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Recent advances in 3D bioprinting for cartilage tissue engineering: Biomimetic strategies, cellular regulation, and future perspectives

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Abstract

Articular cartilage has limited intrinsic repair capacity, and current clinical approaches often fail to restore durable hyaline cartilage. Three-dimensional bioprinting offers spatial control over cells, biomaterials, and bioactive cues, creating opportunities to fabricate patient-specific constructs that recapitulate cartilage architecture and function. However, functional cartilage regeneration cannot be achieved by optimizing printing technology, bioink composition, cell source, or scaffold design in isolation. This review critically examines recent advances in 3D bioprinting for cartilage tissue engineering through an integrated, design-oriented framework. Bioprinting modalities are compared according to their underlying physical mechanisms and their trade-offs in resolution, throughput, bioink compatibility, and cellular stress. Natural, synthetic, and composite bioinks are discussed with emphasis on how rheological behavior, crosslinking, and reinforcement jointly regulate printability, cell-instructive capacity, degradation, and mechanical durability. The roles of chondrocytes, mesenchymal stromal cells, and pluripotent stem cell-derived chondrogenic cells are evaluated in relation to phenotype stability, scalability, safety, and clinical application. At the construct level, pore architecture, mechanical and compositional gradients, fiber alignment, and spatiotemporally controlled factor delivery are considered as interacting regulators of mass transport, matrix organization, regional function, and host integration. A central conclusion is that successful cartilage bioprinting requires balanced optimization of competing objectives, including bioactivity versus printability, printing fidelity versus cytocompatibility, and porosity versus mechanical integrity. Future translation will require standardized, cartilage-specific evaluation of long-term matrix quality, mechanical function, safety, reproducibility, and repair efficacy in clinically relevant models.

Keywords: 3D bioprinting techniques; Tissue engineering; Composite biomaterial; Cartilage regeneration

1. Introduction

As an advanced manufacturing approach for tissue engineering, three-dimensional(3D) bioprinting can realize the high-fidelity recreation of native tissue structure by depositing cells, biomaterials and bioactive agents at different times sequentially¹. In this way, it both replicates the complex gradient micro-structure of native articular cartilage as well as regulate cells' distribution, matrix composition and bioregulatory factors to enhance cell-cell and cell-matrix interactions for promoting cartilage repair^{2,3}. Recently, due to its wide application in 3D bioprinting technology for making cartilage organoids or scaffolds with close function similarity to natural cartilages. Constructing supporting Structures can assist in repairing articular cartilage lesions and enhance the delay of disease progression compared with developing osteoarthritis^{2,4}. Although the current scaffolds are limited by their mechanical properties and long-term strength^{5,6}. But they have the advantages of fast prototype, good environmental control ability and multimodal multi-scale structure-inspired biomimicry for artificial cartilage fabrication in the near future^{1,7}.

Due to the poor blood supply and sensory nerve endings in articular cartilage, its own repair capacity is relatively weak. A full-thickness wound will not heal spontaneously, resulting in chronic pain, loss of function, and later-stage arthritis⁸. Currently, several therapeutic strategies are used clinically to repair damaged cartilage, including microfracture surgery, autologous grafting, allogeneic grafting, cell-based regenerative approaches, and intra-articular platelet rich plasma injection. Although they have achieved some degree of effect so far, problems need to be addressed, including a lack of cell phenotype stability, insufficient mechanical performance after repair, poor adherence to surrounding tissues⁹. 3D bioprinting provides a novel pathway toward anatomical matching and functional regeneration through precise design of scaffold geometry, pore architecture, and bioactive components^{4,8}. Scaffolds produced by gelatinous matrix-mesenchymal stem cells bioink exhibited strong promotion of collagen fibre formation and repair performance in a rabbit model¹⁰. Hyaluronic acid/sodium alginate bio-ink containing human bone marrow mesenchymal stem cells can form self-curved structures through 4D printing to imitate the curvature and multi-layered cellular arrangement of natural cartilage¹¹. However, clinical translation still faces difficulties with insufficient mechanical strength, uncontrolled long-term degradation in vivo, no standardized assessment system for large-scale production, and weak vascularization and innervation^{6,12,13}. Therefore, at present, developing multimodal regeneration

strategies that can jointly achieve the following objectives is urgently needed: structural biomimetic; bioactive support and long-term functional stability.

Several previous reviews have provided important insights into the development of 3D bioprinting for cartilage tissue engineering, mainly focusing on specific aspects such as printing technologies, biomaterial selection, bioink formulation, or scaffold fabrication strategies. These studies have greatly advanced the understanding of how individual components contribute to cartilage regeneration. However, cartilage regeneration is a complex multiscale process requiring the coordinated optimization of manufacturing precision, biomaterial properties, cellular behaviors, and hierarchical tissue organization. The interactions and potential trade-offs among these factors, including biological activity versus printability, structural accuracy versus cellular compatibility, and porosity versus mechanical stability, remain insufficiently discussed. Therefore, an integrated perspective that connects technological innovation with biological regulation and structural-functional reconstruction is needed to guide the development of next-generation 3D bioprinted cartilage constructs.

This review aims to systematically summarize the latest advances in 3D bioprinting for cartilage tissue engineering, focusing on key aspects from fundamental technology selection to clinical translation (as shown in Figure. 1). Firstly, we comprehensively compared different 3D bioprinting technologies with different technical principles and their clinical advantages in orthopedics. Second, material design strategies were explored, including biological properties of biomaterials from different derived sources, synthetic polymers for different uses, and their composites. Subsequently, the characteristics of various seed cells, co-culture strategies, and the effects of epigenetic regulation on chondrogenic differentiation are analyzed. In addition, optimization strategies for key parameters in biomimetic scaffold design, including porosity, mechanical gradients, surface microarchitecture, and growth factor delivery, are described. Finally, future perspectives of 3D bioprinting and tissue engineering are discussed.

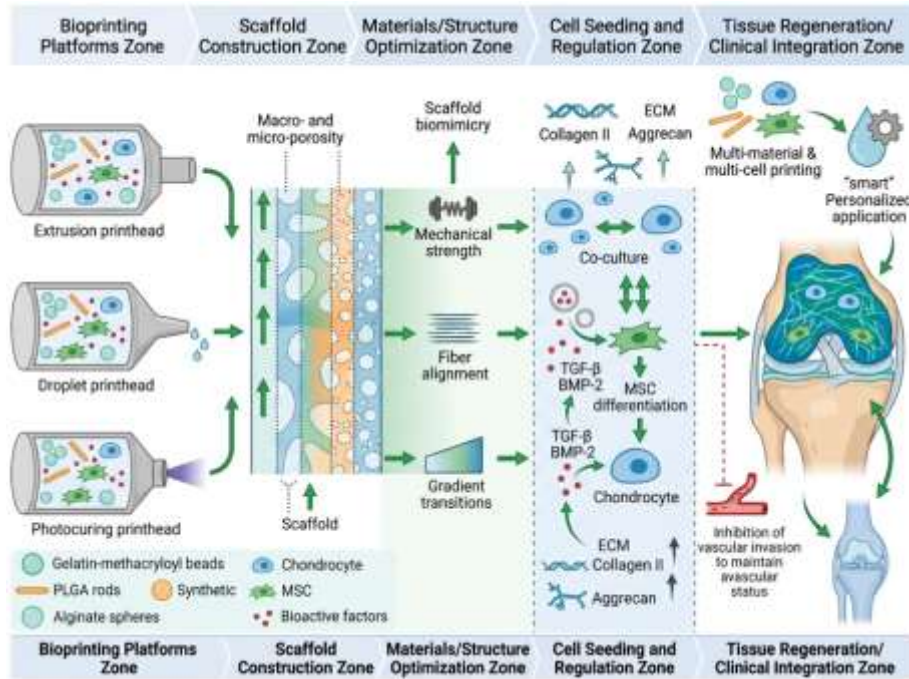


Figure 1. Overview of 3D bioprinting strategies for cartilage tissue engineering. The schematic summarizes the major steps involved in fabricating functional cartilage constructs, including bioprinting platform selection, scaffold design, material optimization, cell regulation, tissue regeneration, and clinical translation. Extrusion-, droplet-, and photocuring-based bioprinting enable the controlled deposition of cells, biomaterials, and bioactive factors. Scaffold properties can be optimized by regulating pore architecture, mechanical strength, fiber alignment, compositional gradients, and biomimetic features. Chondrocytes and mesenchymal stem cells (MSCs) may be incorporated alone or in co-culture systems, while transforming growth factor- β (TGF- β) and bone morphogenetic protein-2 (BMP-2) promote chondrogenic differentiation and extracellular matrix deposition. Multi-material and multi-cell printing further supports the fabrication of spatially organized and patient-specific constructs. After implantation, these engineered tissues aim to restore cartilage structure and function while maintaining the avascular characteristics of native articular cartilage.

2. 3D Bioprinting Technology

The tissue-engineered success depends on whether there is an ability to generate cells in a 3D, biocompatible environment with the morphological structure and functional characteristics as close to natural tissues surroundings. Therefore, technologies to design and fabricate the internal architecture and surface morphology of biomaterial scaffolds are their core foundations for functional tissue engineering. As a high-level manufacturing method for biofabrication of complex hierarchical structures¹⁴. The scaffolds fabricated by this method have an interconnected pores

system and high-specific surface area to promote cell adhesion, proliferation and enhance intercellular communication as well as improve gas-nutrient transportability among cells¹⁴. According to the different printing mechanisms, 3D bioprinting can be mainly divided into: extrusion-based bioprinting, drop-based bioprinting, light-based bioprinting, external assisted bioprinting and other bioprinting (as shown in Table. 1 and Table 2) ¹⁵.

2.1. Extrusion-Based Bioprinting

Recently, extrusion-based bioprinting has gained attention in the field of biological printing. The continuous release of bioink through a nozzle is applied in this method to build 3D scaffolds structure by adding layers sequentially¹⁶. This approach has some advantages, including a lower cost, simple operation, good compatibility with high-viscosity biopolymers, wide-ranging material applications, suitable for high-cell-dense or viscous hybrid bio-ink systems^{17,18}.

2.1.1 Pneumatic bioprinting

Pneumatic bioprinting is one of the most widely used extrusion-based bioprinting modalities, in which compressed air provides the driving force for controlled bioink deposition (as shown in Figure. 2A). For example, a gelatin methacryloyl (GelMA) bioink containing bone marrow-derived mesenchymal stem cells were extrusion-bioprinted into a scaffold for repairing cartilage defects in the rabbit distal femoral condyle. In vivo evaluation showed that the bioprinted scaffold promoted fibronectin deposition and enhanced the chondrogenic activity of the encapsulated cells¹⁰. However, the high shear stress generated during extrusion may cause cell membrane damage or reduced cell viability, thereby affecting subsequent proliferation and differentiation¹⁹. Based on the computer-aided design for cellular stability improvement, a suitable nozzle design was selected by performing computation-fluid-dynamics simulation analysis of shear-stress distributions in the flow channel¹⁹. During extrusion bioprinting, the scaffold may collapse under the influence of gravity, limiting the construction of complex structures²⁰. At the same time, in terms of material selection, extrusion bioprinting often uses high viscosity inks, which makes it difficult to apply low viscosity inks and soft materials. All in all, due to the conventional extrusion bioprinting, the needs of multi-material, multi-structure and multi-component in complex functional scaffolds cannot be met. Many scholars have developed different printing methods with similar printing mechanisms, mainly including coaxial bioprinting and suspended printing.

2.1.2 Coaxial bioprinting

Coaxial bioprinting is a high-precision technique in extrusion-based bioprinting using two concentric channels to repeatedly print cores and shells, which are commonly used to promote the release of growth factors, encapsulate cells, and construct gradient materials (as shown in Figure. 2B). At the same time, it releases both types of bio-ink to provide adequate conditions for cells and tissues to grow and survive under such circumstances²¹. Coaxial bioprinting can be applied for the production of cells encapsulated in a gel structure, which has reproduced physiologically constructed layers as described above²². As an adaptable form of high-end 3D bioprinting technology that can effectively construct osteochondral regeneration models²¹. In addition to, combining this technology with microfluidic systems to improve the interfacial stability and composition control of engineered cartilage scaffolds in a more biologically realistic manner.

2.1.3 Embedded printing

As an emerging extrusion based additive manufacturing technology, embedded bioprinting (suspension bioprinting) enables free-form manufacturing without additional support structures by depositing bioink directly into a temporary support bath, such as gelatin particles or carboxysugar gels (as shown in Figure. 2C). This method is especially suitable for the construction of cartilage scaffolds with overhangs, internal cavities, and complex topological morphology^{23,24}. The core advantage of this technology is that the omnidirectional wrapping and mechanical support provided by the support bath can effectively maintain the shape accuracy of the deposited ink and avoid its deformation before curing. This approach not only eliminates the need for rapid curing and high-viscosity bioinks in conventional extrusion-based printing but also prevents nozzle clogging. At the same time, it significantly reduces the risk of gravity collapse caused by insufficient mechanical strength of the material, thereby improving the molding quality of soft materials in small-scale fine structure manufacturing²⁵⁻²⁷. For example, relevant studies have shown that human bone marrow mesenchymal stem cells (hMSCs) can be encapsulated in hydrogels using this method and a complex three-dimensional structure in the shape of an auricle can be printed. The structure can provide an ideal microenvironment for long-term proliferation and directional differentiation of cells and effectively promote tissue formation²⁸. However, there are still several challenges for the popularization and application of this technology. First of all, due to the large density difference between bioink and support bath, when the gravity or buoyancy

exceeds the yield stress of the support material, the sedimentation structure may sink or float, thus affecting the molding accuracy ²⁹. In addition, the problem of the removal of cross-linking factors cannot be ignored, especially in the case of complex structures or closed cavities, the residual cross-linking agents are difficult to be completely removed, which may have adverse effects on biocompatibility ³⁰. Therefore, one of the important directions for future research is to develop more biocompatible supporting bath materials and systematically evaluate their compatibility with the physiological microenvironment in vivo. In general, suspension bio-printing can effectively maintain the geometric fidelity of the hydrogel structure before cross-linking, avoid collapse or deformation, and show significant advantages in constructing the curved surface and porous network structure of biomimetic articular cartilage, especially for weak gel systems such as GelMA and sodium alginate^{10,31,32}.

Its compatibility with viscous bioinks and multiple material formulations makes it advantageous for producing multilayered cartilage or osteochondral scaffolds. However, the requirement for relatively high viscosity and extrusion pressure may expose encapsulated cells to substantial shear stress, thereby reducing cell viability and impairing subsequent proliferation and extracellular matrix deposition. In addition, the resolution of extrusion-based systems is generally limited by nozzle diameter and filament spreading. These limitations can be partially compensated for by using shear-thinning and rapidly self-recovering bioinks, optimizing nozzle geometry and printing pressure, applying secondary crosslinking after deposition, and integrating coaxial or embedded-printing strategies. Therefore, extrusion-based bioprinting should be selected when structural stability and material versatility are prioritized, provided that rheological optimization is used to preserve cellular function.

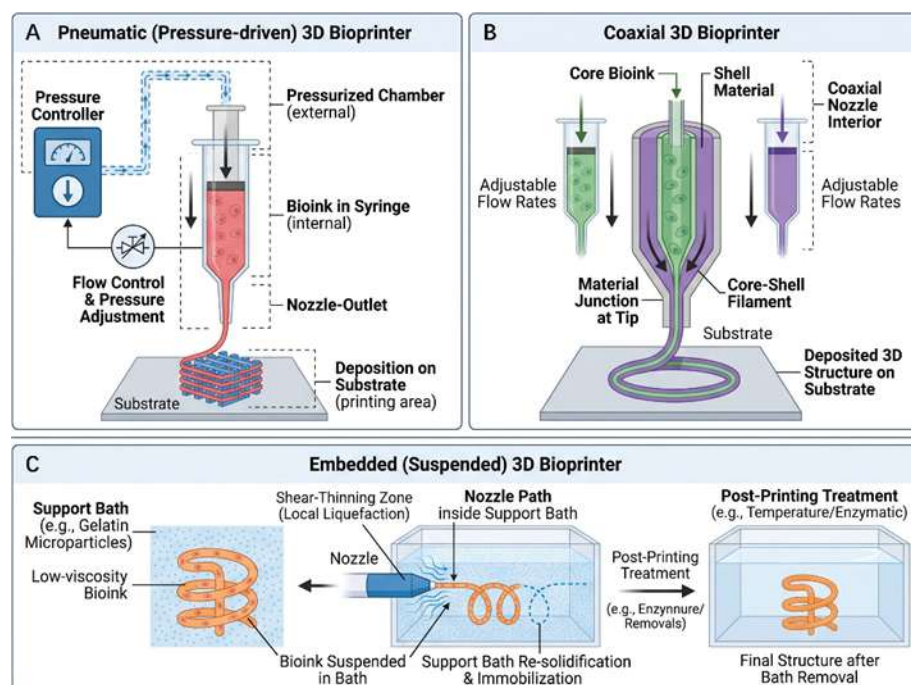


Figure 2. Representative extrusion-based 3D bioprinting strategies. (A) Pneumatic bioprinting uses controlled air pressure to drive bioink through a nozzle and deposit continuous filaments layer by layer onto a substrate. Printing behavior can be regulated by adjusting the applied pressure and flow rate. (B) Coaxial bioprinting simultaneously delivers core and shell materials through a concentric nozzle, enabling the direct fabrication of core-shell filaments with independently controlled flow rates. (C) Embedded bioprinting deposits low-viscosity bioinks within a shear-thinning support bath that locally liquefies around the moving nozzle and rapidly resolidifies to stabilize the printed structure. After printing, thermal, enzymatic, or other treatments remove the support bath and release the final construct.

2.2. Droplet-based bioprinting

Droplet-based bioprinting is a 3D bioprinting technique that uses discrete droplets as its fundamental building blocks. It involves the non-contact deposition of cell- or drug-containing droplets, typically in the picoliter-to-nanoliter volume range, at precisely defined locations; these droplets are deposited layer by layer to construct three-dimensional structures³³. Droplet-based bioprinting offers several advantages for the fabrication of complex 3D structures: (1) high versatility and precise spatial control over small droplets, including deposition onto curved surfaces; (2) non-contact generation of high-resolution patterns and structures; and (3) favorable biocompatibility that helps preserve the viability and functionality of encapsulated cells or bioactive agents³⁴. According to the underlying droplet-generation mechanism, droplet-based

bioprinting can be classified into inkjet bioprinting, electrohydrodynamic jetting, and laser-assisted bioprinting, as illustrated in Figure 3.

2.2.1. Inkjet bioprinting

Bioprinting based on ink-jet printing belongs to the category of modified or upgraded forms of traditional inkjet printing (as shown in Figure. 3A). A droplet-based additive manufacturing technology that has strong spatial resolution, no contact with the workpiece, and low cost³⁵⁻³⁷. Thermal or piezoelectric actuation is used for the thermal or piezo-deposition of cell-bioactive-component-loaded micro-drops at specific positions to form 3D tissues layer by layer³⁸. According to the ejection mechanism of droplets, inkjet bioprinting is generally divided into continuous-inkjet-printers, drop-on-demand printers, and electro-hydrodynamic inkjets. Among them, drop-on-demand inkjet Bioprinting can be divided into thermal inkjet, piezo-electric inkjet and electrostatic bioprinting based on the nozzle-actuating mechanism.

In terms of the construction process of artificial chondrocyte tissue by inkjet bioprinting technology in cartilage tissue engineering. Under dynamic culture conditions, porcine mesenchymal stem cells are implanted to create a gradient structure composed of collagen fibers showing varying orientations at different levels and heights; The glycosaminoglycan content increased by more than 5%(w/w)³⁹. In addition, it was found that inkjet printing induced temporary dedifferentiation of fibroblasts. Upregulated pluripotent marker genes such as Oct-4, Nanog and Sox-2 were observed; activation of the Hippo signaling pathway and inhibition of MAPK/P38 and MAPK/JNK1-3 pathways occurred. This may represent changes in cells states⁴⁰. However, inkjet bioprinting has stringent viscosity requirements for bio-inks and is typically applicable only to low-viscosity hydrogel systems. Moreover, high-cell-density printing may compromise cell vitality and function⁴¹.

2.2.2 Electrohydrodynamic injection bioprinting

Electrohydrodynamic injection(EHD) bioprinting, also known as electroassisted droplet based 3D bioprinting, relies primarily on the electricity generated by an applied electric field (0.5-20 kV) to drive a cell-free/cell-loaded bioink out of the nozzle to form tiny droplets(as shown in Figure. 3B)⁴². The superior advantages of EHD bioprinting mainly include its high accuracy and the wide applicability of bioinks with various viscosities⁴³. In addition, EHD bioprinting has demonstrated

its effectiveness in applications related to cell-loaded 3D bioprinting and drug delivery because of the low cell damage caused by the printing technology itself⁴⁴. EHD bioprinting can achieve a minimum resolution of around 5 μ m⁴⁵. However, the underlying mechanism of EHD bioprinting remains unexplored, and its boundaries with related technologies, including electrospray, drop on demand droplet ejection, electrospinning, and electrowriting, are not well defined⁴⁶.

2.2.3 Laser-assisted bioprinting

Laser-assisted bioprinting (LAB) uses a nozzle-free method by creating high-pressure bubbles with the help of lasers to transport bioinks from one surface to another without obstruction and can accommodate various viscosities of bioinks(as shown in Figure. 3C)⁴⁷. Primarily include: laser direct writing (LDW), laser induced forward transfer (LIFT) and matrix-assisted pulsed laser evaporation (MAPLE). Due to its high-resolution capability (able to reach down to tens of micrometers), good preservation of cells, higher Spatial position accuracy, LAB is more appropriate for detailed Structure recovery from cartilage tissue engineering⁴⁷⁻⁴⁹. LIFT technology can be used to accurately place articular cartilage progenitor cell microspheres in the range of about 80-150 μ m on melt electro-writing fibre scaffolds. According to the result: laser power, size of microsphere and its concentration affected precisely placing larger discrete units by controlling with LIFT technology⁵⁰. However, there are problems with homogeneity of cells encapsulated. Moreover, the high cost and technical complexity of LAB equipment may limit its widespread clinical adoption⁵⁰.

Droplet-based bioprinting is most suitable for applications requiring high spatial precision, non-contact deposition, and the controlled placement of cells, growth factors, or microscale functional units. Inkjet, electrohydrodynamic, and laser-assisted approaches are particularly valuable for generating patterned constructs, depositing multiple cell populations, and reproducing localized cartilage microenvironments. However, these techniques generally have restricted bioink viscosity ranges, limited ability to fabricate mechanically robust large-scale constructs, and potential challenges related to cell loading, droplet uniformity, or equipment complexity. High cell density may also impair droplet formation and compromise cellular function. These limitations may be addressed by combining droplet-based printing with supportive polymer frameworks, using hybrid hydrogel formulations with optimized viscosity, incorporating prefabricated thermoplastic skeletons, or integrating droplet deposition with secondary crosslinking. Accordingly, droplet-

based bioprinting is most appropriate when microscale patterning and spatial control are more important than immediate load-bearing capacity.

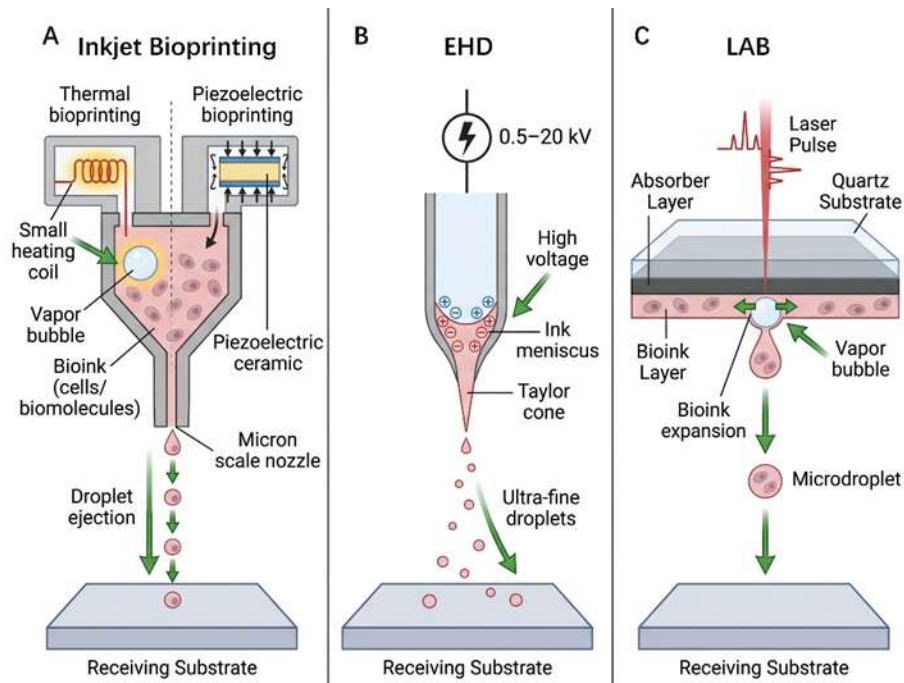


Figure 3. Representative droplet-based 3D bioprinting technologies. (A) Inkjet bioprinting generates discrete bioink droplets through either thermal or piezoelectric actuation. Local heating produces a transient vapor bubble, whereas deformation of a piezoelectric ceramic creates a pressure pulse, driving cell- or biomolecule-laden droplets through a microscale nozzle onto the receiving substrate. (B) Electrohydrodynamic (EHD) bioprinting applies a high electric field to the bioink meniscus, forming a Taylor cone and ejecting ultrafine charged droplets with high spatial resolution. (C) Laser-assisted bioprinting (LAB) uses a pulsed laser focused onto an absorber layer beneath a transparent quartz substrate. Rapid localized heating generates a vapor bubble that expands the bioink layer and propels a microdroplet toward the receiving substrate.

2.3. Photocuring-based bioprinting

Photocuring-based bioprinting is a fabrication technique that employs the photopolymerization of photosensitive materials under precisely controlled light irradiation. In this process, photocurable 3D bioprinting employs photopolymerization to crosslink photosensitive biomaterials. Through optical projection, photosensitive bioinks are selectively patterned onto a substrate and subsequently cured layer by layer to fabricate complex 3D tissue constructs³⁶. Compared with

other bioprinting methods, it usually offers significant improvements in printing resolution and printing speed. It also has the inherent advantage of not having to worry about nozzle blockage or shear stress affecting cell survival. The most common use of light-curing based bioprinting is to create cell-free scaffolds for cell seeding after printing²⁰. However, light-curing based cell bioprinting techniques have also been reported. According to different light scanning modes, light-curing based bioprinting can be further divided into stereolithography, digital light processing and volumetric bioprinting (as shown in Figure. 4).

2.3.1 Stereolithography (SLA) and digital light processing (DLP)

SLA is created by selectively scanning a slot of photosensitive material with UV light, allowing it to cure layer-by-layer (as shown in Figure. 4A). Its technique is often used to print precise tissue scaffolds with controllable geometry and porous structure due to its high resolution. Different from the point-by-point fixation of SLA, DLP solidifies the complete layer at one time. Since the printing time per layer does not increase no matter how complex the structure is, it is not difficult to see that DLP has a significant advantage in printing speed because the printing time per layer does not increase no matter how complex the structure (as shown in Figure. 4B). These technologies have provided resolutions as low as 100 μ m, cell-viability rates exceeding 85%, high-speed printing capabilities, and good structural accuracy. They can construct cartilage mimetic scaffolds with complex heterogeneities and anisotropies^{18,36,41}. A photopolymerization system using a combination of methacryloyl-modified acellular wharton's jelly and methacryloyl-modified gelatin to support the survival, spread and chondrogenic differentiation of bone marrow mesenchymal stem cells (BMSC) in vitro and achieve good healing effect in rabbits with a full-thickness cartilage defect³¹. Advanced photopolymerization technology recently has increased the resolution of print to around 47 μ m and achieved a filaments without any cross-section diameter exceeding 104 μ m, while ensuring the transdermal compatibility and good biocompatibility⁵¹. However, phototoxicity and residual photoinitiators generated during the curing process may adversely affect cell viability. Therefore, optimizing light wavelength, exposure duration, and bioink formulations is necessary to enhance curing efficiency while ensuring biosafety^{18,52}.

2.3.2 Volumetric bioprinting

Volumetric bioprinting is an emerging layerless 3D fabrication technology that projects multi-angle light fields simultaneously to achieve synchronized internal curing of photosensitive resins (as shown in Figure. 4C)⁵³. Its main features are extremely high-speed production capabilities and complete absence of support frameworks⁵³. To date, this technology has fabricated many types of scaffolds for bone, cartilage or perfusable hollow bone shafts⁵⁴. Recently, volumetric printing technology has developed to an extent where it can be used to embed micro-fluidics components within tissues or cells for biomedical research^{10,31,55}. At present, it is limited to using photopolymers and has a higher cost.

Photocuring-based bioprinting is advantageous for fabricating cartilage constructs requiring high geometric fidelity, rapid manufacturing, and complex architectures. By avoiding nozzle-induced shear stress, it can better preserve cell viability than extrusion-based methods. However, improved resolution is often achieved at the expense of biological functionality: increased crosslinking density and light exposure enhance structural stability but may impair cell migration and ECM remodeling. SLA, DLP, and volumetric bioprinting enable precise fabrication of cartilage-like microstructures and patient-specific geometries, yet remain limited by the narrow range of cytocompatible photocurable bioinks, photoinitiator-associated cytotoxicity, light attenuation, and challenges in multi-material or multicellular integration. Strategies including visible-light photoinitiators, cytocompatible crosslinking systems, degradable hydrogels, and hybrid manufacturing approaches may help overcome these barriers. Therefore, photocuring-based bioprinting is particularly suitable for applications prioritizing resolution and shape fidelity, while its biological and functional limitations require further optimization.

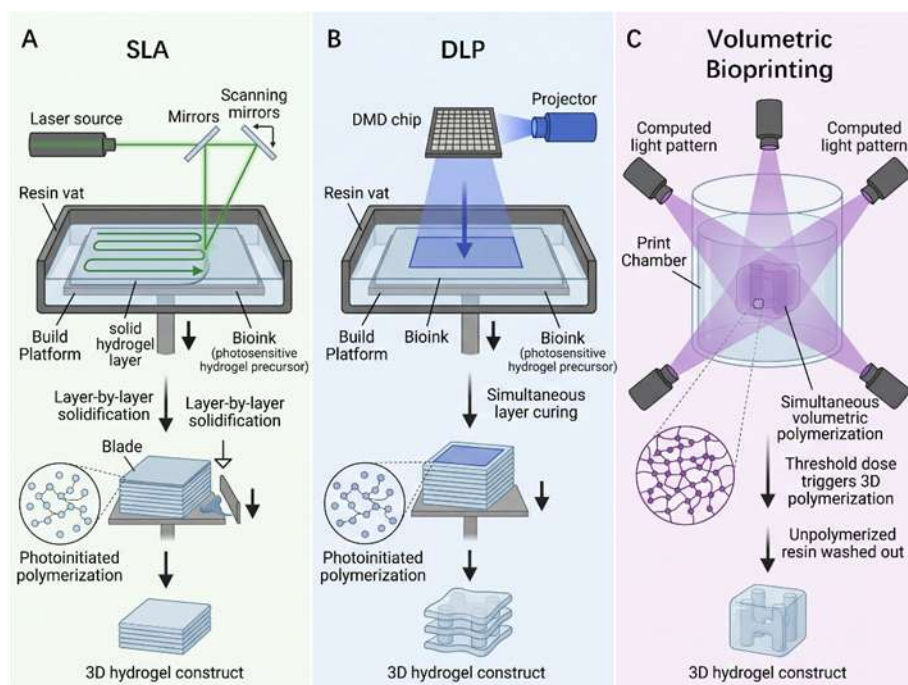


Figure 4. Representative light-based 3D bioprinting technologies. (A) Stereolithography (SLA) uses a focused laser beam, directed by mirrors and scanning mirrors, to selectively polymerize a photosensitive bioink in a point-by-point and layer-by-layer manner. After each layer is cured, the build platform moves to enable fabrication of the next layer. (B) Digital light processing (DLP) projects a patterned image through a digital micromirror device (DMD), allowing simultaneous photocuring of an entire layer and thereby improving printing speed. (C) Volumetric bioprinting projects computed light patterns into a rotating or multi-directionally illuminated print chamber, inducing three-dimensional polymerization once the local light dose exceeds the gelation threshold. Unpolymerized resin is subsequently removed to obtain the final construct.

2.4. External Assisted 3D Bioprinting

2.4.1 Acoustic-Assisted Bioprinting

Acoustic-assisted printing exploits the penetration capability of ultrasound and rapid acoustothermal-triggered free-radical polymerization to shape biopolymer solutions into predefined geometries without direct contact (as shown in Figure. 5). The principal acoustic modalities used in this approach are surface acoustic wave (SAW) and bulk acoustic wave (BAW), as illustrated in Figure 5. Acoustic-assisted biofabrication has been predominantly implemented using bulk-acoustic-wave-assisted bioprinting. The principle is to generate acoustic radiation forces by generating longitudinal-vertical bulk acoustical waves inside the bioink to produce controllable cellular spatial patterns⁵⁶⁻⁵⁸. Key process parameter settings are as follows: ultrasound frequency, signal voltage, bioink viscosity, and actuation duration⁵⁹. Under optimisation of

parameters at that point, acoustic-regeneration forces are sufficient to immediately respond appropriately by regulating cell positions⁵⁶⁻⁵⁸. This method has a shortcoming: it cannot fully restore the spatial details of cells or tissues to prevent subsequent disorders such as an overabundance of extracellular matrix (ECM) network formation⁵⁹. Biomedical applications of SAW primarily focus on cell sorting, separation, mixing and transport; it is generally applicable to two-dimensional models and individual or groups of cells in microfluidics⁶⁰⁻⁶⁴. But these methods cannot be used to create a 3D model of viscous hydrogel for bioprinting⁵⁹.

Designed a special bio-ink system for deep printing of heterogeneous tissue structures using acoustic bioprinting technology to promote the regeneration of bone defects and heart valves⁶⁵. Although there are no direct references to the application of current literature on cartilage engineering. The improvements brought by printing precision, nozzle blockage prevention and promoting cellular homogenization have made theoretical basis compatible with biodegradable inks containing cells or composite microparticles such as graphene oxide⁵⁹. Further verification is needed regarding the compatibility of this method with chondroitin sulphate-bearing biocompatible inks.

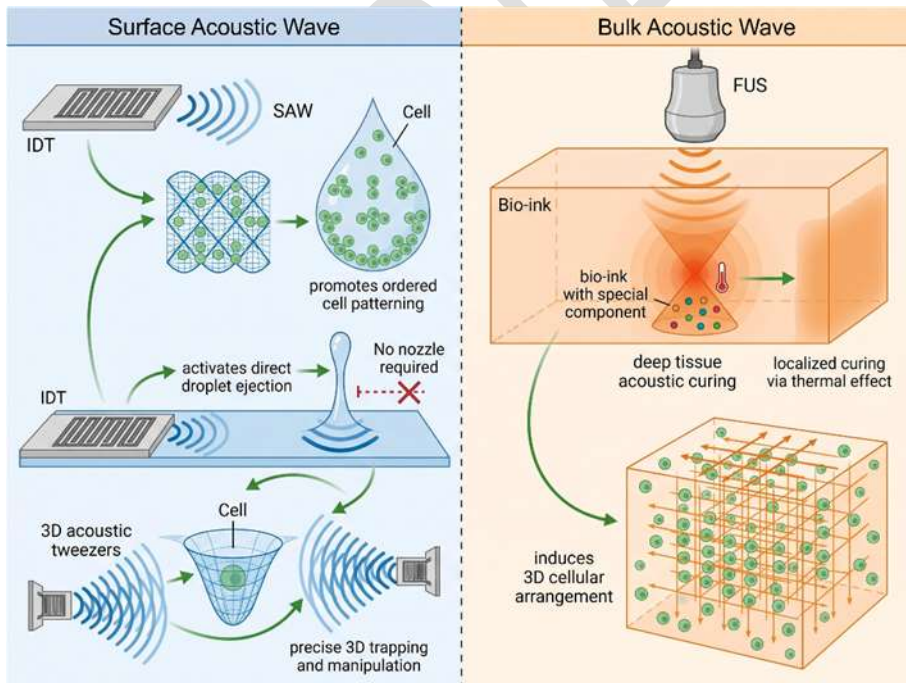


Figure 5. Acoustic-wave-assisted strategies for 3D bioprinting and cellular organization. Surface acoustic waves

(SAWs), generated by interdigital transducers (IDTs), can regulate cell distribution within bioinks, promote ordered cellular patterning, and trigger direct droplet ejection without requiring a nozzle. Opposing acoustic fields can also function as three-dimensional acoustic tweezers, enabling precise cell trapping, positioning, and manipulation. In contrast, bulk acoustic waves, delivered by focused ultrasound (FUS), penetrate bioinks and induce localized thermal or mechanical effects for deep-tissue acoustic curing. By controlling the spatial distribution of acoustic energy, FUS can selectively crosslink bioinks containing responsive components and promote three-dimensional cellular arrangement within printed constructs.

2.4.2 Magnetic-Assisted Bioprinting

Magnetic 3D bioprinting is based on magnetic levitation and can assemble in vitro 3D multicellular co-cultures (as shown in Figure. 6)^{66,67}. This approach provides high-precision spatial control, endogenous formation of the ECM, exclusion of synthetic protein substrates and can rapidly fabricate multi-tissue-like structures⁶⁸. As a contactless method, magnetic 3D bioprinting takes two different approaches to organise the arrangement of cells into specified shapes⁶⁹. The first method introduces magnetic metal nanoparticles into the bioink and applies an external magnetic field during printing to achieve directed positioning of these materials⁷⁰. The second approach employs label-free diamagnetic printing, mixing medium with a paramagnetic buffer and exposing it to a magnetic field to form cellular aggregates^{71,72}.

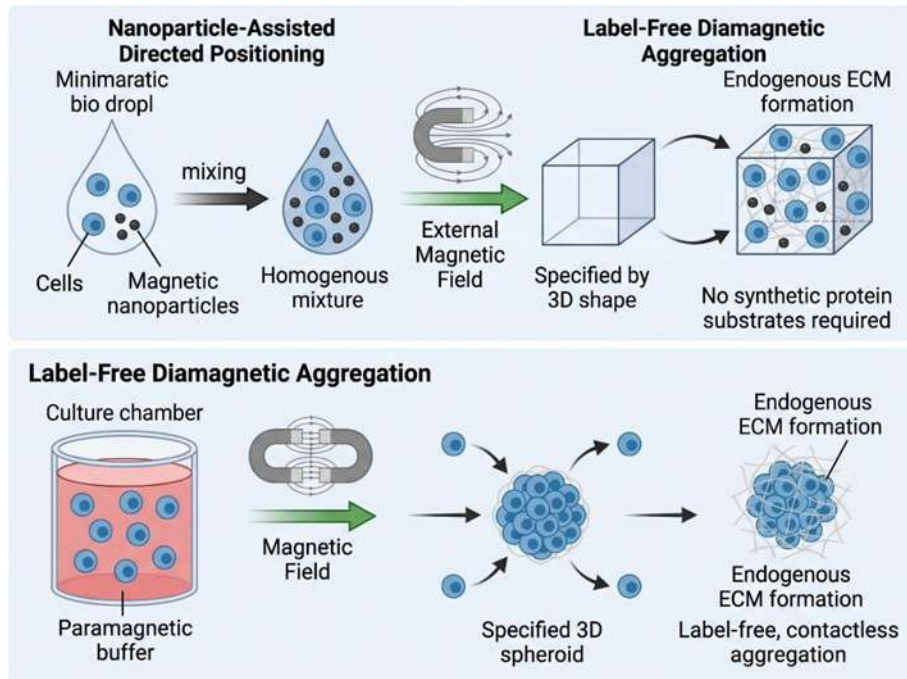


Figure 6. Magnetic-field-assisted cellular positioning and aggregation strategies for cartilage tissue engineering. Nanoparticle-assisted magnetic positioning involves mixing cells with magnetic nanoparticles to generate a homogeneous magnetically responsive bioink. Under an external magnetic field, the labeled cells can be directed into predefined three-dimensional geometries, where subsequent cell–cell interactions and endogenous extracellular matrix (ECM) deposition support tissue formation without requiring additional synthetic protein substrates. In contrast, label-free diamagnetic aggregation suspends unlabeled cells in a paramagnetic culture medium. Application of a spatially controlled magnetic field induces diamagnetic displacement and contactless cellular assembly, producing compact spheroids with specified three-dimensional shapes. These aggregates progressively synthesize and organize their own ECM, facilitating scaffold-free tissue maturation. Together, nanoparticle-mediated magnetic guidance and label-free diamagnetic manipulation provide non-contact approaches for controlling cell localization, aggregation, and spatial organization, thereby supporting the fabrication of structurally defined and biologically active cartilage constructs.

2.4.3 Aspiration-Assisted Bioprinting

Aspiration- assisted bioprinting (AAB) is an innovative technique that precisely regulates suction to grasp, transfer, and spatially position individual bioactive units onto hydrogels (as shown in Fig. 7)⁷³. ABB made glass pipette for generating a negative pressure and overcoming liquid-air interface energy barriers to maintain its viscoelastic characteristics⁷³. Combining sacrificial hydrogels can realize the manufacture of specific shapes of scaffolds-free or scaffolding-biologically-constructed structures precisely⁷³. The method is able to organize functions-diverse cells clusters into stratified layers and promotes the self-organization process that forms osteochondral tissues; therefore, it has a more obvious cartilage-repairing efficacy.

External field-assisted bioprinting, including acoustic-, magnetic-, and aspiration-assisted approaches, enables precise manipulation and spatial organization of cells, spheroids, and bioactive components, offering potential for reproducing the heterogeneous cellular architecture of cartilage and osteochondral tissues. However, current limitations include low throughput, equipment complexity, limited scalability, and insufficient validation in cartilage models. Magnetic approaches raise concerns regarding nanoparticle retention and biosafety, while aspiration-based methods may induce mechanical stress on cell aggregates. Integration with extrusion or photocuring platforms, development of biocompatible degradable magnetic materials, improved automation, and long-term in vivo evaluation may help overcome these challenges. Thus, external field-assisted printing currently serves as a complementary strategy to enhance cellular precision rather than replace established bioprinting methods.

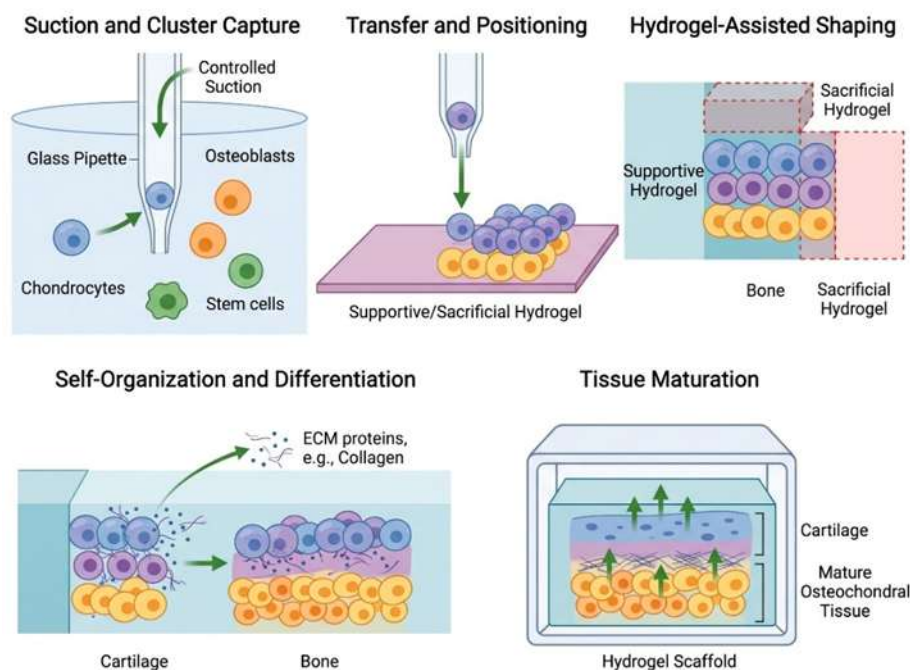


Figure 7. Aspiration-assisted bioprinting of osteochondral tissue constructs. Controlled suction through a glass micropipette enables the selective capture of chondrocytes, osteoblasts, stem cells, or preformed cellular clusters. The aspirated cells are subsequently transferred and precisely positioned onto supportive or sacrificial hydrogels to establish spatially defined cartilage and bone compartments. Hydrogel-assisted shaping provides temporary structural support and guides the formation of the intended three-dimensional architecture, while sacrificial materials can be removed after assembly. Following deposition, cell-cell interactions, self-organization, lineage-specific differentiation, and endogenous extracellular matrix (ECM) secretion promote the development of cartilage- and bone-like regions. Continued culture within a hydrogel scaffold supports matrix remodeling and tissue maturation,

ultimately generating an integrated osteochondral construct with distinct yet interconnected cartilage and subchondral bone layers.

2.5 Other Bioprinting

2.5.1 Multi-Nozzle Printing

Multi-nozzle printing technology represents a hardware architecture with compatibility and modularity. Depending on the feeding system and the material transport mode, the technology can operate according to two distinct physical mechanisms: droplet injection or material extrusion. Therefore, the key criterion to distinguish which type of printing it belongs to is the morphological characteristics of the material when it is released from the end of the nozzle - that is, as a controlled droplet or continuous filament (as shown in Figure. 8). Multiple nozzles are used for multi-channel printing to achieve spatial coordination of different materials or cells and functional components⁷⁴. Multi-nozzle cooperative alternating-printing-path strategy effectively enhances the print speed and geometric accuracy of complex retrogrades tissue through internal path re-distribution and adaptive modes switch⁷⁵. Experimentally verified that under the conditions compared to the single-nozzle system, this approach can increase printing efficiency by 32.4% in symmetrical areas and improve pore diffusivity by 33.8% for small-scale scaffolds. Moreover, dimensional deviation of key structure is less than 4%, which shows good repeatability and accuracy in building complex asymmetric structures of heterogeneous rabbits hepatobiliary models⁷⁵.

In addition, a new type of multifunctional 3D-printing system for handling four kinds of raw materials at the same time (including filaments, granules, liquids), thus coordinating multi-material printing and enhancing production efficiency while also realizing comprehensive integration in multi-functional products⁷⁶. In comparison with other commercial printers, it has reduced the development cost while maintaining compatibility and expandability.

Meanwhile, a microfluidic chip-based multi-material hydrogel filament printing technique forms phospholipid bilayers in an oil phase to achieve high-precision multi-material deposition with minimal cross-contamination, offering a new strategy for constructing multiphasic structures such as the cartilage–bone interface⁷⁷. Furthermore, a dielectrophoresis-driven single-nozzle multi-material sorting approach achieved approximately 95% separation accuracy of gold and silica

nanoparticles at room temperature, demonstrating broad potential for precise multi-material deposition in biofabrication⁷⁸.

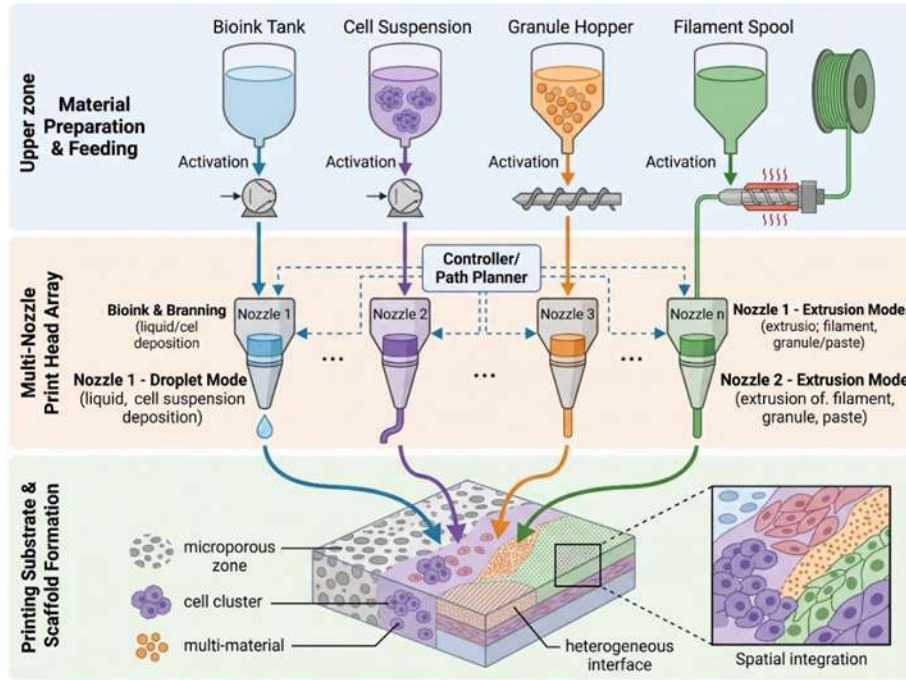


Figure 8. Multi-nozzle, multi-material bioprinting for constructing spatially heterogeneous cartilage scaffolds. The system integrates an upper material preparation and feeding zone, a programmable multi-nozzle printhead, and a substrate-based scaffold fabrication stage. Bioinks, cell suspensions, polymer granules, and thermoplastic filaments are independently activated and delivered to dedicated nozzles. Under the coordination of a controller and path-planning module, different printheads operate in droplet or extrusion modes to deposit liquids, cell aggregates, pastes, granules, or molten filaments with controlled spatial organization. Sequential and synchronized deposition enables the formation of microporous regions, cell-rich domains, multi-material compartments, and heterogeneous interfaces within a single construct.

2.5.2 In Situ 3D Bioprinting

In situ 3D bioprinting refers to the immediate placement of bioinks at the defects in the body to avoid postoperative implants and improve tissue integration and clinical application prospects (as shown in Figure 9)⁷⁹. This method is based on the combined design of portable printing device and quickly cross-linkable bioink to repair damaged skin, bones or cartilage effectively. Researchers have established a novel, direct delivery device named "Biopen", which can immediately introduce GelMA/HAMA bioink with mesenchymal stem cells at the site of injury. Experimental results

showed improved macroscopic and microscopic outcomes compared with controls, along with earlier chondrocyte formation^{80,81}.

Based on this direction of individualization in medical design and minimally invasive treatment; particularly difficult to identify anatomical defects⁸². However, some problems still exist during the process: intraoperative imaging-guided operations, adjusting the compatibility between bioink viscosity and biological environments, stabilizing printing under sterile conditions⁸³.

Of note, there are inherent difficulties in rigorously categorizing 3D printing techniques. On the one hand, multiple printing mechanisms can coexist in the same device, making it difficult for a single label to accurately reflect all its functions. On the other hand, the selection of classification criteria often depends on the research purpose and personal cognition, and there is a lack of unified classification framework among different literatures. Therefore, the classification method adopted in this paper is only used as an analytical tool, and its purpose is to construct a clear discussion context, rather than to make a final judgment on the technical system.

Multi-nozzle and in situ bioprinting are promising for cartilage repair requiring coordinated deposition of multiple biomaterials, cell types, or bioactive factors in anatomically complex defects. Multi-nozzle systems enable compositional gradients and osteochondral interface fabrication, while in situ printing allows patient-specific defect filling during surgery. However, their clinical translation is hindered by challenges in nozzle coordination, material compatibility, crosslinking synchronization, sterility, reproducibility, and intraoperative accuracy under complex physiological conditions. These limitations may be addressed through computer-assisted imaging, robotic positioning, rapid cytocompatible crosslinking, closed-loop control, and standardized bioink systems. Therefore, these approaches possess significant translational potential, but their clinical implementation depends on improving manufacturing reliability and surgical applicability.

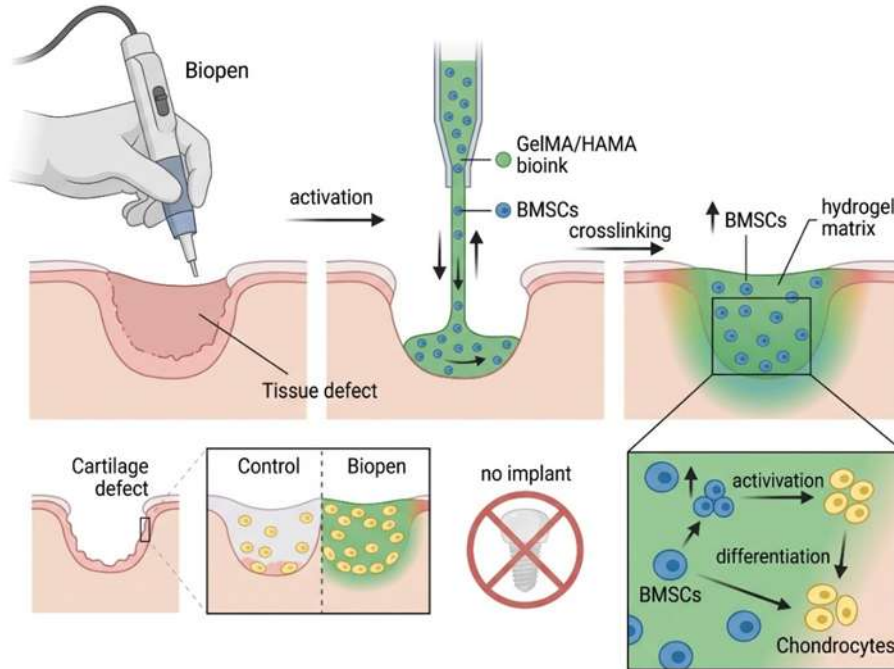


Figure 9. In situ bioprinting of cartilage defects using a handheld biopen. A photocrosslinkable bioink(GelMA/HAMA) containing BMSCs is directly deposited into an irregular cartilage defect using a handheld bioprinting device. Following activation and crosslinking, the printed hydrogel conforms to the defect geometry and forms a cell-laden matrix without requiring a prefabricated implant. The hydrogel provides temporary structural support and a three-dimensional microenvironment for BMSC retention, proliferation, and chondrogenic differentiation. Bioactive stimulation further promotes the transformation of BMSCs into chondrocyte-like cells and supports endogenous extracellular matrix formation.

Table 1. Summary of the features, strengths and weaknesses of various bioprinting techniques

Printing mechanisms	Representative bioprinting modality	Advantages	limitation	References
Extrusion-Based Bioprinting	Extrusion-Based Bioprinting	1.Low cost and simple operation. 2.Excellent compatibility with high-viscosity biopolymers 3.Versatile material applicability	1.Shear-stress-induced cell damage 2.Gravity-induced structural collapse. 3.Limited material versatility	17-20
	Coaxial Bioprinting	1. Strong capability for biomimetic structure fabrication.	1.Complex nozzle design.	21,22

		2.High functional integration 3.Compatibility with microfluidic systems	2.Restricted material selection 3.Post-extrusion crosslinking issues	
	Suspension bioprinting	1.Support-free fabrication of complex structures 2.Enhances cell-laden construct performance 3.Avoiding nozzle blockage and reducing the risk of gravity-induced collapse	1.Density-mismatch-induced instability. 2.Difficult removal of crosslinking agents. 3.Limited support-bath biocompatibility. Available materials require photosensitive modification	10,23-32
Droplet-based 3D bioprinting	Inkjet bioprinting	1. High spatial resolution and precision 2. Non-contact and low-cost operation 3. Demonstrated efficacy in cartilage tissue engineering	1. Narrow bio-ink viscosity window 2. Cell viability concerns at high densities 3. Potential for undesired cellular perturbations	35-37,41
	Electrohydrodynamic injection	1.Ultra-high resolution 2. Wide viscosity compatibility 3. Low cell damage	1. Poorly understood mechanism 2. Blurred technical boundaries 3. High-voltage requirements	43,44,46
	Laser-assisted bioprinting	1. High resolution and high spatial precision 2. Nozzle-free design, eliminating clogging 3. Broad viscosity compatibility	1. Poor homogeneity of cell encapsulation 2. High equipment cost 3. High technical complexity	47-50
Photocuring-based	Stereolithography and digital light processing	1.High resolution and structural precision 2.High printing speed	1.Phototoxicity and residual photoinitiators	18,36,41,51,52

bioprinting		3.Good cytocompatibility	2.Limited material selection 3.Potential interlayer defects from layer-by-layer curing	
	Volumetric bioprinting	1.Extremely high printing speed 2.Support-free fabrication 3.Capability to fabricate complex functional constructs	1.Limited material selection 2. High equipment cost 3.Insufficient technological maturity	10,31,53,55
External Assisted 3D Bioprinting	Acoustic-Assisted Bioprinting	1.Non-contact shaping 2. Controllable cellular spatial patterning 3.Improved printing precision and clogging prevention	1.Insufficient spatial detail reconstruction 2.Limited 3D printing capability 3.Lack of validation in cartilage engineering	56-59
	Magnetic-Assisted Bioprinting	1.High-precision spatial control 2.Endogenous ECM formation 3.Rapid fabrication of multi-tissue constructs	1.Potential cytotoxicity 2.Equipment and operational complexity	66-72,84
	Aspiration-Assisted Bioprinting	1.High-precision single-unit manipulation 2.Layered tissue construction and self-promotion 3.Scaffold-free/minimal-scaffold precise fabrication	1.Operational complexity and limited throughput 2.Insufficient technological maturity 3. Potential damage to active units	73,75
Other Bioprinting	Multi-Nozzle Printing	1.Multi-material collaborative printing capability 2.Significantly enhanced printing efficiency and precision	1.High system complexity 2.Restricted material compatibility	74-76,78

		3.Strong compatibility and cost-effectiveness	3.Insufficient validation of emerging technologies	
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Table 2. Representative quantitative evidence for bioprinting modalities relevant to cartilage tissue engineering

Bioprinting modality	Representative printing metric or condition	Cell viability or post-printing cellular outcome	Tissue-generation capability	Reference
Extrusion-based bioprinting	5% GelMA with rabbit MSCs; 25-G nozzle; 10-30 kPa; 360 mm/min; 0.2-mm layer height; 405-nm photocuring for 30 s	81.2% cell viability after 48 h of 3D culture	Promoted cartilage collagen-fiber regeneration in a rabbit full-thickness cartilage-defect model	10
Inkjet bioprinting	Printing parameters were not reported as a directly comparable numerical set	Numerical viability was not reported	Dynamic culture produced an approximately three-fold increase in glycosaminoglycan and collagen accumulation; GAG content exceeded 5% (w/w)	39
Electrohydrodynamic bioprinting	5% GelMA; uniform microdroplets of approximately 100 μ m	Low cell damage was reported, but no directly comparable numerical viability value was provided	Supported BMSC-laden microsphere fabrication; cartilage-repair outcome was not evaluated	44

Laser-assisted bioprinting/LIFT	Articular cartilage progenitor-cell spheroids with diameters of approximately 80 or 150 μm were deposited into fibrous PCL scaffolds	Post-printing viability was evaluated; a directly comparable percentage should be extracted from the full text before submission	Enabled controlled placement of cartilage progenitor-cell spheroids in reinforced constructs	50
DLP bioprinting	GelMA with cartilage microtissues; DLP-fabricated auricular construct	Day 1 viability: $95.68 \pm 0.71\%$ for GelMA plus chondrocytes and $98.25 \pm 0.43\%$ for GelMA plus microtissues; microtissue group remained above 90% through day 20	Improved extracellular-matrix deposition in vitro and mature auricular-cartilage formation after 12 weeks in vivo	85
Volumetric bioprinting	Centimeter-scale constructs fabricated within seconds to tens of seconds	Cell viability >85% in gelatin-based photoresponsive hydrogels	Chondroprogenitor-laden meniscal grafts synthesized neo-fibrocartilage matrix in vitro	54

2.6. Application of 3D Printing Technology in Orthopedic Clinical Practice

In recent years, due to the continuous improvement of technology, industry and material science development speed up 3D printing application orthopedic clinical practice. As a new form of technology, 3D printing has become popular in hospitals to inform consents, plan surgery, design and manufacture implants⁸⁶. Among all clinical applications of 3D printing, orthopedics has reached about 45.18% in terms of share across different fields⁸⁷. Moreover, in implantable medical devices based on 3D printing technology have been developed widely. Additionally, a variety of

materials with high precision and diverse structures can be fabricated using this technique⁸⁸⁻⁹⁰. All these types of products' advances are closely related to the developments in medicine and materials science, but medical biomedical material development has made notable achievements⁹¹.

3D printed models in orthopedic practice accurately reflect skeletal anatomy, positively improving clinical results. Such a model can help doctors and patients understand the type of injury more clearly⁹². In addition, raise patients' awareness of the surgical program to reduce preoperative preparation time through efficient management of students who take care of them, lowering post-operative costs^{92,93}. Therefore, some surgeons use imaging data to generate 3D printed fracture models before surgery for optimization in reducing fractures and selecting fixation materials⁹². This process ensures that the fixation devices match specific fracture types in simulations and do not need to be reused, thus reducing operating room preparation time⁹². Fractions reproductions can present the injury characteristics, possible complications, surgical plans, etc., for patient explanation^{92,94}. Earlier research has shown that a 3D-printed surgical plan-aid reduces the operating time by around 15% through pre-operative calculations⁹². Help it for a better understanding of its condition by reducing medical malpractice accidents. Conventional implants are less adaptable to patient-specific anatomical differences than 3D-printed ones. Therefore, 3D printing has provided essential support for personalized medicine in orthopedics. Although widely implemented internationally, its large-scale clinical adoption remains limited in world. Therefore, as an essential tool in modern medicine for medical applications at present.

3. Material Selection and Design for 3D Printing

Choosing suitable biomaterials for use in the development of cartilage tissue engineering projects. Ideal biomaterials should simultaneously satisfy the biocompatibility requirements and technical demands for 3D bioprinting. Biologically speaking, it needs to have good biocompatibility so that cells can survive, grow, proliferate and differentiate in its environment close to the native tissue condition outside. Biomaterials need to have the characteristics of printability and stability at a production level to ensure high-precision rapid prototyping results and long-lasting structural strength. Several typical forms of biomaterials used in cartilage tissue engineering are as follows: natural biomaterials, synthetic polymer materials and composite materials.

3.1. Natural Biomaterials

Natural biomaterials are primarily derived from animal, plant, and microbial sources and exhibit distinct compositions, structures, and physiological properties. These materials can provide biomimetic microenvironments that support cell adhesion and proliferation, thereby enabling their broad application in tissue engineering and regenerative medicine^{95,96}. Therefore, after being seeded with autologous or genetically modified cells, the original biomaterials can serve as good templates for developing living implants and are widely used in certain fields of tissue engineering and regenerative medicine. Here, we classify biomaterials according to their biological derived: animal derived, plant derived, algae-derived and microbial derived (as shown in Table. 3 and Figure 10).

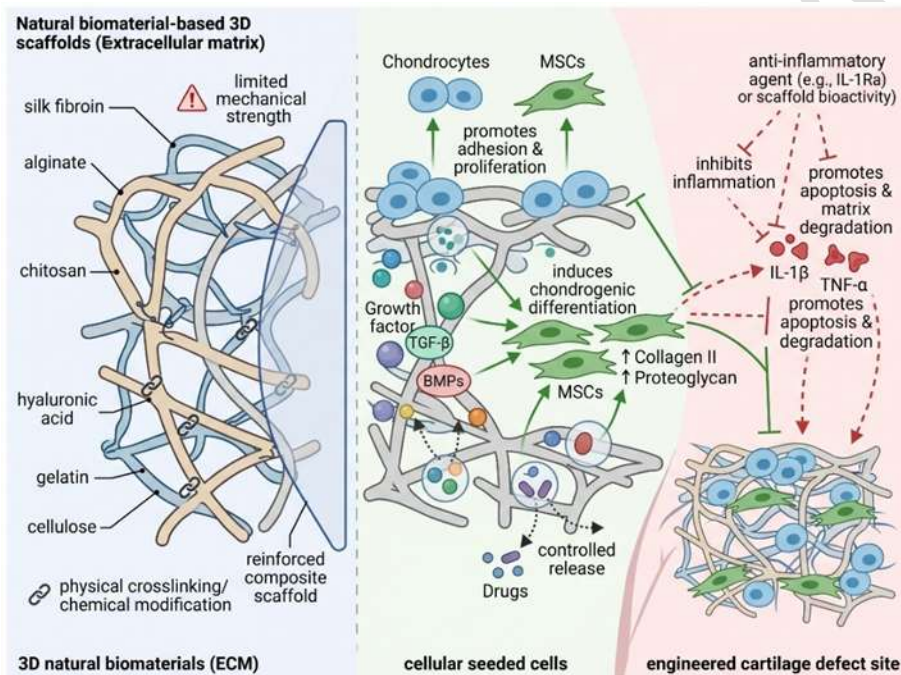


Figure 10. Natural biomaterial-based scaffolds and their biological functions in cartilage tissue engineering. Natural extracellular matrix (ECM)-derived biomaterials, including silk fibroin, alginate, chitosan, hyaluronic acid, gelatin, and cellulose, can be combined through physical crosslinking, chemical modification, or composite reinforcement to improve scaffold stability and compensate for their limited mechanical strength. These biomimetic matrices promote the adhesion and proliferation of chondrocytes and mesenchymal stem cells (MSCs), while growth factors such as transforming growth factor-β (TGF-β) and bone morphogenetic proteins (BMPs) stimulate chondrogenic differentiation and enhance collagen II and proteoglycan production. Natural scaffolds can also serve as controlled-release platforms for drugs and other bioactive agents. At the cartilage defect site, anti-inflammatory cues, such as interleukin-1 receptor antagonist (IL-1Ra), suppress inflammatory signaling mediated by interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), thereby reducing apoptosis and matrix degradation and supporting cartilage regeneration.

3.1.1. Animal-Derived Biomaterials

Animal-derived biomaterials have great potential as a source of scaffolds because of their biocompatibility, bioactivity, and extracellular-matrix-mimicking properties⁹⁷. These mainly include decellularized extracellular matrix(d-ECM), collagen, gelatin, silk fibroin, chitosan and fibrin, etc. These biomaterials provide a native environment for cells to grow and differentiate into tissues⁹⁸. Derived from acellular components of biological tissue, these materials have favorable histocompatibility and biocompatibility; thus, they provide an ideal microenvironment for cell proliferation, differentiation, migration, and deposition of ECM. Animal-derived materials should be used in combination with other materials to achieve the best regenerative repair effect. However, quality control challenges, such as ensuring pathogen safety and maintaining performance consistency, coupled with high production costs, have prevented the widespread application of animal-derived biomaterials. Importantly, animal-derived biomaterials also suffer from certain drawbacks, such as a weak structure of mechanical properties, low porosity that is not suitable for cell growth, narrow source limits.

d-ECM is a novel biomaterial that removes cellular components from tissues by physical, chemical, or enzymatic methods, while retaining the three-dimensional structure of the ECM, bioactive components such as collagen, growth factors, and biochemical signals. Its main advantages include: retaining natural biological activity, providing tissue-specific microenvironment, accurately regulating cell adhesion, proliferation, differentiation and migration, and high degree of bionic; it has excellent biocompatibility and low immunogenicity and significantly reduces the risk of host immune rejection after removing cellular components⁹⁹⁻¹⁰¹. Some products have been approved by FDA for clinical use and with the potential for functionalization and customization, combining with techniques such as photocross-linking to improve mechanical properties, d-ECM are more tunable and safer¹⁰²⁻¹⁰⁴. Some studies have demonstrated that acellular sturgeon cartilage photolinked bioink has good printing performance and biocompatibility. When administered, it promotes efficient regeneration of cartilage tissue¹⁰⁵. However, d-ECM materials also face many challenges, including poor mechanical properties and rapid degradation, which are difficult to meet the repair needs of load-bearing tissues such as bone and cartilage, and they often need to be combined with synthetic polymers such as PCL and PLGA; the instability and high cost between

batches, the difference of raw material sources (species, age, etc.) lead to the inconsistency of batch quality, the complex extraction and purification process, and the high cost of research and development^{102,106}. In summary, d-ECM materials have great application prospects in tissue engineering due to their unique biological activity and biomimetic microenvironment. However, its key defects, such as insufficient mechanical properties and poor batch stability, are still the main bottlenecks to achieve clinical translation. Future studies will focus on recombination or chemical modification strategies to overcome its physical and regulatory shortcomings while retaining its biological activity.

Collagen is a biomaterial commonly found in many vital organs and tissues and is widely used in tissue engineering. It is rich in ECM components that help form cell frameworks and has a fibrous molecular architecture. Therefore, it can be used as an alternative to ECM^{107,108}. Due to its outstanding biocompatibility, biodegradation, bioactivity and processability properties at present, collagen is suitable as a promising material scaffold for the cultivation of organ/tissue-bioprinting applications¹⁰⁹. Collagen breaks down relatively quickly, lacks significant mechanical strength¹¹⁰. In the future, more durable collagen-containing scaffolds will also be available after incorporating more materials¹¹¹.

Gelatin is derived from animals as a product of further processing of collagen and is commonly used in tissue engineering¹¹². Gelatin can induce stronger cell attachment by interacting with cell-surface membrane proteins and receptors. In particular, gelatin can be remodeled in vivo via collagenase-catalysed cleavage¹¹³. Gelatin-based biomaterials contain a higher water content and are suitable for tissue engineering regeneration and repairs. Nevertheless, due to excessive speed of degradation for an extended period, it is challenging to ensure the longevity of the gelatin-based system^{114,115}. A typical natural polymer compound can preserve the viability of MSC and promote regeneration by forming regenerated type II collagen fibrils in rabbits with cartilage defects¹⁰. Participated in more investigation and findings show that the blend of GelMA and HAMA at ratios of 2:1 is an efficient method for producing chondrogenic cell materials. At these concentrations, it shows not only higher storage modulus but also weakened cell motility to stimulate type-II collagen expression efficiently¹¹⁶.

Silk fibroin (SF) obtained from *bombyx mori* has been approved by the FDA for use in clinical practice. SF has good mechanical properties, flexibility and biocompatibility for biomedical

applications. Due to its favorable biocompatibility and predictable degradation characteristics over the past few decades^{117,118}. SF has been widely used in biomedical fields. It is also adjustable with precision at its surface molecular composition, structure, morphology, function modifications are expected to become more versatile in terms of tissue engineering drug delivery protein genes¹¹⁹. A new SF-DNA hydrogel microsphere system has been developed, which exhibits a strong induction effect on chondrogenesis through integrin-mediated adhesion pathways and glycosaminoglycan biosynthesis. It can promote proliferative ability, adhesive capability and chondrogenic-differentiation ability of BMSCs¹²⁰. However, the main limitations of silk fibroin include insufficient mechanical strength for independent load-bearing applications and a limited capacity to regulate its degradation rate, which makes it difficult to match the regeneration rates of different tissues precisely. The processing process is complex, the cost of extraction and purification is high, and there are batch to batch differences influenced by raw materials¹²¹⁻¹²³. These shortcomings usually need to be remedied by recombination with other materials or chemical modification. Overall, SF is a promising biomaterial for constructing and maintaining long-term human cartilage organoid models. These findings provide new insights and material strategies for cartilage regenerative medicine.

Chitosan is a chitin-derived water-soluble polymer that exhibits strong biodegradability and various biological functions such as antibacterial, high-bioactivity materials, low immunogenicity carriers, or blending agents¹²⁴⁻¹²⁶. With these features, it has been widely used in biomedical applications for cartilage repair, wound dressing, drug release, biomedical materials, and tissue engineering. However, the mechanical properties of chitosan are not ideal for matching cartilage tissue. Additionally, it has low solubility and easily becomes brittle when dry^{127,128}. In recent years, through adjusting the molecular weight, degree of de-acetylation, and physical-chemical properties of chitosan molecules, various changes in scaffold stiffness, pore structure, degradation rates can be controlled to meet different needs of chondrogenic differentiation and in vivo integration applications¹²⁹. Chitosan scaffolds have been reported to enhance the proliferation of hyaline cartilage through modulation of M2 macrophage polarity, stimulation of neo-vascularisation, and releasing specific growth factors; thus, promoting recovery after injury^{130,131}. As cartilage tissue-engineering research continues to progress, it is expected that some chitosan-containing materials will simultaneously serve as both cell growth environments and bioreactors providing auxiliary features.

Fibrin is a protein produced by thrombin acting on fibrinogen. Fibrin is a suitable biomaterial for scaffolds because of its biocompatibility and ability to bind proteins and growth factors¹³². In addition, fibrin hydrogels exhibit relatively poor mechanical properties because of their high water content and low protein concentration, which limit their applications in tissue engineering¹³³. Ultimately, its excellent biocompatibility, it is widely used in the regeneration and repair of soft tissues, such as skin, blood vessels, muscles, and nerves^{134,135}. Additionally, it has been widely used in clinical work as a carrier for autologous chondrocyte transplantation¹³⁶. Some researchers have combined 3D printing technology with Fibrin hydrogel to provide a supportive microenvironment for chondrocyte proliferation and ECM secretion, promoting in situ regeneration and repair of meniscus defects¹³⁷.

Animal-derived biomaterials are relatively safe, inexpensive and autologous bio-activators that can provide excellent solutions for the repair of damaged cartilage using combination technology with high-performance scaffolds and optimized cellular treatments. Their relatively weak mechanical strength and fast rate of breakdown limit the duration that they can maintain a biological environment.

3.1.2. Plant-Derived Biomaterials

Plant-derived biomaterials can reduce the dependence on animal-derived materials and are one of the main options for biological scaffold materials¹³⁸. Plant-derived biomaterials have technical and economic advantages such as high nutritional value, biocompatibility, and low cost¹³⁹. However, the limited cell attachment of these biomaterials has driven recent research to develop plant-based scaffolds through various scaffolding techniques¹⁴⁰. Generally speaking, they have a poor degree of rigidity and mechanical strength to meet the needs of cartilage tissue engineering independently¹⁴¹.

Starch is a biodegradable carbohydrate polymer found primarily in corn, wheat, cassava, rice, and potatoes¹⁴². Due to its high availability, low cost, non-toxicity, and biodegradability, starch has been widely used in several industries including the food industry¹⁴³. The low mechanical strength and high hydropathy of starch limit its application as a scaffold fabrication biomaterial, and several studies have addressed these challenges¹⁴⁴. A new type of 3D bioprinting bioink has been developed by adding 1% and 5% starch nanoparticles into a hydrogel composed of 15% gelatin and 1% sodium alginate¹⁴⁵. Meanwhile, the addition of 1% starch nanoparticles to the gelatin-based hydrogel was demonstrated to reduce the viscosity and shear stress of the bioink and promote

the proliferation and differentiation of fish satellite cells, thereby improving the 3D printability and biocompatibility. Overall, starch can be efficiently utilized by conjugation with other biomaterials or structural modification into nanoparticles^{145,146}.

Glycomannan is a polysaccharide in the pecking family commonly found in softwoods, rhizomes, tubers, and plant bulbs¹⁴⁷. Among the various types of glucomannans, the most utilized form is konjac glucomannan, which is extracted from *amorphophallus konjac* tubers¹⁴⁸. Konjac glucomannan is widely used in the food and tissue engineering industries due to its gelation and water retention properties¹⁴⁹. However, pure konjac glucomannan has limitations, including low hydrophobicity, viscosity, thermal stability, and mechanical strength¹⁵⁰. To alleviate these limitations, previous studies have investigated the fabrication of hydrogels by constructing composites of konjac glucomannan with biomaterials such as fibrin or k-carrageenan¹⁵¹. Therefore, the combination of glucomannan with other biomaterials can be an efficient strategy for scaffold fabrication in cultured meat production.

3.1.3. Algae-Derived Biomaterials

Algae are photosynthetic organisms that can be eaten. It has long been known to be rich in bioactive substances such as polysaccharides, proteins, bioactive peptides, fatty acids, and vitamins¹⁵². Algae are usually divided into macroalgae and microalgae. Macroalgae are multicellular organisms, mainly composed of polysaccharides. Microalgae are unicellular organisms consisting mainly of amino acids and bioactive peptides¹⁵³. The pigmentation and high water content of microalgae make them difficult to use as scaffolds for tissue engineering¹⁵⁴. Therefore, macroalgae are generally considered to be more suitable for tissue engineering applications than microalgae. Although alginate and agarose exhibit excellent gelation and thickening properties, their limited cell-binding sites and low mechanical stability limit their application in scaffold fabrication. In order to promote tissue regeneration and repair, these biomaterials often need to be combined with other biopolymers.

Sodium alginate (SA) contains anions and is considered to have good biocompatibility and antibacterial properties, thus being used extensively in life-sciences applications¹⁵⁵. Hydrogel materials have shown broad applications in cell transplantation, tissue engineering, wound treatment and drug delivery, such as protein, small molecule drugs and nanoparticles¹⁵⁶. However,

the use of pure alginate as a scaffold material is limited due to its lack of cell attachment sites¹⁵⁷. One study introduced graphene oxide nanoparticles into a composite bioink containing SA, gelatin, and chondroitin sulphate at a concentration of 0.1 mg/mL to improve the growth efficiency of mesenchymal stem cells³². At this time, it showed strong chondrogenative characteristics. SA still has significant deficiencies in mechanical strength and the controllability of degradation^{114,158,159}. In summary, SA has been applied to cartilage tissue engineering at an accelerating pace towards more precise reconstruction of the native in vivo microenvironment and will bring improvements in clinical results soon.

Agarose is a linear polysaccharide. Since its chemical structure is similar to ECM, it forms a solid porous scaffold suitable for cell growth¹⁶⁰. In addition, the high water retention ability of agarose provides sufficient oxygen and nutrients for cell proliferation and differentiation, and its superior biocompatibility also exists¹⁶¹. However, the lack of cell-binding domain of agarose significantly limits its application in tissue engineering¹⁶². Cross-linking of 2% agarose with 5% soy protein isolate followed by coating with 1% gelatin significantly improved mechanical strength, structural stability, and cell survival¹⁶². Taken together, these studies suggest that incorporation of other biomaterials within agarose scaffolds into the enhanced cell binding domain can significantly improve their applicability for cultured meat production.

3.1.4. Microbial-Derived Biomaterials

Microbial biomaterials are produced by microbial fermentation involving a variety of bacterial genera, yeasts and moulds¹⁶³. Bacterial cellulose and hyaluronic acid are promising biomaterials for enhancing the mechanical strength of scaffolds. However, the low nutritional value of bacterial cellulose and the lack of galan cell binding sites should still be addressed in scaffold applications.

Hyaluronic Acid (HA) is a naturally occurring non-sulfated glycosaminoglycan composed of repetitive D-glucuronic acid and N-acetyl-D-glucosamine disaccharide units. At present, they are mainly produced by microbial fermentation to help maintain tissue homeostasis and regulate other physiological processes. It can serve as a good cell-culture substrate or additive in skin-care products¹⁶⁴. HA exhibits high water-retention capacity, excellent biocompatibility, and biodegradability. In addition, it participates in several physiological processes, including cell signaling, migration, and proliferation. Additionally, HA is also commonly employed in various fields such as dermal or tissue fillers, drugs carriers, scaffolds for tissue engineering¹⁶⁵⁻¹⁶⁷. Low

viscosity, poor gel formation and fast degradation are the main limitations on hyaluronic acid hydrogel application currently^{114,168}. One study developed a type of HA-gelatin hydrogel with good lubricity and bio-compatibility; it could stimulate cartilage regeneration while preventing the early onset of degradation of cartilage¹⁶⁹.

Cellulose is divided into bacterial cellulose and plant cellulose, both of which have a long-chain glucose composition. Importantly, bacterial cellulose exhibits a unique 3D hierarchical nanofiber structure¹⁷⁰. In addition, it is superior to plant cellulose^{151,171}. Bacterial cellulose biomaterials are widely used in tissues engineering, wound healing treatment and drug delivery systems. Their tunable physical-chemical properties and biomechanical characteristics make them suitable as biomedical materials¹⁷². Cellulose-based materials offer a surrounding environment for cell attachment, proliferation, migration, and differentiation¹⁷³. Researcher has built porous scaffolds by combining polycaprolactone/polyethylene glycol polymers with cellulose nanofibers, which show excellent mechanical properties, good biocompatibility, low biodegradation rate and other applications in soft-tissue repair¹⁷⁴. These findings suggest that a deeper understanding of bacterial cellulose is expected to open its potential for wider applications in tissue engineering.

Natural biomaterials are highly valuable for cartilage tissue engineering due to their ECM-like biochemical cues, supporting cell adhesion, chondrogenic differentiation, matrix deposition, and remodeling. Animal-derived materials, including collagen, gelatin, decellularized ECM, and silk fibroin, provide tissue-specific microenvironments, whereas polysaccharide-based materials such as alginate, agarose, hyaluronic acid, and cellulose offer high water content, mild gelation, and favorable cell encapsulation properties. However, natural biomaterials generally suffer from insufficient mechanical strength, poor shape retention, uncontrolled degradation, and batch variability. Their biological advantages may also be limited by source-dependent differences, immunological concerns, sterilization challenges, and inadequate long-term load-bearing capacity. Moreover, biological activity alone does not necessarily indicate effective cartilage regeneration. These limitations can be addressed through chemical modification, controlled crosslinking, nanoreinforcement, or integration with synthetic polymers and thermoplastic frameworks. Therefore, natural biomaterials are best suited for creating cell-supportive cartilage-like microenvironments, while composite strategies are often required for mechanically demanding cartilage repair.

Table 3. Comparison of various characteristic the different natural biomaterials

Material		Advantages	limitation	References
Animal-Derived Biomaterials	Decellularized extracellular matrix	1.Good biocompatibility and low immunogenicity 2.Potential for functionalization and customization	1.Poor mechanical properties and rapid degradation 2.Batch-to-batch instability and high cost 3.Immunogenicity and regulatory challenges	99-106
	Collagen	1.Excellent bioactivity and biomimetic properties 2.Outstanding biocompatibility and biodegradability 3.Good processability	1.Significantly insufficient mechanical strength 2.Excessively rapid degradation	107-109,111
	Gelatin	1.Excellent cell adhesion capability 2.In vivo remodelability and biodegradability 3.High water content and biomimetic microenvironment	1.Excessively rapid degradation 2.Relatively weak mechanical properties 3.Batch-to-batch variability and source dependency	113-116
	Silk fibroin	1.Low immunogenicity and good biocompatibility 2.Predictable degradation characteristics 3.Versatile processability and multiple formats	1.Insufficient mechanical properties 2.Complex processing requirements 3. Challenges in long-term stability	117-119,121,122

		4. Promising potential as a drug delivery vehicle		
	Chitosan	1. Excellent bioactivity and multifunctionality 2. Tunable physicochemical properties 3. Special mechanisms promoting cartilage regeneration	1. Inadequate mechanical properties 2. Poor solubility and brittleness when dry.	124-128
	Fibrin	1. Excellent biocompatibility 2. Broad applications in soft tissue regeneration	1. Weak mechanical properties 2. Rapid degradation rate	132-135
Plant-Derived Biomaterials	Starch	1. Abundant source and low cost 2. Biodegradable and non-toxic 3. Performance enhancement through compounding or modification	1. Low mechanical strength 2. Poor structural stability due to high hydrophilicity	143,144
	Glycomannan	1. Excellent gelation and water retention properties 2. Wide availability and relatively low cost 3. Performance enhancement through composite strategies	1. Poor mechanical strength and thermal stability. 2. Limitations in hydrophobicity and viscosity.	149,150
Algae-Derived Biomaterials	Sodium alginate	1. Excellent biocompatibility and antibacterial properties 2. Broad applicability as hydrogel materials 3. Performance enhancement through	1. Lack of cell attachment sites 2. Significantly insufficient mechanical strength 3. Poor degradation controllability	114,155-159

		nanocomposite modification		
	Agarose	1.ECM-like chemical structure and porous scaffold 2.High water retention and nutrient supply 3.Significant performance enhancement through composite modification	1.Lack of cell-binding domains 2.Inadequate mechanical properties 3.Limited degradation controllability	160-162
Microbial-Derived Biomaterials	Hyaluronic Acid	1. Excellent water retention and biocompatibility 2. Involvement in cell signaling and promotion of migration/proliferation 3. Performance enhancement through composite modification	1. Low viscosity and poor gel-forming ability 2. Excessively rapid degradation 3. Insufficient mechanical properties	114,164-168
	Cellulose	2.Tunable physicochemical and biomechanical properties 3.Good cytocompatibility and low degradation rate	1. Relatively inferior performance of plant cellulose 2. Excessively low degradation rate may hinder tissue remodeling.	172-174

3.2. Synthetic Polymeric Materials

While natural biomaterials provide a biologically instructive microenvironment, synthetic polymers offer greater control over mechanical performance and manufacturing reproducibility. Their complementary properties provide the rationale for the composite-material strategies discussed in the following sections.

The polymerization of synthetic monomers generates synthetic polymers, among which these molecules have been modified via polymerization into those containing specific functional groups or with desired properties. Cells are more difficult to adhere than natural polymers to the surface of synthetic polymer materials¹⁷⁵. These materials exhibit excellent processability, enabling the fabrication of scaffolds with tunable pore size, filament diameter, porosity, and overall geometry. They also offer controllable degradation rates and favorable mechanical properties¹⁷⁶. Although they have obvious technical applications, there are some deficiencies: bioactivity is lacking; potential toxic degradation products exist. The safety for patients has not been fully guaranteed^{177,178}. According to the processing characteristics of each material, polymer materials can be roughly divided into thermoplastic and cross-linked polymer materials (as shown in Table. 4 and Figure. 11). Among them, thermoplastic polymer materials are often suitable for extrusion type 3D printing technology, which can provide rigid support. Cross-linked polymers are often prepared into hydrogel materials by photocrosslinking or chemical cross-linking, which can be used to encapsulate cells.

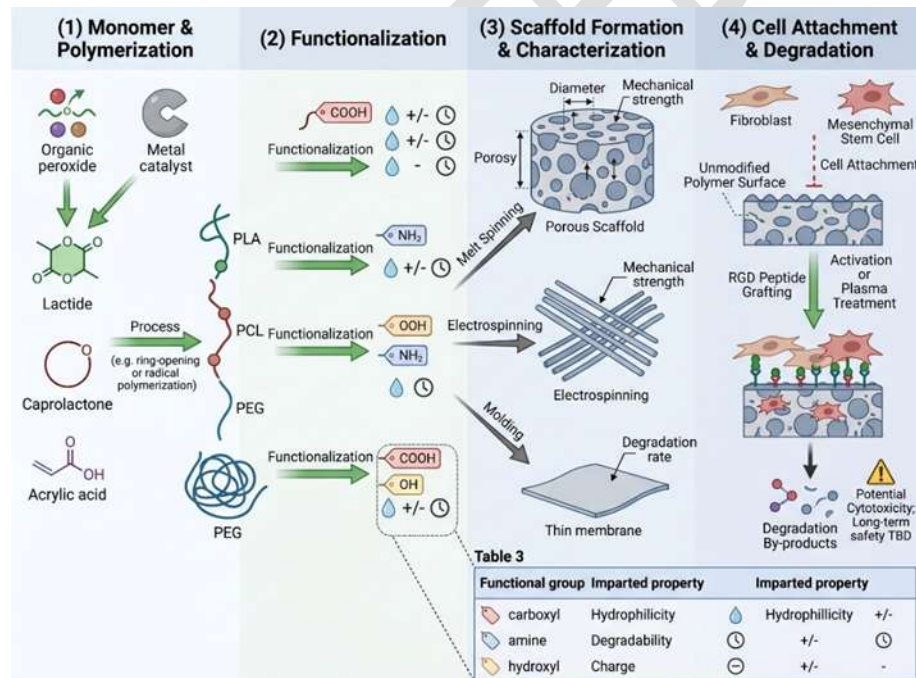


Figure 11. Design and functionalization of synthetic polymer scaffolds for cartilage tissue engineering. (1) Synthetic polymers, including poly(lactic acid) (PLA), polycaprolactone (PCL), and poly(ethylene glycol) (PEG), are produced from corresponding monomers through ring-opening, radical, or other polymerization reactions. (2) Introduction of carboxyl, amine, and hydroxyl groups modulates polymer hydrophilicity, surface charge, and

degradation behavior. (3) Functionalized polymers can be processed by melt spinning, electrospinning, or molding to generate porous scaffolds, fibrous networks, and thin membranes with tunable porosity, fiber diameter, mechanical strength, and degradation rate. (4) Because unmodified synthetic polymer surfaces generally exhibit limited cell adhesiveness, bioactivation through RGD peptide grafting, plasma treatment, or related surface-modification strategies enhances fibroblast and mesenchymal stem cell attachment. Scaffold degradation subsequently releases polymer by-products, whose cytotoxicity and long-term biosafety should be carefully evaluated before regenerative application.

3.2.1. Thermoplastic polymer materials

Thermoplastic polymers are characterized by softening or melting upon heating and solidifying upon cooling, and this thermal cycle can be repeated. Their molecular structures consist primarily of linear or branched polymer chains held together by physical intermolecular interactions, such as van der Waals forces and hydrogen bonding, rather than permanent covalent crosslinks. The absence of permanent crosslinking enables their reversible thermal processing. Representative thermoplastic polymers include polyurethane, polycaprolacton, polylactic acid, and polyglycolic acid.

Polyurethane (PU) is an FDA-approved flexible polymer with unique elasticity, load-bearing capacity, biodegradability, and biocompatibility. It is widely used in biomedical applications, including cartilage, bone, skin, and vascular engineering¹⁷⁹. Studies have shown that a scaffolding composition at the ratio of 60% PU: 40 % PLC has maintained good cell proliferation in vitro and shows excellent degradation performance¹⁸⁰. Modified PU composite materials can improve the bonding strength and regeneration ability of chondrocyte for faster generation of neo-cartilage¹⁸¹. However, PU degradation products are toxic, which seriously limits its application in tissue engineering¹⁸².

Polycaprolactone (PCL) exhibits good biocompatibility, adequate mechanical strength, excellent processability, a relatively low melting temperature of approximately 60 °C, non-toxic degradation products, and favorable rheological and viscoelastic properties. It has been approved by the FDA and is one of the most commonly used polymers for extrusion-based scaffold fabrication¹⁸³⁻¹⁸⁵. However, due to their poor hydrophilicity and difficulties in surface modification, it cannot provide good assistance for cell attachment^{186,187}. Studies show that PCL/Fibrin hydrogels can help reconstruct natural meniscal tissue engineering in animals with artificial meniscal cartilage defects,

promoting vascularisation and healing of the meniscus¹³⁷. Furthermore, reinforcement of PCL with multi-walled carbon nanotubes and bamboo-like carbon nanotubes (BCNTs) has been investigated, and PCL modified with 0.02% BCNT significantly enhanced human articular chondrocyte adhesion and proliferation while improving the material's rheological and mechanical properties¹⁸⁸.

Poly-lactic-acid (PLA) is a commonly used polymeric biomaterial composed of lactic acid (2-hydroxypropionic acid) units¹⁸⁹. Degradation products of PLA have good biocompatibility for tissue repair and replacement¹⁹⁰. In terms of its physicochemical properties, PLA exhibits excellent thermoplastic processability, high tensile strength, a relatively high Young's modulus, and good biocompatibility that supports cell growth, making it well suited for 3D printing applications.^{191,192}. PLA has a serious problem of brittleness; the breaking elongation falls below 10%¹⁹³. Furthermore, PLA has no reactive end-group and cannot easily perform surface or property modifications¹⁹⁴. PLA's low hydrophilicity also has a detrimental effect on cells attaching¹⁹⁵. That is to say, its degradates may cause inflammation^{193,196}. Copolymerization or blending of PLA with polyethylene glycol can increase its hydrophilicity¹⁸⁹. Experimental studies have shown that PLA scaffolds provide favorable mechanical stability, making them suitable for the regenerative repair of bone and cartilage tissues^{191,197}.

Poly(glycolic acid) (PGA) is a highly crystalline biodegradable polymer, has relatively high tensile strength and rapid degradation rate¹⁹⁸. After being degraded into glycolic acid, which is nontoxic to humans and eliminated through metabolism in our bodies naturally¹⁹⁹. The PGA has, therefore, been extensively used in bone tissue engineering materials. However, an excessively rapid degradation rate may compromise its mechanical strength, and it may also lead to the rapid accumulation of glycolic acid, triggering adverse inflammatory responses²⁰⁰.

Poly-lactic-co-glycolic acid (PLGA), which contains both L-lactic acid and glycolic acid, is an FDA-approved material used clinically that has good biocompatibility, a long degradation time, excellent mechanical properties²⁰¹. PLGA scaffolds may induce an increase in chondrocyte proliferation to form hyaline cartilages with enhanced joint function post-transplantation. PLGA scaffolds can stimulate the proliferation of chondrocytes to some extent and help form hyaline cartilage. Thus, it enhances joint function^{202,203}. However, PLGA is poorly hydrophilic and has no cell-recognition or adhesive structures, thus losing cellular affinities²⁰⁴. Moreover, during PLGA degrading and releasing acid, it may trigger local inflammatory reactions²⁰⁵.

In short, due to the favourable degradability, mechanical performance and mouldability of polymeric materials at present time, they have become an essential material for production currently. It has a wide range of applications in biomedical engineering areas, such as bone repair, cartilage tissue repair and regeneration, tissue scaffolding design, and drug delivery systems. Polymers have excellent mechanical properties; also, reproducing micro-environments similar to those in the body is beneficial for cells to grow normally after differentiation is activated and functions are optimized. During the research and development stage, materials degradation or bioactivity-related problems need to be given due attention in time.

3.2.2. Cross-linked polymers materials

Cross-linked Polymers refers to the polymer molecular chains through chemical bonds or physical interaction with each other to form a huge, insoluble three-dimensional network structure of polymer materials²⁰⁶. There is a critical point in the cross-linking process when the system changes from a liquid (mobile sol) to a solid gel (loss of mobility)²⁰⁷. Once the gel point is reached, the polymer forms a crosslinked network that is insoluble in solvents, although it can still swell, and cannot be remelted upon heating. Crosslinking methods can be classified into chemical, physical, and biological crosslinking²⁰⁸. Currently, the most widely used crosslinkable synthetic polymers include polyethylene glycol, polyvinyl alcohol, and methacrylate-functionalized polymers.

Polyethylene-glycol (PEG) has good hydrophilicity and biodegradability, as well as other properties such as water solubility, low immunogenicity, flexibility²⁰⁹⁻²¹¹. Studies have shown that PEG-based composites of hydrogels promote the attachment, proliferation and differentiation of chondrocytes in vitro, they also accelerate the healing of cartilage defects^{211,212}. For example, PEG-based microsphere hydrogels have been developed to effectively protect cartilage tissue and thereby alleviate the progression of osteoarthritis²¹³. Due to the lack of cell adhesion domains, PEG hydrogels alone cannot provide an ideal environment to support cell adhesion and tissue formation²¹⁴. Alternatively, PEG is often chemically modified by an acrylic group to generate photopolymerizable PEGDA, and cells can be rapidly encapsulated²¹⁵. PEGDA polymerized by UV light has been applied in the field of extruding-based 3D printing for fabricating tissue engineering scaffolds with higher mechanical properties.

Polyvinyl alcohol (PVA), as a non-toxic, water-soluble polymer, has high hydrophilicity, easy processability, good biocompatibility and excellent chemical resistance^{216,217}. Because of the

abundance of hydroxyl groups in PVA, it has good water solubility. These properties have driven the matching of hydrophilic groups with drugs and bioactive factors, resulting in a wide range of applications in the field of tissue regeneration²¹⁸. The PVA-hydrogel that bears similarity with the mechanical features of human cartilage is also frequently chosen as a medical intervention material for defective articular cartilage defects²¹⁹. Studies show that as a suitable material for joints, both PVA-chitosan-hydrogel and traditional ones outperform each other. They exhibit high flexibility and low friction coefficients while satisfying more stringent biosafety requirements than many other synthetic polymers^{216,220}. However, the major limitations of crosslinked PVA are its poor biodegradability and limited ability to promote cell adhesion²²¹.

Synthetic polymers are valuable for cartilage bioprinting when mechanical reinforcement, processing reproducibility, geometric stability, and degradation control are required. Thermoplastic polymers, including PCL, PLA, PGA, PLGA, and PU, provide stable frameworks for load-bearing cartilage and osteochondral constructs, whereas crosslinkable polymers such as PEG- and PVA-based systems allow tunable gelation, stiffness, degradation, and printability for cell-laden fabrication. However, their engineering advantages are often accompanied by limited intrinsic bioactivity. Most synthetic polymers lack cell-recognition signals and require functionalization to promote cell adhesion, chondrogenic differentiation, and cartilage-specific matrix formation. Additional challenges include thermal damage during thermoplastic processing, photoinitiator-related toxicity in photocrosslinking systems, restricted cell migration caused by excessive crosslinking, and adverse effects of degradation products. These limitations can be addressed through surface modification, bioactive peptide incorporation, ECM-derived material blending, and hybrid designs combining synthetic frameworks with cell-laden hydrogels. Therefore, synthetic polymers provide excellent structural and manufacturing control but generally require biological functionalization to achieve effective cartilage regeneration.

Table 4. Comparison of various characteristics of the different synthetic polymeric materials

Material		Advantages	limitation	References
	PU	1.FDA-approved medical polymer	1. Toxic degradation products	179,181,182

Thermoplastic polymer materials		2.Unique elasticity and load-bearing capacity 3. Synergistic effects through composite modification	2. Mechanical properties requiring further optimization 3. Difficulty in matching degradation rate with tissue growth	
	PCL	1.FDA-approved with good biocompatibility 2. Low melting point and non-toxic metabolites 3. Significant performance enhancement through composite modification	1.Poor hydrophilicity 2.Difficult surface modification 3.Relatively slow degradation rate	183-187
	PLA	1. FDA-approved biodegradable material 2. Excellent thermoplastic processability and mechanical strength 3. Property improvement through copolymerization	1. High brittleness 2. Lack of reactive end-groups and difficult modification 3. Poor hydrophilicity and potential inflammatory degradation products	190-196
	PGA	1. High crystallinity and tensile strength 2. Non-toxic and metabolizable degradation products 3. Non-toxic and metabolizable degradation products	1. Excessively rapid degradation leading to mechanical loss 2.Degradation product accumulation causing inflammation 3. Poor processing and storage stability	198,199,222
	PLGA	1.FDA-approved clinical material 2.Promotion of chondrocyte proliferation and	1.Poor hydrophilicity 2.Lack of cell-recognition and adhesion structures	201-205

		hyaline cartilage formation 3.Tunable degradation rate	3. Acidic degradation products triggering inflammation	
Cross-linked polymers materials	PEG	1.Excellent hydrophilicity and anti-fouling properties 2.Good biodegradability and flexibility 3.Easily chemically modified for photocrosslinking	1.Lack of cell-adhesion domains 2.Potential cytotoxicity from photocrosslinking 3.Insufficient mechanical properties of pure PEG hydrogels	209-212,214,215
	PVA	1.Excellent hydrophilicity and water solubility 2. Good biocompatibility and processability 3. Mechanical properties similar to human cartilage	1.Poor biodegradability after crosslinking 2. Inadequate cell adhesion capacity 3. Crosslinking process may affect performance	216-221

3.3. Synergistic Optimization of Composite Materials

No single biomaterial can simultaneously achieve the biological activity, printability, mechanical strength, degradation control, and long-term stability required for cartilage tissue engineering. Natural biomaterials and ECM-derived components provide a hydrated, cell-supportive microenvironment, whereas synthetic polymers and reinforcing phases enhance structural fidelity, mechanical performance, and manufacturing reproducibility. Therefore, composite design should not be viewed as simple material combination, but as a rational strategy in which each component addresses specific limitations, including insufficient bioactivity, poor printability, inadequate mechanical support, uncontrolled degradation, or limited functional organization.

3.3.1. Complementary Design of Composite Bioinks

The composition ratio of individual components is a critical determinant of the biological and mechanical performance of composite bioinks. For example, increasing the gelatin content in PEG-PLA/gelatin composite hydrogels enhanced swelling capacity and promoted chondrocyte adhesion, proliferation, type II collagen secretion, and glycosaminoglycan deposition, whereas the compressive modulus decreased accordingly²²³. This finding illustrates a central challenge in composite design: improving the biological microenvironment may compromise mechanical stability. Thus, the optimal composition should be selected according to the intended application rather than by maximizing a single material property.

Composite systems can also be designed to improve printability and cell-instructive function simultaneously. The incorporation of calcium phosphate and glycosaminoglycans into GelMA hydrogels has been reported to promote osteogenic and chondrogenic differentiation of hMSCs, as reflected by increased RUNX2 and SOX9 expression, respectively. In the same system, xanthan gum and nanocellulose improved the printability of the bioink, and DLP-printed constructs showed an approximately two-fold increase in cell number after 7 days of culture²²⁴. These findings suggest that reinforcing or rheology-modifying components can improve processing performance without necessarily eliminating biological activity. However, the concentration, dispersion, and long-term retention of nanomaterials or inorganic additives must be carefully controlled because excessive reinforcement may limit cell migration, alter degradation, or adversely affect matrix remodeling.

Multi-material bioprinting further enables the spatial organization of different biological and mechanical functions within a single construct. For instance, tyramine-modified alginate and carboxymethyl cellulose were crosslinked under visible light to fabricate a gradient osteochondral interface, which induced chondrogenic and osteogenic differentiation after 3 weeks of co-culture²²⁵. Such spatially organized systems are particularly relevant to cartilage and osteochondral regeneration because native articular cartilage exhibits depth-dependent differences in extracellular-matrix composition, cell phenotype, mechanical behavior, and mineralization status. Rather than using a homogeneous scaffold throughout the defect, gradient composite constructs may better reproduce the transition from the cartilage layer to the calcified cartilage and subchondral bone regions.

Nevertheless, improved in vitro cell proliferation, chondrogenic-marker expression, or short-term extracellular-matrix deposition should not be interpreted as direct evidence of durable cartilage regeneration. The translational value of a composite construct should be evaluated using integrated outcomes, including print fidelity, cell viability, cartilage-specific matrix formation, compressive and fatigue properties, degradation behavior, phenotype stability, host integration, and long-term in vivo repair. In particular, the degradation rate of each component should be coordinated with the rate of newly formed extracellular-matrix deposition. If the reinforcing component degrades too rapidly, the construct may lose mechanical support before tissue maturation; conversely, excessively slow degradation may hinder tissue remodeling and integration with the host cartilage.

3.3.2. Photocrosslinking Strategies for Composite Bioinks

Photocrosslinking provides an important strategy for rapidly stabilizing composite bioinks after deposition. Photocrosslinkable biomaterials can be generated by introducing photosensitive functional groups into synthetic polymers, natural polymers, or their composite systems. Upon irradiation with light of an appropriate wavelength, photoinitiator-mediated reactions or photoreactive functional groups can induce the formation of a three-dimensional network within seconds to minutes²²⁶. Common photocrosslinkable chemistries used in tissue engineering and 3D bioprinting include (meth)acrylate, vinyl, thiol-ene, and cinnamate chemistries^{227,228}. Representative materials include PEG, gelatin, silk fibroin, hyaluronic acid, and chitosan derivatives.

Photocrosslinking enables temporal control of gelation and rapid post-printing stabilization, improving filament retention, shape fidelity, and complex architecture fabrication, particularly for soft cell-laden hydrogels prone to deformation. However, these advantages are accompanied by biological trade-offs. Excessive light exposure, high photoinitiator concentrations, or dense crosslinking networks may impair cell viability, migration, and extracellular matrix remodeling. Therefore, photopolymerization parameters should be optimized according to cell type, construct thickness, bioink composition, and intended application.

Commonly used photoinitiators include Irgacure 2959, lithium phenyl-2,4,6-trimethylbenzoylphosphine (LAP), and Eosin Y²²⁹. Their selection should consider wavelength, light dose, radical-generation efficiency, cytocompatibility, and the potential influence of residual initiator on long-term tissue development. Coumarin-functionalized hyaluronic acid/gelatin

systems are of particular interest because they enable photoinitiator-free crosslinking through light-induced dimerization, thereby avoiding the need for radical-generating photoinitiators and potentially reducing associated cytotoxicity risks²³⁰. In addition, combining complementary chemistries may provide greater control over material performance. For example, thiol-ene and (meth)acrylate reactions can be integrated to generate dual-crosslinked networks, whereas reversible cinnamate photodimerization can be used to develop light-responsive dynamic materials²³¹.

In summary, composite bioinks should be designed as integrated systems in which each component serves a defined biological or engineering function. Natural components can enhance cell-matrix interactions and chondrogenic activity, synthetic or reinforcing components can improve mechanical stability and printability, and photocrosslinking can provide rapid structural fixation. However, increasing the number of components does not necessarily improve overall performance. The most effective composite strategy is one that balances biological activity, printability, structural fidelity, degradation, mechanical durability, and spatial functional organization according to the specific requirements of cartilage or osteochondral regeneration.

4. Selection and Functional Modulation of Seed Cells

4.1. Cell-source selection for cartilage bioprinting

Seed-cell selection critically determines the biological performance and translational potential of 3D-bioprinted cartilage constructs. Beyond chondrogenic potential, key considerations include cell availability, expansion capacity, phenotypic stability, tolerance to printing stress, immunological compatibility, tumorigenic risk, and regulatory feasibility. Therefore, the optimal cell source depends on the intended application, from in vitro cartilage modeling to focal cartilage repair and large osteochondral defect reconstruction. Major cell sources include primary chondrocytes, adult mesenchymal stem cells (MSCs), and pluripotent stem cell-derived chondrogenic cells (Table 5 and Figure 12).

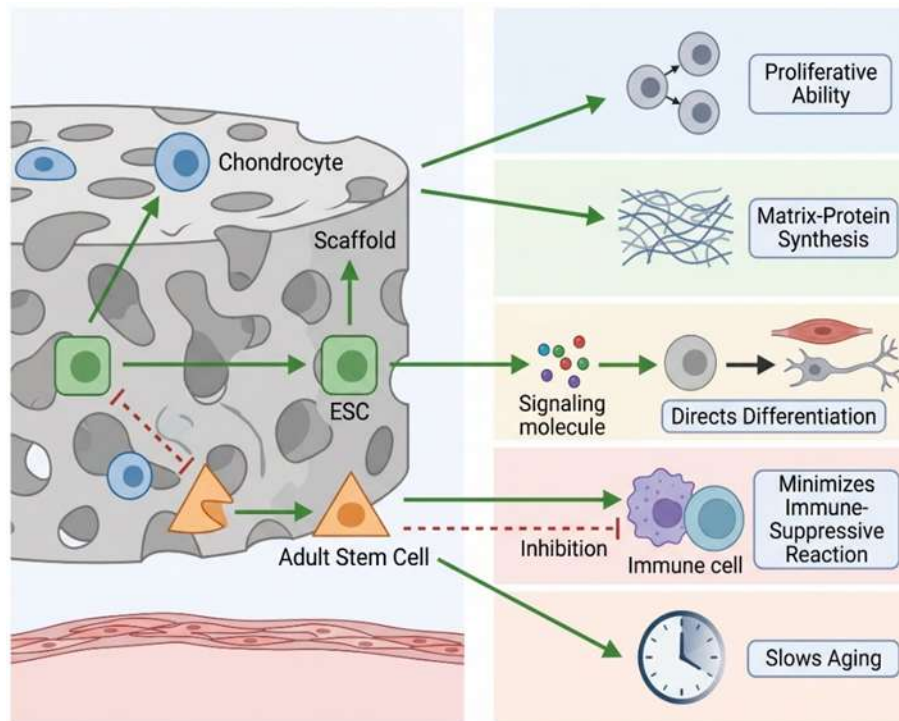


Figure 12. Cell sources and biological functions of stem cell-based scaffolds for cartilage tissue engineering. Chondrocytes, adult stem cells and pluripotent stem cell-derived chondrogenic cells can be incorporated into porous scaffolds to support cartilage formation and regeneration.

4.1.1. Chondrocytes

Chondrocytes are the resident cells of articular cartilage and are directly responsible for the synthesis, maintenance, and remodeling of cartilage extracellular matrix²³². Because they naturally produce cartilage-specific matrix components, including type II collagen and glycosaminoglycans, primary chondrocytes remain an important cell source for cartilage tissue engineering. Encapsulation within three-dimensional hydrogel systems can help preserve their rounded morphology and chondrogenic phenotype by providing biochemical and biophysical cues that resemble the native cartilage microenvironment^{233,234}. In previous studies, hydrogel-encapsulated chondrocytes produced cartilage-related extracellular matrix and formed engineered cartilage with molecular characteristics resembling native tissue after implantation²³⁵.

Primary chondrocytes are particularly suitable when the primary objective is to generate hyaline-cartilage-like extracellular matrix or to repair focal cartilage defects using cells with an established

chondrogenic phenotype. However, their clinical application is limited by restricted donor-cell availability, limited proliferative capacity, and progressive dedifferentiation during monolayer expansion. Dedifferentiated chondrocytes may exhibit reduced expression of cartilage-specific markers and increased fibrocartilage-associated characteristics, thereby compromising the quality and durability of regenerated tissue²³⁶. These limitations can be partially mitigated by minimizing cell passage number, using three-dimensional culture systems, applying appropriate mechanical stimulation, and combining chondrocytes with supportive biomaterials or MSCs. Therefore, primary chondrocytes remain biologically attractive for cartilage regeneration, but their successful use depends on maintaining phenotype stability throughout cell expansion, printing, and post-printing maturation.

4.1.2. Adult Stem Cells

Adult MSCs are widely used in cartilage tissue engineering because they can be isolated from multiple tissue sources, expanded in vitro, and induced toward chondrogenic differentiation under appropriate biochemical and mechanical conditions. Common sources include bone marrow-derived MSCs (BMSCs), adipose-derived MSCs (ADSCs), and synovium-derived MSCs. These cells are particularly useful when a large number of cells are required for bioprinting or when the availability of autologous chondrocytes is limited^{237,238}. However, MSC populations from different tissue sources may differ in proliferation capacity, responsiveness to chondrogenic cues, secretory activity, and long-term phenotypic stability. Therefore, no single MSC source should be considered universally optimal for all cartilage-repair applications.

BMSCs are frequently used because of their established chondrogenic potential and extensive use in musculoskeletal tissue engineering. For example, BMSCs encapsulated in printable gelatin methacryloyl-chitosan methacrylate hydrogels maintained cell viability above 80% and showed increased expression of SOX9, ACAN, and COL2A1, indicating a favorable chondrogenic microenvironment²³⁹. ADSCs provide another clinically accessible source because adipose tissue can be obtained in relatively large quantities. In hyaluronic-acid-based hydrogels, ADSCs showed increased expression of chondrogenic markers by day 5 and enhanced sulfated glycosaminoglycan production between days 7 and 14²⁴⁰. Synovium-derived MSCs may also be valuable for joint-related applications because they originate from the intra-articular environment; however, their

availability, donor variability, and comparative performance in bioprinted constructs require further systematic investigation.

Despite their advantages, MSC-based cartilage regeneration remains challenged by donor-dependent heterogeneity, variable differentiation efficiency, and the possibility of hypertrophic or osteogenic differentiation under inappropriate microenvironmental conditions. Maintaining a stable hyaline-cartilage phenotype therefore requires coordinated control of bioink composition, growth-factor signaling, oxygen tension, mechanical stimulation, and scaffold architecture. MSCs are most suitable for applications requiring scalable cell expansion and adaptable cell-material interactions, but their use should be accompanied by strategies that promote chondrogenesis while suppressing hypertrophic differentiation and phenotypic drift.

4.1.3. Pluripotent Stem Cell-Derived Chondrogenic Cells

Pluripotent stem cells, including embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), provide a potentially scalable source of chondrogenic cells because of their self-renewal capacity and broad differentiation potential. ESCs can be directed through staged differentiation protocols toward mesenchymal progenitors, chondroprogenitor cells, or chondrocyte-like cells^{241,242}. Similarly, iPSCs can be generated from somatic cells and differentiated into mesenchymal or chondrogenic lineages, creating opportunities for patient-specific modeling and personalized regenerative strategies.

Recent evidence suggests that iPSC-derived cell products may provide favorable cartilage-forming capacity. For example, chondrocytes differentiated from iPSC-derived MSCs exhibited a phenotype more similar to native hyaline cartilage than chondrocytes derived from conventional BMSCs in a minipig model²³⁹. These findings indicate that pluripotent stem-cell-derived chondrogenic cells may be valuable for generating standardized and scalable cell sources, particularly for disease modeling, drug screening, and future personalized cartilage repair.

However, the clinical translation of pluripotent stem-cell-derived cells remains limited by the complexity of differentiation protocols, incomplete maturation, heterogeneous cell populations, potential tumorigenicity, and substantial regulatory and ethical requirements. In particular, undifferentiated residual cells and insufficiently controlled lineage commitment may compromise long-term safety after implantation. Therefore, pluripotent stem-cell-derived chondrogenic cells

should currently be regarded as a promising but still predominantly preclinical cell source. Their application in 3D bioprinting will require rigorous cell purification, standardized differentiation protocols, long-term safety evaluation, and validation of stable cartilage-specific function in relevant in vivo models.

In summary, cell-source selection for cartilage bioprinting should be tailored to the intended regenerative objective. Primary chondrocytes are advantageous when direct formation of cartilage-specific extracellular matrix is prioritized, whereas adult MSCs offer greater accessibility and expansion capacity. Pluripotent stem-cell-derived chondrogenic cells provide a potential route toward scalable and standardized cell production but require further safety and regulatory validation. The final choice of seed cells should therefore be coordinated with the printing modality, bioink properties, scaffold design, and required duration of post-printing tissue maturation.

Table 5. Comparison of various characteristics of the different seed cells

Cell types	Advantages	Disadvantages	References
Chondrocytes	1. Direct production of cartilage-specific ECM 2. Established chondrogenic phenotype 3. Suitable for hyaline cartilage-like tissue formation	1. Limited donor-cell availability 2. Limited expansion capacity 3. Dedifferentiation and phenotypic instability during expansion	232-236,243
Mesenchymal stem cells (MSCs)	1. Relatively accessible from multiple tissue sources. 2. High expansion capacity. 3. Chondrogenic differentiation potential and adaptable cell-material interactions.	1. Donor- and source-dependent heterogeneity. 2. Variable chondrogenic efficiency. 3. Risk of hypertrophic or osteogenic differentiation and phenotypic instability.	237-240
Pluripotent stem cell-derived chondrogenic cells (ESCs/iPSCs)	1. High self-renewal and expansion capacity. 2. Potential for scalable and standardized cell production 3. Suitable for disease modeling and personalized applications	1. Complex differentiation and incomplete maturation. 2. Cellular heterogeneity and tumorigenic risk. 3. Substantial regulatory and ethical challenges.	241,242

4.2. Preservation of cell viability and phenotype during bioprinting

Preserving cell viability and phenotype is essential for successful cartilage bioprinting. However, immediate post-printing survival alone does not demonstrate that a construct can support durable cartilage regeneration. Bioprinted cells must also retain proliferative capacity, chondrogenic differentiation potential, extracellular-matrix synthesis, and resistance to hypertrophic or fibrocartilaginous phenotypic drift.

Different printing modalities expose cells to distinct forms of stress. In extrusion-based bioprinting, mechanical stress during nozzle passage may damage cell membranes and impair subsequent proliferation and differentiation^{9,19}. Droplet-based methods reduce continuous nozzle shear but require careful control of cell concentration, droplet formation, and ejection force to avoid impaired cell function⁴¹. In photocuring-based systems, excessive light exposure, photoinitiator concentration, and free-radical generation may reduce viability or limit subsequent cell migration and matrix remodeling^{51,52}. Thermoplastic processing is generally unsuitable for direct cell encapsulation because of the high operating temperature; therefore, thermoplastic frameworks should be combined with cell-laden hydrogels under mild conditions.

The post-printing microenvironment is equally important for maintaining cellular function. Bioinks should support cell-matrix interactions, nutrient exchange, and extracellular-matrix remodeling after deposition. For example, compared with gelatin alone, PEG-PLA/gelatin hydrogels enhanced porcine chondrocyte adhesion and proliferation and increased glycosaminoglycan as well as type II collagen production²²³. Nevertheless, a material that preserves short-term viability may still fail to maintain a stable hyaline-cartilage phenotype if it restricts cell spreading, matrix deposition, or long-term remodeling.

Cytocompatibility should therefore be assessed beyond live/dead staining immediately after printing. Relevant outcomes include cell survival, proliferation, apoptosis, cartilage-related matrix formation, expression of chondrogenic and hypertrophy-associated markers, and long-term phenotype stability. A successful cell-preservation strategy is not one that only maximizes initial viability, but one that supports sustained type II collagen-rich matrix formation and functional cartilage maturation.

4.3. Co-culture Strategies and Compartment-Specific Vascularization

Articular cartilage is intrinsically avascular and receives oxygen and nutrients mainly through diffusion from synovial fluid and the subchondral region. As the effective diffusion distance of oxygen is generally limited to approximately 200 μm , nutrient transport becomes challenging in large or densely cell-laden constructs²⁴⁴. However, vascularization should be regulated according to tissue compartment. The hyaline cartilage layer should maintain an avascular and chondrogenic microenvironment, whereas the subchondral bone region requires vascularization to support osteogenesis and integration with host bone.

Co-culture strategies can improve the biological organization of engineered cartilage. Chondrocytes provide cartilage-specific extracellular-matrix signals, whereas MSCs offer proliferative capacity and chondrogenic potential. Co-culturing hMSCs and chondrocytes at a 1:1 ratio enhanced chondrogenesis without increasing fibrosis in one study²⁴⁵. Nevertheless, this ratio should not be considered universally optimal, because the appropriate cell proportion depends on the cell source, bioink composition, scaffold properties, and intended application.

For osteochondral repair, different compartments should receive distinct cells, materials, and inductive factors. The cartilage layer should promote chondrogenesis and maintain avascularity, whereas the bone layer may incorporate osteogenic and pro-angiogenic cues. For example, hMSCs printed in a fibrin-based bioink on PCL scaffolds promoted vascularization and bone healing in a rat femoral-defect model under chondrogenic and osteogenic induction²⁴⁶. This finding supports vascularization of the bone compartment, but not the cartilage layer. Chondrocytes and MSCs may further regulate tissue formation through paracrine factors, extracellular vesicles, and matrix-mediated interactions²⁴⁷.

In summary, co-culture should be used to create compartment-specific biological functions rather than to simply combine multiple cell types. Future studies should optimize cell ratios and spatial distribution while evaluating cartilage matrix formation, control of hypertrophy, subchondral bone integration, and long-term repair outcomes.

4.4. Epigenetic and Gene-Editing Approaches for Cell-Fate Regulation

Epigenetic regulation influences MSC chondrogenesis by altering gene expression without changing the DNA sequence^{248,249}. Its major mechanisms include DNA methylation, histone modification, and non-coding RNA regulation²⁵⁰⁻²⁵². These mechanisms interact dynamically

during chondrogenesis; for example, histone modifications may influence DNA-methylation patterns, whereas non-coding RNAs can regulate chromatin-modifying proteins and transcriptional activity²⁵³.

MicroRNAs, long non-coding RNAs, and circular RNAs are important regulators of chondrocyte phenotype and MSC differentiation^{254,255}. Exosomes derived from BMSCs, ADSCs, and hiPSCs may deliver regulatory miRNAs to articular chondrocytes, thereby attenuating senescence-associated changes, enhancing glycosaminoglycan and type II collagen synthesis, and suppressing fibrocartilage-associated gene expression²⁵⁶. Although findings from intervertebral-disc research provide mechanistic insights, their applicability to articular cartilage regeneration requires direct validation in cartilage-specific models. For example, MSC-derived exosomes enriched in miR-221-3p attenuated cell senescence through DDIT4/NF- κ B regulation in an intervertebral-disc model²⁵⁷.

Gene-editing technologies may provide a more direct strategy for regulating cell fate. CRISPR-Cas9-mediated disruption of RUNX2 reduced the osteogenic tendency of hMSCs and promoted chondrogenic differentiation in two-dimensional and three-dimensional culture systems²⁵⁸. However, miRNA-based therapy, extracellular-vesicle delivery, and gene-editing approaches remain predominantly preclinical rather than established clinical strategies. Their translation requires rigorous assessment of delivery efficiency, off-target effects, genomic stability, tumorigenic risk, long-term safety, regulatory requirements, and ethical considerations.

The value of epigenetic or gene-editing interventions should not be judged solely by changes in gene expression. Future studies should evaluate the stability of the hyaline-cartilage phenotype, extracellular-matrix quality, suppression of hypertrophic differentiation, mechanical function, repair in relevant animal models, and long-term safety after implantation. Thus, these approaches may provide useful tools for precision cell regulation in bioprinted cartilage constructs, but their clinical applicability requires substantial further validation.

Overall, seed-cell selection should be integrated with the printing modality, bioink properties, scaffold architecture, inductive signals, and intended clinical application. Primary chondrocytes favor cartilage-specific matrix formation but are limited by cell availability and dedifferentiation, whereas MSCs offer greater accessibility but require strict control of phenotype stability. Cell viability after printing alone is insufficient; long-term chondrogenic function, matrix deposition,

and suppression of hypertrophy should also be evaluated. For osteochondral repair, the cartilage and subchondral bone compartments require distinct cellular and vascularization strategies. Therefore, cell-based bioprinting should be assessed using integrated outcomes that include phenotype stability, matrix quality, mechanical function, host integration, and long-term safety.

5. Structural and Functional Design of Bioprinted Cartilage Constructs

The performance of bioprinted cartilage constructs is determined not only by printing technology, material composition, or cell source, but also by the structural and functional design of the final construct. After deposition, scaffold architecture regulates mass transport, mechanical loading, cellular spatial organization, extracellular-matrix remodeling, and the delivery of bioactive signals. This section therefore focuses on the key design variables that govern construct-level performance, including bioink rheology, pore architecture, mechanical gradients, fiber alignment, and spatiotemporally controlled delivery systems. Rather than optimizing these variables independently, functional cartilage regeneration requires their coordinated adjustment according to the biological and mechanical requirements of the target tissue (as shown in Table. 6 and Figure 13).

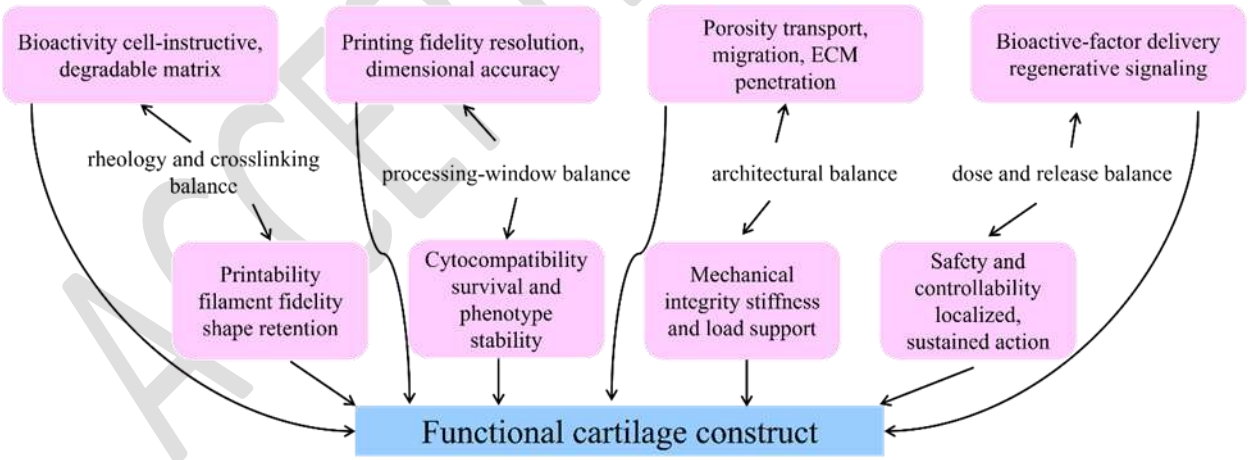


Figure 13. Conceptual framework illustrating competing design objectives in cartilage bioprinting.

Table 6. Key design trade-offs governing 3D bioprinting performance for cartilage tissue

Competing objectives	Variables	Benefits	Cost	Key parameters	Design strategy
Bioactivity versus printability	Polymer concentration, natural-matrix content, yield stress, viscosity, shear-thinning behavior, crosslinking kinetics	A cell-instructive and degradable matrix supports cell spreading, phenotype maintenance, and ECM deposition	Highly bioactive, low-solid-content bioinks often exhibit poor filament fidelity, pore collapse, and limited post-printing stability	Storage/loss modulus, yield stress, filament diameter, spreading ratio, pore fidelity, shape retention	Combine bioactive matrix components with shear-thinning networks, rapid secondary crosslinking, or reinforcing phases to maintain shape without excessively restricting matrix remodeling
Printing fidelity versus cytocompatibility	Nozzle diameter, extrusion pressure, printing speed, residence time, photoinitiator concentration, light dose	Small nozzles, higher driving forces, and rapid curing improve resolution and geometric accuracy	Excessive shear stress, pressure, thermal exposure, or photochemical dose can impair cell survival and phenotype stability	Feature resolution, dimensional error, cell viability, apoptosis, phenotype markers, long-term ECM production	Define a cell-tolerant processing window rather than pursuing maximum resolution; optimize geometry and curing conditions simultaneously
Porosity versus mechanical integrity	Pore size, total porosity, strand spacing, filament diameter, infill pattern, interlayer bonding	Higher porosity improves nutrient diffusion, cell migration, and matrix penetration	Increased porosity and larger pores reduce load-bearing capacity, stiffness, and resistance to deformation	Porosity, pore interconnectivity, compressive modulus, fatigue resistance, nutrient transport	Use zonal or gradient pore architectures: a more open internal region for transport and denser peripheral/superficial regions for mechanical support

Mechanical stability versus matrix remodeling	Crosslink density, polymer network type, degradation rate, reinforcing fibers, nanofillers	A stable construct better preserves geometry and withstands early mechanical loading	Excessive stiffness or slow degradation may constrain cell migration, neotissue deposition, and integration with host cartilage	Compressive modulus, stress relaxation, degradation profile, cell migration, ECM distribution, integration strength	Match degradation with matrix deposition; use viscoelastic or dynamic networks and region-specific reinforcement instead of uniformly increasing stiffness
Bioactive-factor loading versus safety and controllability	Growth-factor dose, release kinetics, carrier type, spatial distribution, gene-delivery approach	Local signaling can enhance chondrogenesis and repair maturation	High or poorly controlled doses may cause burst release, ectopic effects, hypertrophy, off-target responses, or regulatory barriers	Release profile, local retention, hypertrophy markers, repair quality, long-term safety	Use low-dose, sustained, and compartment-specific delivery; evaluate functional repair and safety rather than gene expression alone

5.1. The balance between "printability" and "biological activity"

Bioink rheology is a major determinant of print fidelity and post-printing construct stability. Viscosity, shear-thinning behavior, yield stress, viscoelasticity, and thixotropic recovery jointly regulate filament continuity, filament diameter, pore preservation, interlayer stability, and geometric accuracy²⁵⁹⁻²⁶². For cartilage tissue engineering, the objective is not to maximize viscosity or stiffness, but to establish a rheological window that permits accurate deposition while maintaining an architecture suitable for subsequent extracellular-matrix remodeling and tissue maturation.

During printing, shear-thinning behavior enables material flow under applied stress, whereas rapid structural recovery after deposition helps preserve filament geometry. Yield stress is particularly important for preventing deposited filaments from spreading, fusing, or collapsing under the weight of subsequent layers. Similarly, storage and loss moduli influence the balance between elastic support and flow behavior²⁶³⁻²⁶⁶. Bioinks with insufficient yield stress or slow rheological recovery may produce irregular filaments, closed pores, and unstable multilayer structures, thereby limiting nutrient transport and reducing the architectural complexity that can be achieved.

The structural consequences of inappropriate rheology should be considered in relation to the intended application. Low-concentration gelatin- or alginate-based bioinks are readily deposited but may spread after printing, leading to poor pore definition and reduced mechanical stability²⁶⁷. In contrast, highly viscous formulations may improve shape retention but can narrow the usable processing window and impede uniform deposition²⁶⁸. Insufficient shear-thinning behavior may result in discontinuous extrusion, nozzle clogging, and nonuniform filaments²⁶⁹, whereas inadequate yield stress can cause pore occlusion and impaired mass transport^{270,271}. Poor rheological recovery may further destabilize multilayer constructs during prolonged printing²⁷².

Accordingly, rheological optimization should be guided by construct-level requirements. High-resolution cartilage models may prioritize filament precision and controlled pore geometry, whereas implantable constructs must additionally maintain structural integrity during culture, degradation, matrix deposition, and mechanical maturation. The most effective bioink is therefore not the stiffest or most viscous formulation, but one that balances deposition fidelity, pore interconnectivity, multilayer stability, and long-term functional maturation²⁷³.

5.2. Balancing Pore Architecture and Filament Diameter for Mass Transport and Mechanical Integrity

Pore architecture and filament diameter are key structural variables that determine pore interconnectivity, mass transport, cell distribution, and mechanical stability in bioprinted cartilage constructs^{274,275}. Larger pores and higher porosity can facilitate oxygen and nutrient diffusion, metabolic-waste removal, and cell migration. However, excessive porosity or excessively thin filaments may reduce the effective load-bearing volume of the scaffold, thereby compromising compressive strength, elastic stability, and fatigue resistance. Conversely, thicker filaments and smaller pores may improve initial mechanical support but restrict mass transport and limit the

space available for tissue ingrowth. Therefore, pore size, porosity, and filament diameter should be optimized together rather than treated as independent parameters.

The optimal pore architecture is material- and application-dependent. Native cartilage exhibits zonal differences in structure and mineralization, providing a useful reference for the design of depth-dependent scaffold architectures²⁷⁶. For example, porous chitosan/chondroitin sulfate/silk fibroin scaffolds with a porosity of $77 \pm 4.3\%$ and pore sizes of 55–261 μm were reported to mimic aspects of the cartilage microenvironment²⁷⁷. In PCL scaffolds with average pore sizes of 215, 320, and 512 μm , the 215 μm group promoted MSC proliferation and extracellular-matrix formation in vitro^{278,279}. However, these values should be interpreted as material- and model-specific observations rather than universal design targets for cartilage regeneration.

Gradient pore design may provide a more effective solution than homogeneous architecture. A functionally graded porous scaffold increased surface porosity from 30% to 50%, improving osseointegration while maintaining compressive and flexural strength comparable to those of uniformly porous scaffolds²⁸⁰. Such results indicate that structural heterogeneity can help balance mass transport with mechanical durability, particularly in osteochondral constructs with different functional requirements across cartilage and subchondral bone regions.

In summary, pore architecture should be designed to maintain interconnected transport pathways while providing sufficient mechanical support during tissue maturation. The most suitable scaffold is not defined by a single pore size or porosity value, but by a coordinated balance among pore geometry, filament diameter, material properties, loading conditions, and the biological requirements of the target tissue.

5.3. Gradient Design of Mechanical and Compositional Properties

Native articular cartilage exhibits depth-dependent variations in extracellular-matrix composition, collagen organization, cell distribution, and mechanical behavior. Therefore, the objective of biomimetic scaffold design is not simply to maximize stiffness, but to reproduce regional mechanical function while supporting cell-mediated matrix remodeling and integration with surrounding tissue. In osteochondral repair, this requirement is particularly important because the cartilage, calcified-cartilage, and subchondral-bone regions have distinct biological and mechanical functions.

Gradient constructs can be generated by regulating material composition, pore architecture, mineral content, and spatial distribution of bioactive cues. For example, dual-channel extrusion-based bioprinting has been used to create continuous hydroxyapatite gradients that mimic the transition between non-calcified and calcified cartilage. Compared with stepwise gradients, continuous-gradient constructs showed improved compressive strength and supported MSC adhesion and cartilage-related extracellular-matrix deposition²⁸¹. Similarly, a multilayer chitosan-based hydrogel scaffold containing kartogenin was developed to establish an osteochondral-like construct with spatially distinct biological functions²⁸².

Mechanical reinforcement should be balanced with biological performance. A composite porous scaffold incorporating a poly(glycerol sebacate) microstructure and a type I/II collagen-hyaluronan network achieved a compressive modulus of up to 167.0 kPa, together with satisfactory fatigue resistance and controlled degradation²⁸³. However, mechanical values should be interpreted cautiously because reported cartilage properties vary according to anatomical location, depth, loading mode, and testing conditions. A higher modulus alone does not demonstrate successful cartilage regeneration if it limits cell migration, extracellular-matrix remodeling, or integration with host tissue. In another example, directionally frozen alginate/alginate-sulfated scaffolds integrated with 3D-printed PCL frameworks supported chondrogenic differentiation under dynamic culture while providing cartilage-like mechanical properties²⁸⁴.

Accordingly, gradient design should coordinate material stiffness, degradation, porosity, and cellular microenvironment across different regions of the construct. The most effective osteochondral scaffold is not one with the highest overall mechanical strength, but one that provides continuous interfacial transition, region-specific function, and sufficient stability during tissue maturation.

5.4. Fiber Alignment and Surface Microarchitecture

Surface microarchitecture, particularly fiber alignment and spatial organization, can regulate cell adhesion, migration, polarity, and extracellular-matrix deposition²⁸⁵. Native articular cartilage presents depth-dependent collagen organization: fibrils are arranged parallel to the articular surface in the superficial zone, more randomly in the middle zone, and predominantly perpendicular to the surface in the deep zone. This hierarchical architecture contributes to the anisotropic mechanical behavior of cartilage and provides an important design principle for biomimetic constructs.

Aligned fibrous structures can guide cellular orientation and promote organized matrix formation. For example, inkjet bioprinting combined with dynamic culture has been used to generate cartilage constructs containing aligned collagen networks, with glycosaminoglycan accumulation exceeding 5% (w/w)³⁹. Electrospun fibrous layers can also provide tunable anisotropic microstructures for tissue engineering²⁸⁶. Bilayer scaffolds composed of decellularized extracellular matrix and silk fibroin have been designed by regulating layer composition and fiber orientation to mimic osteochondral organization²⁸⁷. In addition, aligned poly(L-lactic acid)/barium titanate nanofibrous membranes provided more favorable guidance for cell growth than non-aligned fibrous systems²⁸⁸.

However, fiber alignment alone cannot reproduce the full structure and function of native cartilage. Its biological effect depends on fiber diameter, material composition, pore interconnectivity, mechanical properties, and integration with surrounding matrix. Although aligned fibrous scaffolds may improve mechanical compliance and facilitate bioactive-factor retention²⁸⁹. But, excessive structural density may restrict cell infiltration and nutrient transport. Therefore, fiber alignment should be coordinated with pore architecture and mechanical gradients to support both anisotropic matrix organization and long-term tissue maturation.

5.5. Spatiotemporally Controlled Delivery of Bioactive Factors

The delivery of bioactive factors is an important strategy for regulating cell behavior and promoting cartilage regeneration. However, the objective is not to maximize factor loading, but to achieve spatially and temporally controlled signaling that matches the biological requirements of the target tissue. Conventional delivery may result in rapid burst release, short retention time, and uncontrolled local concentrations. For example, high-dose recombinant human bone morphogenetic protein-2 may induce ectopic bone formation and inflammatory responses²⁹⁰. Therefore, delivery systems should provide sustained release while minimizing adverse effects.

Nanocarriers, hydrogel networks, and compartmentalized scaffolds can improve retention and regulate release kinetics. For example, PLGA nanoparticles loaded with VEGF and bFGF enabled sustained local release in a skin-defect model²⁹¹. Although this study demonstrates the general value of nanoparticle-mediated delivery, its results should not be considered direct evidence for cartilage regeneration. In contrast, an in situ monoolein-hyaluronic acid liquid-crystalline gel provided sustained intra-articular release of kartogenin for more than four weeks and promoted

cartilage regeneration while protecting subchondral bone²⁹². Similarly, a TGF- β 1-binding peptide-amphiphile and hyaluronic-acid microgel scaffold enhanced localized cartilage repair in a sheep model compared with growth-factor administration alone²⁹³.

For osteochondral repair, bioactive signals should be distributed according to tissue compartment. The cartilage layer may require factors that support chondrogenic differentiation and extracellular-matrix formation, whereas the subchondral bone region may require osteogenic or carefully controlled pro-angiogenic cues. For example, CSK@G gradient scaffolds incorporating kartogenin-loaded chitosan hydrogels promoted directed stem-cell migration and chondrogenic differentiation through spatially controlled delivery²⁸². In addition, an interpenetrating GelMA/alginate/nanoclay network reduced degradation and prolonged retention of encapsulated therapeutic agents²⁹⁴.

Platelet-rich plasma is another potential source of multiple bioactive factors. It may promote cartilage-related matrix synthesis through TGF- β /Smad signaling²⁹⁵. But intra-articular PRP injection is limited by rapid factor release, short retention, and donor-dependent variability²⁹⁶. Incorporating PRP into silk-fibroin hydrogels can improve local retention and provide a printable scaffold that supports chondrocyte proliferation and cartilage-specific matrix production²⁹⁷.

In summary, effective delivery systems should control factor dose, release rate, and spatial distribution rather than relying on uniform or high-dose delivery. Future studies should evaluate release profiles, retained bioactivity, cartilage-specific matrix formation, compartment-specific effects, long-term safety, and functional repair in relevant animal models.

6. Future Directions and Translational Priorities

Future advances in cartilage bioprinting should not be evaluated solely by printing speed, resolution, or material novelty. Meaningful progress requires the coordinated improvement of manufacturing efficiency, cell compatibility, structural fidelity, mechanical function, long-term tissue maturation, and clinical reproducibility. The following directions represent key opportunities, but each must be validated using cartilage-specific and translationally relevant outcomes.

6.1. High-Speed Bioprinting for Living Constructs

Printing time directly affects the duration of cell exposure to non-physiological conditions and is therefore relevant to cell survival and function²⁹⁸. Volumetric bioprinting has attracted attention because it can fabricate complex structures within seconds. For example, volumetric photopolymerization enables rapid formation of three-dimensional constructs by selectively curing regions where the accumulated light dose exceeds the polymerization threshold²⁹⁹. A volumetric bioprinting study reported cell viability above 85% after 7 days and progressive extracellular-matrix deposition, with the compressive modulus of the construct reaching approximately 265 kPa⁵⁴.

However, faster fabrication does not necessarily ensure better cartilage regeneration. Volumetric systems often depend on homogeneous photocurable resins, which may limit the incorporation of multiple materials, distinct cell populations, and spatial gradients. Future high-speed platforms should therefore combine rapid fabrication with cytocompatible crosslinking, multi-material capability, and reliable control of zonal cartilage or osteochondral architecture.

6.2. High-Resolution and Multiscale Bioprinting

High-resolution bioprinting is important for reproducing the microscale features of native cartilage, including pore geometry, cell distribution, and extracellular-matrix organization. Light-based technologies can achieve high geometric fidelity; for example, stereolithography has been used to fabricate tissue constructs with feature sizes of approximately 30 μm ²⁹⁹. Two-photon polymerization can further achieve submicrometer-scale resolution and has been applied to fabricate scaffolds with controlled microarchitecture^{300,301}.

Nevertheless, high resolution alone is not equivalent to functional tissue reconstruction. Increased resolution may be accompanied by longer manufacturing time, limited construct size, restricted material selection, and potential phototoxicity. Conventional stereolithographic approaches also commonly process a single photocurable material at a time, limiting the fabrication of heterogeneous cartilage constructs³⁰². Future studies should therefore determine whether improved resolution produces meaningful benefits in cartilage-specific matrix organization, mechanical function, and integration with host tissue.

6.3. Multi-Material and Multicellular Bioprinting

Multi-material and multicellular bioprinting provides a practical strategy for reproducing the structural and compositional heterogeneity of cartilage and osteochondral tissues. Spatially organized materials can be used to generate gradients in stiffness, mineral content, degradation, and bioactive signaling. For example, multi-material printing has been used to fabricate osteochondral interfaces with controlled compositional gradients, promoting chondrogenic and osteogenic differentiation of hMSCs²²⁵. Alternating bioinks with different mechanical properties can also generate heterogeneous tissue-like microenvironments³⁰³.

However, increasing material and cellular complexity also increases the risk of interfacial failure, incompatible crosslinking conditions, uneven degradation, and poor manufacturing reproducibility. Emerging strategies, including embedded bioprinting and wavelength-orthogonal photochemistry, may improve the spatial integration of multiple materials^{304,305}. Their translational value will depend on whether they can generate stable interfaces, maintain cell function, and be produced reproducibly under clinically acceptable conditions.

6.4. Dynamically Responsive Smart Bioinks

Smart bioinks can dynamically regulate construct properties in response to environmental stimuli and may better reproduce the changing microenvironment of developing or repairing cartilage. DNA-programmable hydrogels have been used to regulate cell behavior in bioprinted cartilage organoids³⁰⁶, while dynamic covalent bonds can enable reversible control of gelation and mechanical properties³⁰⁷. Shape-morphing constructs fabricated by 4D bioprinting and hyaluronan-alginate bioinks have also maintained high cell viability and generated cartilage-like extracellular matrix during in vitro culture¹¹. In addition, photothermal nanomaterial-based systems may allow externally controlled drug release³⁰⁸.

Despite this potential, smart bioinks remain largely preclinical. Their clinical translation requires demonstration of predictable responsiveness, long-term material stability, safe stimulus application, controlled degradation, manufacturability, and regulatory compatibility. Dynamic behavior should provide a measurable advantage in cartilage regeneration rather than serve only as a material novelty.

In summary, future cartilage bioprinting should prioritize integrated and clinically relevant design. High-speed, high-resolution, multi-material, and smart-bioink strategies should be assessed using

standardized outcomes that include cell phenotype stability, extracellular-matrix quality, mechanical durability, host integration, long-term safety, reproducibility, and repair performance in relevant large-animal models.

7. Summary

Three-dimensional bioprinting offers a promising strategy for cartilage regeneration by integrating cells, biomaterials, bioactive cues, and scaffold architecture. This review emphasizes that these factors should not be optimized independently, but coordinated according to the structural and biological requirements of the target tissue.

Successful cartilage bioprinting requires a balance between print fidelity and biological function. Bioink viscosity, shear-thinning behavior, yield stress, viscoelasticity, and structural recovery should support both accurate fabrication and subsequent tissue maturation. Likewise, pore architecture, mechanical gradients, fiber alignment, and controlled factor delivery must jointly regulate mass transport, matrix organization, and regional function.

Major barriers to translation remain, including phenotypic instability, hypertrophic differentiation, insufficient mechanical durability, limited host integration, and poor manufacturing reproducibility. Future studies should evaluate matrix quality, mechanical function, long-term safety, and repair efficacy in clinically relevant animal models.

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Conflict of interest

The authors declare that they have no competing interests.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

The resources that support this review work are available upon request from the corresponding authors.

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