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REVIEW ARTICLE

The Application of Cartilage Tissue Engineering with Cell-Laden Hydrogel in Plastic Surgery: A Systematic Review

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Abstract

BACKGROUND: As a contour-supporting material, the cartilage has a significant application value in plastic surgery. Since the development of hydrogel scaffolds with sufficient biomechanical strength and high biocompatibility, cell-laden hydrogels have been widely studied for application in cartilage bioengineering. This systematic review summarizes the latest research on engineered cartilage constructed using cell-laden hydrogel scaffolds in plastic surgery.

METHODS: A systematic review was performed by searching the PubMed and Web of Science databases using selected keywords and Medical Subject Headings search terms.

RESULTS: Forty-two studies were identified based on the search criteria. After full-text screening for inclusion and exclusion criteria, 18 studies were included. Data collected from each study included culturing form, seed cell types and sources, concentration of cells and gels, scaffold materials and bio-printing structures, and biomechanical properties of cartilage constructs. These cell-laden hydrogel scaffolds were reported to show some feasibility of cartilage engineering, including better cell proliferation, enhanced deposition of glycosaminoglycans and collagen type II in the extracellular matrix, and better biomechanical properties close to the natural state.

CONCLUSION: Cell-laden hydrogels have been widely used in cartilage bioengineering research. Through 3-dimensional (3D) printing, the cell-laden hydrogel can form a bionic contour structure. Extracellular matrix expression was observed *in vivo* and *in vitro*, and the elastic modulus was reported to be similar to that of natural cartilage. The future direction of cartilage tissue engineering in plastic surgery involves the use of novel hydrogel materials and more advanced 3D printing technology combined with biochemistry and biomechanical stimulation.

Keywords 3D bioprinting · Tissue engineering · Cartilage · Cell-laden hydrogel · Plastic surgery

1 Introduction

As a contour-supporting material, the cartilage has a significant application value in plastic surgery. Auricular and nasal reconstruction requires the auricular and costal cartilages to be cut and carved, resulting in the consumption of autologous materials, which is significantly greater than what is available [1]. Trauma of the donor site and loss of autologous tissue are inevitable [2]. Cartilage tissue engineering, which has been widely discussed and researched in recent times, provides a new method for producing contour-supporting materials for plastic surgery.

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Owing to the poor self-healing and proliferation ability of the cartilage, cartilage regeneration has always been a challenging direction for research and clinical applications [3]. With the development of three-dimensional (3D) culture and 3D bio-printing, tissue engineering technologythat combines cells (somatic cells and stem cells) and biomaterials has shown potential for the preparation of cartilage scaffolds and the repair of cartilage defects [2].

The cell-laden hydrogel scaffold is an emerging area of bioengineering scaffolds. In recent years, with the progress of materials science and 3D printing technology, researchers have been able to obtain cell-laden scaffolds with sufficient biomechanical strength and high biocompatibility [4]. The bioengineered cartilage with cell-laden hydrogel has been studied *in vitro* and in animal experiments, in which there have been many attempts in the field of plastic surgery, including the regeneration of nasal cartilage, ear cartilage, and tracheal cartilage.

In this study, we aimed to systematically review the literature published in the field of plastic surgery in the past 10 years focusing on cartilage tissue engineering based on cell-laden hydrogel scaffolds, and attempted to clarify the following questions: What types of biomimetic scaffolds have been prepared? What hydrogel materials have been used, and what new materials have potential application? What cells have been loaded into hydrogels and have been proven to have good chondrogenesis? Are there any new advances in cartilage bioengineering that may have application in the field of plastic surgery?

2 Methods of systematic review

This was a systematic review of the literature in which cell-laden hydrogels were used for cartilage tissue engineering in the field of plastic surgery. The involved cells included chondrocytes, auricular cartilage progenitor cells, and mesenchymal stem cells in humans and animals, and the 3D bio-printed technique was used to create the tissue constructs or hydrogel models.

The PubMed and Web of Science databases were searched. The following terms were used (including synonyms and closely related words) as index terms or free-text words: “cartilage” or “chondrocyte”; “hydrogel”; “3D” or “printing” or “bio-printed” or “scaffold”; and “plastic surgery.” The articles were restricted to those written in English. The publication date was from January 2010 to June 2021. Studies were included if they investigated a hydrogel scaffold in which cells were loaded inside and reported its potential for cartilage tissue regeneration and reconstruction in plastic surgery application.

3 Results

Using the search terms described above, 42 publications were identified. A flow diagram of the inclusion and exclusion process is shown in Fig. 1. After reading the full-length text of these publications, 18 studies were included in this review [5–22]. Basic information on culture form, seed cell types, sources, and seeding density is presented in Table 1. And basic information on hydrogel and scaffold contents, experimental animal choices, and scaffold morphology is presented in Table 2.

Among the 18 studies, 11 used chondrocytes as the seeding cell [5–15], 1 used peri-chondrocytes (CPCs) [15], and 2 used adipose mesenchymal stem cells (ADSCs) for chondrogenic differentiation [15, 16]. The remaining six studies [17–22] focused on co-culturing using the previously mentioned seed cells to form tissue-engineered cartilage. With regard to the sources of seed cells, five researchers used human cells [5, 6, 16, 19, 20], four used goat/sheep cells [11–13, 17], three used bovine cells [7, 9, 18], three used porcine/swine cells [8, 10, 22], two used rabbit cells [14, 21], and one used horse cells [15]. The density of seed cells varied, but was mostly approximately $10–30\times10^6$ cells/ml.

Collagen was the most frequently applied hydrogel [5, 7–10, 17, 18, 22], followed by alginate [6, 11, 16, 19, 20], hyaluronic acid (HA) [10, 17, 22], gelatin methacrylate (GelMA) [12, 15], extracellular matrix [14, 16], and thermo-sensitive hydroxypropyl chitin (HPCH) [13]. Some used more than one type of hydrogel to combine the advantages and obtain better material properties. Three-dimensional bio-printing of grid cube constructs was commonly used to verify the chondrogenic properties of the cell-laden scaffold. There were also some studies that reported the 3D reconstruction of human facial image data and bio-printed the cell-laden scaffold in the shape of a human auricle or nasal implant, which further promotes the combination of cartilage engineering and clinical application [6, 7, 9–11, 14, 16]. In some studies [6, 7, 9], a pre-fabricated model was used to ensure the morphology and volume of the hydrogel and its scaffolds after solidity. Some studies used poly-ε-caprolactone (PCL) as a reinforcing material to form a skeleton with stronger biomechanical properties studies [8, 10–12, 16, 17, 21, 22].

Nude rats and mice were the most widely used experimental animals. As these studies are aimed at stimulating the ectopic chondrogenic environment of engineering constructs in the clinical application of plastic surgery, the dorsal subcutaneous embedding method was commonly chosen. In addition, in one study [21], in order to simulate

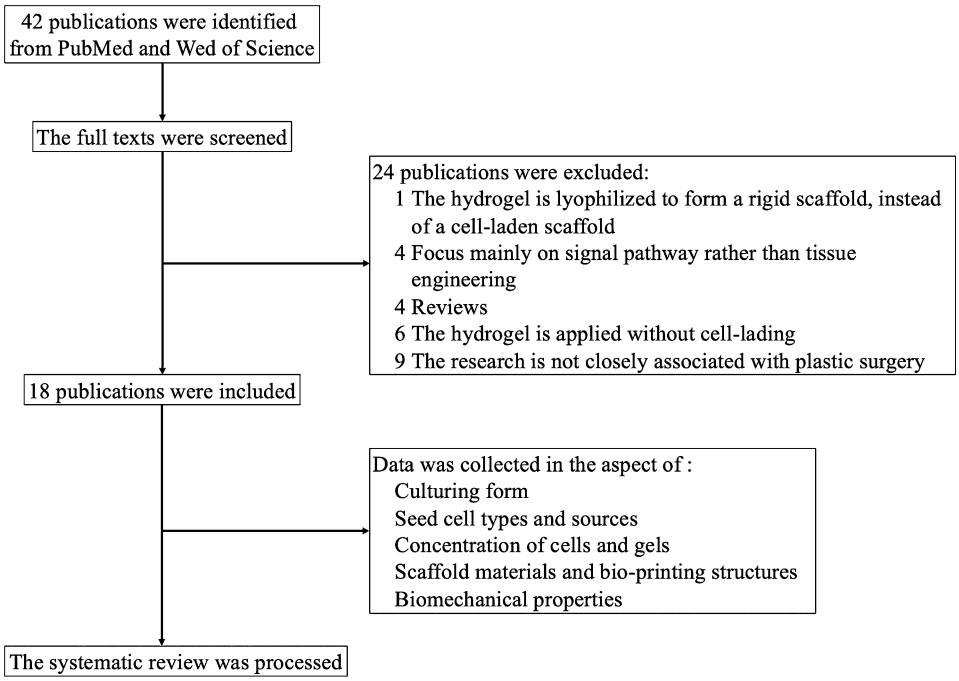

Fig. 1 Flow diagram of the review

the tracheal structure, authors chose to implant the construct under the pedicled muscle flap of rabbits.

The Young's modulus of the scaffolds was tested to determine the biomechanical properties in eight of these studies, which are listed in Table 3. In these reports, the Young's modulus varied greatly with the material of the scaffold. For hydrogel scaffolds without rigid support (four out of eight studies), the average value of the Young's modulus was in the range of 100-380 kPa [7, 9, 15, 18]. For hydrogel scaffolds with PCL support, the Young's modulus is in the range of 0.8-4 MPa [8, 12]. The constructs printed in the polylactide-co-glycolide (PLGA) scaffold filled with collagen had a Young's modulus of 15-25 MPa [5]. Another study reported that the average Young's modulus of PCL cell-laden hydrogel was 8-16 kPa [17]. It was obvious that the engineered constructs with different types of seed cells, that is, mesenchymal stem cells (MSCs), auricular cartilage progenitor cells (AuCPCs), and chondrocytes, had different Young's moduli. However, there was no clear evidence to show which seed cells or which cell proportion of co-culture could result in the best biomechanical performance.

These cell-laden hydrogel scaffolds were reported to show some feasibility of cartilage engineering, including better cell proliferation, enhanced deposition of glycosaminoglycans and collagen type II in the extracellular matrix, and better biomechanical properties close to the natural state.

4 Discussion

4.1 Significant role of cartilage tissue engineering in plastic surgery

Cartilage has been widely applied as a contour-filling material in the fields of plastic surgery and cosmetic surgery. Nasal reconstruction and aesthetic surgery have high strength and shape requirements for augmentation materials. At present, the commonly used augmentation materials include conchal cartilage, costal cartilage, septal cartilage, and alloplastic implants (mainly silicone and expanded polytetrafluoroethylene) [23]. Because of the relative lack of blood supply and thin skin coverage of the external nose, prostheses implanted in the nasal cavity could produce more severe inflammatory reactions compared with those in areas with abundant blood supply [24]. The acquisition of autologous conchal and costal cartilage causes additional pain, surgical wounds, and risks of complications [2]. In addition, the cartilage needs to be cut and carved during the operation to meet the effect requirements to the greatest extent, thus increasing the patient's surgical trauma and autologous tissue loss. In cases of nasal reconstruction and secondary repair of rhinoplasty, there is a further shortage of autologous cartilage materials.

Reconstruction of the auricle is frequently performed using the costal cartilage. During surgery, the costal cartilage is cut and fitted to the shape of the auricle. Because of the high demand for cartilage, children usually need to reach adolescence in order to undergo ear reconstruction

Table 1 Summary of culture form, seed cell types, sources, and seeding density of 18 researches.

Year	Co-culture	Seed cell sources	Species	*In vitro*	*In vivo*	References
2010	×	Chondrocytes: auricular	Human	NA	10-100×10^6 cells/ml laden in 1% atelocollagen hydrogel	[5]
2010	×	Chondrocytes: nasal septal	Human	NA	60×10^6 cells/ml laden in 2% porous PVA-alginate gel hybrid	[6]
2013	×	Chondrocytes: auricular	Bovine	NA	25×10^6 cells/ml laden in 1% collagen I hydrogel	[7]
2014	×	Chondrocytes: auricular	Swine	10×10^6 cells/ml laden in 0.24%collagen I hydrogel	10×10^6 cells/ml laden in 0.24%collagen I hydrogel	[8]
2016	×	Chondrocytes: auricular	Bovine	NA	25×10^6 cells/ml laden in 10 mg/ml collagen	[9]
2018	×	Chondrocytes: auricular	Porcine	25×10^6 cells/scaffold laden in 3 mg/ml hyaluronic acid/6 mg/ml collagen hydrogel	25×10^6 cells/scaffold laden in 3 mg/ml hyaluronic acid/6 mg/ml collagen hydrogel	[10]
2019	×	Chondrocytes: auricular	Goat	4×10^6 cells/ml laden in 3 wt % alginate	NA	[11]
2020	×	Chondrocytes: condyle	Sheep	10×10^6 cells/ml laden in 10%, 15% and 20% GelMA hydrogels	NA	[12]
2020	×	Chondrocytes: auricular	Goat	30×10^6 cells/ml laden in 3 wt% HPCH	100×10^6 cells/ml laden in 3 wt% HPCH	[13]
2021	×	Chondrocytes: auricular	Rabbit	20×10^6 cells/ml laden in 20, 30, and 40 mg/ml cdECMMA	NA	[14]
2018	×	MSCs: bone marrow; perichondrocytes: auricular perichondrium; chondrocytes: auricular	Horse	15×10^6 cells/ml laden in 10 % GelMA	NA	[15]
2019	×	MSCs: adipose tissue	Human	10×10^6 cells/ml laden in 2% alginate	1×10^7 cells/ml laden in 2% alginate	[16]
2016	√	MSCs: subcutaneous adipose tissue; perichondrocytes: auricular perichondrium; chondrocytes: auricular	Goat	20×10^6 cells/ml gel (unknown concentration)	NA	[17]
2017	√	Chondrocytes: auricular; MSCs: bone marrow	Bovine	25×10^6 cells/ml laden in 10 mg/ml collagen	25×10^6 cells/ml laden in 10 mg/ml collagen	[18]
2017	√	Chondrocyte: nasal; MSCs: bone marrow	Human	NA	10×10^6 cells/ml bioink	[19]
2017	√	Chondrocyte: nasal; MSCs: bone marrow	Human	NA	10×10^6 cells/ml bioink	[20]
2018	√	Chondrocytes: auricular; MSCs: bone marrow	Rabbit	10×10^6 cells/ml laden in 20% PEG/PCL	1×10^7 cells/ml laden in 10, 20, 30% PEG/PCL	[21]
2018	√	MSCs: subcutaneous back fat; chondrocytes: auricular and tracheal	Porcine	1×10^6 cells cells/ml laden in 3 mg/ml hyaluronic acid/6 mg/ml collagen hydrogel	1×10^6 cells cells/ml laden in 3 mg/ml hyaluronic acid/6 mg/ml collagen hydrogel	[22]

* NA: not available, PVA: poly (vinyl alcohol), GelMA: gelatin methacrylate, MSCs: mesenchymal stem cells, HPCH: hydroxypropyl chitin, cdECM: cartilage-derived decellularized extracellular matrix, PEG: polyethylene glycol, PCL: poly-e-caprolactone

surgery. Long-term external ear deformities often have a great impact on children's mental health. In addition, the costal cartilage can retain a certain degree of compliance after carving, but it lacks the flexibility required by the external ear, and the contouring outcome is difficult to predict [25, 26]. At present, surgery not only involves the risk of severe hematoma and wound healing disorders, but also requires multiple surgeries to reduce the volume of the graft and to reshape the delicate structures of the helical and anti-helical folds [25].

3D printed polymers are also an option for nasal prostheses or external ear implants. However, these structures

Table 2 Summary of hydrogels and scaffold contents, experimental animal choices, and scaffold morphology of 18 researches.

Year	Hydrogels and scaffold contents	Experimental animal	Scaffold morphology	References
2010	PDLA or PLA/CL or PLGA scaffold, collagen gel	Nude mice, dorsal subcutaneous	3D printing: cube constructs	[5]
2010	Porous PVA-alginate gel hybrid	Nude mice, dorsal subcutaneous	Fabricated in mode: human-shaped auricle	[6]
2013	collagen type I hydrogel	Nude rats, dorsal subcutaneous	Fabricated in mode: human-shaped auricle	[7]
2014	PCL scaffolds, collagen gel	Nude mice, dorsal subcutaneous	3D printing: three cube constructs with different parameters	[8]
2016	Collagen gel	Nude rats, dorsal, subcutaneous	Fabricated in mode: human-shaped auricle	[9]
2018	PCL scaffold, hyaluronic acid/collagen hydrogel	Nude rats, dorsal, subcutaneous	3D printing: human-shaped auricle with different pole sizes	[10]
2019	PCL scaffold, alginate gel	NA	3D printing: human-shaped auricular and cube constructs	[11]
2020	PCL scaffold, GelMA	NA	3D printing: cube constructs	[12]
2020	HPCH hydrogel	Nude mice, dorsal, subcutaneous	3D printing: cube constructs and letter-shaped constructs	[13]
2021	Photo-crosslinkable hydrogel using methacrylation (cdECMMA)	NA	3D printing: human-shaped auricular and cube constructs	[14]
2018	GelMA-based hydrogel	NA	Mode: hydrogel discs	[15]
2019	PCL scaffold, cartilage-decellularized ECM hydrogel	Nude mice, dorsal, subcutaneous	3D printing: nasal implant mode and cube constructs	[16]
2016	3D-printed poly-ε-caprolactone cage collagen I/III scaffold FB/HA hydrogel	NA	3D printing cage: hydrogel-collagen scaffold	[17]
2017	Type I collagen hydrogel	Nude mice, dorsal, subcutaneous	8 mm discs	[18]
2017	Nanofibrillated cellulose/alginate (NFC-A) bioink	Nude mice, dorsal, subcutaneous	3D printing: lattice-shaped constructs	[19]
2017	Nanofibrillated cellulose/alginate (NFC-A) bioink	Nude mice, dorsal, subcutaneous	3D printing: cube constructs	[20]
2018	PEG/PCL hydrogel, luminal silicon stent	Rabbits, dorsal, wrapped by a pedicle muscle flap	Mode: hydrogel discs	[21]
2018	PCL scaffold, hyaluronic acid/collagen hydrogel	Nude rats, dorsal, subcutaneous	3D printing: PCL porous scaffold filled with hydrogel	[22]

* PDLA: poly (d-lactide), PLA/CL: poly(lactide)/caprolactone, PLGA: polylactide-co-glycolide, 3D: three-dimensional, PVA: poly (vinyl alcohol), PCL: poly-e-caprolactone, NA: not available, GelMA: gelatin methacrylate, HPCH: hydroxypropyl chitin, MSCs: mesenchymal stem cells, cdECM: cartilage-derived decellularized extracellular matrix, FB/HA: fibrin/hyaluronic acid, PEG: polyethylene glycol

still have disadvantages in terms of flexibility and increasing the long-term risk of skin extrusion [27]. Hence, tissue-engineered cartilage, in which the addition of stem cells and bioactive molecules was performed to enhance the functionality of a biomaterial and to transform the generated construct into natural tissue after degradation of the biomaterial, has provided a new method for the repair of cartilage defects and the improvement of aesthetic contour.

4.2 Hydrogel options

At present, there are many types of hydrogel materials used as cell-laden scaffolds, such as collagen, sodium alginate, HA, and gelatin. These gels have good biocompatibility for chondrocytes and MSCs, but their mechanical strength is relatively weak. They usually need to be combined with rigid scaffolds or formed with prefabricated molds to form bio-constructs with concrete shapes [6, 7, 16, 17].

To further enhance their strength and make them more suitable for 3D printing, hydrogels gels have been highly modified. GelMA and methacrylated hyaluronic acid (HAMA) are typical crosslinked modified hydrogels that

Table 3 Composition of scaffolds and their biomechanical properties in each study

Year	Scaffold materials	Seed cell types	Species	Young's modulus *in vitro*	Young's modulus *in vivo*	Young's modulus of natural cartilage	References
2010	PDLA or PLA/CL or PLGA scaffold, collagen gel	Chondrocytes	Human	NA	15–25 MPa	NA	[5]
2013	Collagen type I hydrogel	Chondrocytes	Bovine	NA	380 kPa	200 kPa	[7]
2014	PCL scaffolds, collagen gel	Chondrocytes	Swine	2–4 MPa	NA	NA	[8]
2016	Collagen gel	Chondrocytes	Bovine	NA	170 kPa	250 kPa	[9]
2020	PCL scaffold, GelMA	Chondrocytes	Sheep	800 kPa	NA	980 kPa	[12]
2018	GelMA-based hydrogel	BMSC	Horse	BMSC: 179 kPa	NA	NA	[15]
		AuCPC		AuCPC: 109 kPa			
		Chondrocytes		Au: 103 kPa			
2016	3D-printed poly-ε-caprolactone cage collagen I/III scaffold FB/HA hydrogel	ADSC	Goat	Cartilage-ADSC: 16 kPa	NA	NA	[17]
		AuCPC		AuPCP-ADSC: 10 kPa			
		Chondrocytes		Cartilage: 8 kPa			
2017	Type I collagen hydrogel	BMSC	Bovine	NA	50% cartilage-50% MSC: 374 kPa	388 kPa	[18]
		Chondrocytes			100% cartilage: 375 kPa		

* PDLA: poly (d-lactide), PLA/CL: poly(lactide)/caprolactone, PLGA: polylactide-co-glycolide, NA: not available, PCL: poly-e-caprolactone, GelMA: gelatin methacrylate, BMSCs: bone marrow mesenchymal stem cells, 3D: three-dimensional, AuCPCs: auricular cartilage progenitor cells, ADSCs: adipose mesenchymal stem cells, FB/HA: fibrin/hyaluronic acid, MSC: mesenchymal stem cells

have been proven to be adequate for chondrocyte and MSC culturing. The combination of GelMA and HAMA results in the integration of the mechanical strength of HAMA and the great biocompatibility of GelMA to form a modified hybrid gel that further provides an ideal chemical and mechanical microenvironment for chondrocytes and chondrogenic differentiation of MSCs [28, 29].

Hybrid GelMA hydrogels combined with other components have also been reported to enhance the cartilage phenotype in scaffolds. Nano-patterned hybrid scaffolds made from GelMA, HA, and polyethylene glycol (PEG) dimethacrylate have been proven to enhance chondrogenesis in dental pulp stem cells [30]. The covalent bonding between modified PCL and GelMA was reported to improve the resistance to repeated axial and rotational forces at the interface. Human chondrocytes embedded within the hybrid constructs were able to form cartilage-specific matrices *in vitro* and *in vivo* [31]. Other combinations such as GelMA/silk fibroin [32], and GelMA/chondroitin sulfate [33] have also been reported to enhance the outcome of cartilage regeneration. However, an important challenge in designing scaffolds for cartilage is achieving mechanical properties that closely mimic native tissues, which requires continuous development of hydrogel materials [34].

4.3 Seed cell options

For hydrogel scaffolds, seed cells are loaded inside the gel, and the gel is internally solidified to form pores, allowing cells to proliferate, migrate, and differentiate. There are three types of seed cells in cartilage tissue engineering: chondrocytes, chondrocyte progenitor cells, and MSCs. The proliferation ability of human adult chondrocytes was the weakest among the three types of seed cells; cells in passage 2 were mostly chosen in the reviewed studies. At present, human nasal septal chondrocytes are often used as the source of cartilage seed cells because they are easy to obtain, and the isolated chondrocytes have a stronger proliferative ability [6, 19]. However, the number of chondrocytes in the human nasal septum is small, making it very difficult to prepare a bio-engineering scaffold of a certain size. Despite having relatively larger cell volumes, acquiring human costal cartilage and ear cartilage requires donor site (costal and retroauricular) incisions. However, because of the clear and stable phenotype of the cartilage, chondrocytes are still the most widely applied seed cells in the research of cell-laden scaffolds.

Chondrocyte progenitor cells have stronger proliferation ability and more accurate chondrogenic properties than MSCs [35]. However, the tissue source of cartilage progenitor cells is limited, and donor site incisions are inevitable. At present, the application of chondroprogenitor cells

is limited, but it still has good research and application prospects.

MSCs, including amniotic mesenchymal stem cells (AMSCs) [36], bone marrow mesenchymal stem cells (BMSCs) [19–21], and ADSCs [17, 18, 22] have been extensively studied as seed cells in cartilage tissue engineering in recent years. They have been reported to have certain chondrogenic abilities *in vitro* and *in vivo* in hydrogel scaffolds.

Research on ADSCs in cartilage tissue engineering is not as extensive as that on BMSCs, but as the most easily available source of stem cells in plastic surgery, ADSC ectopic chondrogenesis can be more widely used. An *in vitro* study showed that human ADSCs derived from different anatomical sites (breast, abdomen, and hip) displayed good cell yield, stemness, mesenchymal phenotype, proliferative ability, and viability, regardless of the cell tissue harvesting site [37]. Studies have shown that ADSCs with specific subpopulations have better chondrogenic differentiation potential [38]. The expression of CD146, CD73, CD90, CD105, and CD106 markers is necessary for ADSC differentiation into cartilage [39]. In addition, the combination of PDGF and insulin [40], TGF-beta [41], GF-1 [42], and BMP [43] with hydrogel was reported to effectively promote cartilage differentiation in ADSCs.

As a novel 3D culture method, spheroids of different seed cells have been applied in cartilage tissue engineering. Chondrocyte spheroids with a diameter of approximately 200 μm were used as micro units to form the ensemble cartilage tissue in agarose. Compared with chondrocytes cultured traditionally, chondrocyte spheroids produced more abundant cartilage extracellular matrix and had a higher expression of hyaline cartilage-related genes, which was close to that of natural cartilage [44]. Other studies reported that human BMSC spheroids were adaptable for bio-printing, and could help maintain cell viability, 3D architecture, chondrogenic phenotype, and fusion capacity in the hydrogel scaffold [45, 46]. The spheroid-laden hydrogel may pave the way to the future of cartilage engineering in the field of plastic surgery.

4.4 Prospects for mechanical bionic scaffolds

The chondrogenesis of MSCs in biological scaffolds is not only related to the choice of seed cells, but also closely related to the biomechanical environment, including the applied forces and cell-generated forces [47]. In recent years, the "mechanobiology of MSCs" has become an important research topic. Studies have shown that in 3D culture, the mechanical properties of the hydrogel matrix affect the differentiation outcomes of MSCs. Adipogenic differentiation of MSCs tends to occur in environments with lower forces, whereas osteogenic differentiation tends to occur in environments with higher forces [48, 49]. Studies have also shown that applied forces influence differentiation outcomes. Compressive force promotes chondrogenic differentiation of stem cells, while tensile force promotes osteogenic differentiation of stem cells [50]. With regard to cell-generated forces, recent studies have implicated multiple mechanical properties of the extracellular matrix as key elements of the stem cell microenvironment. Substrate rigidity [51], nanometer-scale topography [52, 53], and substrate patterning [54] were reported to have an impact on MSC differentiation.

In terms of articular cartilage regeneration, Yu et al. [55] studied the chondrogenic effect of a bionic mechanical environment. They used a customized dynamic tension-compression loading system to stimulate MSCs seeded into a biomimetic scaffold, and finally induced zonal, layer-specific expression of type I and type II collagens with similar structure and function to those present in the native meniscus tissue. In plastic surgery, a hydrogel biomimetic scaffold with an adequate mechanical strength is constructed according to the stress condition of the cartilage scaffolds needed for patients undergoing nasal reconstruction and ear reconstruction. This may also be one of the development directions for bioengineering cartilage scaffolds.

The limitation of this review is that the included studies are limited to those related to plastic surgery. As a subdivision, the application of tissue engineering in plastic surgery must lag behind the most frontier progress, so we may not be able to present the latest technological breakthrough. In addition, because the experimental design, materials, cell species and result evaluation parameters of each study are different, it is difficult to review quantitatively. However, we hope that through this detailed and enumerated review, we can bring readers an overview of the existing research on cartilage tissue engineering in plastic surgery.

Based on the review of the literature, cell-laden hydrogels have been found to be widely used in cartilage bioengineering research. Through 3D printing, the cell-laden hydrogel can form a bionic contour structure, including the shape of human auricular and nasal implants. Better cell proliferation, enhanced deposition of glycosaminoglycans, and collagen type II in the extracellular matrix were observed *in vivo* and *in vitro*, and the elastic modulus was reported to be similar to that of natural cartilage. Thus, the future direction of cartilage tissue engineering in plastic surgery involves the use of novel hydrogel materials and more advanced 3D printing technology, combined with biochemical and biomechanical stimulation.

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Declarations

Conflict of interest The authors declare that they don't have any conflict of interest.

Ethical statement There are no animal experiments carried out for this article.

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