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# 3D Biofabrication of Microporous Hydrogels for Tissue Engineering

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**Microporous hydrogels have been utilized in an unprecedented manner in the last few decades, combining materials science, biology, and medicine. Their microporous structure makes them suitable for wide applications, especially as cell carriers in tissue engineering and regenerative medicine. Microporous hydrogel scaffolds provide spatial and platform support for cell growth and proliferation, which can promote cell growth, migration, and differentiation, influencing tissue repair and regeneration. This review gives an overview of recent developments in the fabrication techniques and applications of microporous hydrogels. The fabrication of microporous hydrogels can be classified into two distinct categories: fabrication of non-injectable microporous hydrogels including freeze-drying microporous method, two-phase sacrificial strategy, 3D biofabrication technology, etc., and fabrication of injectable microporous hydrogels mainly including microgel assembly. Then, the biomedical applications of microporous hydrogels in cell carriers for tissue engineering, including but not limited to bone regeneration, nerve regeneration, vascular regeneration, and muscle regeneration are emphasized. Additionally, the ongoing and foreseeable applications and current limitations of microporous hydrogels in biomedical engineering are illustrated. Through stimulating innovative ideas, the present review paves new avenues for expanding the application of microporous hydrogels in tissue engineering.**

## 1. Introduction

The hydrogel, functioning as a water-absorbing polymer network, exhibits both solid and liquid properties due to its crosslinked polymer structure, allowing for the infiltration of water and creating a 3D microenvironment akin to that found in the human body.[1] Hence, hydrogels can function as vehicles for cell transplantation. The regenerative capacity of adult cells is inherently limited, leading to compromised function following repair.[2] Currently, drug therapy and surgical therapy are commonly employed for in vivo and in vitro injury repair; however, they are unable to restore necrotic tissue.[3] Tissue engineering is a multidisciplinary field that combines biology, engineering, and medicine to create functional tissue with scaffolds, cells, and biologically active molecules that can replace or support damaged or diseased tissues, thereby restoring normal function and promoting healing.[4] Cell-laden scaffolds are widely investigated in tissue engineering because they can provide homogenous cell distribution after long culture periods, and deposit multiple types of cells into a designed region.[5] However, although traditional non-microporous hydrogels have been widely used as cell-loaded scaffolds in tissue engineering, their nanoscale molecular network impedes cell function. These hydrogels suffer from poor permeability, limited cell survival rates, and ineffective tissue repair due to the restricted penetration of oxygen and nutrients, which is typically limited to a depth of ≈200. [6] This limitation restricts intercellular communication within and beyond the scaffold, hindering the natural regeneration of tissue structure and physiological function during the healing process. To overcome these challenges, there is an urgent need for the development of more effective cell carriers—specifically, microporous hydrogels—that can enhance cellular vitality, promote cell proliferation, and support the restoration of physiological tissue function.[7]

Microporous hydrogels can effectively serve as a favorable platform for cell vitality and restoration of physiological tissue function as an efficient cell carrier. Over the past two decades, the exploration of microporous hydrogels commenced and there has been a gradual accumulation of evidence demonstrating the advantages of porous hydrogels in tissue engineering, including

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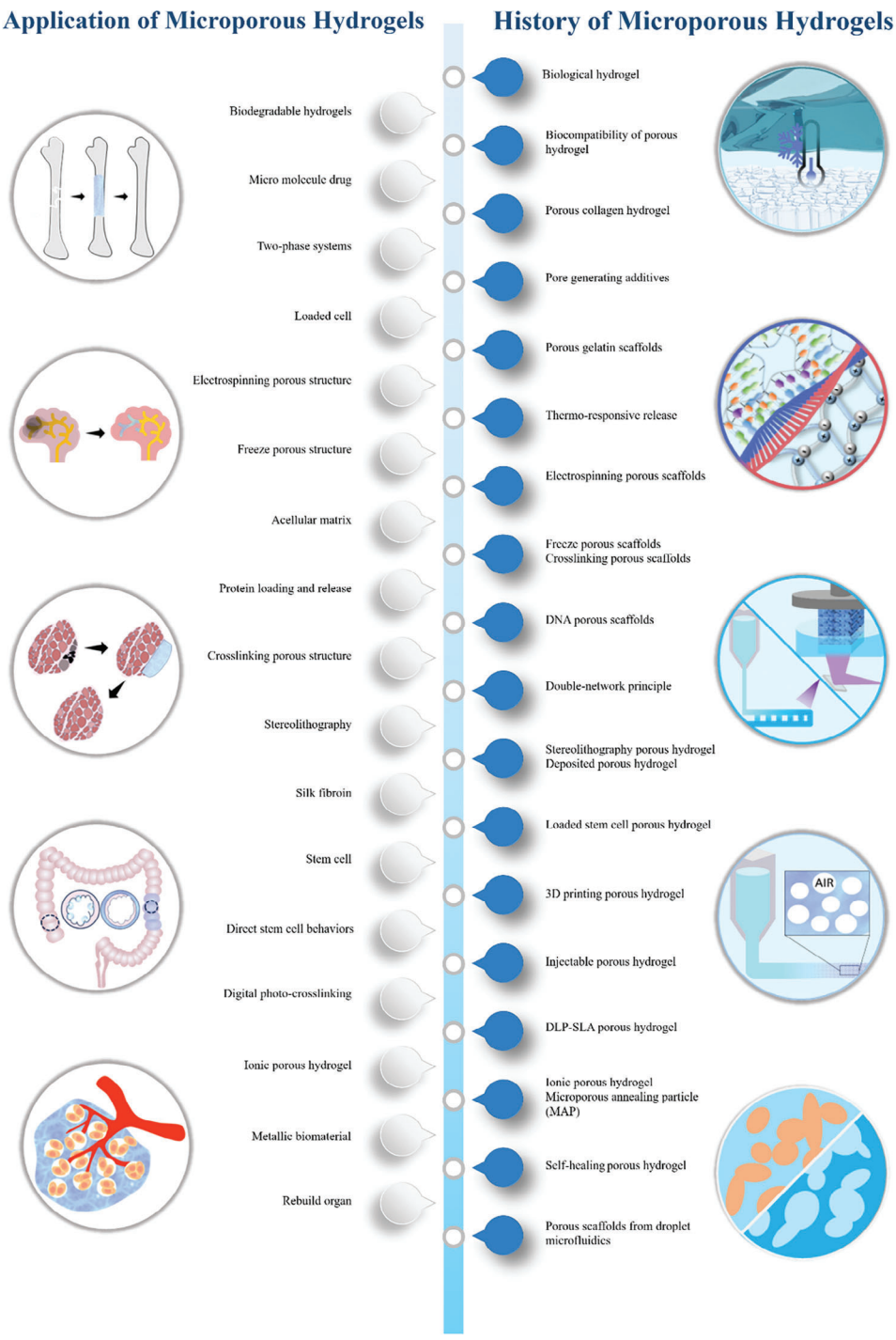



**Figure 1.** Microporous hydrogel evolution. (Application of microporous hydrogels[1a,17]; History of microporous hydrogels[9b,17d,e,h,i,l,m,18]).

promoting cell growth, migration, and differentiation.[8] Modulating porosity can enhance the mechanical properties required for specific cell functions. Precise control of porosity in hydrogels enhances permeability, strength, and support for cells.[9] The distinguishing characteristic of a porous hydrogel resides in the precise distribution of pore sizes and the organized or disorganized nature of the pore structure, encompassing closed pores, and open pores.[9d,10] Additionally, it serves as an effective platform for tissue engineering, facilitates the supply of essential nutrients to cells residing deep within the hydrogel matrix, and enhances the excretion of metabolic waste[11] (**Figure 1**). With the advancement of 3D network structures in hydrogels, there is a growing recognition of the excellent cell-level biocompatibility exhibited by microporous hydrogels, characterized by their porosity


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and interconnected spatial features.[8e,9a,d] These unique characteristics render microporous hydrogels a versatile material that plays an indispensable role in the field of tissue engineering and regenerative medicine research, offering superior tissue restoration compared to conventional methods. Therefore, this review focuses on high porosity microporous hydrogels (pore size exceeding 10 micrometers) to facilitate tissue engineering and regenerative medicine.[6,12] The versatility of microporous hydrogels enables their application in tissue and organ regeneration encompassing wound healing[13], vessel restoration,[14] bone tissue reconstruction,[15] tumor immunization,[16] among others.

In recent years, various methods have been employed to obtain microporous hydrogels with enhanced biocompatibility. These include utilizing two aqueous phases to prepare extremely biocompatible microporous hydrogels and acquiring such structures through freeze-drying or low-temperature freezing.[19] This approach applies to most hydrogel carriers and exhibits a certain level of universality. Furthermore, 3D biofabrication techniques like electrospinning, 3D bioprinting, and microfluidics enable the production of microporous hydrogel scaffolds encompassing micropores to macropores.[20] Additionally, the microporous hydrogel pattern utilizing microgels as fundamental units is distinguished by exceptional fluidity and injectability[21].

In summary, this review provides a comprehensive overview of the preparation of microporous hydrogels and their biomedical applications in biomedicine for cell therapy for tissue engineering. We comprehensively elaborate and present two fabrication methods: fabrication of non-injectable microporous hydrogels and fabrication of injectable microporous hydrogels. The discussion of non-injectable microporous hydrogels primarily focuses on freeze-drying microporous method, two-phase sacrificial strategy, 3D biofabrication technology, while the discussion of injected hydrogels mainly pertains to microgel assembly. In addition, we also provide a summary of microporous hydrogels fabricated through the use of click chemistry, MXene, DNA, and polypeptide. Regarding biomedical applications, our primary focus lies in using microporous hydrogels for various biomedical applications, including but not limited to bone, nerve, and muscle regeneration, vascularization, 3D cell culture, dental care, and intestinal tract utilization. Lastly, by bringing the existing challenges under the spotlight, current challenges and prospects in related research fields are addressed in this review. We believe this review will accelerate the development of advanced microporous hydrogels and inspire future biomedical research efforts.

## 2. Fabrication of Cell-Loaded Microporous Hydrogels

A variety of fabrication methods for microporous hydrogels have been proposed for the production of microporous hydrogels, including freeze-drying microporous method, two-phase sacrificial strategy, and 3D biofabrication technology. Initial investigations have concentrated on optimizing freeze-drying and mineralization levels, with the potential for further enhancement.[22] The advancement of photochemistry and temperature-sensitive materials has facilitated the development of microporous hydrogels through the sacrificial two-phase method, which utilizes photo-responsive and thermo-responsive materials as its foundation.[8e,23] In addition, extensive research has been conducted on microporous hydrogels obtained through 3D manufacturing technology. By manipulating the printer's parameters, precise manipulation of the hydrogel's structure and design can be achieved.[17d,24] Microporous hydrogels with excellent injectability are essential for tissue regeneration, as they can be minimally implanted to minimize tissue damage and precisely deliver cells, growth factors, and other bioactive molecules to specific sites in the body for localized targeted therapy.[18j,25] Although the aforementioned three methods can produce microporous hydrogels with injectable properties under specific conditions, it is important to note that utilizing microgels as fundamental units for constructing microporous hydrogel structures offers broad fluidity and injectability. In summary, the fabrication of microporous hydrogels in this section is classified into two categories according to their injectability: fabrication of non-injectable microporous hydrogels including freeze-drying microporous method, two-phase sacrificial strategy, 3D biofabrication technology, and fabrication of injectable microporous hydrogels via microgel assembly.

### 2.1. Fabrication of Non-Injectable Microporous Hydrogels

#### *2.1.1. Freeze-Drying Microporous Method*

The freeze-drying method is a widely employed technique for fabricating microporous structures.[17e,26] Throughout the past century until the present, it has remained a prevalent approach for generating microporous hydrogels. The preparation of microporous hydrogels through freeze-drying is based on the principle of ice crystal sublimation. In a high vacuum environment, the water in the frozen hydrogel directly transitions from solid ice to vapor without melting into liquid, leading to the formation of tiny pores as the hydrogel matrix transforms into ice crystals during the sublimation process.[27] This straightforward and effective freeze-drying method can be applied to most hydrogels, creating widely microporous structures. Specifically, the hydrogel modules are obtained and subjected to freeze-drying to form microporous hydrogels. This technique can be applied to fabricate bulk or microspherical microporous hydrogels. However, it is critical to note that the network structure may undergo damage during freeze-drying due to factors such as humidity. To address this issue, gel cross-linking can be combined with this technology to stabilize the resulting microporous structure to a certain extent. For instance, microdroplets formed from GelMA (gelatin methacryloyl) solution were deposited onto a freeze-dried platform using microfluidic technology. Subsequently, these freeze-dried microspheres were transformed into stable microporous scaffolds through ultraviolet light-induced solidification, thereby forming stable microporous hydrogel microspheres [28] (**Figure 2A**). Furthermore, adjusting the freeze-drying temperature allows for precise control of pore size and size within a specific range, thereby facilitating the loading of cells with varying sizes.[9a]

Manipulating and controlling the formation of ice crystals can result in microporous structures with specific morphology and size. The manipulation of ice crystal formation during freeze-drying enables the development of distinct microporous

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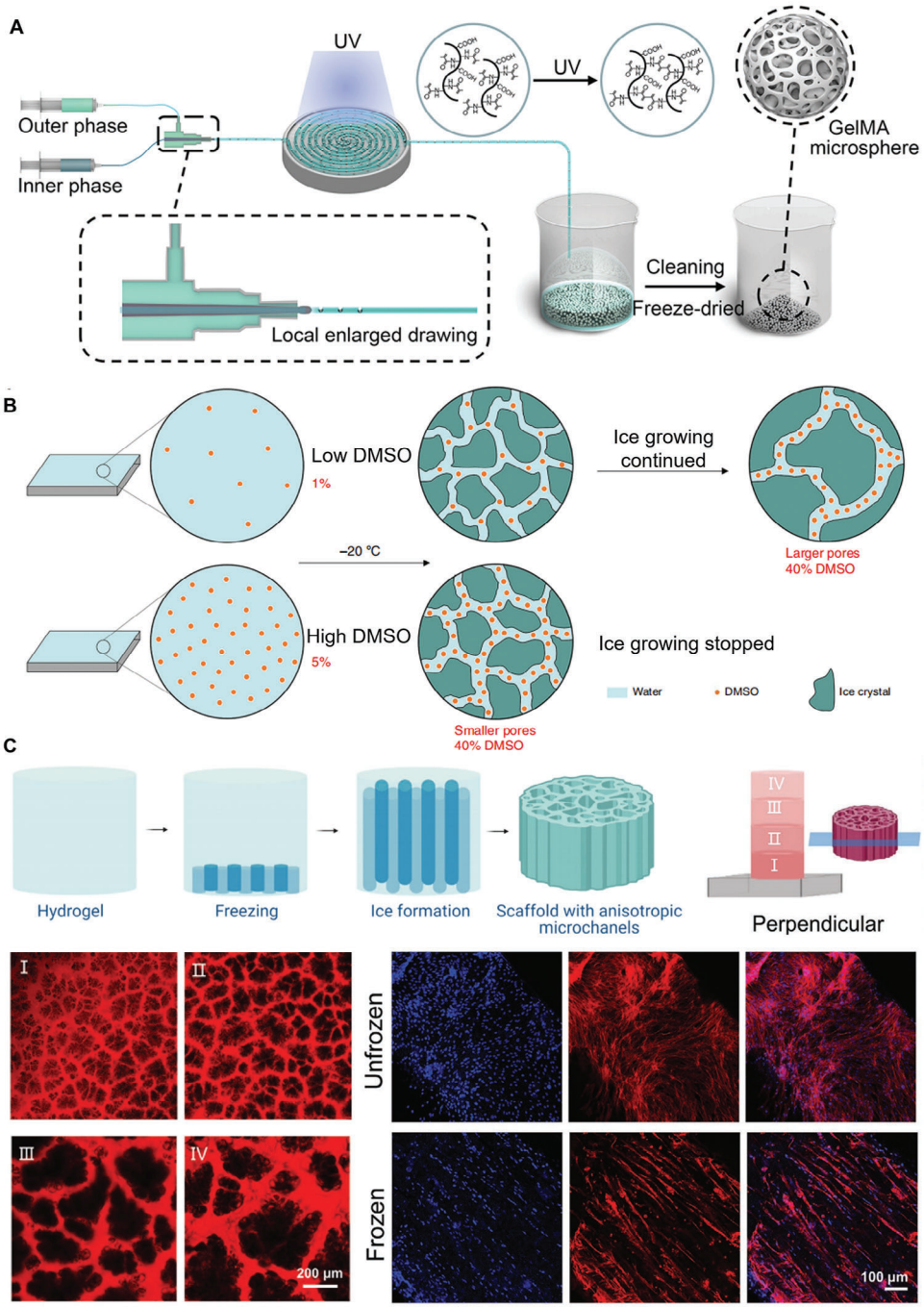



**Figure 2.** Fabrication of microporous hydrogels via freeze-drying method. A) Schematics of fabrication of freeze-dried microporous microspheres. Reproduced with permission.[28b] Copyright 2021, American Chemical Society; B) Schematics of fabrication of Microporous structure by regulating ice crystal growth. Reproduced with permission.[22a] Copyright 2019, Speinger Nature; C) Bioprinting of microporous structure by combining bio-printing and ice template methods. Reproduced with permission.[30] Copyright 2022, John Wiley and Sons.

structures with a diverse range of sizes and extreme levels of porosity. By integrating ice template materials or solution-forming additives into the freeze-drying process, it becomes feasible to direct the formation of desired ice crystal structures and fabricate microporous structures in terms of size and shape.[19,29] Du's research group utilized the cryoprotectant DMSO's ability to regulate ice crystal growth in order to precisely control the pore size and stiffness of the scaffold[22a] (Figure 2B). The transition from smaller, softer pores to larger, stiffer pores within microporous scaffolds results in a shift in macrophage behavior from a pro-inflammatory to an anti-inflammatory phenotype. Ice crystal conditioning has the potential to enhance cell viability during freeze-drying. The conventional freeze-drying process results in a microporous hydrogel that requires cell

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seeding on a previously freeze-dried microporous hydrogel instead of suspending cells within it, allowing for cell growth within the structure. By manipulating ice crystal formation, cells can directly adhere the microporous hydrogel and utilize its unique structures (such as directional and layered porosity) to promote outward cellular growth and improve tissue repair efficacy. Zeyu Luo et al. utilized a combination of DMSO and melezitose as cryoprotective agents and employed 3D extrusion bio-printing and ice template methods to produce vertical, vertical microporous hydrogel structures with direct cell-loading capability and interconnected, anisotropic gradient microchannels[30] (Figure 2C). The directional microporous structure also can be achieved by incorporating specific directional obstructions during the freeze-drying process. Additionally, adjusting the temperature and duration of the freeze-drying process can also lead to the formation of a directional microporous structure.[31] By simultaneously introducing digestible components into the hydrogel matrix along with the oriented structure, oriented graded microporous structures at multiple scales can be obtained. Subsequent solution leaching techniques such as salting out or metal ion solutions further enhance this approach.[26b,32] Overall, freeze-drying is a simple and convenient method for preparing microporous hydrogels that is compatible with most hydrogel matrices.

#### 2.1.2. Two-Phase Sacrificial Strategy

This technique involves harnessing the phase separation phenomenon of mutually insoluble two-phase solutions to create intricate porous structures. In this process, one phase undergoes solidification while the other phase is dissolved and subsequently washed away, resulting in the formation of a highly interconnected network of pores within the hydrogel matrix. By carefully controlling various parameters such as temperature, concentration, and solvent composition, it is possible to achieve different pore sizes and distributions within the hydrogel structure. Moreover, the two-phase sacrificial strategy offers numerous advantages over conventional techniques utilized in the fabrication of microporous materials. It presents a straightforward yet highly efficient approach to generating well-defined pore structures without necessitating sophisticated equipment or extensive processing procedures. Additionally, this technique can be easily scaled up for mass production due to its simplicity and effectiveness.

The utilization of incompatible properties between water and oil is commonly employed to fabricate porous networks. This approach entails blending hydrophilic and organic solutions, curing the hydrophilic solution, and subsequently removing the organic phase to generate a porous structure.[33] While this method shows promise for tissue engineering materials, it may not be suitable for encapsulating sensitive biological molecules or cells due to adverse effects associated with oils. The two-phase sacrificial strategy exhibits significant potential as a strategic methodology, and its straightforward manipulation and exceptional compatibility with cells render it an appealing choice for researchers seeking advanced materials for tissue engineering. This section will outline the biphasic sacrificial strategy for fabricating porous hydrogels, encompassing three stages: aqueous two-phase strategy (liquid-liquid phase), microparticle sacrificial strategy (liquid-solid phase), and bubble sacrificial strategy (liquid-gas phase).

*Aqueous Two-Phase Strategy*: The encapsulation of sensitive biomolecules or cells in oil-water sacrificial templated porous hydrogels presents a significant limitation due to the potential adverse effects of oil on cell growth and biological responses. To improve the biocompatibility of the two-phase sacrifice method, microporous hydrogels have been prepared by using two-phase emulsion.[8e,34] The aqueous two-phase system is employed as an efficient approach for fabricating microporous hydrogels, with one of the aqueous phases serving as the cross-linkable hydrogel matrix, such as photocurable GelMA,[9e] poly (N-isopropyl acrylamide)[35] and sodium alginate.[36] The other aqueous phases serve as the sacrificial matrix such as PEO (polyethylene oxide), which can modify the hydrogen bond strength between molecular chains of GelMA to produce a typical aqueous two-phase emulsion.[37] The fabrication of microporous hydrogels by the aqueous two-phase sacrifice method in the past five years is summarized in Table S1 (Supporting Information). The microporous hydrogel prepared by the aqueous phase sacrificial strategy can be efficiently and rapidly prepared with different pore sizes by adjusting the proportional concentration of the two phases and the phase separation time.

Importantly, the aqueous two-phase microporous hydrogel demonstrated enhanced biocompatibility by promoting direct cell spreading within its microporous structure[8e] (**Figure 3A**). Therefore, the hydrogel with a microporous structure obtained by sacrificing the aqueous phase is more advantageous for tissue repair and regeneration. Mongeau et al. employed a coordinated approach involving phase separation and covalent crosslinking to fabricate injectable double-network hydrogels that possess porosity while maintaining cell viability[38] (Figure 3B). This demonstrates the feasibility of in situ injection of an aqueous two-phase emulsion to dissolve the sacrificial phase and form a microporous hydrogel, thus highlighting the potential of microporous hydrogels for clinical applications in tissue engineering and regenerative medicine. Furthermore, combined with the 3D bioprinting strategy, the macro- and micro-porous hydrogel modules with grading and good mechanical properties can be obtained.[9e,39]

When the undisturbed uncured aqueous two-phase emulsion undergoes gradual phase separation over time, it can have a detrimental impact on printing quality due to potential significant alterations in pore size before and after the printing process. Therefore, it is necessary to have a corresponding substance to stabilize the separation of the two phases and obtain a suitable aperture size and span. Liu et al. developed a sacrificial phase comprising of a GelMA solution and $\beta$-LG ($\beta$-lactoglobulin) nanoparticles/dextran solution, wherein the dextran droplets are dispersed within the GelMA solution while the $\beta$-LG nanoparticles are anchored onto the surface of these droplets to enhance emulsion stability[40] (Figure 3C). Upon polymer solution curing, the dextran is subsequently removed, resulting in the formation of a microporous structure. Zhang et al. enhanced the stability of the GelMA/PEO hydrogel matrix by incorporating rhamnolipid as a biosurfactant, resulting in a well-maintained microporous structure.[41]

*Microparticle Sacrificial Strategy*: The construction of microporous structures often lacks highly adjustable pore structures.


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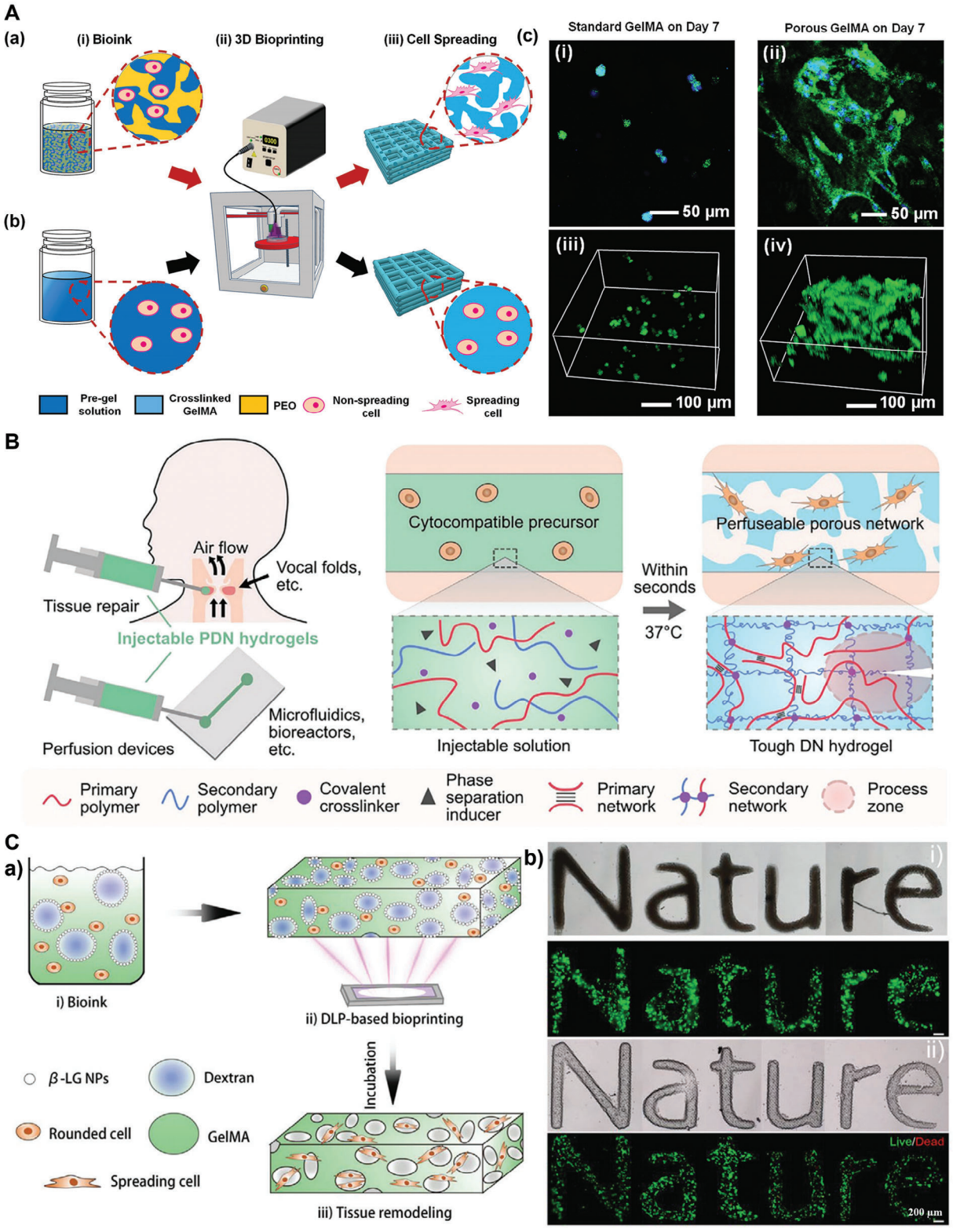



**Figure 3.** Fabrication of microporous hydrogels via aqueous two-phase strategy. A) Schematics of the aqueous two-phase microporous hydrogel and confocal image of cell growth and spreading within these microporous constructs. Reproduced with permission.[8e] Copyright 2018, John Wiley and Sons; B) Schematics of injectable microporous hydrogel. Reproduced with permission.[38] Copyright 2022, Wiley-VCH GmbH; C) Schematics of microporous hydrogel with pore size stability and confocal image of cell growth and spreading within these microporous constructs. Reproduced with permission.[40] Copyright 2022, John Wiley and Sons.


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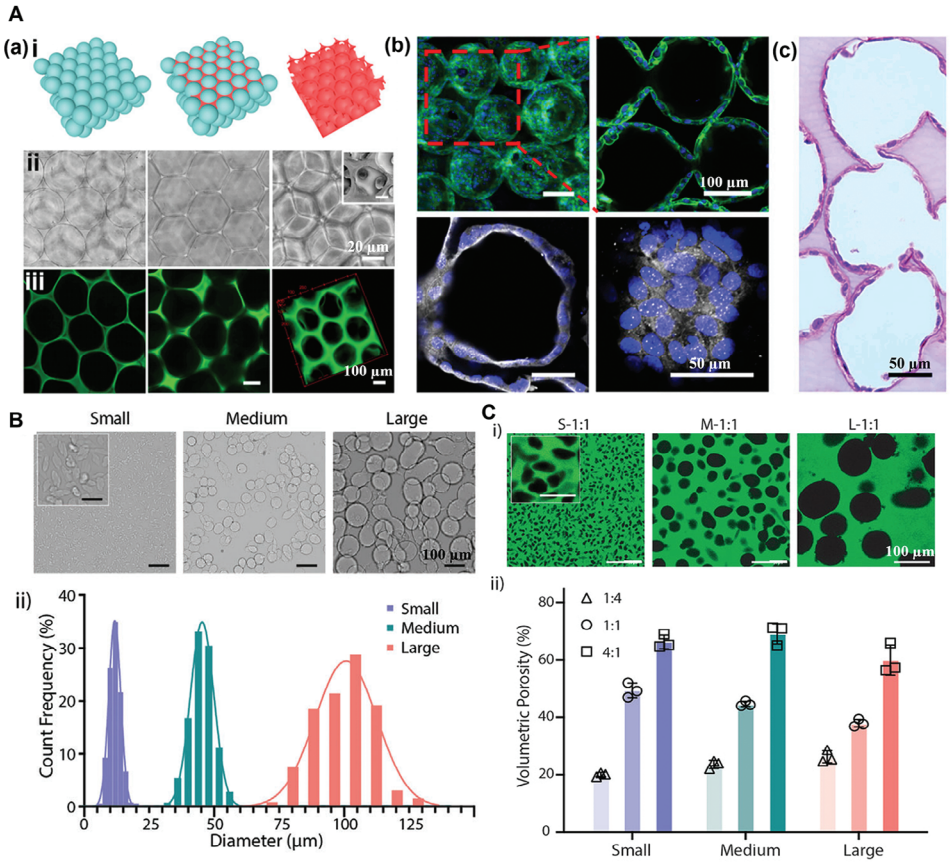



**Figure 4.** Fabrication of microporous hydrogels via microparticle sacrificial strategy. A) Schematics of microparticle sacrificed microporous hydrogel and fluorescence image of cells within the microparticle sacrificed microporous hydrogel. Reproduced with permission.[44] Copyright 2021, PNAS; B, C) Microparticle sacrificed microporous hydrogel with adjustable pore size. Reproduced with permission.[45a] Copyright 2022, John Wiley and Sons.

In response to this issue, the sacrificial strategy of microsphere-based has emerged. The microsphere sacrificial strategy refers to the incorporation of engineering microspheres into a hydrogel matrix solution, and after solidifying the outer layer of the gel matrix, the microspheres are sacrificed to form a uniformly sized porous hydrogel scaffold.[42] This innovative approach enables precise control over the microporous structure and properties of the scaffold, rendering it well-suited for tissue engineering applications. The consistent pore size facilitates cellular penetration and distribution within the scaffold, leading to enhanced tissue regeneration and integration[43]. Furthermore, this strategy allows researchers to customize the porosity of hydrogel scaffolds to mimic specific tissues or organs, thereby enhancing their potential for regenerative medicine and drug delivery systems. Di Huang et al. utilized sodium alginate microspheres arranged in a tightly packed cuboidal lattice, into which the GelMA solution was permeated and cross-linked, followed by the removal of the sodium alginate microspheres.[44] Subsequently, primary human alveolar epithelial cells adhered to the surface of regular pores within microporous hydrogels to form a single layer of epithelium, simulating cyclic inhalation/exhalation motions in an alveolar-lung model (**Figure** 4A).

Temperature-sensitive materials like porcine skin gelatin are utilized to generate sacrificial phase microspheres of specific sizes or pre-cured digestible microspheres.[45] These prepared microspheres are introduced into the photosensitive hydrogel, resulting in the formation of a microporous structure within a defined range of pore sizes after curing and subsequent rewarming or digestion (Figure 4B,C). This method offers enhanced stability and greater control over microsphere size compared to the aqueous two-phase strategy.

*Bubble Sacrificial Strategy*: The bubble sacrificial strategy is a technique utilized for the fabrication of a porous hydrogel through manipulation of the liquid and gas phases. This process entails the introduction of air into the hydrogel matrix and the incorporation of air facilitates the generation of interconnected voids within the hydrogel, leading to the development of a porous structure with cavities.[46] The bubble sacrificial strategy primarily involves two methods: introducing air into the hydrogel to create pores and generating air within the hydrogel to form pores[47] (**Figure** 5A,B). By further leveraging the capabilities of this technology, bubble microporous hydrogel fabrication devices can be seamlessly integrated onto extrusion printers to fabricate 3D printed structures with predetermined geometries and internal microporous architectures that govern spatial variations, encompassing diverse geometric models and bone constructs[47b,48] (Figure 5C).


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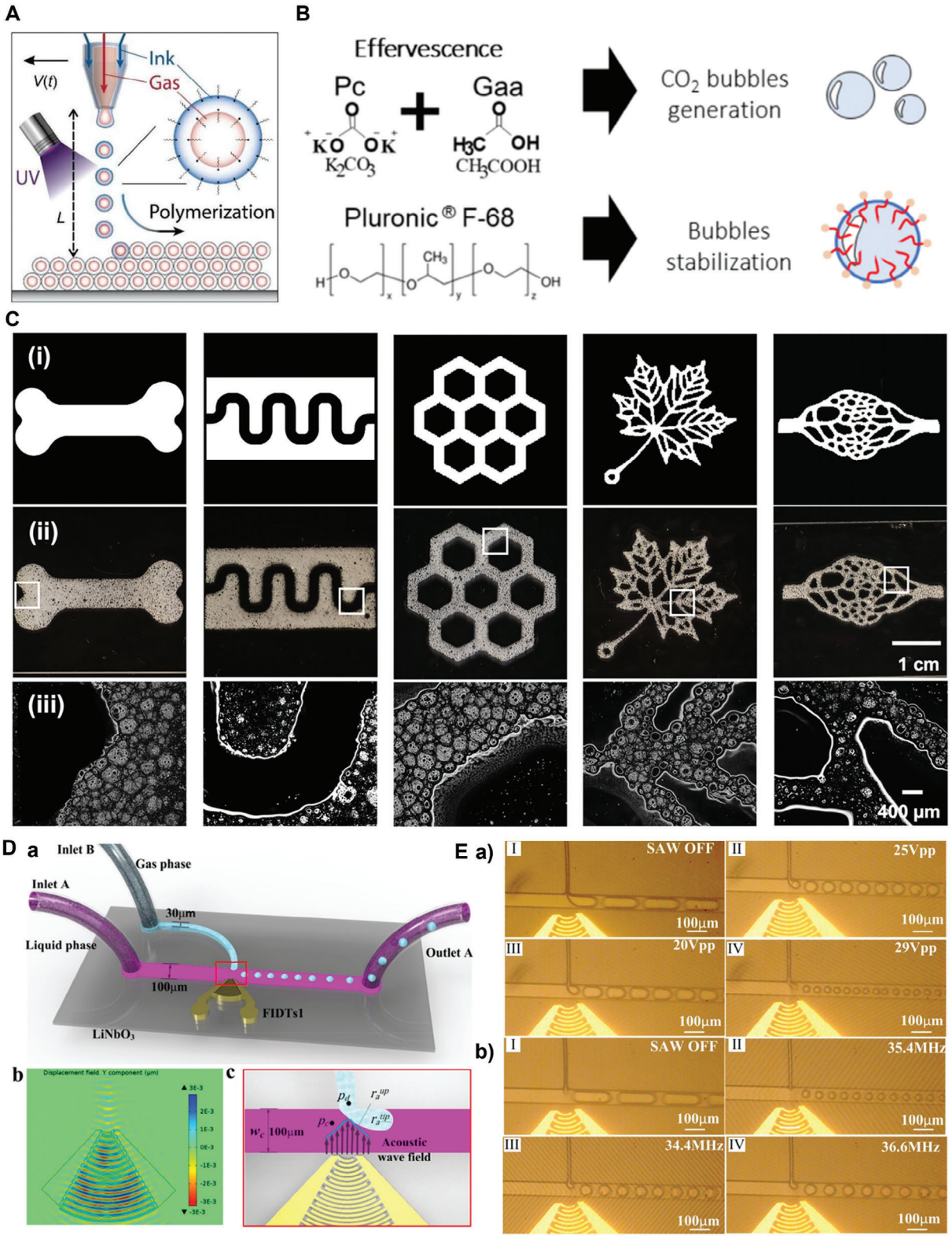



**Figure 5.** Fabrication of microporous hydrogels via bubble sacrificial strategy. A, B) Schematics of bubble sacrificed microporous hydrogel. Reproduced with permission.[47] Copyright 2019, John Wiley and Sons; C) 3D bioprinting microporous structures with bubble sacrificial strategy. Reproduced with permission.[48b]; Copyright 2023, John Wiley and Sons; D, E) Schematics of fabrication by surface acoustic wave and live video capturing the process of micro-pore formation. Reproduced with permission.[49] Copyright 2020, American Chemical Society.


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In a microfluidic device, the designed gas is in the inner phase while the curable liquid is in the outer phase.[47b,49] By controlling the flow rate of both phases and other relevant specific parameters, a stable cavity structure can be achieved. For instance, by adjusting the gas flow rate and pressure, cavities with diverse sizes and pore size structures exhibiting varying anisotropy can be generated.[46b,47b] It is worth noting that the presence of oxygen in the gas can partially impede the polymerization of the hydrogel, resulting in the rupture of the adjacent microporous film and the formation of an open microporous hydrogel, and substituting nitrogen for oxygen leads to the formation of a closed microporous hydrogel.[47b] The generation of microbubbles in water using acoustic-controlled microbubble generation based on the focused surface acoustic wave (FSAW) is deemed appropriate. Furthermore, the size of microbubbles can be dynamically regulated by adjusting the frequency or driving voltage of FSAW for the fabrication of microporous hydrogels comprising microbubbles[49] (Figure 5D,E). Furthermore, a specific valve device can be integrated at the bubble sacrifice device joint to facilitate gradual extrusion based on applied pressure. The dynamic regulation of pore width can lead to diverse bubble sizes without modifying the input flow of the two immiscible phases[48]. This type of valve is not only suitable for generating a wide range of monodisperse microporous materials using a microfluidic device but also for producing graded microporous structures with spatially varying pore sizes through manipulation of bubble sizes according to predefined protocols. The dimensions of the micropores influence the resulting microporous structure, thus enabling the preparation of hydrogel scaffolds with gradient pore size structures. Additionally, gradient pore structures can be created using microfluidic valves or by altering the gas type to establish interconnected pore networks.[48,50] It is possible to create microporous hydrogels with customized mechanical properties and interconnected porosity at different length scales by incorporating specific particles to stabilize the air–water interface.[51]

Bubbles can be introduced into the hydrogel system by incorporating bubble-producing components or methods and subsequently curing the system in a specific mold to yield microporous hydrogels. For example, carbon dioxide bubbles can be generated through the addition of potassium carbonate and glacial acetic acid to the hydrogel system, while carbon dioxide and ammonia bubbles can be produced via thermal decomposition of ammonium bicarbonate or acetate salt.[47a,52] Additionally, air can be introduced into the hydrogel solution using a syringe.[46a] This method is advantageous for creating injectable hydrogels as the gas originates from within the hydrogel, offering simplicity and convenience while maintaining cytocompatibility, thereby promoting rapid cell attachment, proliferation, deep infiltration, and extracellular matrix deposition.[46a,47a]

Overall, the fabrication of microporous hydrogels comprises three stages: aqueous, solid-liquid, and gas-liquid, which is called aqueous two-phase strategy, microparticle sacrifice strategy, and bubble sacrifice strategy, demonstrating tunable pore size properties within the micrometer range by manipulating solution concentration, two-phase ratio, and molecular weight. The distinctive internal cavity of these microporous hydrogels facilitates cellular adhesion and proliferation, thereby promoting efficient cell spreading.

#### 2.1.3. 3D Biofabrication Technology

3D bioprinting, also referred to as additive manufacturing in the field of tissue engineering, employs 3D printing technology to fabricate intricate structures composed of hydrogel bioinks. This cutting-edge technique facilitates precise control over the design and manufacturing process, enabling the creation of elaborate scaffolds and interconnected pores that mimic natural tissue-like structures.[53]

The utilization of hydrogels in 3D bioprinting has unlocked novel possibilities across various domains, including tissue engineering, regenerative medicine, and even organ transplantation.[17o] These biomimetic structures can be tailored to specific applications by adjusting factors such as pore size, shape, density, and mechanical properties. Despite being in its nascent stages, microporous hydrogels based on 3D biological printing technology have made significant advancements and are expected to address the challenges of tissue and organ replacement therapy. This section delves into a comprehensive discussion on 3D biofabrication encompassing a range of technologies primarily consisting of digitally designed 3D bioprinting, spinning 3D biofabrication, and granular 3D biofabrication.

*Digitally Designed 3D Bioprinting Technology*: The light-curable biohydrogel exhibits excellent formability, with monomer molecules of hydrogel being larger in comparison to small molecule polymers. Upon exposure to UV light, unsaturated double bonds are cleaved by free radicals to generate crosslinks, thereby interlinking with each other to form a polymer. The crosslinking process of the hydrogel results in the formation of 2D network structure units, unlike the linear structure units formed in small molecule polymerization, enabling hydrogels to be printable[54]. The design of digital models provides a feasible solution to realize pore size positioning, adjustable mechanical properties, and precise control of the internal and external structure of microporous hydrogels.[55] The computer-aided design distinguishes biological 3D printing from the two-phase sacrificial method and freeze-dried microporous fabrication. Digital design can be used to fabricate microporous hydrogels for 3D printing. The microporous structure was established by digital modeling technology, and then the printing ink was placed in the printer, and the established microporous structure could be directly printed out by stacking the 3D model layer by layer[56] (**Figure 6**A,B).

Furthermore, the combination of 3D printing and aqueous two-phase sacrificial methods can also be utilized for the fabrication of microporous hydrogels. The two-phase sacrifice method respectively can be used to configure two tubes of the sacrificed template bioink and the hydrogel forming bioink to establish a non-void multi-material structure through 3D printing. Sacrificing the template phase after crosslinking the cured intersect allows a microporous network structure to be formed after sacrificing the phase ink, creating a well-defined 3D network of interconnected tubular channels.[57] (Figure 6C) The microporous size of the structure is generally attributed to the digital model established, the printable properties of the ink preparation, and the precision of the printing equipment. However, no matter what kind of mentioned printing method or what kind of printing equipment is employed, such as extruded printing or digital light-curing printing, it will be affected by the accuracy of the printer


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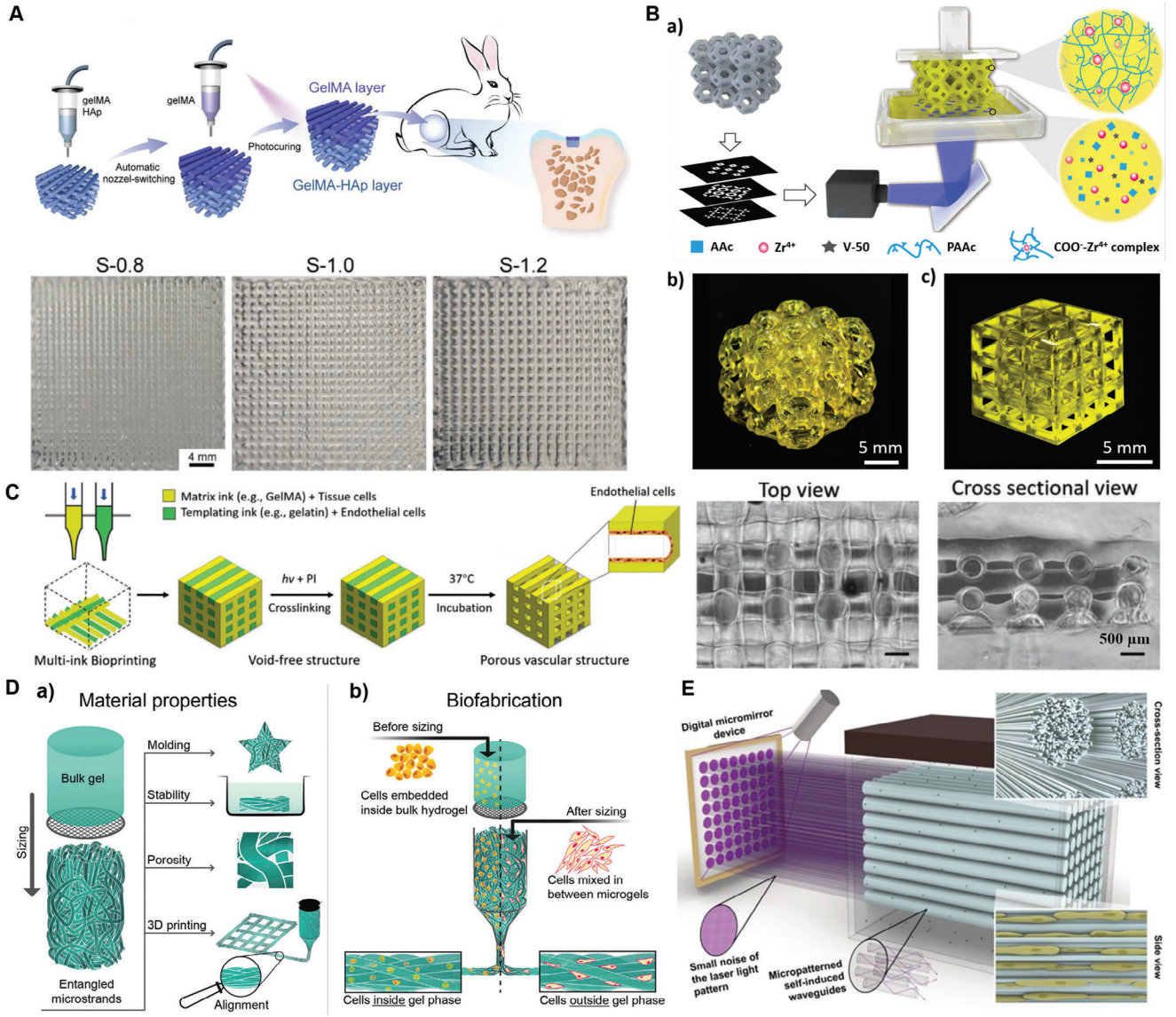



**Figure 6.** Fabrication of microporous hydrogels via 3D biofabrication. A) Schematics of fabrication of microporous hydrogels via extruded 3D printing and top view photograph of the printed scaffolds with different interfilamentous spacings. Reproduced with permission.[56b] Copyright 2020, John Wiley and Sons; B) Schematics of fabrication of microporous hydrogels via digital light processing 3D printing and photograph of the printed scaffolds with various shapes. Reproduced with permission.[56c] Copyright 2022, John Wiley and Sons; C) Schematics of fabrication of microporous hydrogels via the combination of sacrifice template method and digital design. Reproduced with permission.[57c] Copyright 2020, John Wiley and Sons; D) Schematics of the bulk hydrogel compressed into microstrands and schematics of cell-loaded microstrands via extruded 3D printing. Reproduced with permission.[58b] Copyright 2020, Wiley-VCH GmbH; E) Schematics of fabrication of highly aligned microporous constructs by filamented light. Reproduced with permission.[64] Copyright 2022, John Wiley and Sons.

and the accuracy of the G-code file to a certain extent due to the computer design of microporous scaffolds, so the printed aperture is often large.[58]

In general, the utilization of digital model printing is relatively straightforward to initiate, allowing for convenient adjustments to the aperture structure and model style as required. However, the resulting diameter of microporous network often exceeds 100 microns, posing challenges in achieving smaller microporous structures due to limitations imposed by the printing devices.

*Spinning 3D Biofabrication Technology*: The porous hydrogel created through spinning technology is a result of random linear packing under the superposition of spins, as opposed to the typical pore-like structure formed by cross-linking or sacrifice fabrications.[59] The most common spinning technology is electrospinning, in which the bioink is formed into filaments under the guidance of positive and negative electrodes and magnetic fields, and then can be fabricated into thin-film microporous hydrogels.[60] These microporous hydrogels often form nano-microfibers and have the advantages of high porosity, large surface area, transparency, and ultra-high flexibility[61]. However, fiber scaffolds for spinning primarily comprise rigid prefabricated microporous solids, which may


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not be suited for cell encapsulation or repetitive bioprinting. Butcher's group has successfully developed gelatin fibers by shear-thinning a high-concentration gelatin solution in the presence of extremely viscous polymers.[62] These fibers are subsequently photocrosslinked to create microporous fibrous hydrogels possessing mechanical properties akin to soft tissues. This type of microporous fibrous hydrogel exhibits a certain degree of stretchability and can be arranged directionally, thereby promoting the formation of anisotropic cellular or tissue structures.

The microporous hydrogels obtained through the spinning technique tend to exhibit a sheet-like structure, making it challenging to achieve specific shape features. In their study, Burdick et al. employed mechanical fragmentation of electrospinning hydrogel fiber pads to obtain fiber suspensions, which were then assembled into networks at desired densities.[63] The resulting fiber network was subsequently stabilized using optical crosslinking techniques, leading to the formation of fiber-hydrogel assemblies. Finally, by utilizing a light-curable fibrous hydrogel for printing purposes, an easily loadable highly microporous fiber network could be constructed. In addition, Zenobi-Wong et al. employ mechanical extrusion via a grid system to effectively break down the bulk hydrogel into fine microstrands.[58b] (Figure 6D)In this intricate procedure, individual microstrands intricately interweave to create entangled microstrands – an inherently stable substance that exhibits key characteristics essential for tissue engineering purposes such as plasticity, stability in aqueous environments, porosity for enhanced functionality and printability along with precise control over their arrangement during extrusion. Furthermore, 3D printing enables the direct fabrication of fibrous hydrogels with precise directional alignment. Zenobi-Wong's group has pioneered a biomanufacturing technique called FLight (Filamented Light), which allows for the meticulous construction of hydrogels composed of a unidirectional network of microfilaments[64] (Figure 6E). By adjusting the projection direction in FLight, multidirectional microfilament bundles can be incorporated within a single hydrogel structure. These channels formed by microfilament bundles not only facilitate cell migration but also provide an optimal 3D environment for cellular activities such as proliferation, vascularization, and extracellular matrix deposition.

In general, the fabrication of microporous hydrogels through spinning can achieve a relatively enhanced oriented structure, which serves as a favorable platform for significant organ and tissue damage repair. However, further expansion of the compatibility of this method with secondary printing technology is necessary.

### 2.2. Fabrication of Injectable Microporous Hydrogels

In addition to block-shaped microporous hydrogels, the interstitial voids created by the stacking of 3D microgels also exhibit characteristics of a macro-microporous hydrogel scaffold, forming a highly interconnected microporous structure. As a result, particulate hydrogels in the form of microgels can serve as versatile biomaterials for tissue engineering with a wide range of biomedical applications. The fabrication of injectable microporous hydrogels typically takes advantage of the shear-thinning properties of microgels, enabling easy injection into targeted areas within the body, and making them ideal for local tissue engineering in minimally invasive procedures such as tissue healing.[18i,28a,65] Furthermore, microgel-based models can be constructed using crosslinking agents and specific polymer compositions to create interconnected pore networks among microgels, as seen in applications like 3D printing.[50,66]

Traditional hydrogel injection encounters challenges due to the limited injectability of large pieces of hydrogels in uniform precursor solutions.[67] Microgels assembly offers a solution by enabling the injection of individual microgels and their in-situ assembly.[24b,68] Injectable microgels include a type known as MAP (microporous annealed microgel), which consists of microgels and is widely microporous construction in scaffolds due to its exceptional injectability and in-situ annealing characteristics.[69] Through functional annealing of the microgel surface, these microgels can be injected into various shapes while providing a mechanically stable scaffold for cell growth. The application of MAP microporous scaffolds has shown promise in brain tissue repair and holds potential in other fields of regenerative medicine and tissue engineering, including the treatment of myocardial infarction.[24b,68] Notably, microgel assemblies with reversible dynamic bonding exhibit fluid-like behavior under certain injection forces, transitioning to viscoelastic solid gel properties as the applied force decreases. For example, the positive and negative charges of biomaterials can be leveraged to fabricate microporous hydrogels through electrostatic interactions.[24a,70] (**Figure** 7A).

The assembly of microgels driven by cell-cell interactions can be achieved by seeding cells onto the surface of the microgels.[71] This spontaneous microporous hydrogel assembly does not require additional chemicals or external stimuli, such as UV light or cross-linking agents. Instead, it allows cells to migrate and proliferate from inside the cell-loaded microgel to the surface, ultimately forming macroscopic 3D structures through a self-assembly process.[72] Cells on the microgel surface form intercellular junctions, while the cell culture medium diffuses through the cavities between the microgels, providing essential nutrients.[73] The addition of self-healing properties further enhances the stability and practicality of microgel assemblies in minimally invasive therapies.[65] When injected into a damaged tissue cavity, the microgel assembly easily fills the space and adapts to the cavity's shape, much like the precursor hydrogel solution. This process creates an cellular microenvironment for somatic cell growth and tissue repair.[68,70] (Figure 7B) Injectable and interconnected granular microporous hydrogel scaffolds, assembled from particle-based hydrogel building blocks promote rapid cell proliferation and the formation of extensive, interconnected 3D networks in vitro. In vivo, the scaffold facilitates cell migration, resulting in accelerated skin tissue regeneration and tissue structure formation.[65,74] The shape of the particles can be tailored to influence cellular growth outcomes. Burdick's group explored how the particle shape—whether isotropic spheres or anisotropic rods—affects the properties and cell growth of granular hydrogels[75] (Figure 7C). Burdick's group explored how the particle shape—whether isotropic spheres or anisotropic rods—affects the properties and cell growth of granular hydrogels, and moreover, the principal axis of rod-shaped particles may play a crucial role in supporting the directional growth of endothelial buds.


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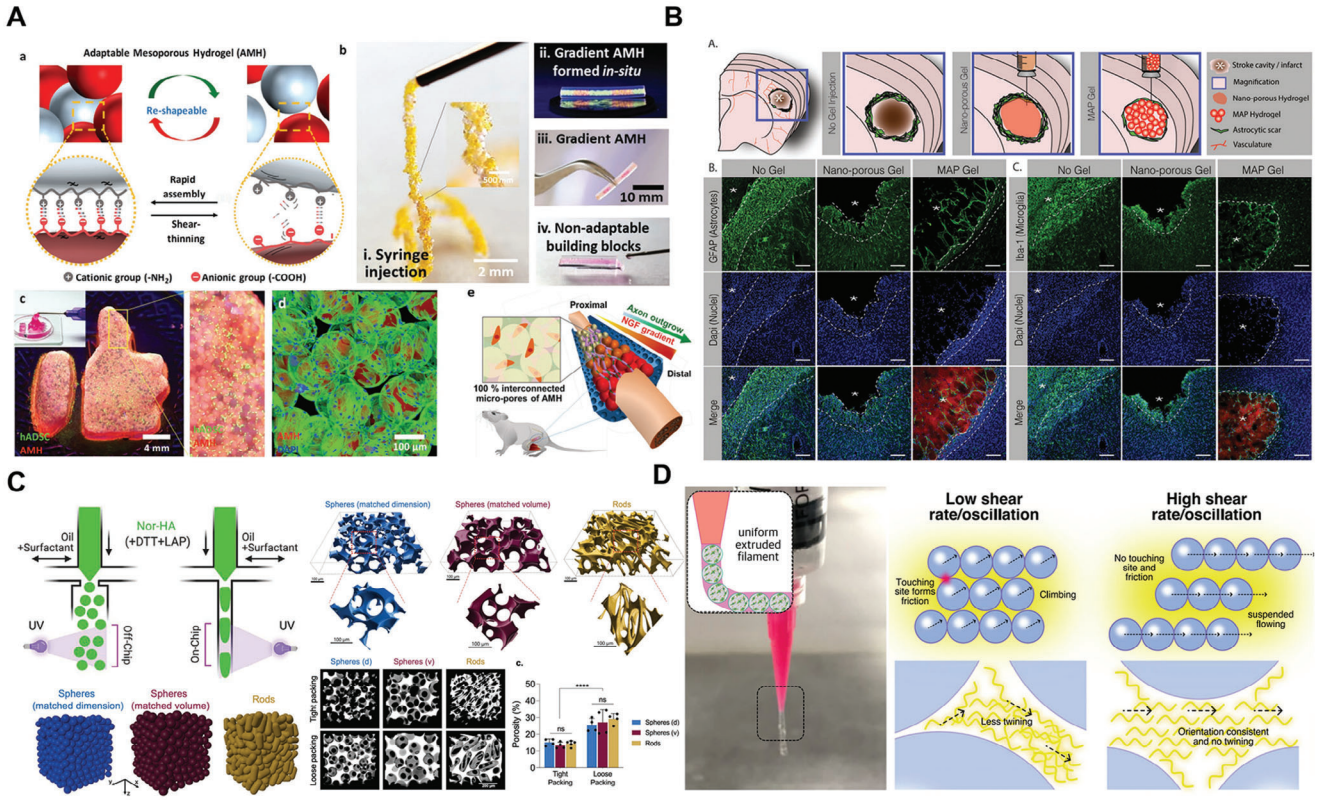



**Figure 7.** Fabrication of granular microporous hydrogels. A) Schematics of microporous hydrogel by microspheres electrostatic interaction, photograph of injected microgel in syringe extruded and fluorescence of cell microspheres. Reproduced with permission.[24a] Copyright 2019, Wiley-VCH GmbH; B) Schematic representation of granular hydrogel injection and fluorescence images of depicting post-stroke astrocytic responses following stroke under various conditions. Reproduced with permission.[68] Copyright 2017, John Wiley and Sons. Scale bar: 100 μm; C) Fabrication of highly adjustable granular microporous hydrogels with anisotropic and interconnected pores. Reproduced with permission.[75] Copyright 2022, John Wiley and Sons; D) Photograph of 3D printing microgel in syringe and the mechanism of the shear-thinning feature of microgel bioink. Adapted with permission.[21b] Copyright 2022, Springer Nature.

Loose granular hydrogel scaffolds face challenges in meeting the treatment needs of various diseases due to their large pores, high density, and limited adjustable range. Hydrogel matrix microspheres, precisely controlled through microfluidic techniques, can be further assembled using 3D printing. This enables the adjustment of key scaffold properties, such as morphology, porosity, and pore interconnectivity, allowing for more precise customization to suit specific therapeutic applications.[76] Bioinks composed solely of microgels have limited stability and are difficult to use for printing complex structures. To overcome this limitation, another liquid phase is combined with the microgels to enhance printability and shape fidelity. The resulting bioink, whether composed of pure microgels or a microgel-liquid mixture, offers versatility in selecting appropriate biomaterials, sizes, and shapes based on processing requirements. Additionally, this bioink can be easily extruded through smaller diameter nozzles, thanks to its shear-thinning behavior.[21a,77]For instance, GelMA acts as an adhesive between microgels, utilizing its strong rheological properties, fluidic nature, and wide temperature range to ensure excellent printability of microgel-based bioinks.[21b] (Figure 7D). Microgels can be fabricated through extrusion printing, digital light processing, or by sifting bulk hydrogels for mixed cell 3D printing.[66,78] Particle hydrogels not only provide a microporous structure but also exhibit injectability and secondary printability.

In general, the granular hydrogel can be regarded as an extension of microsphere secondary printing, enhancing their injectability while maintaining their microporous structure. The injectability aspect means that particle hydrogels can be directly administered via injection without the need for invasive surgery. Highly porous hydrogel modules provide significant advantages in tissue engineering for medical applications. The assembly and injection of microgels hold promising potential to improve medical treatments. However, further research is required to optimize microgels and fully exploit their benefits.

### 2.3. Other Methods

In addition to the three commonly employed methods for preparing microporous hydrogels, microporous hydrogels can also be synthesized chemically. Microporous hydrogels generated via chemical reactions are easily manipulable; however, typical


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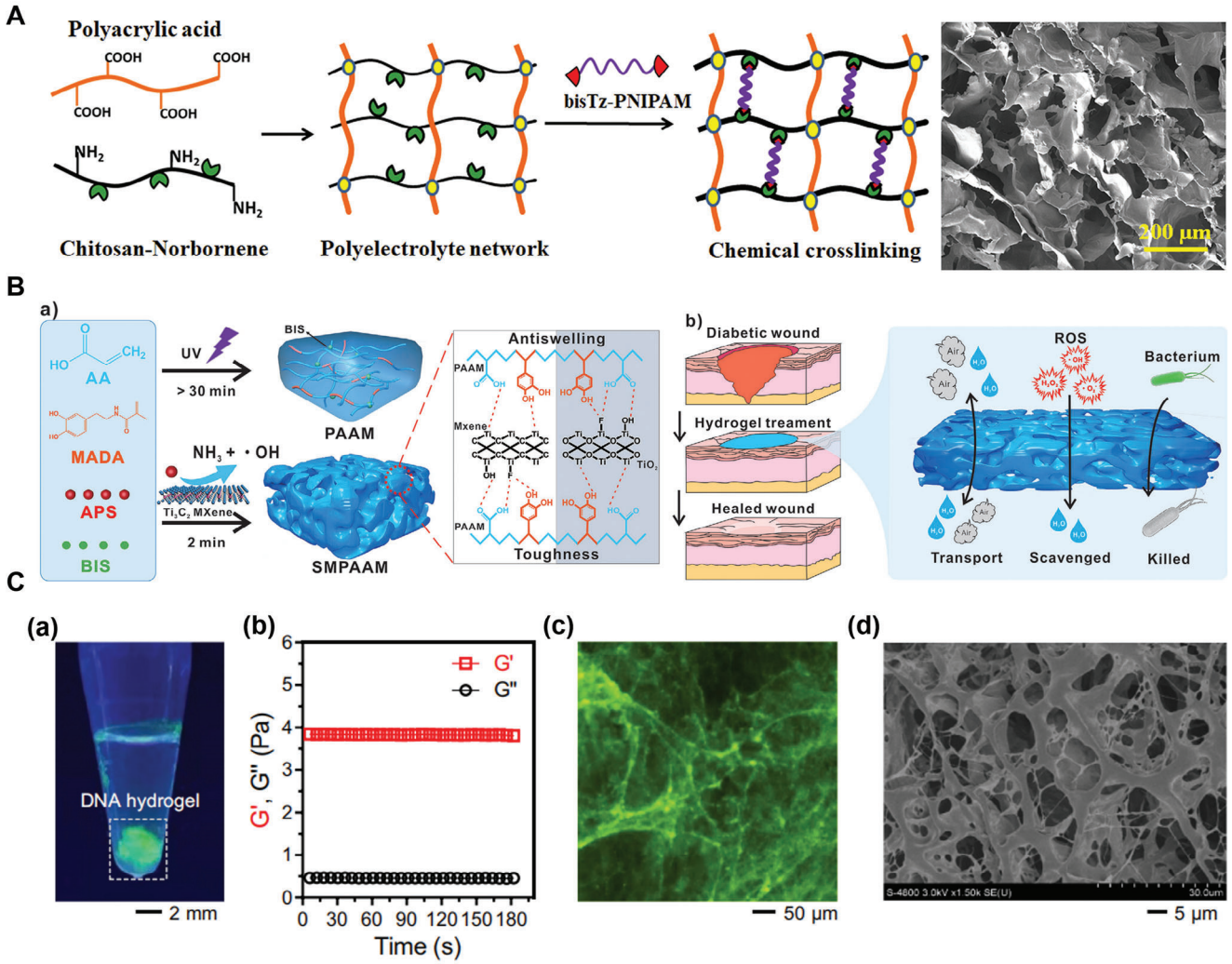



**Figure 8.** Fabrication of microporous hydrogels via other methods. A) Schematics of polyelectrolyte microporous hydrogel formation via click chemistry and SEM image of microporous hydrogels. Reproduced with permission.[79b] Copyright 2021, Elsevier; B) Schematics of sponge-like microporous hydrogel using Ti3C2 MXene. Reproduced with permission. [81a] Copyright 2022, John Wiley and Sons; C) Microporous networks of DNA hydrogel. Reproduced with permission.[83] Copyright 2023, PNAS.

chemical synthesis methods yield nanoporous structures, necessitating specific materials or crosslinking techniques.

Microporous hydrogels can be created by blending solutions of macromolecules capable of undergoing chemical reactions with each other, leading to the formation of specific side chain groups on the structural molecules of the hydrogel. This process includes click chemistry and esterification[14b,79] (**Figure 8A**). MXene, a class of 2D materials, has played a crucial role in tissue regeneration for tumors, infections, and inflammation due to their high surface area, adjustable properties, strong absorption of near-infrared light, and effective surface plasmon resonance.[80] The MXene system undergoes REDOX reactions to produce hydroxyl radicals that can be integrated into the hydrogel matrix, resulting in the construction of a porous hydrogel with micropores.[81] Zhang's group developed a sponge-like microporous hydrogel using $Ti_3C_2$ MXene which exhibits anti-swelling, anti-fatigue, and antibacterial properties.[81a] This microporous hydrogel serves as a platform for chronic diabetic wound healing (Figure 8B).

In addition, the incorporation of DNA and polypeptides into hydrogel creates a microporous structure, which enhances cell growth and tissue regeneration in tissue engineering. Within the hydrogel matrix, molecules are organized into fibrous microporous network structures through nucleic acid interactions based on the complementary base pairing principle.[82] Drawing inspiration from the process of forming DNA microporous hydrogels, each peptide sequence consists of two peptide structural domains with opposite charges at their ends, enabling them to assemble into bundled fibers for constructing polypeptide microporous hydrogels[83] (Figure 8C). By forming hydrogen bonds similar to DNA cross-linking or covalent bonds formed by positive and negative charges, polypeptides are specifically cross-linked in hydrogels to form microporous networks.[84] Protein microporous hydrogels mimic the ECM environment


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well, providing biochemical signals and structural support for tissue repair. Therefore, glycoprotein and collagen molecules and the fibrous protein structure of microporous hydrogels have been proposed. Such hydrogels provide good biochemical signals while providing good structural and mechanical support for tissue repair and development.[84b] Peptides can be synthesized to obtain protein structure and biochemical benefits with specific benefits or microporous hydrogels can be constructed by extracting proteins with specific pharmacological activities and biological benefits from existing animals.[69a,85]

The pore size in microporous hydrogels can be modified by adjusting the concentration of synthetic substrate and other conditions, typically ranging from nanometers to microns.[15a,85a,86] Additionally, they possess dynamic properties that promote cell growth by enabling cells to adhere to specific proteins or binding sites on the molecular porous network.[87] This characteristic can be incorporated into the fabrication of microporous hydrogels to optimize the microenvironment for cell proliferation, adhesion, differentiation, and facilitate cell transplantation and tissue regeneration.

## 3. Cell-Loaded Microporous Hydrogels for Biomedical Applications

Incorporating cells into microporous hydrogels is a common strategy in cell therapy for tissue engineering to address the low retention and survival rates of cells in damaged microenvironments. Microporous hydrogels advantage is widely exploited in the field of biomedicine. First, microporous hydrogels are frequently utilized as biomaterials for tissue engineering due to their exceptional biocompatibility and capacity to minimize secondary damage at the injured site. The hydrogels can provide an optimal environment for cellular growth and proliferation, while the presence of pores facilitates efficient nutrient exchange and migration between the scaffold and tissue.[8e,88] Furthermore, microporous hydrogels possess the ability to autonomously regulate their pore size and shape during the preparation process, thereby facilitating cellular proliferation and differentiation within the cavity.[30,45a,89] The autonomous construction of microporous networks provides significant advantages in tissue engineering. Additionally, the reversible compressibility and shape-memory properties of porous hydrogels offer injectability,[9e] which is currently a focus of research in the field of microporous hydrogel cell therapy for tissue engineering. Unlike solid scaffolds used in traditional tissue engineering, injectable hydrogels can be administered through minimally invasive surgery without requiring extensive procedures Another advantage of cell-loaded microporous hydrogels lies in their ability to mimic the natural ECM found in living tissues.[15a,17f,84b] The interconnected pores within the hydrogel structure facilitate the efficient diffusion of nutrients and oxygen, thereby promoting cellular metabolism and signaling activities.

In conclusion, the utilization of microporous hydrogel in cell therapy for tissue engineering exhibits tremendous potential for applications in regenerative medicine due to its ability to replicate native tissue environments and provide controlled delivery platforms for therapeutic cells. In this section, the advantages of microporous hydrogels in tissue engineering are discussed with respect to various tissue repair applications, including bone regeneration, nerve regeneration, muscle regeneration, vascular regeneration, muscle regeneration, and other regeneration.

### 3.1. Microporous Hydrogels for Bone Regeneration

Due to the highly microporous nature of both bone structure and microporous hydrogels, microporous hydrogels have been developed for applications in bone tissue repair.[22b,90] The microporous structure not only conforms to the structural characteristics of bone tissue but also provides an advantageous platform for cell growth, differentiation, and proliferation. It has been acknowledged that the presence of open and interconnected pores promotes cell growth and facilitates bone structure reconstruction.[91] The open and microporous nature of the microporous hydrogel facilitates cell migration and promotes effective integration and repair between the microporous hydrogel scaffold and the surrounding bone tissue to a certain extent. Bone repair necessitates the introduction of exogenous cells to enhance the efficacy of damage restoration. Microporous hydrogels can be utilized for tissue engineering in bone repair tissue engineering, allowing the loading of stem cells and the differentiation of osteoblasts, chondrocytes, and osteoclasts[15a,20a,22b,33c,58b,92] (**Figure 9**A). The optimization of microporous hydrogel carriers can promote their resilience in harsh environments and enhance their effectiveness in tissue regeneration. Chen's group proposed using injectable "peptide-cell-hydrogel" microspheres to mitigate the local inflammatory response, modulate the metabolic equilibrium of ECM, and enhance cellular survival in acidic environments[28b] (Figure 9B).

As research on bone repair advances, there have been additional developments in understanding the structure and purpose of microporous hydrogels. In terms of mechanical properties, bone tissue typically possesses a certain level of hardness. To address this issue, Mineralized hydrogels offer a promising solution for bone repair and regeneration by combining superior mechanical properties with excellent osseointegration. Ren's research group proposed the utilization of in-situ mineralization with HAp (hydroxyapatite) nanocrystals for the production of microporous hydrogels.[22b] The mineralized HAp layer has demonstrated an ability to enhance osteoblast adhesion and proliferation, effectively stimulating bone differentiation. The mechanical strength can significantly impact the adhesion, growth, proliferation, and differentiation of osteogenic lineage cells. Camci-Unal group conducted sequential mineralization using calcium chloride dihydrate and sodium phosphate dibasic dihydrate, resulting in microporous hydrogel modules with enhanced mechanical properties.[93] A microporous hydrogel was prepared by incorporating an amino-functionalized hydrogel 45S5 BG into an sodium alginate/gelatin matrix.[15b] During the formation of the microporous structure, the superior apatite formation activity of the microporous hydrogel, while maintaining the amino-modified BG and suitable mechanical strength, may also positively affect M2 polarization of macrophages by improving cytoskeletal structure. This suggests that the microporous structure with mechanical strength significantly affects adhesion, growth, proliferation, and differentiation of osteoblasts. Furthermore, the radial gradient microporous


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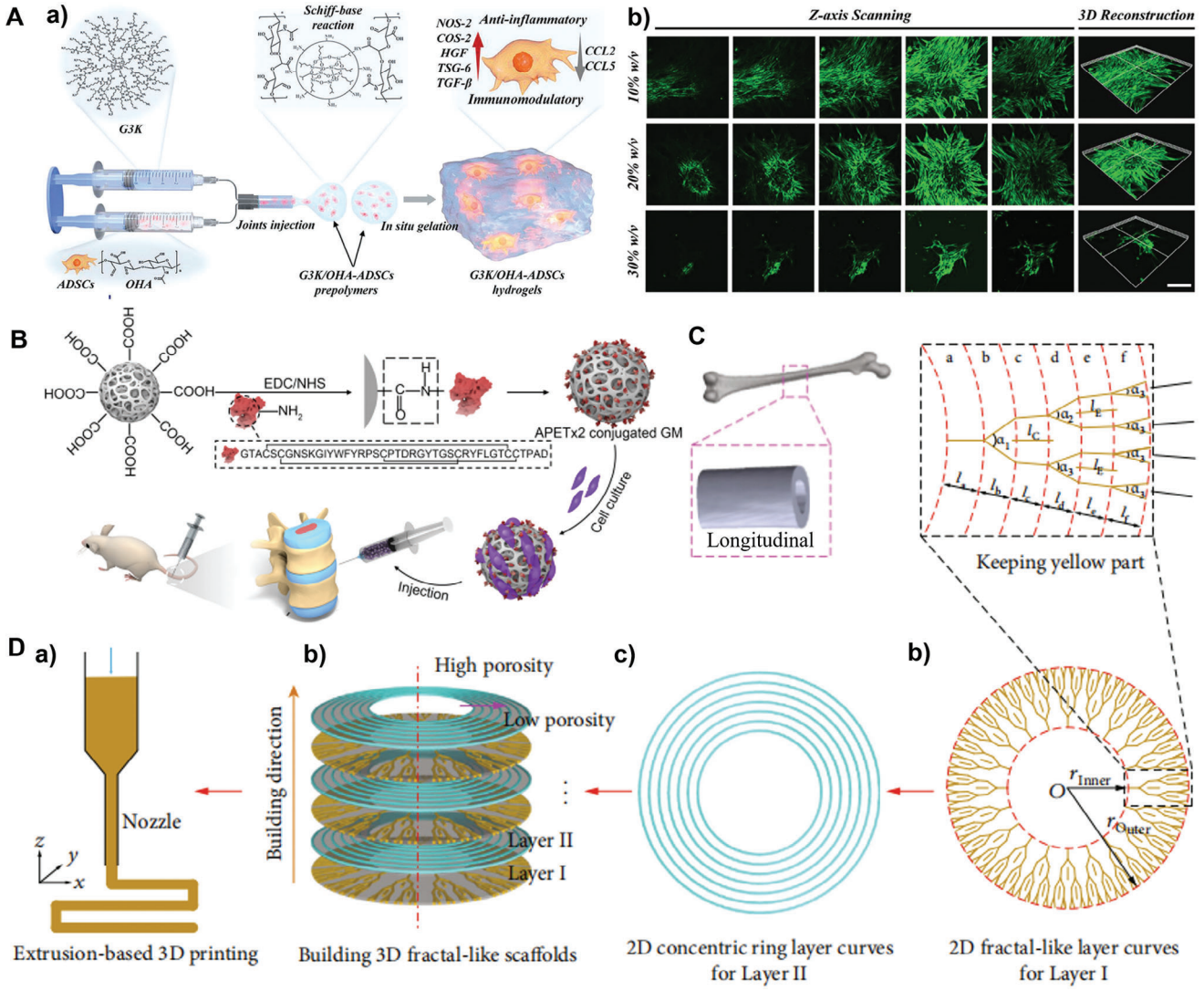



**Figure 9.** Cell-loaded microporous hydrogels for bone regeneration. A) Confocal imaging of cellular proliferation in an acidic environment within peptide-based microporous hydrogels. Reproduced with permission.[15a] Copyright 2023, Wiley-VCH GmbH; B) Schematics of microporous hydrogels loading stem cells for bone regeneration. Reproduced with permission.[28b] Copyright 2021, American Chemical Society; C, D) The radial gradient microporous structure. Adapted with permission.[94] Copyright 2021, American Association for the Advancement of Science.

structure can more accurately mimic the microstructure of typical human bone tissue in its overall architecture. The Ruan group proposed a fractal microporous scaffold with controllable radial hierarchical gradients, achieved through advanced 3D printing technology[94] (Figure 9C,D). This innovative radial gradient structure effectively mimics the gradual reduction of native bone porosity from cancellous to cortical bone, demonstrating significant potential for biomedical applications. Furthermore, it is crucial to form vascularization in the process of bone regeneration. More than that, vascularization also plays a crucial role in tissue engineering for repair and regeneration, which will be discussed separately. The focus here is on the combination of bone repair and vascularization, with the potential for simultaneous bone mineralization and vascularization through seeding stem cells and endothelial cells.[6,9a,57a]

### 3.2. Microporous Hydrogels for Muscle Regeneration

Muscle tissue exists in various tissues and organs of the human body, so the process of muscle repair includes not only the reconstruction of muscle fibers but also the restoration of tissue structure at the cellular level.[95] Microporous hydrogels with adjustable porous structure and high porosity can serve as carriers for muscle cells, providing mechanical strength and a certain degree of deformability in vivo, thus providing a platform for re-establishing a 3D structure during muscle cell regeneration.[9e,96] The anisotropic microporous structure promotes the aggregation and alignment of muscle fibers in the correct direction, thereby providing necessary mechanical and physical support for cell and tissue development.[97] In addition, Microporous hydrogels, characterized by their high water content and interconnected microporous structure, closely mimic the natural ECM.[84b] This unique


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architecture facilitates efficient nutrient and oxygen transport, as well as cell infiltration and proliferation within the hydrogel scaffold during muscle repair. The microporous hydrogel created through 3D printing demonstrates effective tissue repair, and the unique flexibility of 3D printing allows for enhanced customization of muscle tissue scaffolds. By adjusting the cell type within the printing bioink, fibroblasts can be printed in the muscle layer while facilitating epidermal hair growth.[98] Cho's group utilized various types of ECM to assemble into printing inks for constructing ECM environment and increasing cell viability.[99] The process of muscle tissue repair not only involves targeting muscle cells but also necessitates attention to the surrounding tissue structure and vascularization. Dvir's group developed a customized thermo-reactive hydrogel bioink through the processing of the acquirement separated from the matrix.[14a] The cells were reprogrammed into pluripotent stem cells, differentiated into cardiomyocytes and endothelial cells, and then encapsulated in a hydrogel bioink for 3D printing to create a porous hydrogel with well-defined hollow pipes to achieve the vascular structure (**Figure 10**A). The resulting autologous engineered tissue can be transplanted back into the patient with a reduced risk of rejection, offering a promising approach for repairing or replacing damaged/diseased organs.

The microporous structure of hydrogels can provide the specific architectural and cellular microenvironment required for muscle tissue repair. Furthermore, the flexible compressive mechanical characteristics of microporous formations establish conducive environments for cellular regeneration and tissue reconstruction.[9e,100] The interconnected network of the microporous hydrogel functions as a highly adaptable buffer, capable of withstanding significant elastic strains and alleviating external loads on the entire elastic structure.[101] It demonstrates exceptional mechanical properties with reversible compressibility. This characteristic was further validated in cell culture, as none of the compression processes had any discernible impact on cell viability, proliferation, or spreading within the microporous hydrogel structure[9e] (Figure 10B). The mechanical characteristics of microporous hydrogels and matrix materials can be customized to mimic the properties of natural muscle tissue, providing essential scaffolding and guidance for tissue regeneration.[102]

The adjustable microporous structure can be tailored to accommodate the physiological characteristics of various cells, thus broadening the potential uses of anisotropic and layered microporous hydrogels. This distinctive feature contributes to muscle repair at junction sites and facilitates the enhancement of cell growth status. Zeyu Luo et al. proposed observing a network of microchannels in the cross-section following 3D printing using directional ice templates, demonstrating a gradient distribution of pore sizes throughout the height of the structure.[30] This enables the construction of a vascularized tissue scaffold with organized microchannels at junctions between muscle and tendon components. Additionally, these microporous hydrogels possess anisotropic properties that are advantageous for guiding specific morphologies, such as skeletal muscle. The directional arrangement of this hydrogel promotes the formation of skeletal muscle and bone junctions by facilitating the directional growth of cells.[89] Furthermore, microporous structures ranging from the nanoscale to the micrometer level as Janus porous hydrogels, facilitate directional cell growth, with cells exhibiting a preference for favorable microporous structures over nanopores. Wu's research group has developed a novel biocompatible Janus microporous poly(vinyl alcohol) hydrogel, featuring a dense microporous and smooth bottom surface on one side to reduce fibroblast adhesion and prevent visceral adhesion.[9d] On the other side, a loose extracellular matrix microporous and rough top surface promotes significant improvement in fibroblast adhesion and tissue growth. Additionally, Janus microporous hydrogels can be engineered by modifying the design of multi-hydrogel matrix materials. Qiu's group has developed an asymmetrically adherent Janus hydrogel that exhibits rapid attachment to the heart surface, allowing for controlled stimulation for detachment and preventing postoperative tissue adhesion[103] (Figure 10C). The top layer effectively resists cell adhesion and fouling, thus preventing tissue adhesion. In contrast, the bottom hydrogel layer not only securely adheres to cardiac tissue and can be easily removed when needed but also serves as a therapeutic agent for myocardial infarction. Additionally, microporous hydrogels have the capacity to be loaded with bioactive molecules, growth factors, or other components conducive to tissue repair under conditions of high cell growth, thereby further enhancing their regenerative potential.

Microporous hydrogels provide an innovative approach to muscle regeneration and tissue repair in tissue engineering. The ECM-like microporous structure of these hydrogels can be customized for diverse tissue repair needs. Moreover, the integration of materials like graphene oxide, polypyrrole, and carbon nanotubes enhances their conductivity, which is critical for the repair of cardiomyocytes.[100,104] A notable innovation is the creation of a gradient bimetallic microporous hydrogel through the synergistic cross-linking of copper and zinc ions, designed to reconstruct the tendon-bone insertion microstructure.[105] The implantation of hypoxia-inducible factor-1$\alpha$ mutant muscle-derived stem cells has yielded significant improvements in cavernous tissue morphology, pressure, elasticity, and contraction, thus aiding in the recovery of male reproductive functions.[106]

### 3.3. Microporous Hydrogels for Neural Regeneration

Neural regeneration is the process of repairing and regrowing damaged or lost nerve cells in the nervous system, including restoring internal functionality and connectivity of nerve cells.[107] The intersection of neuroscience and tissue engineering holds great promise for advancing this field. The nerve scaffold should provide physical support for axonal extension by connecting severed nerve endings with sutures, while also being nontoxic. The porous hydrogel effectively meets the aforementioned criteria while offering a compact structure to promote nerve growth[79a]. In cases where there is a significant gap between the proximal and distal nerve stump, 3D network scaffolds are necessary to bridge the gap and guide the growth of nerve fibers.[108] As a 3D biological culture material, microporous hydrogels provide an effective platform for neural cells to develop into neural networks[109] (**Figure 11**A). Similar to the utilization of biological materials for clinical regeneration induction, microporous hydrogels can support and facilitate the growth, spreading, and formation of modulated key processes required for spontaneous action potentials in spinal cord injury.[110] The decellularized


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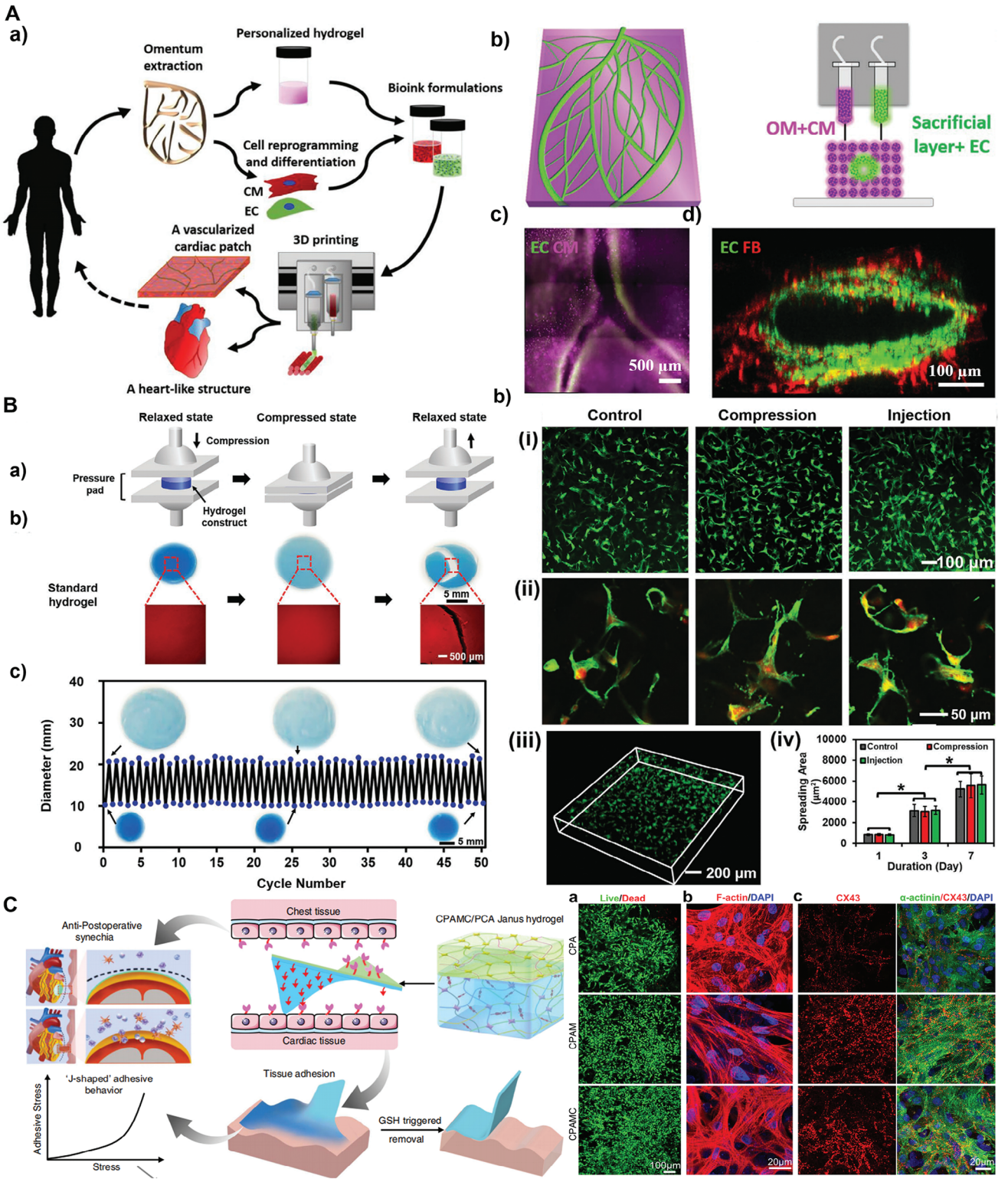



**Figure 10.** Cell-loaded microporous hydrogels for muscle regeneration. A) Schematic diagram of illustrating 3D printing scaffold for vascular repair of myocardial tissue, and fluorescence image of cell growth after seeding. Reproduced with permission.[14a] Copyright 2019, Wiley-VCH GmbH; B) Schematic diagram of the reversible compressive mechanical properties of microporous hydrogels and a confocal microscopy image of cell growth after compression injection. Reproduced with permission.[9e]. Copyright 2020, John Wiley and Sons; C) Schematic diagram of asymmetrically adherent Janus hydrogel and fluorescence image of cell growth. Reproduced with permission.[103] Copyright 2022, Springer Nature.



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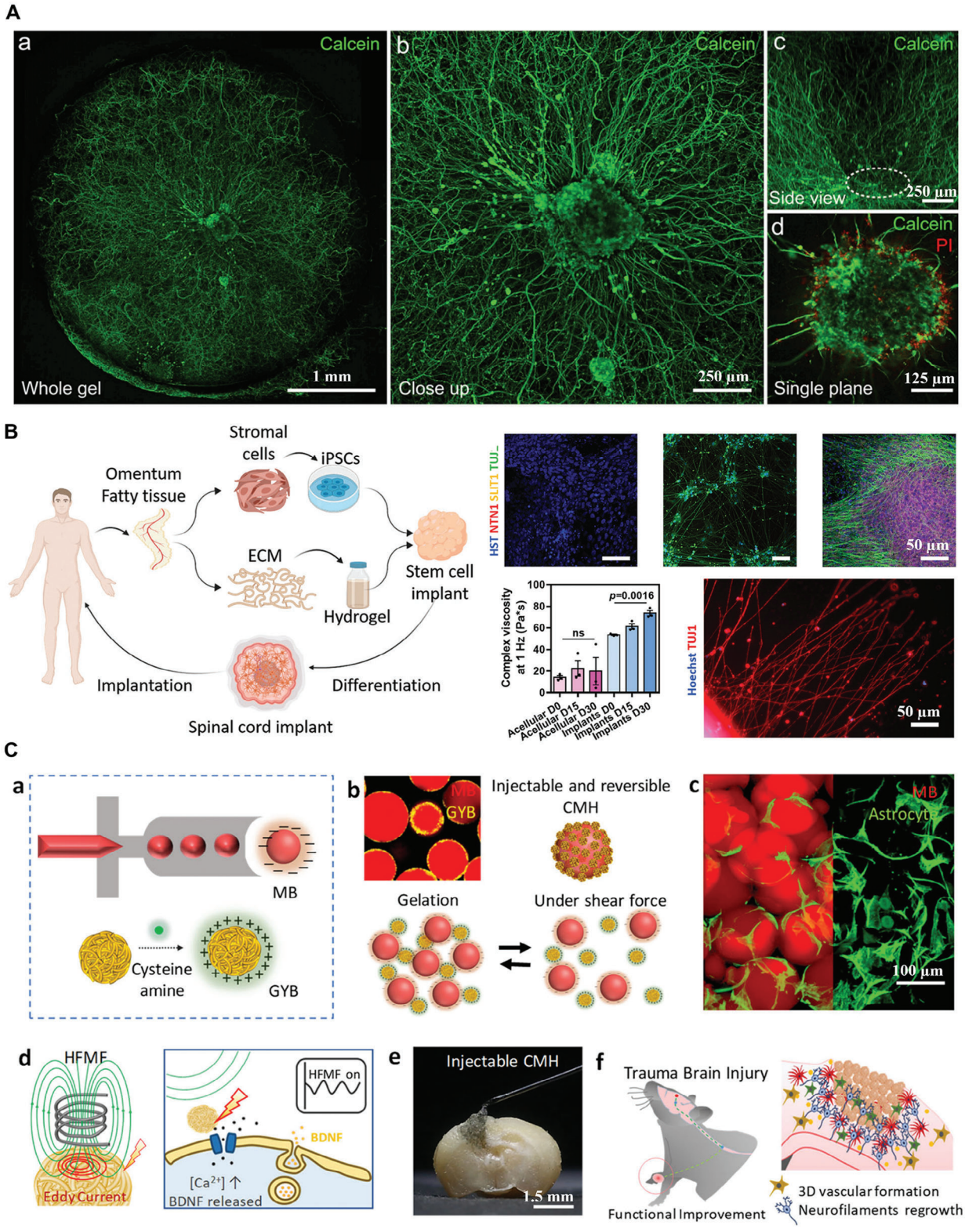



**Figure 11.** Cell-loaded microporous hydrogels for neural regeneration. A) Fluorescence image of neuronal cells growing in a microporous hydrogel. Reproduced with permission.[109] Copyright 2019, Elsevier; B) Schematic illustration of producing personalized hydrogels based on ECM using fat tissue from the patient. Reproduced with permission.[111a] Copyright 2022, Wiley-VCH GmbH; C) A schematic diagram and fluorescence image of the microspheres microporous hydrogel used for nerve regeneration. Reproduced with permission.[70] Copyright 2022, Springer Nature.


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microporous hydrogel bioink closely mimics natural tissue, possessing a natural hardness and fiber structure conducive to the growth of nerve cells, which are essential for tissue integration following implantation.[31,111] The human regenerative cells, such as neural stem cells, housed within the microporous hydrogel can fully differentiate into neurons. Additionally, the interconnected cavities embedded in the microporous hydrogel significantly enhance the extension of neuronal axons and the formation of myelin sheaths, thereby effectively restoring neurological function.[111b] Additionally, patient-derived adipose tissue is used to produce ECM-based personalized microporous hydrogels following the reprogramming of cells into induced pluripotent stem cells (iPSCs).[111a] The goal is to encapsulate patient-specific iPSCs in customized microporous hydrogels to promote efficient differentiation within a 3D microenvironment that mimics the embryonic development of stem cells (Figure 11B).

The unique morphology of nerve cells necessitates the use of appropriate 3D scaffolds to effectively support their elongated growth. Oriented microporous hydrogels can serve as an ideal platform for this purpose. The directional microporous structure, featuring elongated penetrating pores, partially meets the requirements of nerve cells, enabling them to maintain a stretched and spreading state.[112] Quan's group integrated a longitudinally oriented microchannel structure into a decellularized nerve matrix microporous hydrogel derived from porcine sciatic nerve using controlled unidirectional freeze-drying.[31] Culturing dorsal root ganglion explants on the longitudinal section of the scaffold demonstrated that axially arranged microchannels effectively guide and significantly enhance neurite extension and Schwann cell migration, which is advantageous for nerve regeneration. Additionally, granular hydrogel scaffolds provide a conducive environment for nerve cell growth. Notably, specific pores frequently occur between particles, particularly when microspheres aggregate to form microporous hydrogel scaffolds[18l,70,113] (Figure 11C). The microspheres embedded within the scaffold remain independent, facilitating cell migration within the specified pore range and providing ample space for growth. This environment supports cellular development, acting as a foundational platform for the migration of regenerated nerve cells and the formation of biological channels.[24a]

### 3.4. Microporous Hydrogels for Vascularization

The development of new blood vessels and vasculature is closely linked to the growth, repair, and regeneration of human tissues.[114] When tissue defects occur, the vascular network often ruptures, leading to inadequate nutrition supply and delayed healing. Porous hydrogels with cavity structures can effectively mimic the layered and structurally penetrating specificity of natural vascular networks in tissues.[115] In tissue engineering for vascularization repair, implantation of vascularized porous hydrogel scaffolds can accelerate surrounding tissue repair by rapidly constructing a mature vascular network and promoting material exchange at transplant sites while stabilizing the biochemical microenvironment for tissue cells.[116] Their microporous nature mimics the intricate structure of the extracellular matrix in soft tissues, providing an ideal environment for cellular attachment, growth, and proliferation. This microenvironment not only supports angiogenesis, and the formation of new blood vessels, but also aids in the migration and proliferation of various cell types crucial for tissue regeneration. The physicochemical properties of microporous hydrogels make them excellent candidates for creating scaffolds that effectively mimic the natural environment of tissues, thus advancing the field of regenerative medicine.[14b,92b,117]

The 3D sacrificial printing technique revolutionizes the fabrication of microporous hydrogels, enabling the creation of intricate vascular channel structures with precise control. The inner surface of the channels can be effectively cellularized through the integration of endothelial layers[57a,c,118] (**Figure 12**). This in situ endothelialization approach offers improved uniformity in cell seeding compared to traditional post-seeding methods. Additionally, the granular microporous hydrogel promotes the outward growth of endothelial cells, leading to the establishment of a prominent vascular network within the interstitial spaces between granules.[9a,78a] By employing 3D printing within a gelatin microparticle receiving bath, Feinberg's research group intentionally liquefies and eliminates captured gelatin microparticles during the printing process, enabling the integration of these particles into the collagen of 3D bioprinting structures to generate microporous microstructures that facilitate cell infiltration and micro vascularization.[17o] Additionally, the microporous hydrogel matrix can potentially impact the vascularization process by modulating its type, adjusting its chemical composition, and influencing cell-to-cell interactions.

Microporous hydrogels are employed in skin tissue engineering to replicate the 3D structure of the skin, promote the proliferation and differentiation of fibroblasts and vascular endothelial cells, and induce angiogenesis.[69a,98a] In bone regeneration, microporous hydrogels act as carriers for osteocytes to facilitate new bone formation and vascularization[9a,119]. Additionally, microporous hydrogels have been utilized in cardiac tissue engineering to enhance the proliferation and vascularization of cardiomyocytes by mimicking the microenvironment of myocardial tissue.[24b,100]

### 3.5. Microporous Hydrogels for Other Applications

The previous discussion delves into the utilization of microporous hydrogel tissue engineering for repairing significant cellular tissues within the human body. Furthermore, the structural adjustment of microporous hydrogels and the control of loaded cells or factors can be leveraged for the repair and reconstruction of diverse organs and tissues. Microporous hydrogels hold promise as biomaterials that support cell growth, differentiation, and proliferation while displaying the decreased vulnerability of the microenvironment.

The local delivery of cellular microporous hydrogels offers a promising alternative to intravenous drug administration for bypassing the blood-brain barrier and enhancing anti-tumor effectiveness. For example, T-cell microporous hydrogels mimic lymph nodes to facilitate targeted therapy for cancer cells.[120] Microporous hydrogels play a pivotal role in facilitating the proliferation, survival, and migration of bone marrow mesenchymal stem cells, as well as in promoting the regeneration of pulp-like tissues and the formation of new microvessels.[121] Janus


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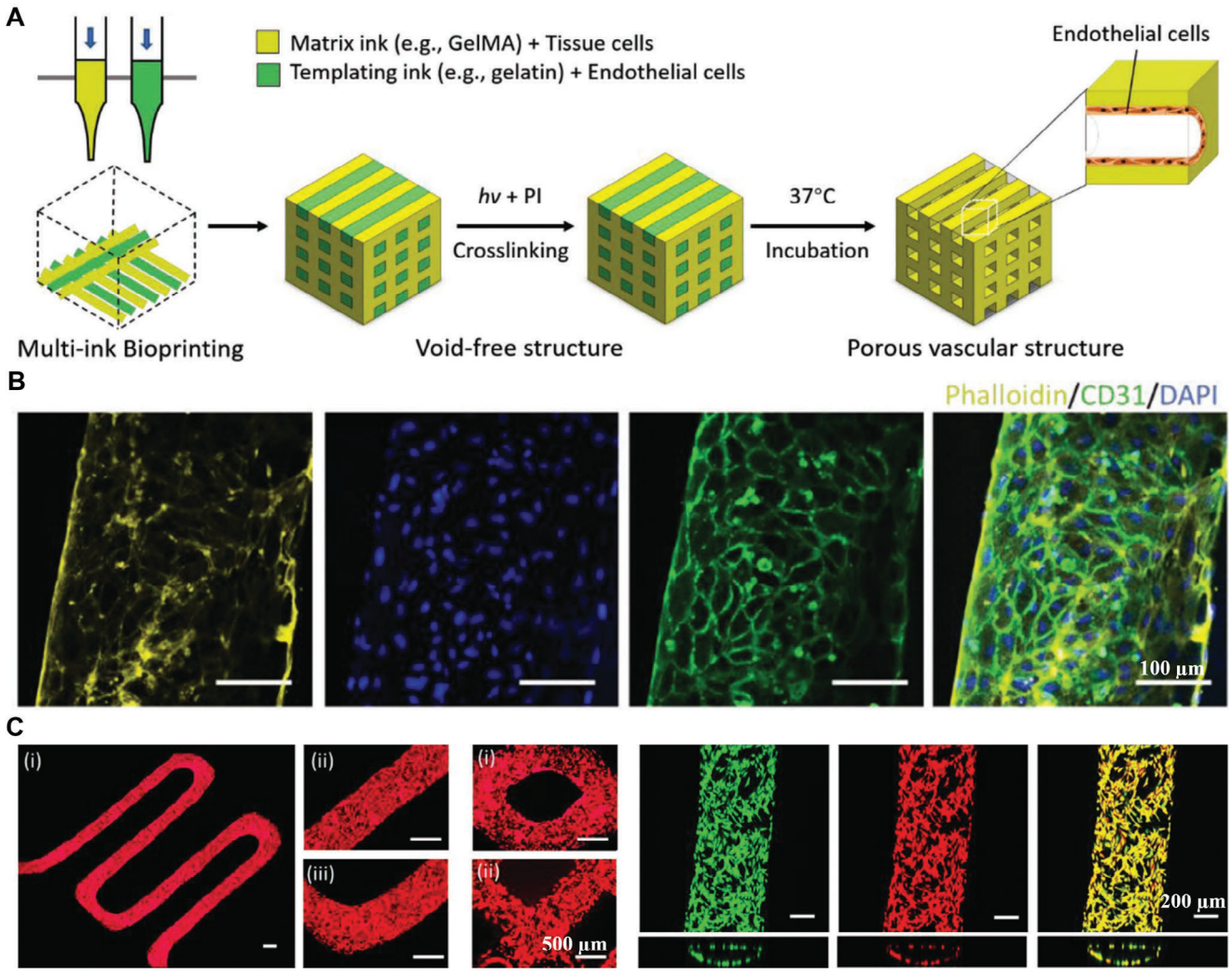



**Figure 12.** Cell-loaded microporous hydrogels for vascularization. A) Schematic of the Void-free 3D Bioprinting process printed side by side via a biocompatible templating bioink (green) and a matrix bioink (yellow); B) High-magnification confocal fluorescence microscopy images of HUVEC in situ endothelization; C) Confocal fluorescence microscopy images of HUVECs of perfusion culture. Reproduced with permission.[57c] Copyright 2020, John Wiley and Sons.

microporous hydrogels demonstrate distinctive asymmetric cell adhesion behavior, exceptional mechanical and anti-swelling properties, as well as superior anti-adhesion, pro-healing, and anti-deformation characteristics, rendering them highly efficacious in the repair of abdominal wall defects.[9d] The interconnected pores of microporous hydrogels can be harnessed for tissue regeneration and in situ perfusion in a cell-compatible manner to restore mechanically dynamic tissues, such as vocal cord tissue, thereby demonstrating potential applications in regenerative medicine[38]. Furthermore, microporous hydrogels can induce structurally modulated cellular mechanical responsiveness through physical constraints imposed by pores or osmotic pressure.[22a] Microporous hydrogels with micro-nanoporous structures and enhanced ionic conductivity mimic the astringency perception mechanism of the human tongue.[122]

Significant advancements have been made in the development of organoids that replicate natural organs, with ongoing investigations into the various factors influencing their growth.[123] The cultivation of cells within 3D porous hydrogels offers a sophisticated platform for simulating the internal environment of the human body, enabling researchers to gain deeper insights into cellular behavior and function.[124] Moreover, it provides a controlled environment for manipulating the physical and chemical properties of the gel, facilitating the study of cell behavior as carriers and disease models. 3D cell culture within microporous hydrogels has found wide application in various research domains, including in vitro osteogenesis, vascularization,[45a] drug screening for cancer cells and disease modeling,[125] artificial organ construction,[76] and long-term preservation of microporous microfibers as cell carriers.[88b] (**Figure 13**A). For example, Di Huang et al. developed an interconnected microporous inverse opal hydrogel to investigate the pathological effects of smoking and SARS-CoV-2 pseudovirus infection.[44]

A novel strategy for cell replacement therapy involves the encapsulation of cells in microporous hydrogels. By precisely controlling the pore size, cells can maintain high biological activity


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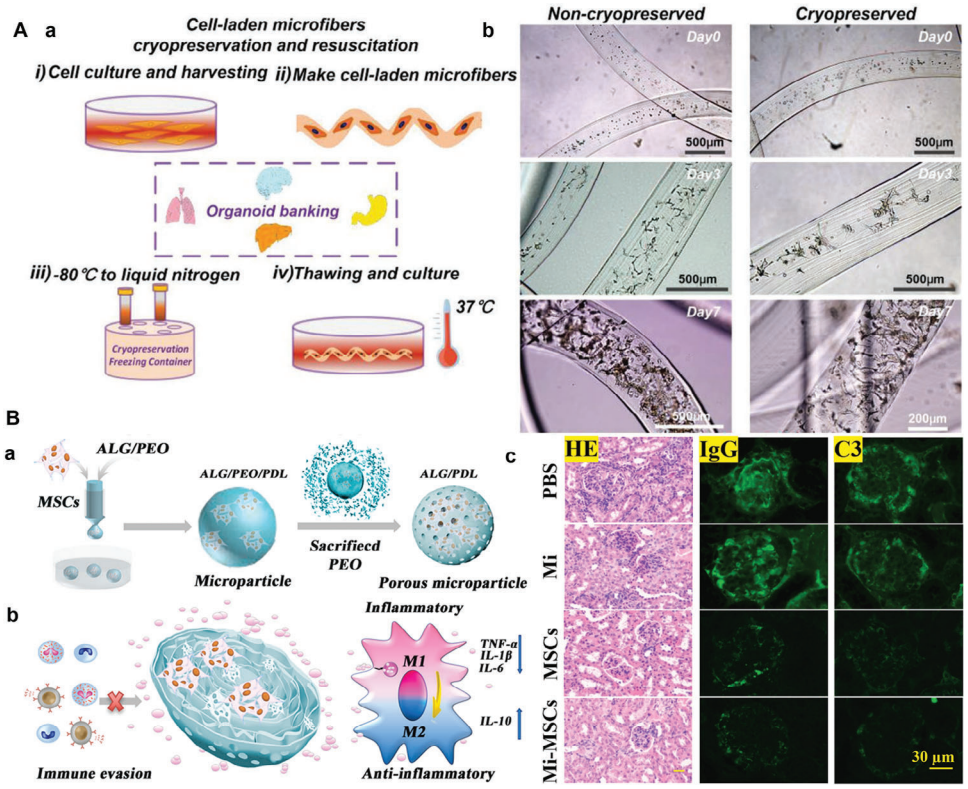



**Figure 13.** Cell-loaded microporous hydrogels for other biomedical applications. A) Schematic diagram of long-term preservation of microporous microfibers as cell carriers and microscopy images of microporous microfibers loading cells. Reproduced with permission.[88b] Copyright 2019, John Wiley and Sons; B) Schematic diagram, histological and cell fluorescence images of encapsulation of cells in microporous hydrogels for release active substances. Reproduced with permission.[126a] Copyright 2021, Elsevier.

within the hydrogels while being shielded from cellular immune rejection[15a,126] (Figure 13B). This microporous hydrogel enables the ingress and egress of cell-secreted proteins, facilitating sustained drug secretion. Importantly, this microporous structure does not impose any noticeable limitations on the types of encapsulated cells, encompassing $\beta$-cells for diabetes,[15a,127] mesenchymal stem cells for systemic lupus erythematosus, T-cells, and NK cells for tumor immunotherapy,[126b,127a] as well as tumor immune vaccines.[16b]

The microporous structure offers advantages in promoting cell growth and can also be applied in dental restorations. Moreover, adjusting pore size from micropores to nanopores can effectively target intestinal repair, facilitating inward cell growth without membrane adhesion. Additionally, cells loaded with nanopores can be utilized to establish drug production facilities, enabling pancreatic cells to consistently secrete insulin over an extended period and inducing long-term immune responses in certain cancer cells while regulating the body's resistance.

## 4. Conclusion and Future Perspective

This review provides a comprehensive overview of fabrication for microporous hydrogels and their applications as cell carriers in tissue engineering and regenerative medicine. The fabrication of microporous hydrogels was classified based on their injectability: fabrication of non-injectable microporous hydrogels including freeze-drying microporous method, two-phase sacrificial strategy, and 3D biofabrication technology, and fabrication of injectable microporous hydrogels, via microgel assembly. Microporous hydrogels have undergone extensive investigation for their potential in cellular delivery across various biomedical applications, including bone repair, nerve repair, muscle repair, and vascularization. Utilizing microporous hydrogels as a tissue engineering strategy effectively addresses critical clinical needs and provides versatile platforms for cutting-edge research in biomedicine and regenerative medicine. Additionally, they present numerous opportunities for advancing novel biomaterials.

The vast potential of microporous hydrogels for scaffold construction, both in vitro and in vivo, remains largely untapped (**Figure 14**). The micro hydrogels can be incorporated into microporous microspheres and microfibers, and then assembled to form scaffolds, thereby amplifying their biological benefits and therapeutic impacts when integrated into various systems.[25b,128] The layered microporous configuration of these carriers renders them suitable for bio-ink printing and opens up possibilities for applications in tissue regeneration.[129] It's worth noting that there are works of literature regarding the loading of probiotics and genetically engineered bacteria into microporous hydrogels. Phages offer an alternative approach for preparing microporous hydrogels, serving as an alternative to antibiotic-loaded systems aimed at mitigating adverse drug effects.[130]


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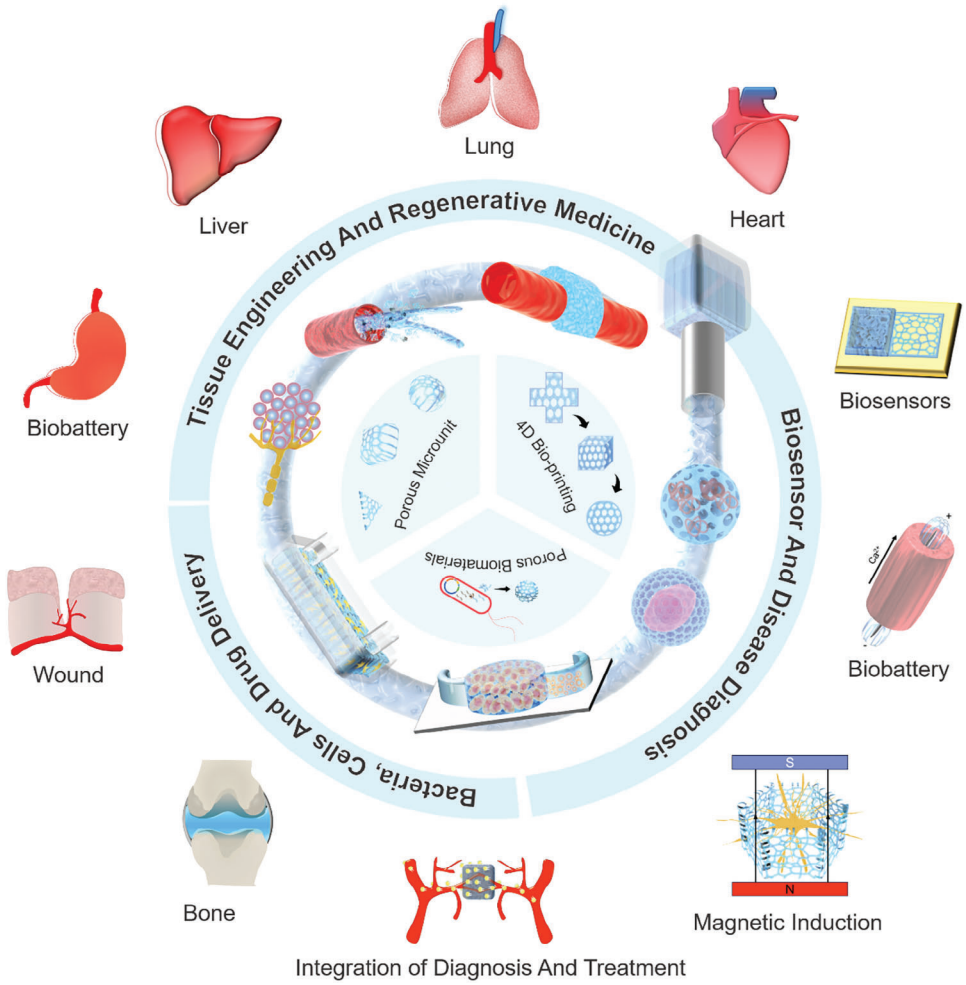



**Figure 14.** The future perspective of applications of microporous hydrogels, for which implants, diagnostic functions, 4D bioprinting, etc. as well as their convergence is inevitable.

While 3D printing technology holds promise for creating personalized structural models for specific wound injuries, accurately modeling complex hierarchical tissue structures and constructing microporous networks remains a significant challenge. Volumetric bioprinting has the potential to facilitate bioprinting of microporous hydrogel system models.[131] Another potential application involves the utilization of 4D printing to fabricate programmable neurovascular conduits and trachea or to mimic natural tissue structural surfaces, which can contribute to the repair of neurovascular injuries.[132] Additionally, leveraging 3D printing technology to fabricate microporous hydrogels also opens up new opportunities for advancement in medicine and biology. Through personalized customization, patients can receive a more tailored treatment plan, which could potentially lead to advancements in living 3D printing.[133] The most prevalent method for utilizing microporous hydrogels post-printing is through surgical implantation. Hence, there's a growing need for injectable microporous hydrogels capable of retaining their intended microporous structure.[24a,28a] Additionally, there's been a scant investigation into taking advantage of the microporous hydrogel as conventional therapeutic agents such as aerosols, while pioneering treatment and detection approaches like microneedles and microgels robots remain largely untapped.[134]

Despite advancements in tissue engineering and regenerative medicine, the restoration of function, including microvasculature, remains a challenge; however, the properties of microporous hydrogels that promote cell growth offer a potential solution to this issue. Bioprinting microporous hydrogels can be integrated into the body to enhance cell infiltration, thereby mitigating excessive or chronic inflammation in vitro and in vivo.[135] This makes them more effective in repairing damaged tissues and organs. The advancement of materials for constructing microporous hydrogels is continuously evolving, with the potential to achieve elevated porosity and refined printing through the application of microporous hydrogels in these regions. Microporous hydrogels offer great potential for biomedical research and therapies by closely mimicking the body's natural environment and providing precise control over biochemical signals. Their versatility and adjustable properties make them suitable for applications in tissue engineering and drug delivery. The utilization of microporous hydrogels in the absence of cytokine supplementation can significantly augment immunomodulatory responses,


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thereby playing a pivotal role in the field of tissue engineering and regenerative medicine.

To bolster the design and optimization of microporous hydrogel systems, there's a rising trend in employing digital model calculations and material approach design. The utilization of multiscale models allows for a thorough exploration of microporous hydrogel composite systems, covering microscopic level analysis to macroscopic mechanical evaluation, thus aiding in predicting internal properties and behaviors. Furthermore, this approach could potentially be enhanced through the integration of deep learning modules.[84a,136]

Overall, the ongoing advancements of microporous hydrogel have the potential to further enhance their impact in biomedical applications such as regenerative medicine. Microporous hydrogel will continue to drive progress in biomedicine due to its unique advantages.

## Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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## Conflict of Interest

The authors declare no conflict of interest.

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cell-loaded scaffolds, microporous hydrogels, tissue engineering and regenerative medicine

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