Bio-Design and Manufacturing (2019) 2:41–49
https://doi.org/10.1007/s42242-018-0031-0

REVIEW

Biomaterials for repair and regeneration of the cartilage tissue

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Received: 20 October 2018 / Accepted: 8 December 2018 / Published online: 17 December 2018

Abstract
The repair and regeneration of the diseases and damaged cartilage tissue are one of the most challenging issues in the field of tissue engineering and regenerative medicine. As the cartilage is a non-vascularized and comparatively acellular connective tissue, its ability to the self-restoration is limited to a large extent. Although there is a countless deal of experimental documents on this field, no quantifiable cure exists to bring back the healthy organization and efficacy of the impaired articular cartilage. Tissue reformative approaches have been of excessive curiosity in restoring injured cartilage. Bioengineering of the cartilage has progressed from the cartilage focal damages treatment to bioengineering tactics progress aiming the osteoarthritis procedures. The main focus of the present study is on the diverse potential development of strategies such as various categories of biomaterials applied in the reconstruction of the cartilage tissue.

Keywords Biomaterials · Cartilage · Tissue engineering · Repair · 3D bioprinting

Introduction

As a division of translational investigation in tissue engineering, regenerative medicine has observed the initiation of the novel, biomaterial established approaches for treating, supporting, or substituting the unhealthy or damaged tissue. Effective scientific use of these methodologies involves emerging biomaterials and scaffolds proficient in interfacing appropriately with tissues on a physical, mechanical, and biological level [1–4]. So as to avoid extra degeneration of the tissue and the adjacent milieus in restoring cartilage, it is vital to regard the complicated progression of the typically happening tissue healing and use a combinative curative method to attain regular structure and functionality of the damaged tissue [5]. A numeral of engineering methods for cartilage healing have acquired notice that uses a mixture of cells, biodegradable scaffolds, and signaling factors proficient in improving regular procedures involved in tissue renewal [6, 7]. Cartilage restoration happens over a conventional of biological procedures organized by different cytokines and growth factors creating signals at the definite destruction situate, which consecutively permit the therapeutic procedures to be started by progenitor and provocative cells [8, 9]. A methodology for renovating need generates a satisfactory space and helpful surrounding to grow cartilage; moreover, to permit the tissue growing or renewal after damage, it has to avoid immune reactions and it needs to degrade for the period of a particular extent of time [10, 11]. Up till now, none of the concocted replacement tissues have totally imitated the characteristics and the organization of natural cartilage.

In this review, numerous of the most important bioengineering approaches in cartilage restoration are abridged that use biomaterial.

Cartilage regeneration approaches

Bioengineering uses the ideologies of engineering and biotic skills to progress biological replacements which are talented for regenerating distorted tissues natural ability [11, 12]. The emerging field of engineering strategies is based on the assortment of nanotechnology, various biomaterials, stem cells, and signaling biomolecules. Progresses made in biomedical engineering and the function of stem cells and growth factors in restoring damaged tissue have been an excessive advantage for bioengineering of cartilage [13].

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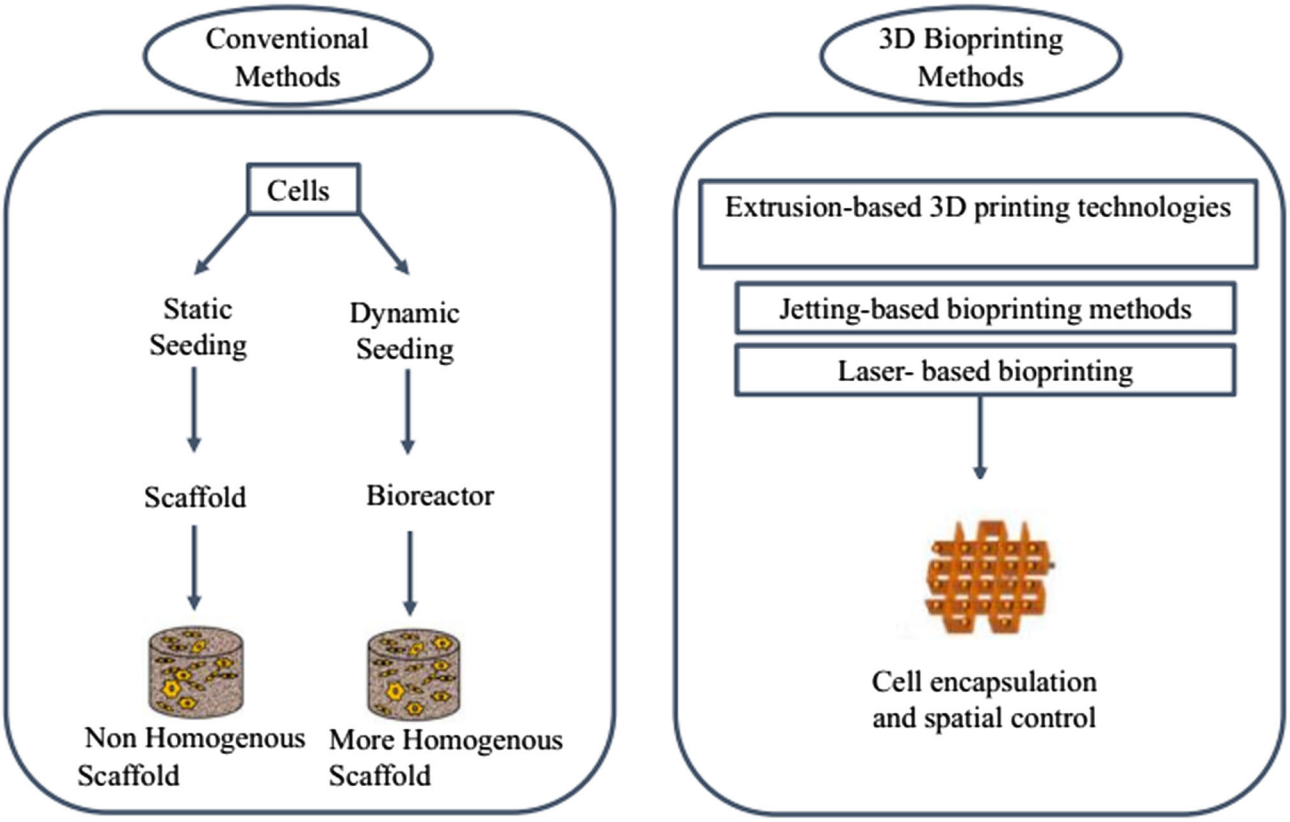

Fig. 1 Recent progress in cartilage repair

Developments in three-dimensional printing have improved possibility toward the production of living tissues. Well known as 3D bioprinting, this method includes the accurate layering of cells, biologic scaffolds, and signaling factors with the aim of producing bioidentical tissue for a diversity of applications. Initial achievements have confirmed individual advantages over conventional tissue engineering approaches (Fig. 1).

Biomaterials

Similar to other tissues engineering-based strategies, there are two main types of biomaterials which are used for the restoration of the cartilage including natural and synthetic substances [14]. However, several modifications have been applying for generating short-term or long-lasting constructions for improving cellular performance as well as generating appropriate niche for the growth of new tissues [15, 16]. In the following sections, we discuss all the aspects around thesis biomaterials and the three-dimensional constructs made of them.

Natural materials

Between natural materials commonly used in cartilage tissue engineering are gelatin, chitosan, cellulose, alginate, chondroitin sulfate, chitosan, agarose, fibrin, hyaluronic acid, and collagen [17]. These diverse categories of biomaterials are capable of interacting with cells due to particular superficial receptors, which cause cell to migrate instinctively and dynamically and facilitate cell proliferation and protein fabrication [18, 19].

Synthetic materials

Because of the great quantity and the simplicity of fabrication of scaffolds with modifiable and tailored properties, synthetic polymers are frequently applied to fabricate scaffolds for tissue engineering. Polyvinyl alcohol (PVA), polyethylene glycol (PEG), poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), poly(NiPAAm), poly(α-hydroxy esters), poly(propylene fumarates) (PPF), and polyurethane (PU) are among the greatest broadly used synthetic polymers for cartilage engineering [20–22].

The function of biomaterials in cartilage repair

The restorative methodology for regeneration of cartilage purposes rapid cartilage repair. With the aim of having an efficacious result in engineering method, it is necessary to prudently ponder diverse factors for instance scaffold's struc-

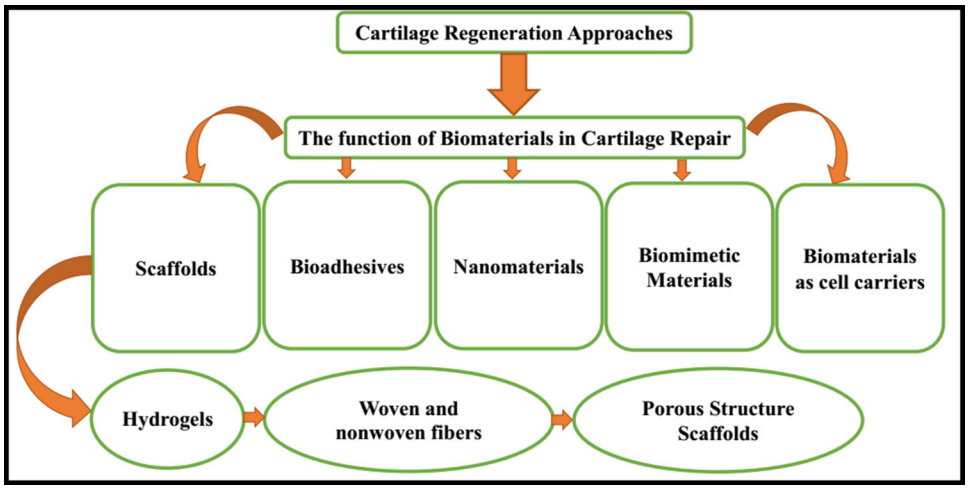

Fig. 2 Approaches to treat and repair of cartilage tissue

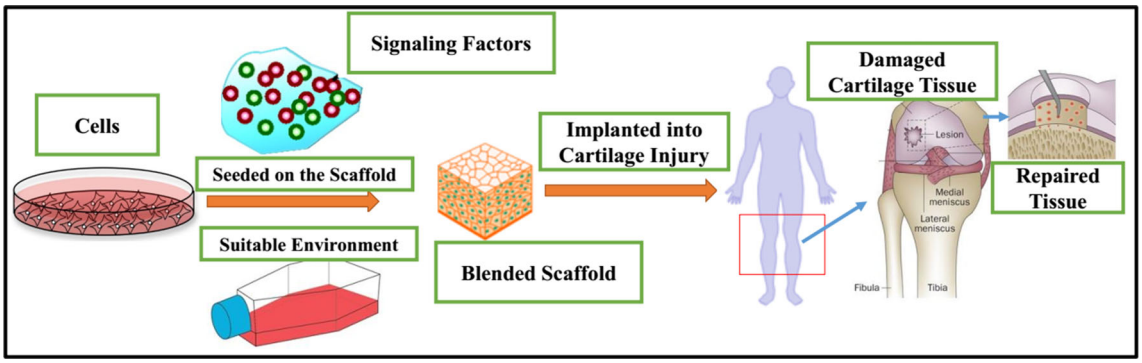

Fig. 3 Treatment of damaged cartilage using tissue engineering

tural design and features, tissue properties, and supporting signaling factors [23]. The concentration of the former tissue engineering methods was on particular subjects, but endeavors have lately been prepared to look for a combinatory methodology wherein a biomaterial and scaffold are incorporated with cells and growth factors [24–26]. As a result of its avascular structure, cartilage has slight inherent capability for restoration. Numerous treatment approaches have been suggested for cartilage restoration, but the ideal treatment is yet to be identified (Fig. 2). Engineered structures targeted toward emerging a suitable substrate may assist in cartilage regeneration.

Scaffolds

Generally, scaffolds are considered as a physical substrate, but in biological surroundings, they interrelate through cells and the neighboring tissue over definite chemical exchanges and physical stimulus [3]. For that reason, a scaffold is principally expected to provision cell culture, permeation, proliferation, and differentiation initiated by signaling factors and mechanical stimulation [27]. As stated by their application and morphology, scaffolds are alienated into seven classes, containing nanomaterials, biomimetic materials, bioadhesives, porous scaffolds, hydrogels, biomaterials as cell carriers and fibers [28, 29]. Scaffolds can be combined with cartilage cells and placed in the defective cartilage (Fig. 3).

Hydrogels

By way of cross-linked polymeric constructions, hydrogels captivate an abundant amount of water or other physiological liquids making them a motivating choice for tissue engineering [30]. Polymeric hydrogels are manufactured in two main systems, containing injectable or implantable system. This polymer demands polymerization, cross-linking, and a gelation process. The mechanical and biochemical properties of the hydrogel are totally founded on cross-linking method or amount and the polymers employed in the method. On the topic of the character of the cross-linking binding among the hydrogel constituents, physical or chemical cross-linking is attained [31, 32]. In cartilage regeneration, numerous hydrogel-centered approaches have been employed by means of diverse cross-linking approaches and materials [33].

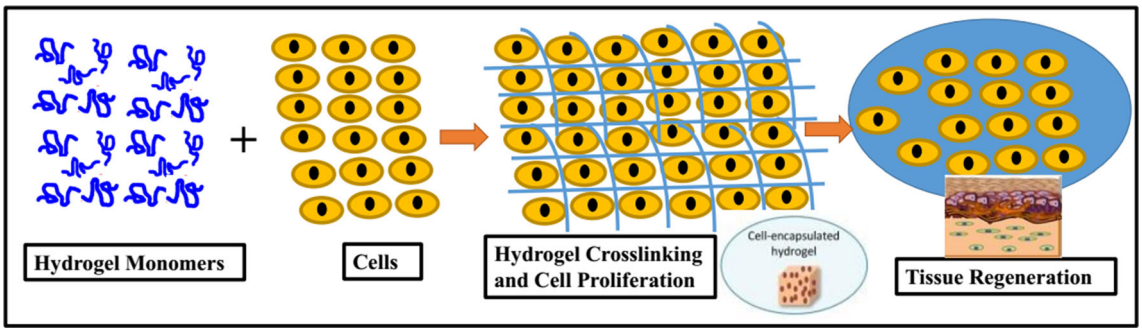

Fig. 4 Schematic illustration of injectable hydrogel for cartilage tissue regeneration

For instance, hyaluronic acid (HA) has a substantial result in growth and performance of the cartilage, and hyaluronic acid scaffolds have appealed excessive consideration. Chemical change of the HA has great importance in the studies. Hydrophobic agents were attached on the hyaluronic acid backbone, and the HA polymer has been cross-linked by means of a reagent tetraethylene glycol ditosylate. As a consequence of hydrophobic exchanges, the method brings about the manufacture of polymer with shear thinning characteristics. With the purpose of assessing cytotoxicity, proliferation, and mineralization, the hyaluronic acid hydrogels have been investigated in the research laboratory by employing chondrocyte cells.

Furthermore, to modify the mechanical structure of the injectable hyaluronic acid hydrogel, by the use of photopolymerization of methacrylate agents to the hyaluronic acid backbone, HA has been cross-linked [34, 35].

Afterward, silanized hydroxypropyl methylcellulose self-setting hydrogel has been presented. The main characteristics of this structure are the dependency of its cross-linking result on the pH of its adjacent milieu. The chemically modified silicone groups on the cellulose backbone were employed to respond to a definite pH variety. The silanized hydroxypropyl methylcellulose self-setting hydrogel improved cytocompatibility, enhanced chondrocyte cell growth, and development of cartilaginous tissue [36].

Due to the passive and hydrophilic features of the polyethylene glycol (PEG), hydrogels for the tissue engineering application have involved the consideration of scientists. Furthermore, cross-linked porous PEG by hydrolyzable polyrotaxane scaffold has been formed to design appropriate surroundings for primary culture of chondrocyte cells. The biological assessment showed their capability to be employed as cartilage replacements [37].

Additionally, photopolymerizable polyethylene glycol diacrylate semi-interpenetrating structure provided a suitable milieu to be fabricated for the in vitro chondrogenesis of human stem cells. Further, evaluation of the architectural factors and the documents of in vivo tests confirmed that the destiny of the structure inside a biological situation is verified by cell–matrix exchanges.

With the aim of improving the geometrical, mechanical, chemical, and physical properties of porous scaffolds, many structures have been created by means of copolymerizing biomaterials with diverse features [38].

In another study, poly(ethylene glycol) (PEG) and poly(vinyl alcohol) (PVA) copolymer gels were produced, and then, these scaffolds were assessed to be employed in cartilage tissue regeneration. The chondrocyte cells were photoencapsulated in the copolymer. The in vitro and in vivo studies have been investigated for about 6 weeks. The achieved outcomes designated neo-cartilaginous tissue growth containing a rich gratified of proteoglycans and collagen [39].

So as to assess the composite and the porous scaffold geometry properties on cell function and ECM fabrication, a 3D structure was produced by means of polypropylene fumarate and was in conjunction with an HA hydrogel. Then, the samples were imbedded in immunocompromised mice for 4 weeks. The attained data indicated that the composite scaffold can be considered as a functional tissue engineering substitutes for cartilage repair due to the tissue regeneration and appropriate mechanical possessions [22]. Hydrogel can be cross-linked with the cells and growth factor. This hydrogel is injectable with a low cross-linking time and strongly adheres to cartilage tissue. Hydrogel is stable in vivo where it maintains its adhesive properties and supports tissue maturation (Fig. 4).

Woven and nonwoven fibers

Fibrous constructions, which represent altered cell behavior, are designed from woven and nonwoven fibers. Investigation on cellular behavior has confirmed diverse factors, containing the thickness of the fiber, directionality, and distance among fibers that influence cellular behavior. As a result of fibers three-dimensional distribution and surface area, nonwoven fibrous constructions are appropriate for tissue restoration [40]. By reason of the biodegradable features

of poly-α-hydroxy esters are widely used polymers in tissue engineering [41]. In a research, the capability of nanofibrous polycaprolactone scaffolds containing TGF-β to preserving its integrity and the ability to encourage chondrogenesis of MSCs was assessed in vitro after 21 days [42]. In a different research, extremely porous with high interconnectivity polyethylene glycol terephthalate–polybutylene terephthalate copolymer scaffold has been evaluated in vitro. Due to appropriate and controllable mechanical and physical properties such as pore geometry and porosity level, a uniform spreading of cells and following cartilage-like tissue development was observed in polymer cultured by chondrocyte cells [43].

In another study, poly-L-lactide and poly-D, L-lactide-co-glycolide copolymer scaffolds have been modified biofunctionally using collagen and an RGD. The attained outcomes represented a growth in cell proliferation and GAG formation; however, a reduction has been observed in immune reaction [44]. Furthermore, a soft hyaline-resembling tissue was produced as a result of the cultured MSCs on PLGA which supports during 12 weeks of study in vivo [45].

Natural fibrous constituents have also been employed in cartilage tissue engineering, for instance agarose, cellulose, and fibrin. Besides, the chondrocyte cells attaching amount on the cellulose–calcium phosphate scaffolds, in which cellulose was activated by $Ca(OH)_2$, enhanced in comparison with the raw cellulose and in the course of the researches [46].

3D woven scaffold is made up of polyglycolic acid combined with agarose, and fibrin hydrogel was produced. Findings indicated the capability of scaffold to be progressed for cartilage regeneration in several phases [47].

Porous structure scaffolds

Porous scaffold features such as dimensions (control cell and nutrient/metabolite transport), porosity percent (necessary for cell adhesion), and interconnectivity (affect transport within the scaffold) justify its performance in a biological surroundings [48, 49]. In addition to developing geometric conformations, combining physiological elements develop cartilage tissue regeneration (e.g., growth factors, cytokines), cells, or pharmaceuticals by way of encapsulation or modifications [50–53]. Besides, a hybrid PLLA and collagen porous scaffold was fabricated by particulate leaching and evaluated. Subsequently, by means of glutaraldehyde, the composite has been cross-linked and further freeze-dried. The acquired chondrocyte cells seeded PLLA and collagen scaffold were imbedded in nude mice. The results discovered an extensive growth and homogeneous cartilaginous tissue formation in contrast to control samples [54].

In an investigation, porous structures were fabricated from polyethylene glycol terephthalate and polybutylene terephthalate using compression molding and paraffin templating. In order to verify which scaffold was proficient of promising chondrogenesis, the in vivo and in vitro evaluation was accomplished. It was understood that the scaffold manufactured as a result of paraffin templating represented greater chondrogenesis [55]. Biodegradable elastomers such as poly-1, 8-octanediol citrate scaffolds represented suitable mechanical and physiological characteristics for load-bearing usages (e.g., in the knees). To fabricate POC scaffolds for cartilage regeneration, the salt leaching methods were used; afterward, their elasticity was evaluated. Furthermore, chondrocyte cell adhesion and proliferation were developed by the POC scaffolds in vitro during 4 weeks of incubation [56]. In another research, with the purpose of fabricating natural porous scaffolds, chitin and chitosan composite was cross-linked with genipin, and then, the composite has been freeze-dried. Afterward, the attained structure was coated with HA to enhance chondrocyte cell adhesion and proliferation [57].

Among biomaterial scaffolds, because of supportive and generative properties for chondrogenesis in comparison with collagen scaffolds, silk fibroin has been contemplated to be an applicable alternative [58, 59]. In a work, by means of salt leaching method, porous silk fibroin substrates have been prepared. The in vitro study was done using human bone marrow to seed scaffolds after 3 weeks of incubation. Excessive cell proliferation and the generation of GAG, aggrecan, and collagen type II were enhanced by the silk substrates, in comparison with the collagen substrates [60].

The composite biomacromolecule and polyester scaffolds, which can potentially be used in cartilage tissue engineering applications, were investigated. In a work, poly-γ-glutamic acid–graft–chondroitin sulfate–blend–polycaprolactone (γ-PGA-g-CS/PCL) composite was prepared as scaffold for cartilage tissue engineering. These composite scaffolds have been analyzed by means of H NMR, ESCA, water-binding capacity, mechanical assessment, degradation percentage, and CS analyze.

After 28 days of culture, the mechanical strength of composite structure was enhanced progressively and chondrocyte cells have been encouraged to perform typically in vitro. Additionally, a greater extent of produced GAGs has been existed in the scaffold than in the control sample. Hydrogels and polymeric porous structures have been independently used as equivalents of the natural ECM though each of these types of constituents has its particular benefits and limitations.

In the current research, the advantages of these two kinds of materials are combined. Poly-L-lactic acid porous structures with virtuous mechanical characteristics have been produced by way of phase separation and then blended with agar hydrogel, which express a function to encourage chondrogenesis, and were carefully chosen to capture chondrocyte cells, performing as correspondents of natural ECM, in order to facilitate entrapment of cells within scaf-

folds. The morphology, distribution, and growth behaviors (glycosaminoglycan (GAG) secretion) of the chondrocyte cells were studied. After 1 and 2 weeks of the incubation, the chondrocyte cells in the scaffold were round and encapsulated by the hydrogel. Cell viability and the cell reproduction in the chondrocytes/agar/scaffold have been similarly greater than that of the control samples. Subsequently employing in the dorsum of nude mice duration of 28 days, cartilage-like samples keep their native shapes. Histological investigation presented that neo-cartilage was redeveloped and a great amount of collagen and GAG were reproduced.

Bioadhesives

Based on studies in regenerative medicine, tissue bonding is implemented by means of polymeric based sutures and tissue adhesive. Main parameters in bonding design are biocompatibility, sufficient strength, and tissue integration [61].

In a work, a fibrin gel has been modified to increase its strength. Furthermore, the modified fibrin gel was evaluated in vitro for cartilage tissue repair application. The attained outcomes discovered the reproduction and generation of the extracellular matrix constituents employing bovine chondrocyte cells [62]. Furthermore, the injectable fibrin glue containing fibrinogen and chondrocytes for cartilage repair was assessed. The results represented fibrin glue as an applicable injectable scaffold for the development of cartilage in the nude mouse model [63].

In addition, the function of a fibrin gel for improving the polyurethane substrate potential has been investigated in vitro. Findings exhibited that employing of fibrin gels conducts a greater cell attachment and proliferation [22]. Lately, application of chondroitin sulfate, the chief element of cartilage ECM, as bioadhesive was studied owing to its quick action. Functionalization of the chondroitin sulfate has been done in order to generate a 'tissue primer' which is capable of developing molecular links among a substrate and the surface of the tissue. Findings point out biocompatibility and growth of cartilage after 5 weeks of incubation [64].

Besides, polyamino acid-based adhesives with capability to adhere to tissues were studied. Blends of different polyamino acids were prepared as bioadhesive. Bioadhesive functioning was assessed in tension on glass surfaces, chondroitin sulfate surfaces, as well as bovine cartilage surfaces. The amino acid constructions contained acidic, basic, or polar side chains and were observed to bond sensibly well to the surfaces. In the other study, chondroitin sulfate–cysteine conjugate (CS-cys) was produced as intra-articular bioadhesive and then evaluated. As stated by results, CS-cys supports developed bioadhesive features that can be suitable as an intra-articular instrument for repairing of osteoarthritis [65].

Nanomaterials

Nanobiomaterials have lately taken considerable focus in the studies as a result of the high surface-to-volume proportion. Nanobiomaterials extensively employed in cell seeding and cartilage tissue regenerating [66–69]. In a study, polycaprolactone scaffolds were prepared in random, aligned, and round-ended electrospun nanofibrous conformations. The growth of chondrocyte cells was investigated in vitro. The obtained results indicated that round-ended nanofibers scaffold presented greatly satisfactory to adhesion, proliferation, and generation of cells ECM components [70]. Cell and matrix orientation can be inducted by aligned nanofibrous substrates. The main problem is low cell infiltration as a result of close-fitting packing fibers throughout preparation. Adjustable nanofibrous composite scaffolds containing polyethylene oxide and poly-ε-caprolactone can increase pore size leading to increase fibers infiltration of cells [71]. Appropriate surface modification of nanofibrous scaffolds increases biocompatibility and bioactivity of them. Moreover, nanofibrous scaffolds exhibited low cytotoxicity, enhanced cells attachment, and result in ECM components reproduction. Nanofibrous poly-L-lactic acid scaffolds were fabricated using electrospinning method for cartilage regeneration and then exposed to direct current (DC) pulsed oxygen plasma treatment. Subsequently, acrylic acid attaching and collagen covering were done by collagen molecular binding to carboxylic moieties of the polyacrylic acid. The results presented that chondrocyte cells seeding onto the scaffolds led to cell attachment, great growth, and viability [72, 73].

Biomimetic materials

Biomimetics is an interdisciplinary field in which principles from engineering, chemistry, and biology are applied to the synthesis of materials, synthetic systems, or machines that have functions that mimic biological processes. Biomaterials are any natural or synthetic material that interacts with any part of a biological system. Biomimetic designs could be used in regenerative medicine, tissue engineering, and drug delivery. Fibrous substrates mimic partially a natural configuration to create cartilage ECM. It was demonstrated that trilaminar scaffolds mimicked principal structural features of natural cartilage, encouraged the development of cartilage formation in vitro, and improved mechanical features [74–76].

In an investigation, biomimetic porcine chondrocytes cells seeded polycaprolactone fibers were fabricated, and after that, a cell–agarose solution was gelated in the center. The findings showed higher mechanical properties; furthermore, cells viability and well distribution were observed [70]. Besides, with the aim of imitate cartilage-like tissue in vitro, a threefold wedge-shaped silk seeded with human fibrob-

lasts and chondrocytes in a spatially parted were produced [77]. Furthermore, to mimic the ECM, the scaffolds may be encapsulated proteins, drugs, or cytokines. In a study, nasal chondrocyte cell-seeded fibrin/hyaluronic acid scaffold was produced and then functionalized with an antiangiogenic drug. The results presented angiogenesis control and enhanced the percentage of survival cells and cartilage regeneration. TGF-β1 transformation shows a substantial function in chondrogenesis [78].

In another study, bovine AFCs were seeded on fibrous poly-L-lactide scaffold containing TGF-β1. The results showed that AFCs grown on PLLA/TGF and expressed a considerably larger quantity of glycosaminoglycans and aggregate collagen with greater neo-ECM thickness after 3 weeks [70]. Besides, photo-cross-linkable, injectable sericin hydrogel as 3D biomimetic extracellular matrix for minimally invasive repairing cartilage has been studied. The mechanical properties and degradation rates were investigated. Particularly, the in vivo implantation of chondrocyte-laden SerMA hydrogels successfully developed synthetic cartilages after 8 weeks. Furthermost significantly, the synthetic cartilages molecularly are similar to native cartilage as demonstrated by high generation of cartilage-specific ECM constituents and upregulated expression of cartilage–critical genes [79].

Biomaterials as cell carriers for cartilage regeneration

Cell carriage and viability have been taken excessive attention in experimental to medical studies. Chondrocyte cells of different sources such as autologous and allogeneic are able to synthesize and deposit collagen and glycosaminoglycan. The supplementation of the survival cell minus scaffolds can be useful for cartilage regeneration. Mesenchymal stem cells, or adipose-derived stromal cells, as well as allogeneic or xenogeneic embryonic stem cells; mesenchymal stromal cells from multiple sources; and primary or chondrocytic origin have been assessed in a great amount of experimental reports [80, 81].

In another research, extracellular matrix powder from cultured cartilage-like tissue as cell carrier for cartilage repair was studied. Cartilage extracellular matrix (ECM) is a promising material for cartilage repair because of its bioactivity. In the current study, a 3D culture approach to prepare injectable, bioactive, biodegradable cell carriers for cartilage tissue engineering. This culture approach blended hanging drop culture with suspension culture technique and was very proficient to generate cartilage-like tissue. The in vitro results showed that MSCs seeded on DEMP differentiated to chondrocytes progressively and expressed GAGs and collagen II at 21 days. The in vivo results presented that the DEMP not only assisted reparation of hyaline cartilage, however, similarly supported the restoration of subchondral bone.

Additionally, nanofibrous hollow microspheres self-assembled from star-shaped polymers as injectable cell carriers have been fabricated. To regenerate complicated formed tissue deficiencies, an injectable cell carrier is appropriate to attain a precise fit and to decrease invasive intervention. The nanofibrous hollow microspheres, incorporating the ECM imitating construction with an extremely porous injectable system, were revealed to resourcefully assist cells and increase cartilage regeneration, in comparison with control microspheres [82].

Discussion and conclusion

Over the past three decades, the subject of cartilage tissue regeneration has expressively developed, mainly in clinical investigations. It seems that a widespread clinical acceptance is being achieved by cartilage tissue regeneration. As a result, it is necessary to develop in the cartilage destruction tissue regeneration by considering engineering approaches introducing several features of the defects. A tissue engineering method, containing MSCs and biomaterials which deliver signaling factors, may be encouraging to progress the regeneration of cartilage imperfection.

Compliance with ethical standards

Conflict of interests The authors declare that they have no conflict of interests.

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