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REVIEW ARTICLE

Application of cell and biomaterial-based tissue engineering methods in the treatment of cartilage, menisci and ligament injuries

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Abstract Over 20 years ago it was realized that the traditional methods of the treatment of injuries to joint components: cartilage, menisci and ligaments, did not give satisfactory results and so there is a need of employing novel, more effective therapeutic techniques. Recent advances in molecular biology, biotechnology and polymer science have led to both the experimental and clinical application of various cell types, adapting their culture conditions in order to ensure a directed differentiation of the cells into a desired cell type, and employing non-toxic and non-immunogenic biomaterial in the treatment of knee joint injuries. In the present review the current state of knowledge regarding novel cell sources, in vitro conditions of cell culture and major important biomaterials, both natural and synthetic, used in cartilage, meniscus and ligament repair by tissue engineering techniques are described, and the assets and drawbacks of their clinical application are critically evaluated.

Keywords Biodegradation · Biocompatible · Cartilage tissue engineering · Collagen · Fibrin · Scaffold · Silk

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Introduction

As a result of ageing populations and the consequent increasing incidence of musculoskeletal disorders, attention has recently been focused on the regeneration of joint structures, primarily knee joints. This task requires the employment of novel tissue engineering (TE) techniques necessary to regenerate cartilage, menisci, or ligaments [1, 2]. However, the application of the TE techniques face numerous challenges, including: the appropriate choice of the cell source and the culture methods used for tissue repair, suitable scaffolds and proper bioreactors [3, 4].

Among the cell types, which qualify for the repair of damaged joint structures the most suitable are chondrocytes, fibrochondrocytes, mesenchymal stem cells (MSCs), human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) [5]. The design of a suitable scaffold requires its proper architecture, which ensures optimal conditions for cell growth. When the scaffolds are loaded with the appropriately selected cells, supplied with proper growth factors, subjected to mechanical stimuli in a suitable bioreactor and implanted into the injury site, then the intrinsic healing response can begin [6].

The aim of the present report is to review the current literature on the cell-based regeneration of knee cartilage, menisci and ligaments. The review includes in vitro, ex vivo and in vivo studies as well as clinical trials.

Cell sources

Of the numerous methods available, cell-based techniques are the most advanced approaches. The cells, first considered suitable for transplantation into the lesion site of articular cartilage

were autologous chondrocytes [7]. The procedure, which was introduced in an animal model in the early 1980s is called autologous chondrocyte implantation (ACI). In the early 1990s, Brittberg et al. [7] in their initial clinical studies on the effectiveness of ACI, reported good or excellent results in 14 out of 16 patients. Two subsequent clinical trials, conducted in larger groups and longer follow-up terms, showed good-to-excellent results in 76 % [8] and 88 % [9] of patients respectively, indicating that the emerging TE technique would soon replace traditional methods of treatment for cartilage, menisci and ligaments injuries and more suitable cells would be searched for.

Chondrocytes and fibroblasts

Autologous chondrocytes, first used for the repair of articular cartilage injuries, have also been found as a good cell source for the meniscus tear repair [10]. It has been well-established that current methods of meniscus repair are only effective in treating tears located in the vascularized (red-red) zone of the meniscus, while ruptures of the avascular (white-white) zone still present a challenge for cell-based therapies [11]. Since meniscectomy contributes to the premature development of osteoarthritis (OA) [12], research has turned towards meniscus replacement methods that use cell/biomaterial constructs. The potential advantage of chondrocytes over meniscus cells is mainly due to the higher production rate of type II collagen and glycosaminoglycans (GAGs) by chondrocytes [13]. Investigations in animal models have shown that the treatment of a meniscus rupture within the avascular zone with autologous chondrocytes provides a good bonding of the lesion borders [10]. Moreover, it is extremely difficult to obtain a sufficient number of autologous meniscus cells from patients who have already undergone meniscectomy. For these reasons, both autologous and allogenic chondrocytes have been used in the replacement of menisci [14, 15].

Fibroblasts have been used to regenerate ligamentous tissue. Cooper et al. [16] compared four cell sources used for anterior cruciate ligament (ACL) reconstruction. Cells were harvested from the ACL, medial collateral ligament (MCL), Achilles tendon, or patellar tendon. The results showed that fibroblasts from the Achilles and patellar tendons showed the highest proliferation rate. However, only the ACL fibroblasts demonstrated a significantly higher expression of differentiation-specific ligament genes. Ge et al. [17] found that fibroblasts derived from ACLs or MCLs produced type I collagen and α-smooth muscle actin, and did not synthesize type II collagen. In that study, however, fibroblasts showed a lower proliferation rate and ability to survive when compared to mesenchymal stem cells (MSCs). In addition, the use of fibroblasts is troublesome due to several factors, including: (i) reduced number of native cells available for implantation, (ii) cell dedifferentiation in vitro and (iii) the need for an additional operation.

Mesenchymal stem cells

The use of MSCs as an alternative source for therapy is advantageous since the number of cells available for implantation is much higher, cells differentiate in vitro into desired cells and there is no need for a second operation. The major obstacle in the application of MSCs in articular cartilage repair, however, is an uncontrolled process of endochondral ossification, which may occur after cell transplantation [18, 19]. In several studies commonly used bone marrow-derived stem cells or stem cells isolated from various tissues were compared. Pei et al. [20] reported that in MSCs derived from synovial tissue, potential for endochondral ossification was lower than in bone marrow-derived MSCs. When, in an animal model, MSCs were applied to restore full-thickness osteochondral defects, bone marrow, periosteal and synovial MSCs showed a higher potential for lesion repair than adipose-derived and muscle-derived MSCs [21]. Adipose-derived stem cells, have a low potential for differentiation into cartilage because they do not express the transforming growth factor-β (TGF-β) receptor and showed a reduced expression of bone morphogenetic proteins (BMPs) [22]. Nevertheless, in cells isolated from the infrapatellar fat pad, the chondrogenic potential in vitro is similar to that of the MSCs derived from synovium [23, 24]. A disadvantage in using bone marrow-derived MSCs is their lower proliferation rate in the elderly and in the OA patients [25]. The MSCs have been tested in several different animal species [26, 27] as well as in clinical studies in humans [28, 29]. The results of these studies confirm the high chondrogenic potential of MSCs in vivo and the outcomes were similar to those obtained using ACI. In order to reach final conclusions, further research in larger groups of patients is required.

Several researchers have also investigated (in animal models) the effectiveness of autologous MSC transplantation to repair meniscus tears. The results of those experiments showed that MSCs implanted into the avascular area of the meniscal tear proliferate and expand, thus producing large amounts of ECM components and thus accelerating the healing process [30, 31].

MSCs have also been used in ligament regeneration due to the ability to effectively differentiate into the ligament fibroblasts [32]. These cells exhibit the fibroblasts' phenotype both in vitro [17] and in vivo [33]. Recent advances in elucidating the basic molecular mechanisms underlying cell differentiation and signalling pathways involved in this process, together with the progress in cell homing and implantation techniques could lead to the application of this method in clinical trials.

Human embryonic stem cells

In addition to MSCs, other cell types that present chondrogenic or fibrogenic potential are human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs). The first of these, hESCs, derive from human blastocysts and have the potential to differentiate into all three germ layer cell lines. Over the last several years, various protocols were used to differentiate hESCs into chondrocytes [34, 35]. Chondrocytes obtained from hESCs show an immature phenotype; therefore, in order to achieve cell maturation, further refinement of this technique applying special biological and environmental factors as well as biomaterials is required. The potential of hESCs to differentiate into fibrochondrocyte-like cells has been investigated by Hoben et al. [36], who showed that the co-culture of hESCs with chondrocytes or meniscus cells results in a significant increase in tissue-specific collagen production. Results from that study have proven that hESCs are suitable for the repair of the meniscus with fibrocartilage cells. However, because of legal considerations and ethical controversies, the clinical use of hESCs is still under consideration.

Induced pluripotent stem cells

Induced pluripotent stem cells are reprogrammed pluripotent cells, which like hESC, also show the potential to differentiate into three germ layer cell types. Most human iPSCs derive from fibroblasts and they are reprogrammed using the forced expression of transcription factors, which are known oncogenes [37]. For this reason, the clinical application of iPSCs is currently being investigated with great caution, given the high potential for oncogenicity that may result from the use of these factors [38]. However, it should be noticed that the use of iPSCs rather than hESCs avoids an ethical issue since the genetic information contained in iPSCs derives from the patient's own genome and is also less likely to induce an immune response [39]. The use of iPSCs in TE is an emerging field of research, and may lead to a wide range of alternative methods that can be used in the treatment of injuries of knee joint structures. Preliminary studies have demonstrated that iPSCs derived from mouse fibroblasts differentiate towards chondrocytes, which synthesize ECM components, type II collagen and GAGs. These chondrocytes, in an in vitro model of cartilage defects, integrate with the native tissue when implanted in agarose scaffolds [25].

Culture conditions

The use of cells expanded under conditions that preserve their differentiation potential and phenotype is crucial in the cell-based TE protocols. Cell growth depends on several important factors, including: temperature, pH, oxygen concentration, nutrients, growth factor/cytokine supply, concentration of metabolic waste and culture type (monolayer or 3D) [40]. Typically, cells are cultured at 37 °C, although some reports suggest that oxidative stress can be reduced by culturing MSCs at 32 °C [41]. The pH is normally 7.4 and it decreases when the concentration of metabolic waste products increases in the medium. This parameter should be carefully controlled, since major changes in the pH may be detrimental for the cell culture [42]. Continuous oxygen supply is essential to provide proper dO_2 concentration, which decreases as the biomass increases. The atmospheric oxygen level, however, may cause the oxidative stress of the cells, thereby decreasing their viability [43]. It has been reported that MSCs expand more efficiently at 2 % O_2 [44, 45], whereas hESCs grow better at 20 to 30 % oxygen levels [46]. Moreover, Foldager et al. [47] demonstrated that oxygen tension (pO_2) as low as 9 % in a 3D culture stimulates the expression of genes that encode chondrogenic markers (Sox9, aggrecan and Col2a1).

Nutrient supply is obviously crucial at each stage of cell differentiation. During cell expansion, cell metabolism is mainly based on energy obtained from glycolysis, whereas at the differentiation stage, there is a switch to oxidative phosphorylation as the energy source [48]. It has been well-established that chondrocytes dedifferentiate when cultured in monolayers, whereas they are able to retain their phenotype in the 3D culture [49]. Cell dedifferentiation results in the decreased expression of type II, IX and XI collagens, as well as SOX9 and aggrecan, with a change to "more fibroblastic" collagens such as type I, V collagen and versican [49, 50]. In large 3D constructions, however, the number and metabolism of cells located in the inner part decreases [51]. A lower concentration of cells in the 3D culture would compromise the mechanical strength of the implant. However, this problem can be overcome by applying bioreactors with dynamic fluid circulation, such as a rotating-wall-vessel bioreactor (RWV) or stirred-flask bioreactor [52]. To date, no consensus has been reached concerning optimal cell densities in cell-based therapeutic methods. In different reports cell numbers ranged from 2.5×10^5 [53] to 1×10^7 per cm^2 [54]. Another study reported that MSCs require an even higher cell density during the chondrogenesis process [55].

The principal growth factors directing chondrogenesis and fibrogenesis are members of the TGF-β family [56]. Cell expansion and differentiation are also affected by bone morphogenetic proteins (BMPs) and the following growth factors: insulin-like growth factors (IGFs), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and growth and differentiation factors (GDFs) [53, 57].

Cell culture is labour-intensive, time-consuming and expensive. Therefore, efforts have been made to optimize this

procedure by using bioreactors to obtain fully controlled, stable, automated cell cultures at a reduced cost [42].

Biomaterials used for cartilage, menisci and ligaments repair

Collagen

Collagen as the major component of cartilage, menisci as well as the ligaments and ECM has long been used in TE as a natural biomaterial [58, 59]. Nowadays, a wide range of collagen-based biomaterials are commercially available. Collagen matrices are characterized by relatively low immunogenicity and a proper structure, which mimic a native tissue environment, thus preventing cell dedifferentiation. However, collagen scaffolds are difficult to handle and sterilization may alter their structure [60]. In collagen matrices type I collagen is commonly used. In vitro studies of type I collagen hydrogel scaffolds has shown that the cells embedded in the hydrogel easily adhere and proliferate well and the MSCs seeded on type I collagen matrix, retain their differentiation potential for a long time. In one of the studies, it was reported that proteoglycan and type II collagen content were similar to that obtained by the same number of cells seeded on clinically used type I/III collagen scaffolds and cultured under the same conditions for 42 days [61]. Yuan et al. [62] demonstrated the immunomodulatory properties of type I collagen hydrogel. Chondrocytes cultured in this gel for 14 days increased the synthesis of both MHC class I and II proteins. These cells produced ECM components, mainly type II collagen and GAGs continuously over the culture period. Gierloff et al. [63] compared the proliferation rate of MSCs and chondrogenesis using various commercially available collagen and hyaluronan scaffolds including: non-cross linked bovine type I matrix, type I/III collagen scaffold, type I collagen sponge and hyaluronic acid gel. Chondrogenesis mediated by MSCs was documented by the elevated expression of the *SOX-9* gene, chondroadherin, cartilage oligomeric matrix protein (COMP) and type IX and XI collagens. The cells seeded on the spongy type I collagen scaffold, showed the highest proliferation rate and number of viable cells (over 54 %) compared to the other two collagen matrices and hyaluronan gel.

The collagen-based meniscus implant (CMI) was the first technique of this type used for meniscus regeneration [64]. CMI is a resorbable type I collagen scaffold and was arthroscopically sutured to the remaining parts of the meniscus. This technique is recommended for the repair of the outer parts of the meniscus and is not suitable for the whole tissue [64]. Martinek et al. [65] conducted an in vitro study in an animal model using CMI seeded with autologous fibrochondrocytes. In the experimental group (n = 9), the meniscus tissue was restored after 3 months. In that group, the implants were seeded with cells containing a larger ECM volume, whereas the implants in the control group (non CMI-seeded) were filled with a high number of cells with a small ECM volume. Another preliminary study involving eight patients who were observed for 24 months showed clinical improvement in all patients. Macroscopic evaluation during the second-look arthroscopy revealed tissue regeneration, and histological assessment confirmed the formation of fibrocartilage [66]. Niemeyer et al. [67] performed a long-term clinical study to prove the superiority of standardized collagen membrane over first generation ACI for the treatment of cartilage defects. Another study, conducted in a group of 160 patients who were observed for 12 months, supports previous observations. Although clinical improvement was reported in most patients, the meniscus-like tissue was present in only 50 % of cases [68]. Pabbruwe et al. [69] investigated another commercially available type I/III collagen membrane, used as a carrier for human bone marrow MSCs, in the treatment of meniscus tears of the avascular zone. Cell-loaded and cell-free scaffolds were cultured in vitro on the white zone of ovine menisci. The MSC-loaded constructs integrated well with the host tissue and this group showed significantly better results in tensile strength compared to the acellular constructs.

Gelatin

Gelatin derives from collagen and is a form of denatured collagen fibre. Due to denaturation, gelatine exhibits lower antigenicity than the collagen itself, and is biocompatible and biodegradable. The most commonly used form of gelatine scaffolds is hydrogel, which is created by fibre crosslinking. The fibres are degraded enzymatically, with the degradation time depending on water content [70]. In addition, these scaffolds retain the Arg-Gly-Asp (RGD) sequence, which promotes cell adhesion and proliferation. However, the poor mechanical properties of gelatine gels preclude the use of this polymer alone as a cell-carrier in cartilage, meniscus or ligament regeneration [71]. In order to improve the mechanical strength, in most studies the cross-linked gelatine scaffolds or multilayer constructs were applied [72, 73]. Lien et al. [72] studied a multi-layered gelatine-ceramic construct for osteochondral lesion repair. In the rat model, they showed that a gelatine layer seeded in vitro with chondrocytes led to the development of cartilage tissue in less than four weeks. From the 1st to the 4th week of culture, the GAGs content increased about 20-times, the cells overgrew the scaffold and filled the pores, while only a small number of hypertrophic cells were observed. The same group investigated the influence of gelatine scaffolds pore size on rat chondrocyte growth and synthesis of the ECM components. The authors concluded that these cells secrete more GAGs and overgrow better scaffolds when the pores are larger (from 250 to 500 μm in size). The authors

also observed an increase in chondrogenic markers: type I, II and X collagens, as well as aggrecans [74].

For meniscus regeneration, a gelatine-based, three-layered scaffold has been developed by Sarem et al. [75]. These authors seeded heterogeneous gelatine/chitosan matrices with human meniscus cells and, showed increased cell number and proliferation over the culture time. Moreover, they reported that cells seeded on scaffolds with higher gelatine content presented a higher proliferation rate and that the biomaterial was more cytocompatible.

Hyaluronan

Hyaluronan is a polysaccharide polymer most often used for orthopaedic applications in the form of benzyl ester of hyaluronic acid (HA). Its degradation process and HA release has been well-documented [76]. HA is as an important component of GAGs, and it shows major chondrogenic and chondro-protective properties [77, 78], although the clinical application of non-cross-linked hyaluronan-based scaffold is limited due to its weak mechanical strength [79]. Hyaluronan has been used to modify the synthetic PCL (polycaprolactone) scaffold of proper mechanical strength and has been shown to improve the distribution and differentiation of chondrocytes seeded on the PCL scaffolds. Type I and II collagen and aggrecan synthesis was also increased when the HA-modified versus an unmodified PCL were used [80]. More recently, Wu et al. [81] investigated the impact of HA on chondrogenesis in human adipose-derived stem cells (ADSCs). Cells were cultured in a 2D monolayer system using either HA/fibrin or fibrin hydrogels. ECM formation assessment showed that cells seeded on HA/fibrin gel induced higher levels of chondrogenic markers expression (SOX-9, type II collagen and aggrecan). Type II collagen and GAG synthesis on HA/fibrin gel was also superior to that of fibrin gel alone. The authors indicated that induction of chondrogenesis in the HA-enriched scaffold was due to the HA and CD44-cell surface receptor involved in HA interactions.

In the TE of the meniscus, HA was used as a scaffold composite together with gelatine [82], collagen [83, 84] and PCL [85]. In a rabbit model of meniscus defect, MSCs seeded on hyaluronan/gelatine matrices and implanted to the injury site, integrated well with the host tissue, filled the defect and three months, newly formed fibrocartilage, with hyaline-like cartilage zones, was observed [82]. In a more recent study, Zellner et al. [84] compared the effects of repairing meniscus tears in the avascular zone of rabbits using four different treatment methods: untreated tear, suture of the meniscus, a PRP-loaded composite and a scaffold loaded with autologous MSCs. At 12 weeks, no signs of healing were observed in either the untreated or sutured tear groups. The PRP-loaded composite resulted in poor tissue regeneration, while the MSC-seeded scaffold filled the defect with meniscus-like tissue comprising low cell numbers and high type II collagen content. Kon et al. [85] investigated hyaluronan/PCL constructs with improved mechanical properties to assess their value as a cell-carrier of autologous chondrocytes. One-year after surgery, cell-seeded scaffolds showed significantly better fibrocartilage formation when compared with the cell-free implants and the group that underwent meniscectomy.

Fibrin

Fibrin is generated by the proteolytic cleavage of fibrinogen by the enzyme thrombin. Since fibrinogen could be formed from the patients' fibrin, this biomaterial is immunocompatible and has been widely used in clinical medicine in the form of fibrin glue for cardiovascular, skin, liver, or muscle repair [86]. The mechanical properties and integrity of fibrin hydrogels depend on Ca^{2+} concentrations and the pH. Similar to gelatine, fibrin scaffolds are characterized by low mechanical strength and rapid degradation. Fibrin-based scaffolds have been used in the TE of cartilage, meniscus and ligaments, although they are usually modified with the addition of more resistant polymers [87]. It has been well-established that fibrin promotes cell proliferation and differentiation [88]. Kreuz et al. [89] investigated the use of scaffold-assisted ACI to repair focal cartilage defects. In that study, 52 patients underwent cartilage repair with autologous chondrocytes embedded in a fibrin scaffold. Four-year clinical observations showed significant improvement in over 80 % of patients, with moderate to complete filling of the lesion observed on MRI.

Fibrin hydrogel has also been investigated in meniscal repair [90]. In that study, chondrocytes embedded in the fibrin scaffold and cultured in vitro bonded to the surrounding tissue and restored the fibrocartilage, while no tissue formation was observed in the cell-free constructs.

Silk fibres

Silk fibres are another emerging and attractive alternative to ECM-derived polymers, mainly due to their outstanding mechanical properties, which are crucial for cartilage, meniscus and ligament regeneration. Silk is a fibrous protein synthesized by several different species of worms, although the best-characterized and most frequently used fibres are produced by the silkworm (*Bombyx mori*) [91]. Silk fibres show a low immunogenicity and antigenicity, and thus are good candidates for the use as cell-carriers in the TE [92]. In a rabbit model of articular cartilage defect, bone marrow MSCs seeded on silk/chitosan (SF/CS) scaffolds restored the cartilage surface with smooth and well-integrated newly-formed tissue. In contrast, in rabbits who received the cell-free scaffold, only a distinct margin between the native and the regenerated tissue

was visible. At 12 weeks after surgery, neither group showed scaffold fibres and no immunogenic reactions occurred [93].

A three-layered silk scaffold has been developed as a cell carrier for meniscal tear repair [94]. The multi-layered structure mimics the fibre alignment of a native human meniscus. The outer parts of silk matrices were seeded with human fibroblasts and the central part was loaded with chondrocytes. At the 28th day of in vitro culture, the cells were evenly distributed across the three layers. GAGs and type I and II collagens were detected in all parts of the construct. The same research group also evaluated the use of MSCs seeded on a multi-layered silk scaffold [95]. In that study, the authors found that MSCs differentiated into chondrogenic lineages after four weeks. The cells stained positive for GAGs and collagen and the differentiated cells showed mature chondrocyte phenotype.

Silk fibres have also been used in numerous in vitro and in vivo studies of ligament regeneration. Liu et al. [96] compared rabbit MSCs and fibroblasts harvested from the ACL and seeded on silk scaffolds. The results of the in vitro study showed that MSCs showed a higher proliferation rate, synthesized more ECM components and exhibited the increased expression of genes encoding type I and II collagen and tenascin-C. The same group investigated the in vivo effects of MSCs seeded onto silk scaffolds and used in ACL reconstruction in the rabbit model [97]. The authors compared two groups, one which received cell-loaded scaffolds and the other (control group) receiving acellular scaffolds. In the 24th week, the cellular scaffolds restored the ACL tissue in the experimental group, while in the control group less of the fibrous tissue formation with visible silk fibres in the regenerated ligament were observed. Histological assessment revealed the intense production of the ECM components, high type I collagen expression and fibroblast-like morphology of the cells. In the control group, all samples stained negative for the ECM components. When converted into a large animal model and evaluated after 24 weeks, the MSCs seeded on the silk scaffold differentiated into fibroblasts and their morphology resembled the native tissue. The follow-up study revealed the complete degradation of silk fibres and the regenerated ACL was able to withstand nearly 52 % of the maximum load compared to the native ligament [33].

Synthetic polymers

Synthetic polymers include poly (lactic acid) (PLA), poly (glycolic acid) (PGA), PLA and PGA copolymer, poly (lactide-co-glycolide (PLGA) and polycaprolactone (PCL).

PLA is used in two isomeric forms: poly L-lactic acid (PLLA) [98] and poly DL-lactic acid (PLDLA) [99], both are biocompatible and biodegradable, with a degradation time of PLA ranging from one to two years [100]. In vivo, PLA is subjected to hydrolysis and the degradation rate depends on the size and shape of implant [101]. Like all synthetic polymers, PLA is easily produced and processed. Polymeric PLDLA-PCL scaffolds were used to repair meniscal tears in a rabbit model [102]. In that study, matrices were seeded with meniscus cells and implanted into the site of the defect. The results of the cell-loaded and cell-free groups were compared at 12 and 24 weeks after implantation. In the 24th week, the tissue that formed in the pre-seeded cell group resembled the native meniscus, while the cell-free scaffolds failed to restore the area of meniscus incision and developed fibrosis at the implantation site. Both the isomeric forms of PLA have been tested for ligament reconstruction. Cells seeded on the PLLA-braided scaffold adhere, proliferate and exhibit ECM component production after three weeks of culture [16].

PGA degrades to glycine, which enters the tricarboxylic acid cycle, and is thus metabolized through the natural metabolic pathways [103]. PGA is an FDA-approved polymer that has long been used in biodegradable sutures. In a pig model study of articular cartilage defect, autologous chondrocytes were seeded and implanted (after two weeks of culture) onto a PGA/PLA scaffold and evaluated after six months [104]. At the 6th-month after the surgery, the cells completely filled the site of the defect with mature cartilage-like tissue. In the newly-formed cartilage, type II collagen and GAG contents were similar to the surrounding tissue. In contrast, the cell-free PGA/PLA construct implantation resulted in the formation of fibrous tissue that did not integrate with the native cartilage, collapsed into the site of the defect and no synthesis of type II collagen or GAGs were detected.

Kang et al. [105] reported the regeneration of rabbit menisci using the PGA/PLGA scaffold seeded with allogenic meniscal cells implanted into the knee joint. At the 10th week, meniscal regeneration was observed and collagen and PG content in the newly-formed tissue was similar to that of native tissue. Saha et al. [106] studied three different cell types cultured under various conditions in vitro and in vivo on the PLGA-based scaffolds. Human bone marrow MSCs, human neonatal chondrocytes and adult chondrocytes were cultured in the chondrogenic medium on the cartilage phase of a commercial osteochondral scaffold. All cell types revealed a high proliferation rate, ECM secretion and cell growth. After the intra-peritoneal implantation of cell-loaded constructs into nude mice, cells formed a cartilage-like tissue. However, in both MSCs and neonatal chondrocytes, some fibrocartilage-like tissue insertions were observed, while the adult chondrocytes managed to maintain their chondrogenic phenotype.

The effect of chondrocyte-seeded PLGA scaffold was examined in meniscal regeneration using porcine meniscal discs implanted in vivo in a heterotopic mouse [107]. In ten out of 12 samples of PLGA cell-loaded constructs, the newly formed tissue filled the entire lesion with a fibrous and cartilaginous tissue, while fibrocartilage was found in seven cases, whereas

when acellular scaffolds were used, no signs of healing were observed.

PCL is a soluble polymer with a degradation time of two to three years [108]. A three-layered heterogeneous PCL scaffold that mimics the fibre organization and alignment of native tissue has been developed and one of the studies compared cell attachment, proliferation and differentiation using bovine chondrocytes seeded either on a homogenous PCL scaffold or on the three-layered PCL construct. In that study, no differences in cell adhesion, GAG content, type I and II collagen production were found [109]. Moutos and Guilak [110] studied an anisotropic PCL/fibrin gel scaffold seeded with human ADSCs. Although cells cultured for 28 days under "chondrogenic" conditions synthesized the ECM components, the phenotype of the cells was fibrocartilage-like.

Conclusions

Combining various types of cells, including stem cells, with new biomaterials presents enormous possibilities to engineer the damaged tissues, including knee joint structures. To date, many efforts have been made to overcome the limitations in cell harvesting, in vitro culture and implantation techniques. Novel methods of manufacturing and the emergence of 3D printing have opened new horizons and in the near future the growing expectations of clinical applications will likely appear. Recent developments in cell-based therapeutic methods, especially those using stem cells, ensure a heterogeneous cell environment and provide the biological and mechanical stimuli that mimic the conditions existing in the native tissue. A thorough understanding of the biological processes underlying the TE at both cellular and molecular levels will ensure the safety and effectiveness of these innovations. All these developments, taken together, may in the future, lead to the successful and cost-effective transfer of the TE methods and the use of novel cell/biomaterial constructs from the bench top to the bedside.

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Compliance with Ethical Standards

Conflict of interest The authors declare that there is no conflict of interest.

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