Types of Scaffolds in Cartilage Regeneration

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There are two main types of scaffolds: natural polymers and synthetic polymers. On the one hand, natural polymers are proteins (e.g., collagen, SF) and polysaccharides (e.g., Alg, CS, and HA derivatives). Natural polymers already have a long history of application in wound treatment. They are the closest substances to human tissue and show biocompatibility and biodegradability without toxic byproducts, and their technologies and properties have been widely investigated. Furthermore, in the form of hydrogels, they can retain a great amount of water. However, natural polymers are normally poor in mechanical strength. On the other hand, synthetic polymers have different properties. They allow the better control of formation, surface morphology, mechanical strength and physicochemical properties than natural polymers. Among them, poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL) and poly(urethanes) (PU) are the most popular candidates in osteochondral regeneration. The limitations of synthetic polymers are poor hydrophilicity, proinflammatory degradation byproducts, and unmatched degradation rates. It is noticeable that these two types of polymers are not independent.

Keywords: osteoarthritis ; cartilage repair ; tissue engineering ; mesenchymal stem cells ; Scaffold

1. Natural Polymers

1.1. Type I/II Collagen

Collagen is the most abundant protein in the human body and the primary component of ECM in cartilage. Collagen is frequently chosen as the material of scaffolds and displays excellent performance; it has gone through in vitro, in vivo and small-scale long-term follow-up clinical trials, which makes it one of the most promising materials. For type I collagen, in vitro, Filardo et al. [1] recently fabricated 3D bioprinting type I collagen scaffolds, utilising a microvalve-based inkjet dispensing technique. This ‘cell-friendly’ type I collagen bioink allowed mesenchymal stem cells (MSCs) to be homogeneously suspended in the bioink priming for printing and then to manufacture anatomical and patient-specific constructs. Their results show that collagen-based hydrogels enhanced the proliferation and chondrogenesis of hBMSCs by providing biochemical signals and revealed a predominant clinical translation potential. Calabrese et al. [2] and Chen et al. [3] drew a similar conclusion that both hACSs or hWJSCs embedded in type I collagen cultured in chondrogenic medium had significant increases in chondrogenic marker gene expression and type II collagen and GAG formation. Moreover, another study indicated that hBMSCs embedded in cross-linker-free type I collagen microspheres exhibited chondrogenic matrix accumulation in vitro, and cartilage-like tissue formed after being subcutaneously injected into mice, and finally witnessed calcification [4]. Similarly, type II collagen scaffolds combined with quickly released chondroitin sulfate successfully guided hBMSCs’ chondrogenesis in the absence of GFs, and this scaffold demonstrated excellent biocompatibility and properties [5].

In vivo large animal experiments revealed that predifferentiated autologous ovine MSC-seeded type I collagen hydrogels implanted within sheep medial femoral condyle defects induced hyaline cartilage, type II collagen and better ICRS histologic scores than undifferentiated MSC-seeded hydrogels at six months postimplantation [6].

Regarding the clinical trial, although it is still in the small-scale phase, it has revealed some encouraging results. Five patients who had isolated medial meniscal tears were treated with hBMSC-laden type I collagen scaffolds. At the time the follow-up ended, three patients were asymptomatic and had clinical improvement in knee function scores at 24 months without magnetic resonance imaging evidence of recurrent tears. Two required subsequent meniscectomy due to retear or nonhealing of the meniscal tear at approximately 15 months after implantation. No other adverse events occurred [7]. Another clinical trial carried out by Sadlik et al. [8] indicated that five patients with femoral condyle chondral defects received hWJSC-embedded porcine type I/II collagen scaffold implantation, and all of them achieved significant pain relief in their knees without adverse effects. Furthermore, two patients with lateral femoral condyle cartilage defects received type I collagen scaffolds and autologous hBMSCs implantation and witnessed great defect filling and incorporation into

the adjacent cartilage after 30–31 months of long-term follow-up [9]. These positive clinical results warrant further large-scale investigation in the future to assess the repair capability of MSC-embedded collagen scaffolds.

1.2. Alginate (Alg)

Alg is a linear polysaccharide extracted from brown algae. It has a structure similar to native ECM, with hydrophilicity, biocompatibility, biodegradability and nonimmunogenicity, and can be used as a scaffold for regeneration bioengineering. Alg can absorb a large amount of water, which allows the rapid diffusion of nutrients and metabolites and is thus capable of being used as a scaffold for embedding MSCs. Nevertheless, Alg displays limitations such as a fast degradation rate and insufficient mechanical properties [10]. In vitro, hBMSCs embedded in Alg hydrogels and filled in osteochondral explants for four weeks were associated with hyaline cartilage, consistent with high *COL2* and *ACAN* gene expression and GAG content [1]. In another study, D1 murine MSCs were grown in Alg scaffolds in the absence of GFs, and this composition successfully induced chondrogenesis [11]. To enhance the mechanical properties of the sponge-like Alg structure, a more solid CS could mix with Alg, and this combination demonstrated better chondrogenic differentiation of hBMSCs and higher GAG and total collagen production than Alg alone [12]. Yang and coworkers [13] tried another mixed formulation in which they fabricated porous gelatin-Alg scaffolds and implanted them together with murine BMSCs into SCID® mice. However, in vivo experiments demonstrated that both osteogenesis and chondrogenesis were suppressed compared to in vitro culture, which revealed different responses between in vitro and in vivo. Additionally, neocartilage only formed on the scaffold surface due to the small pore size (90 μm) and insufficient interconnectivity.

1.3. Agarose (AG)

AG is a polysaccharide containing residues of L- and D-galactose harvested from marine algae. It has been used as an analogue to mimic proteoglycans of cartilage and has been verified to increase the production of cartilage-specific pericellular matrix. AG scaffolds have mostly been investigated in vitro. hBMSC-seeded AG microbeads doped with 10% type II collagen could promote better chondrogenesis than pure AG matrices, demonstrating that incorporating type II collagen could enhance the cartilage regenerative abilities of AG [14]. In another study, different cell types (differentiated/delifferentiated chondrocytes or TGF-β3-pretreated calf MSCs) seeded on AG scaffolds were tested in vitro, demonstrating that differentiated chondrocyte-embedded AG scaffolds showed the highest quality of integration, amount of accumulated ECM and biomechanical properties compared to scaffolds seeded with all other cell types. TGF-β3-pretreated calf MSC-laden scaffolds also displayed sustained chondrogenesis and superior ECM deposition and integration compared to dedifferentiated chondrocytes [15]. AG hydrogels seeded with porcine MSCs were injected into defects created in cartilage explants and showed an abundance of type II collagen and GAG accumulation after six weeks of culture [16]. Because of the poor degradation of AG, it has scarcely been studied in vivo.

1.4. Hyaluronic Acid (HA)

HA is a class of GAG that exists in the human body, particularly in bone joints. It carries a negative charge and has hydrophilicity, anti-abrasive and compressive-resistant properties in the joints. HA enfolds chondrocytes and absorbs water molecules through negatively charged chains, which in turn contributes to the resilience of the cartilage [17]. HA has weaker mechanical strength than collagen, but it can be utilised as a scaffold since it is one of the significant components in ECM and plays a crucial role in regulating chondrogenesis [18][19]. The cross-linking density has a significant impact on HA hydrogels, and a low cross-linking density showed better chondrocyte morphology, while a high cross-linking density led to fibrocartilage and calcification [20][21]. To date, many commercial HA scaffolds have been tested in small animals. For instance, using commercial Hyalofast® HA scaffolds together with hBMSCs + cartilage pellets (CPs) supported faster cartilage regeneration in vivo in full-thickness tibial articular defects of rabbits. Neocartilage close to normality was evidenced by an intact superficial layer, typical chondrocyte arrangement, tidemark and cartilage matrix staining in histology, along with the highest International Cartilage Repair Society (ICRS) score (75%) and magnetic resonance observation of cartilage repair tissue (MOCART) score (76.26) compared to using HA scaffolds alone or HA combined with either hBMSCs or CP [17]. Rabbit BMSC-HA scaffolds (Hyaff®-11) were utilised to treat the rabbit OA model, and the results revealed that the BMSC-HA group produced hyaline-like cartilage, which was proven by morphological, histological, and immunohistochemical data. The regenerated cartilage was significantly thicker in the BMSC-HA group compared to the HA scaffold alone and the untreated control group at six months, as reported by Grigolo et al. [22]. These results may support the industrialisation of HA scaffolds.

1.5. Silk Fibroin (SF) and Cellulose

Generally, SF was extracted from silkworm *Bombyx mori* cocoons. In comparison to other natural polymers, SF displays a balance among suitable mechanical strength, toughness, and elasticity due to its crystallinity, hydrogen bonding, and

numerous small β-sheet crystals [23]. SF has great biocompatibility and a controllable slow degradation rate with nontoxic amino acids and peptides as byproducts. In addition, SF can withstand common sterilisation techniques because of its high thermal stability. Cellulose is the most abundant natural linear polysaccharide comprising a linear homopolymer of glucose (C6H10O5)n, with n ranging from 500 to 5000. It is biocompatible, degradable, mechanically robust and able to be easily fabricated into various shapes [24]. In vitro, the recent literature indicates that SF films/scaffolds fabricated by air-drying or freezing were seeded with canine ASCs, and both SF films and SF scaffolds showed cartilage-like tissues. The chondrogenic markers *SOX9* and *ACAN* were statistically significantly upregulated on SF films without the addition of GFs in comparison to the negative control, while the author failed to evaluate mRNA on SF scaffolds [25]. SF could be mixed with a bundle of polymers to acquire better performance. Different SF proportions have various efficiencies; for instance, SF made from 12% *w*/*v* concentration seeded with hADSCs showed the most effective promotion of chondrogenic differentiation, compared to 8% *w*/*v* and 12% *w*/*v* [26]. Jaipaew et al. [27] tested SF/HA scaffolds in different ratios (*w*/*w*) seeded with hWJSCs. The results indicate that the 80 SF:20 HA and 70 SF:30 HA groups possessed spherical cell shapes and expressed cartilage-specific markers, along with an accumulation of ECM. Higher SF concentrations also increased the mechanical strength of scaffolds [26]. Another study revealed that a 75 cellulose:25 SF scaffold coated with fibronectin (FN) significantly upregulated *SOX9*, *ACAN* and *COL2* without adding GFs. Ch chondrogenesis was undetected in the cellulose/SF 50:50 blend composition [24]. Furthermore, a blend composed of 40 fibrin:8 Alg (*w*/*w*) also induced chondrogenic differentiation; the fibrin fraction offered flexibility and improved cell proliferation, while the Alg fraction enhanced biostability and upregulated the expression of chondrogenic genes, GAGs and type II collagen [28].

1.6. Chitosan (CS)

CS is the second most abundant natural linear polysaccharide after cellulose, derived from partial deacetylation of chitin, which can be commonly isolated from crab and shrimp exoskeletons [29]. CS has appealing biocompatibility, bioactivity, nonimmunogenicity and biodegradability. In particular, CS has a similar molecular structure to HA, which facilitates osmotic swelling and resistance within cartilage [30]. Thus, it has been used as a scaffold in cartilage regeneration and showed positive results [31]. Recently, CS microspheres with an ECM-mimicking nanofibrous structure were fabricated via a physical gelation process and microfluidic technology. When CS microspheres were cocultured with rabbit primary chondrocytes, they displayed enhanced cell attachment and proliferation. Additionally, the microsphere–cell mixtures could form a macroscopic 3D cartilage-like composite with mechanical elasticity, as reported by Zhou and colleagues [32]. However, natural CS does not have adequate mechanical strength, so it is often combined with other stiffer materials to enhance stability. For example, Meng et al. [33] fabricated CS scaffolds combined with a demineralised bone matrix and E7 peptide sequence, which revealed increased cell viability and ECM production and improved chondrogenic differentiation ability of murine BMSCs in vitro. In parallel, the scaffolds induced hyaline cartilage after four weeks of implantation in vivo. Combining CS with other natural polymers also resulted in improved chondrogenesis. CS mixed with HA improves chondrogenesis due to the interaction between HA and CD44, which enhances cell–cell signalling. CS-HA membranes could induce faster spheroid shape formation of MSCs than CS alone and help prevent dedifferentiation. CS-HA membranes exhibit higher levels of *SOX9*, *ACAN* and *COL2* gene expression and higher GAG and type II collagen contents than CS alone and cells cultured in plates [34]. When combined with collagen, collagen offers abundant binding sites for cells. MSC adhesion, matrix production, and chondrogenic gene expression were improved in type II collagen-coated CS scaffolds, according to Ragetly and colleagues [35].

1.7. Decellularised Extracellular Matrix (dECM)

In recent years, dECM scaffolds derived from in vitro cultured cells have drawn researchers' interest. The dECM has the advantages of possessing intrinsic native GFs and biological features. There is evidence that the dECM could contribute to the stability of MSC stemness after long-term expansion [36]. Usually, the ECM is first deposited by hBMSCs on tissue culture plates and then subjected to a decellularisation process to remove hBMSCs, after which they are seeded with chondrocytes. Yang et al. [37] reported that chondrocyte-embedded decellularised hBMSC-ECM scaffolds exhibited a significantly enhanced proliferation rate, better robust chondrogenesis, suppression of chondrocyte hypertrophic genes and chondrocyte phenotype maintenance in vitro than chondrocytes cultured on plates, in parallel with similar in vivo results of hBMSC-ECM scaffolds implanted into SCID® mice. Cai et al. [38] fabricated hBMSC-ECM scaffolds mimicking the early stage of chondrogenesis, which could promote the chondrogenesis of hBMSCs. Additionally, Lu et al. [39] tested hBMSCs or chondrocyte-derived ECM scaffolds, and the results reveal that these scaffolds could facilitate hBMSC adhesion, proliferation, chondrogenesis, and cartilage formation compared to hBMSCs in pellet culture. Aside from hBMSCs, hWJSCs also showed enhanced chondrogenesis on decellularised chondrocyte-derived ECM in a pellet culture system [40]. The dECM scaffolds have some limitations. For example, the preparation of ECM deposition incurs additional time costs and expenditure, and the exact mechanism by which the hBMSC-ECM enhances chondrogenesis is not yet fully understood. In the future, researchers may need to investigate signalling pathways and vital bioactive factors.

2. Synthetic Polymers

2.1. Polycaprolactone (PCL)

PCL belongs to a family of poly(α-hydroxyl esters), and it is a flexible, biocompatible and biodegradable synthetic polymer that can be fabricated into fibres or porous structures via many different methods. PCL has a relatively slow degradation rate and harmless byproducts and thus has become the most widely used polyester in many fields of medicine. PCL-based scaffolds are widely studied both in vitro and in vivo, and they can be fabricated via 3D weaving or electrospinning.

In vitro, 3D woven PCL hemispherical scaffolds were seeded with human ASCs transfected with lentiviral vectors containing interleukin-1 receptor antagonist (IL-1Ra) transgenes. When constructs were cultured for 28 days, they displayed a decrease in matrix metalloprotein production induced by the proinflammatory molecule IL-1 and an increase in total collagen and GAGs, and smooth ECM evenly infiltrated the interior and exterior of the scaffolds [41]. Electrospun PCL scaffolds with a nonwoven mesh structure provide a larger surface-to-volume ratio for cell attachment and infiltration. Moreover, coating PCL with natural polymers exhibits enhanced chondrogenic ability. Liao et al. [42] manufactured electrospun PCL coated with acellular ECM composite scaffolds containing GAGs and collagen. The composite upregulated *ACAN* and *COL2* expression, suppressed the fibroblastic phenotype of differentiated rabbit BMSCs and displayed an enhanced response to TGF-β1 treatment. The hBMSC-seeded PCL/Pluronic F127 scaffolds with surface treatment of type I collagen supported cell survival and chondrogenic differentiation, and the PCL/F127/collagen scaffolds produced the highest SOX9 and COL2A1 mRNA levels compared with PCL/F127, PCL/collagen and PCL alone. Additionally, the PCL/F127/collagen and PCL/collagen scaffolds showed abundant matrix deposition and suppressed hypertrophy. These results reveal that both F127 and collagen enhanced chondrogenic gene expression and that collagen was more effective [43].

In vivo, a 3D-printed PCL artificial trachea combined with rabbit chondrogenic predifferentiated BMSCs and respiratory epithelial cells revealed successful induction of neocartilage formation in a tracheal defect rabbit model [44]. Another small animal study tested 3D woven PCL scaffolds both in vivo utilising a nude murine subcutaneous pouch model and in vitro under simulated conditions, and indicated that the PCL scaffold was highly positive in promoting rapid hBMSC infiltration, both chondrogenesis and osteogenesis [45]. A large animal study was carried out by Vahedi et al. [46]. They treated sheep knee defects using sheep ASCs coincubated with gold precoated PCL scaffolds and demonstrated hyaline cartilage-like tissue, as well as the highest *ACAN*, *SOX9* and *COL2* gene expression, compared to a thinner layer of cartilage-like tissue and lower gene expression in the single ASC group and single PCL scaffold group.

2.2. Poly(Lactic-Co-Glycolic Acid) (PLGA)

PLA, PGA and their copolymer PLGA are widely used in tissue engineering. Among them, PLGA has drawn more attention in recent years. Liu et al. [47] manufactured a roll-up PLGA scaffold wrapped in a rabbit BMSC macroaggregate sheet, which gradually degraded with the increasing formation of cartilage and finally successfully produced an artificial trachea after four weeks of in vitro incubation. This result indicated that PLGA bulk scaffolds possessed potential in cartilage regeneration.

However, pure PLGA generally shows a poor ability to promote cell adhesion and proliferation due to its negative charge on the surface, which impedes cell attachment. Thus, PLGA is usually doped with bioactive molecules or materials to enhance affinity. Moreover, aside from being made into bulk scaffolds, a growing number of studies are investigating the potential of PLGA microparticles. Go and coworkers [48] developed novel magnetic microbeads composed of PLGA bodies and amine-functionalised magnetic nanoparticle (MNP)-coated surfaces. The microbeads successfully loaded D1 murine MSCs to 2D/3D target sites using external magnetic fields and induced MSC proliferation and chondrogenic differentiation in vitro. More importantly, these microbeads can be injected into synovial fluid via syringe, which makes minimally invasive surgery possible. However, this method requires a wearable magnetic device postoperation to assist in maintaining the local attachment of magnetic microbeads, which raises concerns regarding compliance, reliability and convenience. Furthermore, in some cases, a large-scale defect may require a large dose, so another issue is that the acceptable dose of MNPs has not yet been determined. Nevertheless, magnetic microbeads have a high application value and are worth improving. PLGA microbeads with hydroxyl (−OH) groups also displayed chondrogenic differentiation potential without adding GFs [49]. Another type of microbead is composed of PLGA-poloxamer 118 (P118)-PLGA, hBMSCs and the controlled release of TGF-β3. The composition could enhance the proliferation and expression of specific chondrogenic markers in vitro in the absence of any GFs [50], and the following in vivo series experiment showed successful induction of cartilage-like neotissues and protection of endogenous murine cartilage degradation in a mouse knee OA model by PLGA-P118-PLGA [51]. In vivo, hBMSCs and PLGA microspheres coated with an FN surface and engineered to release TGF-β3 were implanted into SCID® mice, and the results revealed the formation of neocartilage stained positive for type II

collagen and aggrecan. This complex allowed MSCs to quickly adhere and differentiate on the surface of the microspheres while under chondrogenic induction from controlled released GFs.

2.3. Polyurethane (PU)

PU is among the most popular synthetic polymers because of its biocompatibility, flexibility and exceptional mechanical strength. Most of the conventional synthetic scaffolds displayed static stiffness, while dynamic mechanical changes persistently exist in native cartilage, so the scaffolds need to adapt to this environment. According to this, Wu et al. [52] developed a poly(urea-urethane) (PUU)-polyhedral oligomeric silsesquioxane (POSS) polymer (PUU-POSS) with a thermal responsive 'stiffness memory' ability via a 3D printing-guided thermally induced phase separation (3D-TIPS) technique. The PUU-POSS scaffold can transition to a soft rubbery phase at body temperature without noticeable shape change because the hard segments are responsible for the permanent shape, and the soft segment of PUU chains that soften by reverse self-assembly at a specific transition temperature is responsible for the temporary shape. The biological properties of this scaffold were investigated in vitro by seeding with human dermal fibroblast cells [52] or hBMSCs [53], showing promoted adhesion and proliferation of both cells and facilitating the osteochondral synthesis of hBMSCs. The PUU-POSS scaffold provides a wide range of tunable, dynamic physical and mechanical properties with little change to the microstructure. Before their stiffness relaxation, the PUU-POSS scaffold reached a maximum compression modulus of 0.80–0.10 MPa, which makes them potential candidates for cartilage regeneration. In vivo, rabbit ASC-seeded 3D-printed PU/HA scaffolds incorporating the small molecule drug Y27632 were implanted into a rabbit femoral condyle defect model. The composite significantly promoted GAG and type II collagen synthesis [54].

2.4. Polyethylene Glycol (PEG) and Polyethersulfone (PES)

PEG is a low cytotoxic and low immunogenic polymer, but it has weak biological activity and lacks cell adhesion sites, so pure PEG has no apparent positive effect on MSC adhesion and chondrogenic differentiation [55]. Nevertheless, adding RGD peptides or ECM molecules to PEG can enhance the cell response. In vitro, researchers tested different concentrations and different peptide modifications for PEG hydrogels. Screening results showed that the 6.5% (*w*/*v*) PEG constructs cross-linked with the GPQGIWGQ peptide and containing the RGD peptide sequence sustainably facilitated cellular viability, proliferation and chondrogenic differentiation of human periosteum-derived cells (hPDCs) and murine ATDC5 cells [56]. Ravindran et al. [57] incorporated RGD peptide into PEG microspheres and cocultured them with hBMSCs, illustrating that cells aggregated in the presence of RGD-PEG microspheres, while PEG microspheres without RGD peptide failed to adhere to cells. Moreover, the hBMSCs/RGD-PEG microspheres showed higher *COL2A1* expression than the hBMSCs pellet culture. Nevertheless, it is noteworthy that the existence of microspheres may impede cell–cell adhesion and paracrine or cell–matrix interactions.

PES nanofibers show suitable mechanical strength, thermal and chemical resistance, and remarkable biocompatibility [58]. There is evidence that the nanosized structures imitating the biomechanical and biological structure of ECM play a critical role in promoting cell attachment, function, proliferation and infiltration. Mahboudi et al. [59] reported a PES nanofibrous scaffold prepared by electrospinning, and its surface was modified by plasma treatment and collagen grafting and then seeded with hBMSCs. The results show that hBMSCs-PES scaffolds appeared to display a cartilage-like morphology, containing abundant ECM, as seen by SEM and immunocytochemistry, and the level of cartilage-specific genes in the hBMSCs-PES scaffold group was higher than that in the scaffold-free group. These results support the suggestion that nanofibrous PES scaffolds successfully improve hBMSCs chondrogenesis.

2.5. Hydroxyapatite (HAp) and Graphene Oxide (GO)

HAp is usually combined with natural polymers to provide suitable stiffness in scaffolds with osteochondral regeneration ability. Yu and colleagues [60] tested Alg/HA and Alg/HAp scaffolds combined with hWJSCs in vitro and found that Alg/Hap scaffolds showed better cell viability, and both types of scaffolds displayed equivalent ECM production at day 30. Zhou and coworkers [61] fabricated a bilayer scaffold with an upper collagen layer and a lower collagen/Hap layer that could induce hBMSCs into chondrocytes and osteocytes, respectively. In a third study, the HAp-collagen matrix induced rabbit BMSCs into the osteogenic lineage, while the HAp-synthetic hydrogel matrix favoured chondrogenesis. This result is consistent with another earlier in vivo study that tested these two materials subcutaneously in rabbits [62]. Clinical case reports are sporadic. One patient with a large osteochondral knee defect and postseptic arthritis was treated with interconnected porous HAp ceramic and hBMSCs, and cartilage-like tissues were successfully regenerated [63]. A clinical study of level III evidence was carried out, and trilayer scaffolds composed of collagen and HAp were tested in 33 patients with 'complex cases' in their knees and achieved positive results, but they were cell-free scaffolds without the engagement of MSCs [64].

GO can absorb substantial transforming growth factor β3 (TGF-β3) through electrostatic attraction and protect TGF-β3 from being enzymatically degraded. Moreover, GO showed remarkable GF-retaining properties, releasing <0.35% TGF-β3 over 72 h and <1.72% in 28 days, which ensured long-term sustained chondrogenic stimuli without GF supplementation [65]. Based on this, in vitro, Zhou et al. [65] reported a collagen hydrogel incorporated with GO flake-adsorbed TGF-β3 and cocultured with encapsulated hBMSCs in the same gel, inducing higher chondrogenic gene expression and a more significant cartilage matrix in 28 days compared to exogenously adding TGF-β3 to media.

Abbreviations

Abbr.	Full Name
OA	osteoarthritis
GFs	growth factors
ACI	autologous chondrocyte implantation
MSCs	mesenchymal stem cells
hBMSCs	human bone marrow-derived MSCs
hASCs	human adipose-derived MSCs
hWJSCs	human Wharton's jelly derived MSCs
hPDCs	human periosteum-derived cells
2D	two-dimensional
3D	three-dimensional
3D-TIPS	3D printing-guided thermally induced phase separation
dECM	decellularised extracellular matrix
GAGs	glycosaminoglycans
SF	silk fibroin
HA	hyaluronic acid
Alg	alginate
HAp	hydroxyapatite
COMP	cartilage oligomeric matrix protein
CS	chitosan
PLA	poly(lactic acid)
PGA	poly(glycolic acid)
PLGA	poly(lactic-co-glycolic acid)
PCL	poly(ε-caprolactone)
PU	poly(urethanes)
PUU	poly(urea-urethane)
POSS	polyhedral oligomeric silsesquioxane
PES	polyethersulfone
PEG	polyethene glycol
AG	agarose
CP	cartilage pellet
ICRS	International Cartilage Repair Society
MOCART	magnetic resonance observation of cartilage repair tissue
FN	fibronectin

MNPs	**magnetic nanoparticles**
GO	**graphene oxide**
RGD	**Arg-Gly-Asp**
TGF	**transforming growth factor**
IGF	**insulin-like growth factor**
−OH	**hydroxyl group**
−COOH	**carboxyl group**
HP	**hydrostatic pressure**

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