying scaffolds [85]. Currently, intra-articular injections of microspheres are used as a minimally invasive method in the treatment of cartilage defects. Cytodex 1, CultiSpher S and SphereCol are some samples of commercial microspheres that are used for cartilage regeneration [86,87]. Intra-articular injection of microspheres containing growth factors to treat cartilage defects like osteoarthritis is another application of microspheres used in the clinic. Platelet-Rich Plasma (PRP), Fibroblast Growth Factor (FGF), and Transforming Growth Factor-1 (TGF-1), are some biological factors that were injected to stimulate proliferation of chondrocyte or chondrogenic differentiation from stem cells. As well as anti-inflammatory cytokines, are used to repress arthritis-related inflammation [87].

Arthroscopic method: Arthroscopic surgery is used as an orthopedic surgery method to diagnose and treatment of articu-

lar defects. In this procedure, the size and shape of the cartilage defect are measured using an arthroscopically graded probe [88]. In addition, many operations can be performed by arthroscopy. It's appropriate for moderate cartilage defects. Among the advantages of this method is the low cost of arthroscopy operation and minimizing the invasion and thus improving rehabilitation. In previous study, by arthroscopic surgery method, several cartilage matrices were isolated from two cadaver cartilage and used in a hip model. Cartilage implants based on cell-free Polyglycolic Acid- (PGA-) hyaluronan scaffold with a flat surface were implanted by with a thickness of 10 mm × 15 mm. The implants were fixed on the hip cartilage defect by fibrin glue. The results have been shown the implant was reinforced by PGA scaffolds [89].

Open surgery method: Open surgery as a common method widely applied in cartilage tissue engineering. Although arthroscopy is less invasive, but in some cases, such as cartilage defects in areas like the posterior femoral condyle, patella and larynx, as well as arthroscopic surgery for some scaffolds is not applicable [88]. Scaffolds designed by tissue engineering are typically transplanted through open surgery. These scaffolds are made by various techniques such as foam casting, electrospinning [90], solvent casting and particle leaching [91], faze separation as well as 3D bioprinting before operating [92]. 3D bioprinting implants contain a wide range of materials and compounds such as calcium polyphosphate and PVA, hydroxyapatite and calcium phosphate, tricalcium phosphate, PCL and chitosan, collagen, and mesenchymal cells are grafted by open surgery for cartilage regeneration [80]. Biopen is a novel 3D bioprinting machine that allows surgery to print bionic and cells during surgery, this technique can revolution in cartilage regeneration. Simultaneous in situ printing of scaffolds and cells on cartilage defect, performed in an open surgical session.Bella et al. [93] used biopen for cartilage regeneration un sheep model. HA-GelMaBioink, was used as a shell layer and allogeneic fat-derived mesenchymal stem cells as a core layer. The material and cells simultaneously were printed on the lateral and internal condyles of both femurs. The results indicated that in situ printing of cell and scaffold simultaneously on cartilage defect had no side effects, in all cases. Biopen can be used in a similar way like other surgical instruments. The shape and thickness of the 3D printed material as well as the speed of printing can be control by surgeon. Biopen could produce a 3D-printed scaffold that completely matched the profundity and shape of defects.

Microfracture surgery method: Microfracture method as a surgical procedure is used to treat cartilage defects. In this method, by making several small holes in the bone under the cartilage defect, the Mesenchymal Stem Cells (MSCs) are stimulated and oriented from the bone marrow and differentiate into cartilage cells [94]. Steadman et al. [94] was designed this method in the early 1980s. At present, micro-fracture surgery is considered as an alternative treatment instead of open surgery for full-thickness cartilage disorder [95]. According to the research, cartilage regeneration was done better in young than older patients [96]. This method can also be used to transplant clinical engineering products. In a study to improve the regeneration process of cartilage repair, 3 D printed scaffolds from aggrecan without cells were grafted with micro-fracture method in a Lapin model [97,98]. The results showed that aggrecan has a high potential for cartilage regeneration and this surgical method was effective and cost effective [99].

Mosaicplasty method: Mosaicplasty is another method for cartilage regeneration. Hangody and el al. [100] was designed this method in 1992 for clinical usage. This surgery method is the mosaic like implantation of some tiny cylindrical plugs of osteochondral to regenerate a cartilage surface [101].Cartilage grafting from a place that is not under mechanical pressure to place that is exposed to mechanical load is prone to damage due to structural and mechanical differences between the two areas of cartilage [102]. Osteochondral allograft can be resolve this problem, but the recipient's immune reaction remained [103]. Bartha et al. [104] evaluates porous Poly (Ethylene Oxide) Terephthalate / Poly (Butylene Terephthalate) (PEOT / PBT) implants to repair the cartilage defect. PEOT / PBT implants were successfully transplanted and reduced donor complications, bleeding, and inflammation after mosaicplasty surgery.

Available Products

Business research predicts that the market for cartilage repair products will grow definitely between 2020 and 2027. Data Bridge Market Research analyses the market to account for USD 4.5 billion by 2027 growing at a CAGR of 6.30% in the above-mentioned forecast period. Increasing sports injuries, obesity, a growth in the elderly population and raise awareness of osteoarthritis will be important reasons for this development in market size. Of course, the high cost of repair procedures, inappropriate surveillance policies, and problems with the insurance and repayment system will be obstacles to market growth. Cartilage repair is known as treatments used for damaged cartilage which can cause pain and inability to move for patients. The main joints involved are the hip, knee, ankle and spine. Analgesics and some medications are used for this purpose but do not produce a significant therapeutic response. The cartilage repair market is segmented on the basis of the type of cartilage, treatment modality, treatment type, application site, and surgical procedure. These segments will help you analyze valuable market overview and market insights to help you in making strategic decisions for the identification of core market applications.

- On the basis type of cartilage, the cartilage repair market is divided into fibrocartilage, hyaline cartilage and other

- Based on treatment modality, the cartilage repair market is divided into cell- based and non- cell based. Cell based is divided into smaller subgroups: chondrocyte transplantation and growth factor technology. The non-cell-based segment consists of tissue scaffolds and cell- free composites.

- The treatment type part of the cartilage repair market is divided into palliative and intrinsic repair stimulus. Palliative segment itself includes 2 sections: viscosupplementation and debridement & lavage

- Application segment of the cartilage repair market includes different parts of the body namely knee, spine, ankle, hip and others

- Based on surgical procedure, the cartilage repair market is segmented into micro fracture, debridement, abrasion arthroplasty, autologous chondrocyte implantation, osteochondral autograft and allograft transplantation, allogeneic chondrocyte implantation, cell-based cartilage resurfacing and others

the U.S., Canada, and Mexico in North America, Germany, France, U.K., Netherlands, Switzerland, Belgium, Russia, Italy, Spain, Turkey, Rest of Europe in Europe, China, Japan, India, South Korea, Singapore, Malaysia, Australia, Thailand, Indone

Table 1: Cartilage products available in the market.

Company	Product	Description	References	Country
Anika Therapeutics SRL	HYALOFAST®:	HYALOFAST non-woven 2×2 cm or 5×5 cm biodegradable hyaluronic acid-based scaffold. Single 3D fibrous layer of HYAFF®, a benzyl ester of hyaluronic acid (HA), mesenchymal stem cells (MSCs), embryonic-like environment, Bio-resorbable and strong safety profile	[105-107]	USA SRL Italy
Osiris Therapeutics, Inc.	Cartiform®	Cartiform®: cryopreserved viable osteochondral allograft, 3-dimensional scaffold of hyaline cartilage. Improve the healing potential of bone marrow stimulation procedures. Mesenchymal stem cell (MSC).	[108, 109]	USA
Arthrex, Inc.	OATS® (As part of the Allograft)	Dovetail Meniscal Allograft Set/ The technique used with the Dovetail Meniscal Transplant Set creates a trapezoidal bone block allograft.	[110-112]	Florida/ USA
BioTissue	BioSeed®-C Chondrotissue®	BioSeed®-C autologous 3-dimensional graft for chondrocyte with maximum mechanical resistance and form stability,compare to other collagen or gel-like grafts Chondrotissue® a one-step, CE marked, cell-free implant Stem cells are obtained by performing standard marrow stimulating procedures, such as micro fracturing or Pridie drilling.	[113] [114]	Germany
Lifenet health	FlexiGRAFT® meniscus Matrigraft®	Meniscus transplantation/ Processed with tibial bone block to allow for surgical technique flexibility such as double bone plug technique, keyhole technique or dove tail technique. Consists of two types of shafts and fibular wedge. Fibular wedge type is Natural shaped, parallel fibular wedge, Shafts Matrigraft consists of Cortical/cancellous shafts, designed to provide immediate structural support to restore segmental bone loss. Joint Arthroplasty ,Tumor Resection and Reconstruction, Fracture Management , Deformity Correction , Corpectomy , Anterior Cervical Fusion	[115] [116]	Virginia/ USA
B. Braun Melsungen AG	Novocart® Basic	Novocart® Basic biphasic, three-dimensional collagen-based matrix consists of a collagen membrane cover and a collagen sponge lying underneath. Biomaterials of bovine origin. Chondral and osteochondral lesions of grade III°-IV° (ICRS Classification) – for smaller defects Focal, traumatic defects and Osteochondrosis dissecans	[117]	Germany
ConMed Corporation	CartiMax Osteochondral Allografts Cartilage Allograft Matrix	CartiMax® is viable, cartilage fibers combined with cartilage allograft matrix to make a biologically-active scaffold with putty-like handling characteristics used to treat focal cartilage defects. Available exclusively from CONMED through MTF Biologics, MOPSTM (Missouri Osteochondral Preservation System) preservation and storage services create osteochondral allografts with consistently high viable chondrocyte density. Taken from the distal femur and processed using MTF's proprietary methods	[118] [119, 120] [121]	NY/ USA
Swedish Orphan Biovitrum AB SOBI	ChondroCelect	Chondro celect the first cell-based product to be approved in Europe which is a medicinal product for use in autologous chondrocyte. This product has been approved by the European Medicines Agency with Agency product number EMEA/H/C/000878	[122]	Swedish Belgium
Medipost	CARTISTEM®	Allogeneic umbilical cord blood-derived mesenchymal stem cells has been market-approved with Biologics License Application (BLA) for commercial sale by the Ministry of Food & Drug Safety (MFDS) in January 2012.	[123]	Korea
Histogenics	Neocart	1NeoCart harvesting cartilage cells from the non-weight-bearing cartilage surface of the patient's femur. Histogen research for Neocart trial seems to have failed and stopped to reach endpoints[1]	[124]	USA
MEDTRONIC		Infuse™ Bone Graft, Grafton™ demineralized bone matrix (DBM), Magnifuse™ Bone Graft, The Mastergraft™ are some examples for their products.		Ireland
Stryker	Prochondrix CR	ProChondrixCRcryopreserved, fresh osteochondral allograft contains live cells and biological components	1- [125]	USA
Smith & Nephew PLC	CARGEL	CARGEL Bio-scaffold single-step bone marrow stimulation procedure. mixing a buffer, a chitosan solution and the patient's whole blood	[126, 127]	UK
Vericel Corporation	MACI®(autologous cultured chondrocytes on porcine collagen membrane)	The symptomatic repair, full-thickness cartilage defects of the knee in adult patients. FDA approved	[128]	Europe USA
Zimmer Biomet Holdings, Inc	Chondrofix (Osteochondral Allograft) DeNovo NT	Minimally manipulated human tissue graft shelf-stable graft. Immediate post-operative weight bearing, DeNovo®NT Natural Tissue Graftoff-the-shelf human tissue, reducing the need for periosteal flap unlike ACI	[129] [130]	Switzerland
Orthox	FibroFix™ Cartilage		[131]	UK
Allosource	ProChondrix® CR	ProChondrix CR, a laser-etched, fresh cryopreserved osteochondral allograft Presence of native growth factors and Viable chondrocytes	[125]	CO/ USA
Cartiheal	Agili-C	Agili-C™ is a cell-free, off-the-shelf implantporous, biocompatible, and resorbable bi-phasic scaffold,	[132]	Israel New Jersey/ USA
MTF Biologics	Profile® Cartimax	MTF Biologics' line of costal human cartilage grafts are primarily used for revision rhinoplasty procedures, both reconstructive (post-trauma or Mohs procedure for basal cell and squamous cell carcinoma of the nose), and cosmetic. Grafts are available in both segment and thinner, pre-cut sheet (Profile®) forms. CartiMax is a ready-to-use, off-the-shelf viable cartilage allograft that can fill cartilage defects up to a 5cm2 lesion. MTF Biologics, Research and Development Department.	[133] [134]	USA
Collagen Solutions PLC	Collagen scaffolds	Collagen scaffolds are ideal for repairing hyaline joints due to their perforated structure and reconstructive structure.	[135, 136]	London/UK

RTI Surgical, Inc.	Fresh-Stored Osteochondral Grafts Allograft Dermis	Implants includes Fresh-stored OC Femoral Condyle, Fresh-stored OC Talus, Fresh-stored OC Humeral Head, Fresh-stored OC Femoral Distal Tibia, Fresh-stored OC Femoral Trochlea and Fresh-stored OC Femoral Patella Matrix HD® Allograft Dermis is an acellular human dermis allograft sterilized to a Sterility Assurance Level (SAL) of 10-6 using the Tutoplast® Tissue Sterilization Process. The three-dimensional intertwined multidirectional fibers and mechanical properties of the native dermis tissue.	[137] [138]	USA
JRF ortho	osteochondral allografts	Femoral Condyle, Precut Fresh OCA Cores (great alternative for focal lesions of up to 20 mm or for Autograft OATS® backfill.), Bi-Compartment Allograft (Combination Femoral Trochlea and Condyle),Custom Allografts (joint, and size-specific osteochondral grafts), Distal Tibia(for resurfacing ankle or shoulder), Femoral Head, Femoral Trochlea (utilized for reconstructing the complex curvature of the trochlear region),Humeral Head(shoulder), Metatarsal Bone (toe), Patella Bone, Talus, Tibia Plateau (with attached Meniscus), Whole Femoral Condyle (allograft includes the entire distal femur) and Whole Tibia Plateau (with intact Menisci)	[139]	USA Colorado
NANOCHON	3D print-nano implant	Using for treat tears, sports injuries, early onset osteoarthritis and other forms of full-thickness cartilage loss. 3D printed from a novel, nanostructured synthetic material. Recently Nanochon was awarded a Phase I SBIR from the National Science Foundation, and is planning to undertake a human study in 2019.	[140]	US Study
Regentis biomaterials	Gelrin C hydrogel	After standard microfracture, the hydrogel is injected as a liquid, conforming to the lesion size, shape and depth. Hydrogel Implant GelrinC Demonstrates Impressive Recovery Rates for Patients with Knee Cartilage Damage. Besides there is an ongoing clinical trial about this product.	[141]	Israel
Cytex	3-Dimensional woven implants	Bone marrow derived mesenchymal cells The implant includes a three-dimensional woven textile scaffold and a three-dimensional rigid, porous substrate.	[142]	US
DePuy Synthes	COR® Autograft	The Arthroscopic Technique for Repair of Osteochondral Defects Which focuses on the extraction of graft tissue in the autograft process	[143]	Indiana USA
Azellon cell therapeutic	Azellon's (Stem cell on membrane)	Azellon's meniscal repair technology will combine patient's bone marrow stem cells with a special membrane that helps to deliver the cells into the injured site.	[144]	UK
Educell	ChondroArt TM	ChondroArt TM are tissue-engineered products for cartilage repair in knee and other joints, based on implantation of autologous chondrocytes.	[145]	Slovenia

sia, Philippines, Rest of Asia-Pacific (APAC) in the Asia-Pacific (APAC), Saudi Arabia, U.A.E, South Africa, Egypt, Israel, Rest of the Middle East and Africa (MEA) as a part of the Middle East and Africa (MEA), Brazil, Argentina and Rest of South America as part of South America are countries covered in cartilage market reporting. North America is expected to overtake the cartilage engineering market between 2020 and 2027 (adapted from https://www.databridgemarketresearch.com)

In this section, we decide to describe some trend products available in the market in the field of cartilage allogeneic transplantation and biological scaffolds for chondrocytes.

At the end, we introduce some famous company with autologous products. As shown at mccourier.com and our searches, the major players covered in the cartilage repair market report are Histogenics, Vericel, Swedish Orphan Biovitrum AB., MEDIPOST, Zimmer Biomet, Osiris, B. Braun Melsungen AG., Stryker, Smith & Nephew, Medtronic, CONMED Corporation., Arthrex, Life Net Health, Anika Therapeutics, Inc., BioTissue, among other domestic and global players. At the end, we report on several other companies and products in table 1. (Adapted from https://www.mccourier.com).

Table 1: Cartilage products available in the market

Rejection of allograft transplantation due to the immune response remains a common and serious challenge in allogeneic tissue or organ transplantation that leads to loss of durability [146]. In tissue engineering, MSCs used on 3D scaffolds can adjust the immune system by reducing inflammatory agents and increasing the release of anti-inflammatory cytokines like Prostaglandin E2 (PGE2), Transforming Growth Factor-β (TGF-β), and Hepatocyte Growth Factor (HGF) [147]. Increase amount of TGF-β and other anti-inflammatory cytokines could induced the regulatory T cells (Tregs) [148] and macrophages activity [149]. MSCs with immunosuppressive properties can directly inhibit the activity of immune cells. The binding of Fas Ligand (Fas-L) and Programmed Death-Ligand 1 (PD-L1) on the surface of MSCs to surface receptors of immune cells, lead to decrease the immune responses [150].

The selected 3D scaffolds in tissue engineering, in addition of mimic the mechanical and physical properties of the tissue, should also not stimulate inflammatory agents [146]. Natural biomaterials like collagen have more biocompatibility and minor immunogenicity [146,151]. Some natural biomaterials are inherently anti-inflammatory, including high molecular weight Hyaluronic Acid (HA) and chitosan [152], which can decrease the type of reactive oxygen [153]. However, the use of anti-inflammatory drugs is common for most biomaterials [154]. According to studies, the structure, shape and geometry of the scaffold can also affect inflammation. In an experimental study it was shown that spherical material was implanted in various biological materials have better biocompatibility and the amount of fibrosis and FBR depend on the dimension of the material [155,156]. In addition, the researches have been shown that MSCs enclosed in 3D scaffolds due to the microstructure of scaffold had less inflammation compared to Two-Dimensional (2D) culture after transplantation. In three-dimensional culture, the amount of macrophages was reduced and production of anti-inflammatory proteins like PGE2 and TSG-6 were increased [156].

Yang et al. [157] to overcome immune response challenge in osteochondral grafting, used basal Fibroblast Growth Factor (bFGF) in combination with agarose gel to modulate and control full-thickness cartilage grafting. This procedure could reduce inflammation at the graft site and prolonged the survival of allogeneic cartilage implants [157]. This study has shown that bFGF can prevent the activation of inflammatory factors that lead to

the secretion of cytokines and the destruction of transplanted tissue. AlsobFGF increased the levels of CD4+, CD25+, Foxp3+ and regulatory T cells (Tregs) in the recipient blood. Increasing Tregs can protect implanted tissues against immune rejection [158].

In another method using immunosuppressive drugs simultaneous with allograft Mesenchymal Stem Cell (MSC) transplantation can reduce the host immune response. Immunosuppressive drugs could modify the mesenchymal stem cells efficacy by extending the viability of allograft tissue or organ transplants, and in turn, mesenchymal cells can control the side effects of immunosuppressive drugs [159,160]. Ge et al. [160] used the Rapa to suppressed the immune responses of allograft- MSC transplantation. Previous studies have shown that allograft-MSC genetic modification can be effective in controlling inflammation [161]. The MHC-1 expression decreased by US11 gene modification in bone marrow derived MSC. This modification also led to the protection of MSC by cytotoxic lymphocytes and prolonged the survival of mesenchymal stem cells in the allogeneic receptor [162]. Chen et al. [163] showed that genetic modification of mesenchymal stem cells could control the inflammation of osteoarthritis after allograft transplantation. Previous studies have shown that articular inflammation activates the IL-1b and TNF-α pathways and inhibits the chondrogenesis of mesenchymal stem cells [164], and can prevent fusion of grafted cartilage tissue [165]. Based on studies to control inflammation after allograft transplantation, use of IL-1b inhibitory growth factors such as IGF-1, Platelet-Derived Growth Factor (PDGF) -bb, Bone Morphogenetic Proteins (BMP-2 and BMP-9), GAG compounds (such as glucosamine), hyaluronic acid, and chondroitin sulfate, as well as Platelet-Rich Plasma (PRP), have been shown to be effective [166,167].

The use of PRP as an autologous source containing chemokines / cytokines, adhesive proteins, and effective growth factors for tissue repair is increasing in the therapeutic system. By inducing the synthesis of hyaluronic acid, proteoglycans and collagen type II have a protective effect on chondrocytes and stimulates their proliferation [168,169]. It also has anti-inflammatory and immunosuppressive effects by inhibiting macrophages as well as suppressing inflammatory factors such as metalloproteinases [170,171].

Conclusions

In summary, reconstruction of articular cartilage defects is a complex procedure. Despite the efforts of researchers, there is still no effective and long-term treatment for articular cartilage damage. Common treatments include surgical procedures such as debridement and arthroscopy, chondrocyte implantation, plastic mosaic, micro fracture, periosteal transplant, heart transplant, osteotomy, and bone marrow stimulation. Cartilage tissue engineering approaches by using different stem cell sources along with appropriate biological scaffolds, chondrogenic factors and physical stimuli, can be a promising way to overcome current limitations and cartilage reconstruction.

Researchers are trying to advance current cartilage therapies toward a consistently successful approach for articular cartilage regenerating. Despite many advances, tissue engineering techniques have limitations for clinical applications, the main problem being in terms of translation, modulation of the host immune system, transplant behavior in the host body, and recovery steps.

Genetic engineering, 3D bioprinting method and cell therapy are being developed alongside other technologies. In the future, combining current strategies with tissue engineering approaches could be a viable solution for the final treatment of cartilage defects.

Author Statements

Author Contributions

All authors have contributed equally to the article conception, data gathering, preparation, draft writing, image drawing, and submission processes.

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Declarations of Interest

The authors have no financial conflicts of interest.

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