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REVIEW ARTICLE

3D-printed hydrogels for treating diabetic wounds: Recent developments

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Abstract

Diabetic wound healing disorder is one of the common complications in diabetic patients, characterized by chronic inflammation, impaired angiogenesis, abnormal extracellular matrix (ECM) remodeling, and markedly elevated oxidative stress. Although traditional treatment models have achieved some success, they still face challenges such as prolonged wound healing duration, increased risk of infection, and continuous formation of scar tissue, particularly in gastrointestinal surgical incisions, breast surgery incisions, orthopedic surgical incisions, and neurosurgical incisions. In recent years, the integration of biomaterials and advanced manufacturing technologies has brought new opportunities for diabetic wound healing. Hydrogels have gained increasing attention due to their excellent biocompatibility, degradability, and significant wound healing ability. As an emerging advanced manufacturing method, 3D printing technology could accurately fabricate hydrogels according to the shape and size of the wound, providing an ideal microenvironment for wound healing. This work systematically reviewed the latest research on 3D-printed hydrogels in diabetic wound healing in the past 5 years. It also thoroughly discussed the preparation methods, including physical, chemical, and biological cross-linking methods, and the specific mechanisms of promoting wound healing, such as regulating inflammatory response, promoting angiogenesis, and guiding the normal remodeling of ECM. This review aimed to provide a solid theoretical and experimental basis for the continued development and eventual clinical application of 3D-printed hydrogels for diabetic wounds.

Keywords: 3D-printed hydrogel; Diabetic wound; Mechanism; Preparation method; Surgical incision

1. Introduction

Diabetes mellitus (DM), as a typical metabolic disorder, is characterized by persistently abnormally elevated blood glucose levels. Its pathological basis is closely related to insufficient insulin secretion or functional defects, causing multiple organ damage and a series of serious complications, such as renal impairment, visual impairment,

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neuropathy, and cardiovascular diseases.[1,2] According to epidemiological data and the Diabetes Atlas of the International Diabetes Federation, the global prevalence of diabetes rose dramatically to 536 million patients by 2021 and is projected to reach 783 million by 2025.[3–5] It is noteworthy that China ranked first worldwide in terms of the diabetic patient population, with the number of adult diabetics reaching a staggering 148 million in 2022, representing approximately 18% of the global total. This situation significantly impacted patients' lives and imposed a considerable strain on the healthcare system.[6]

During normal wound healing, superoxide anion (O^{2-}) and hydrogen peroxide (H_2O_2) are essential to prevent infection. Small amounts of reactive oxygen species (ROS) can promote collagen and fibronectin production, neovascularization, fibroblast proliferation and migration, and epithelial tissue regeneration. However, in diabetic patients, hyperglycemia not only provides a favorable environment for bacterial proliferation but also leads to a significant increase in ROS levels in the body by activating polyol pathways and accumulating advanced glycation end products. These cause changes in skin structure and function, damaging the mechanical integrity of the skin, and weakening its self-healing ability. Eventually, chronic wounds form.[7] From the molecular mechanism perspective, hyperglycemia persistently exerts negative impacts on cell functions, vascular endothelial growth factor (VEGF) expression, and inflammatory responses. For example, it inhibits the proliferation and migration of fibroblasts, down-regulates the expression of VEGF, induces neovascularization dysfunction, leads to insufficient blood supply in local tissues, and excessive expression of pro-inflammatory factors, further aggravating the complexity of wound healing.[8]

Diabetic wound healing is a complex and dynamic process; the chronic inflammation, oxidative stress, and cellular dysfunction caused by hyperglycemia significantly delay the healing process and often fail to complete normal healing.[9–12] Research hotspots for different stages are emerging, including new hemostatic material development, macrophage polarization regulation,[13,14] ROS clearance,[15] angiogenesis and nerve regeneration, collagen deposition, and scar regulation. Nevertheless, the current traditional treatment methods, such as dressing coverage, debridement, and antibiotic therapy, have obvious limitations. For example, it is difficult to precisely regulate the wound microenvironment, cope with complex pathophysiological changes, adapt to the diversification of wound morphology, and treat deep ulcers or complex infections.[16] Besides, antibiotic therapy is also facing the risk of drug resistance, and there exists a notable shortage of individualized treatment strategies. An ideal modern wound dressing should possess excellent moisturizing ability, air permeability, and exudation management capabilities to establish a suitable humid environment while effectively preventing the accumulation of effusion and subsequent infections.[15] At the same time, it is imperative for the dressing to exhibit excellent antibacterial capabilities, mechanical strength, and biocompatibility, enabling it to effectively repel external bacterial intrusion, safeguard the wound against external trauma, and minimize the likelihood of rejection.[17,18] Furthermore, the design of the wound dressing should prioritize ease of clinical handling, ensuring that medical staff can effortlessly perform essential operations.

Recently, the field of wound dressings for healing prolonged diabetic wounds has witnessed remarkable progress, achieving a leap from traditional dressings to a variety of new material systems. Among them, hydrogel dressings can mimic a natural moist environment due to their high water content, thereby fostering cell migration and proliferation.[19] Additionally, the 3D network structure allows the free exchange of oxygen and nutrients while blocking the invasion of pathogens.[20] Moreover, certain hydrogels can be engineered to incorporate bioactive ingredients, such as antibacterial agents and growth factors, enabling precise regulation of biological activity and thereby expediting the wound healing process.[21–24] However, traditional hydrogels still exhibit limitations, including insufficient mechanical strength, uncontrollable pore structures, and the uneven release of antibacterial components.[25]

As bio-manufacturing technology advances rapidly, 3D printing has broken through traditional hydrogel preparation limits, achieving an upgrade from structural biomimicry to functional integration and providing smarter, personalized solutions for diabetic wound healing. For example, through precise adjustment of printing parameters and material composition, it is possible to optimize the moisturizing and breathable characteristics of the dressing, while also enabling the accurate incorporation of antibacterial agents. Its layer-by-layer manufacturing ability enables the construction of biomimetic gradient structures to mimic the mechanical properties of natural tissues, further improving the adaptability of dressings to wounds. Thus, this modern dressing, with its multifunctional and optimized design, is of great significance in addressing the limitations of traditional dressings, accelerating wound healing, improving patient prognosis, and shortening the rehabilitation cycle.

In view of the unique advantages and great potential of 3D-printed hydrogels in diabetic wound healing, it is of scientific and clinical significance to explore their preparation methods and mechanisms of action. This review systematically summarizes the research progress in 3D-printed hydrogels over the past 5 years, aiming to provide a solid theoretical basis and technical support for the development of a new generation of smart wound dressings for diabetic wound healing.

2. Preparation methods for 3D-printed hydrogels

As a cutting-edge technology, 3D printing is deeply integrated with hydrogels, opening up a new path for the biomedical field and effectively overcoming the limitations of traditional cross-linking methods. Currently, the preparation methods for 3D-printed hydrogels primarily include physical cross-linking, chemical cross-linking, and biological cross-linking methods (Figure 1 and Table 1).

2.1. Physical cross-linking method

The physical cross-linking method is one of the primary methods in the preparation of 3D-printed hydrogels. The core principle of this method is the use of non-covalent bond interactions, including hydrogen bonds, electrostatic attraction, and hydrophobic effects, to build a 3D porous network structure of hydrogels.[26] This method preserves the natural structure and biological activity of the raw materials—benefits that are of great significance for tissue engineering, drug delivery, diabetic wound repair, and the treatment of gastrointestinal surgical incisions.[27] However, hydrogels generated through a physical cross-linking method have shortcomings, such as relatively poor uniformity, mechanical strength, and long-term stability. The introduction of 3D printing technology has led to significant breakthroughs in this area, playing an important role in the development of improved materials for diabetic wound healing.

The temperature-induced cross-linking method is an important type of physical cross-linking. It regulates the non-covalent interactions between molecules to

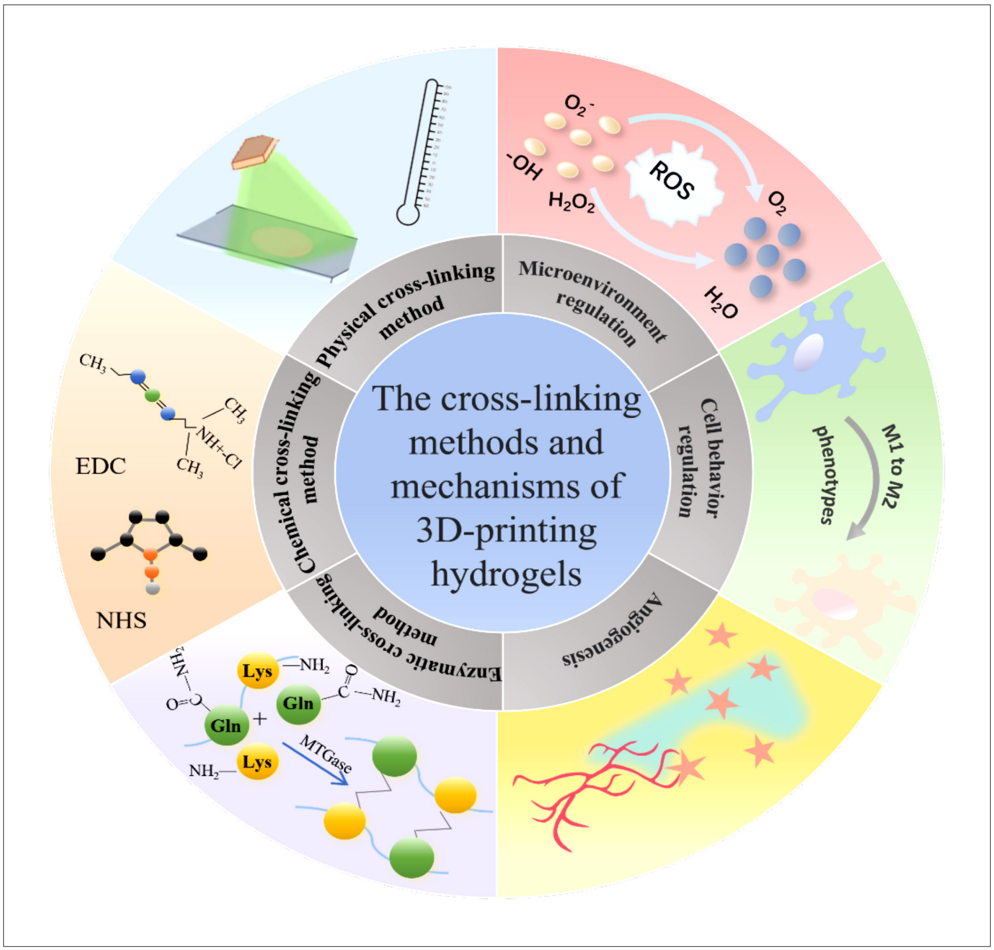

Figure 1. The cross-linking methods and mechanisms of 3D-printed hydrogels. Abbreviations: EDC, 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide; Gln, glutamine; Lys, lysine; MTGase, microbial transglutaminase; NHS, N-Hydroxysuccinimide; ROS, reactive oxygen species.

achieve gelation through temperature changes. At low temperatures, raw materials remain stably in a soluble state; when the temperature rises to physiological range, they spontaneously assemble to form fiber networks through non-covalent forces. For example, Drzewiecki *et al.*[28] used microbiota-modified collagen to generate collagen methacrylamide (CMA). This hydrogel retained the self-assemblability, biodegradability, and natural biological activity of collagen. Under the physiological temperature and pH conditions, CMA exhibited rapid and temperature-dependent reversible self-assembly. Rombouts *et al.*[29] prepared a silk fibroin–collagen hydrogel that achieved reversible state changes through temperature switching (Figure 2A). When the temperature was increased to 40°C, the silk proteins self-assembled, whereas upon cooling to 20°C, the self-assembly process became synchronized with the formation of triple helix structures. Moreover, the introduction of anionic polypeptide poly(γ-glutamic acid) into the CMA hydrogel effectively enhanced the temperature-dependent phase transition behavior of collagen, resulting in a low-viscosity solution at room temperature and a non-flowing gel at approximately 37°C.[30] However, it is still challenging to precisely control the gelation time, porosity, and mechanical properties of collagen hydrogels.

Through the integration of computer-aided design (CAD) and precise temperature gradient control, 3D printing technology enables the realization of structural precision and functional customization in hydrogel fabrication. Studies have shown that bovine serum albumin demonstrates a concentration-dependent gelation when heated at or above its melting point at a pH far from its isoelectric point. Naik *et al.*[31] incorporated aloe vera into bovine serum albumin and prepared a hydrogel using 3D printing technology. The results revealed that the local application of this hydrogel effectively stimulated collagen deposition, thereby promoting wound healing in diabetic patients, increasing VEGF expression, and improving the delivery of nutrients required for angiogenesis and collagen synthesis. Based on a template replication and 3D printing strategy, Zhang *et al.*[32] developed a novel type of biomimetic adaptive indwelling microneedles, which consisted of adjustable polyvinyl-alcohol-hydrogel needle tips encapsulating mesenchymal stem cell-derived exosomes, along with a removable 3M medical tape serving as the supporting substrate. The results showed clinical values in the treatment of diabetic complications. Likewise, Xia *et al.*[33] used 3D printing technology to construct scaffolds by mixing gelatin methacrylate (GelMA) with adipose-derived stem cells (ADSCs) and incorporating the anti-inflammatory antioxidant curcumin, achieving 85% porosity and a cell survival rate of 92%. The temperature-induced cross-linking method rapidly fabricated the scaffold at 37°C, while the interlayer bond strength was improved by optimizing the temperature gradient (gradually increasing from 20 to 37°C) to two times that of the traditional method, thereby significantly enhancing the mechanical stability.

Wound-site bioelectrical stimulation can accelerate wound healing processes by supporting regular collagen deposition and proper extracellular matrix (ECM) remodeling. Kumi *et al.*[34] used 3D printing technology to develop a customized antibacterial porous flexible electrode (APFE) hydrogel dressing that combined the antibacterial properties of modified chitosan (CS) derivatives with the conductivity of poly(3,4-ethylenedioxythiophene):polystyrene sulfonic acid (PEDOT:PSS). This electrical stimulation dressing enabled the delivery of targeted treatment to promote the healing of infected diabetic wounds.

In addition, Metwally *et al.*[35] fabricated a bilayer hydrogel scaffold via hyaluronic acid/CS (HA/CS) inks (Figure 2B). The scaffold consisted of an upper dense planar hydrogel layer and an antibacterial/regenerative nanofiber layer integrated with poly (lactic acid) nanofiber microspheres. Compared with traditional hydrogels, this hydrogel represents a transition from passive dressings to actively regulated, precision treatment platforms through digital extrusion printing. It not only replicates the bionic bilayer structure of the skin but also generates a customizable multi-level pore network through the incorporation of drug-loaded nanofiber microspheres, thus structurally surpassing the uniform random pores of traditional hydrogels. Furthermore, this design enables the efficient loading, uniform distribution, and sustained release of ZnO nanoparticles and didecyldimethylammonium bromide, ultimately producing a synergistic effect of strong antibacterial properties, modulation of the inflammatory microenvironment, and significant acceleration of tissue regeneration. In diabetic wound infection models, it achieved an ultra-high healing rate of 95%, a level difficult to attain with traditional hydrogels.

Although the physical cross-linking method offers unique advantages, it also presents notable drawbacks. For example, inadequate control over cross-linking uniformity can produce hydrogels with compromised mechanical properties, reduced strength, and diminished stability. During *in vivo* applications, the rapid degradation rate of certain materials may render them unsuitable for scenarios demanding high mechanical strength or prolonged implantation periods. This accelerated degradation can compromise the hydrogel's structural integrity over time, thereby adversely affecting the overall therapeutic outcome.

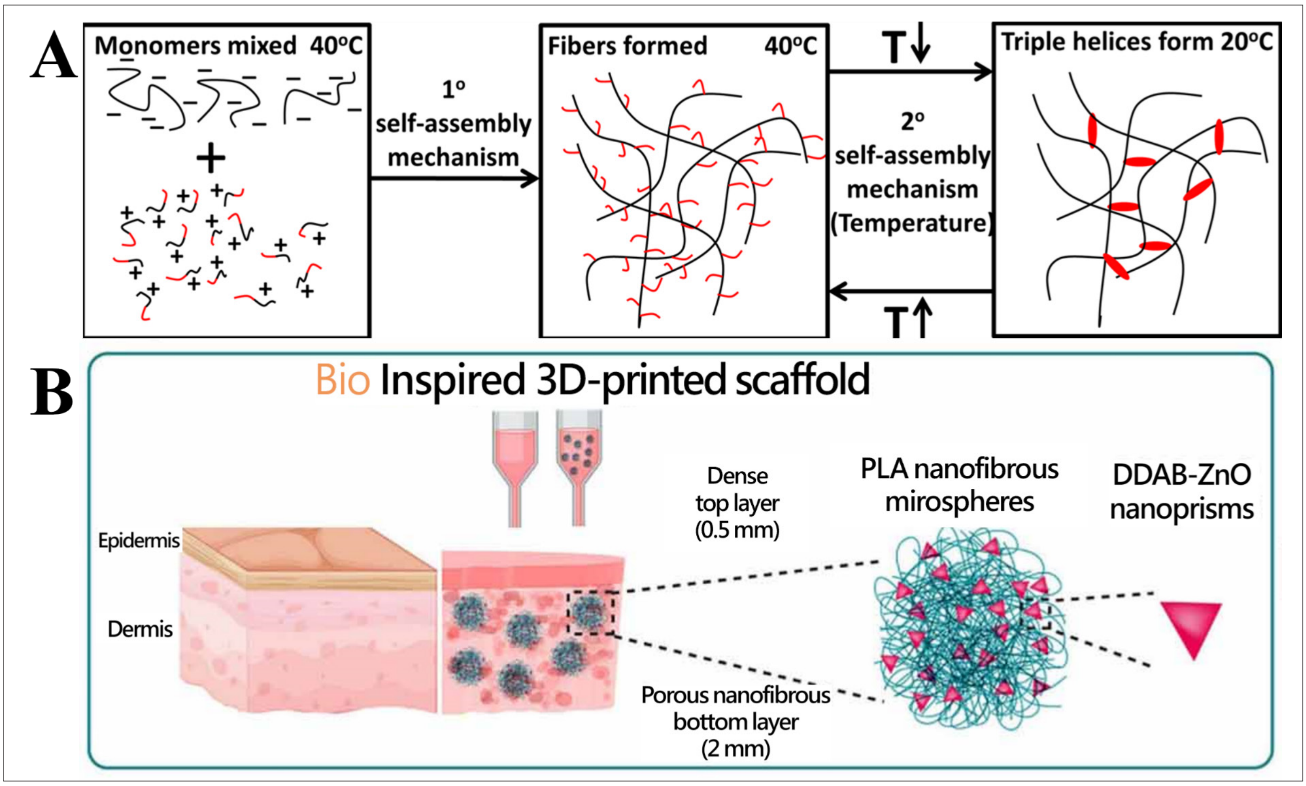

Figure 2. Schematic diagram of the preparation of physical cross-linked hydrogels. (A) The states of collagen hydrogel at different temperatures. Adapted with permission from Rombouts *et al.*[29] Copyright © 2015 American Chemical Society. (B) Schematic process for the developed, bioinspired composite DZ-MS@scaffold. Adapted from Metwally *et al.*[35] Abbreviations: DDAB, didecyldimethylammonium bromide; DZ, DDAB-treated ZnO nanoparticle; MS, microsphere; PLA, poly (lactic acid).

2.2. Chemical cross-linking method

Due to the unique mechanism of action and significant advantages, the chemical cross-linking method has become a research hotspot in the field of biomaterials. The method can precisely control the degradation rate of hydrogels by precisely regulating the types and concentrations of cross-linking agents, meeting the varied requirements of different treatment scenarios. The key factor in preparing hydrogels via the chemical cross-linking method lies in selecting appropriate cross-linking agents, which significantly influence a hydrogel's properties, degradation rate, and overall performance. With the directional modification of key functional groups, such as –CHO and $-NH_2$, within a molecular structure, specific chemical reactions are triggered to facilitate the formation of cross-linking between molecular chains. This tailored approach enables the fabrication of hydrogel structures that are precisely engineered to meet distinct functional requirements for targeted applications.[36] 3D-printed hydrogels obtained through the chemical cross-linking method are an ideal solution for solving personalized medical requirements, particularly in the treatment of diabetic wounds.

2.2.1. Photo–cross-linking method

The photo–cross-linking method represents a pivotal approach in chemical cross-linking. It utilizes photosensitizers, such as riboflavin and methacrylic anhydride, to initiate free radical reactions under specific wavelengths of light sources. This process leads to the formation of covalent bonds or dynamic coordination bonds, ultimately constructing a 3D network structure within the hydrogel.[37] Besides, the photo–cross-linking method exhibits rapid gelation, with gelation times reaching the sub-second range under optimal conditions. This property aligns well with the immediate molding requirements of 3D printing technology and is particularly suitable for rapid wound closure in diabetic wound healing. Chen *et al.*[38] fabricated a 3D-printed dual-network hydrogel incorporating ceria-based metal–organic framework (MOF) nanoenzymes, consisting of a cerium–cross-linked sodium alginate network and a polyacrylamide network. During the printing process, 365 nm ultraviolet light was used to promote the polymerization of acrylamide. After printing, the sample was further cured under ultraviolet light for 10 min to achieve rapid cross-linking. Owing to the anti-inflammatory and hypoglycemic effects of the nanoenzyme hydrogel, wounds of 1 cm^2 in size in diabetic rats were completely healed within 21 days. Similarly, Cao *et al.*[39] addressed excessive ROS and the imbalance between pro-inflammatory and anti-inflammatory cells/factors by preparing a wound dressing consisting of doxycycline hydrochloride-loaded, ROS-responsive polyurethane membranes combined with 3D-printed hydrogel strips using the photoinitiator lithium phenyl-2,4,6-trimethylbenzoylphosphinate (LAP). This multifunctional dressing significantly accelerated the healing of chronic wounds, exhibiting enhanced epithelialization, angiogenesis, and collagen deposition.

Li *et al.*[40] developed a highly self-supporting CS-based hydrogel ink using the photoinitiator Irgacure 2959 for the *in situ* 3D printing of diabetic wound dressings. The ink formed a reversible, physically cross-linked structure through multiple electrostatic interactions and hydrogen-bond networks between carboxymethyl CS and clay nanoparticles. Even after autoclaving, the ink retained its ability to undergo ultraviolet cross-linking, and the photoinitiator remained intact, non-toxic, and biocompatible. The resulting 3D-printed dressings exhibited both antibacterial and pro-angiogenic properties, significantly accelerating wound healing, achieving complete healing within 17 days, accompanied by hair follicle regeneration and angiogenesis. This work not only provides a new strategy for developing highly self-supporting biopolymer inks but also paves the way for advanced, personalized wound dressings.

Ding *et al.*[41] fabricated a multifunctional hydrogel dressing via digital light processing (DLP) technology, inspired by the ECM properties of *Acomys* (African spiny mouse) during wound healing. They introduced methylacryloyl groups into GelMA and HA methacrylate (HAMA), endowing the molecular chains with photosensitive groups capable of undergoing free radical polymerization under ultraviolet light in the presence of photoinitiators, thereby forming a covalently cross-linked network. The precise control over the structural, mechanical, and biological properties of hydrogels was achieved through the photosensitivity of GelMA/HAMA and DLP-based light-curing printing.

Hu *et al.*[42] fabricated an ECM-based 3D-printed dermal hydrogel scaffold loaded with Cu–epigallocatechin gallate capsules. They reacted decellularized ECM (dECM) derived from pigskin with glycidyl methacrylate anhydride, introducing photo–cross-linkable methacrylate groups to form a methacrylated decellularized extracellular matrix (EM). Then it was mixed with the photoinitiator LAP to prepare the bio-ink. Upon ultraviolet (350 nm) irradiation, the double bonds in EM underwent photo-initiated free radical polymerization, forming covalently cross-linked hydrogels. Notably, the EM hydrogel also exhibited temperature-sensitive properties, remaining in a gel state at low temperatures and transitioning into a gel state near body temperature. This combination of physical and chemical cross-linking not only facilitated printing and shaping but also endowed the scaffold with excellent mechanical properties and biological activity. Furthermore, the hydrogel scaffold inhibited excessive inflammation by promoting macrophage polarization from M1 to M2, while supporting the organization of endothelial cells into stable tubular structures essential for neovascularization.

Xia *et al.*[33] used the same method, simultaneously loading curcumin into a 3D-bioprinting hydrogel to create a suitable microenvironment for ADSCs. They demonstrated that curcumin enhanced the reparative effects of ADSCs on diabetic wounds by targeting the advanced glycation end product (AGE)/AGE receptor/p65 signaling pathway. Likewise, Wan *et al.*[43] synthesized modified Has, including maleinated sodium hyaluronate (MHA) and thiolated sodium hyaluronate (SHHA), with highly substituted acrylate groups. MHA/SHHA hydrogels were prepared by blending the modified HA with mercaptoacrylate via Michael addition pre-cross-linking, followed by covalent cross-linking through thiol–acrylate and acrylate–acrylate photopolymerization. These hydrogels represented promising hydrogel scaffold candidates for diabetic wound healing.

2.2.2. Schiff base reaction

The Schiff base reaction, a mild and efficient condensation reaction between –CHO and –NH$_2$ groups forming an imine bond (C=N), plays a crucial role in hydrogel preparation. It allows adjusting the proportion of reactants and precisely controlling the reaction conditions, such as temperature, pH value, and reaction time.[44] The introduction of 3D printing technology enables the precise fabrication of hydrogels through layer-by-layer stacking based on pre-designed models. By precisely controlling printing parameters and the conditions of the Schiff base reaction, hydrogel scaffolds with complex 3D structures can be directly fabricated. Moreover, adjusting the degree of Schiff base cross-linking allows the optimization of the mechanical properties and pore structure of the 3D-printed hydrogels to better match the specific requirements of different tissue engineering applications.

Common cross-linkers used in Schiff base reactions include genipin, dialdehyde cholesterol-modified starch, and oxidized konjac glucomannan. They can react with different polymer matrices to tailor the properties of 3D-printed hydrogels. Fu *et al.*[45] used multi-cross-linking strategies, including free radical polymerization, Michael addition, Schiff base reaction, and hydrogen bonding, to fabricate a cell-loaded collagen-based bio-ink consisting of CMA and dihydromyricetin. Following oxidation, dihydromyricetin generates aldehyde groups that participate in Schiff base formation, while unreacted phenolic hydroxyl groups retain ROS-scavenging ability. This multiple cross-linking strategy accelerated gelation by 375%, increased stiffness by 161%, enhanced mechanical elasticity by 231%, and improved biodegradability by 208%.

Yang *et al.*[46] prepared 3D-printed grid-like hydrogels loaded with deferoxamine, cross-linked via Schiff base bonds between –CHO from oxidized mannan oligosaccharides and $-NH_2$ from hyaluronic acrylamide. These hydrogels not only exhibited antioxidant effects and regulated inflammatory responses but also promoted wound angiogenesis, providing a novel strategy for diabetic wound healing. Lin *et al.*[47] utilized Schiff base reactions between the aldehyde group of oxidized sodium alginate and the amino group of gelatins to prepare bio-inks containing sodium alginate, oxidized sodium alginate, gelatin, and $CaCO_3$ microspheres, thereby enhancing their printability. The resulting porous 3D-printed hydrogel scaffolds featured a stable structure (pore area: 4.43 ± 0.14 μm^2; wire diameter: 184 ± 25 μm), providing a potential solution for improving diabetic wound healing.

While dynamic hydrogels are valuable for tissue healing, improving their adaptability to complex chronic wounds without additional active substances remains a major challenge. To address this, Ding *et al.*[48] developed a 3D-printed hydrogel scaffold from aldehyde-modified dextran and benzaldehyde (DEX-BA) and MoS_2 nanosheets. This hydrogel scaffold formed dynamic Schiff base bonds with tissue protein $-NH_2$ on the surface of wounds through –CHO provided by DEX-BA, achieving strong adhesion to the wound surfaces. Application of 3D printing of the scaffolds into chronic diabetic wounds accelerated wound healing, promoted wound closure, mitigated oxidative stress, and eradicated bacterial infections, highlighting its potential as a multifunctional *in-situ* 3D-printed hydrogel scaffold for diabetic wound healing and other tissue engineering applications.

2.2.3. Click chemical cross-linking reaction

The click chemical cross-linking method is another common method to prepare 3D-printed hydrogels. It enables rapid and site-specific cross-linking through bio-orthogonal reactions to construct highly uniform 3D network structures. Hydrogels prepared via click chemistry typically exhibit exceptional hyperelasticity, shear-thinning behaviors, self-healing properties, and extremely low swelling ratios. Besides, the click chemical cross-linking process effectively avoids the generation of toxic by-products, significantly improving cell survival rates and ensuring long-term encapsulation stability.[49] Common reactions include copper-catalyzed azo-alkynyl cycloaddition, copper-free click reactions, strain-enhanced azo-alkynyl cycloaddition, and sulfyl-Michael addition.[50]

The combination of click chemical cross-linking and 3D printing technology represents a novel approach for fabricating hydrogels with precise structures and superior functional properties, thereby offering promising opportunities in biomedical applications. The structure and shape of 3D-printed hydrogels can be accurately designed according to specific requirements, while click chemical cross-linking ensures the formation of stable 3D network structures during the printing process, facilitating the fabrication of complex structures with sub-micron precision.

However, limited research has been reported on the preparation of 3D-printed hydrogels via the click chemical cross-linking strategy, limiting their broader adoption and advancement in the field. Huang *et al.*[51] developed a full-peptide 3D-printed hydrogel platform using a one-step thiol-ene click chemistry method, enabling the encapsulation of VEGF165-overexpressing cells under physiological temperatures (Figure 3). Through DLP technology, they fabricated hydrogel scaffolds with high resolution (up to 10 μm) and intricate structures such as branching vascular networks, providing a novel strategy for constructing advanced bioactive scaffolds.

2.3. Enzymatic cross-linking method

The enzymatic cross-linking method refers to an efficient cross-linking process under mild reaction conditions, leveraging the specific catalytic activity of enzymes to facilitate rapid and biocompatible material modification. This method effectively preserves the native structure and bioactivity of collagen and other biomolecules by circumventing damage caused by harsh conditions, such as high temperature, extreme pH (strong acid/alkali), and ultraviolet radiation, thereby maintaining their biological integrity to the greatest possible extent.[52] Moreover, enzymatic cross-linking eliminates the need for toxic chemical cross-linking agents, enhancing the biocompatibility of the final products, thus making it particularly well-suited for *in vivo* applications or the development of advanced biomedical materials. In addition, enzymatic reactions exhibit high substrate specificity, enabling the accurate identification and targeting of specific cross-linking sites, thereby achieving precise regulation of the cross-linking process. This precise regulation not only preserves the functional activity of biomaterials but also significantly reduces potential side effects, providing a strong guarantee for the preparation

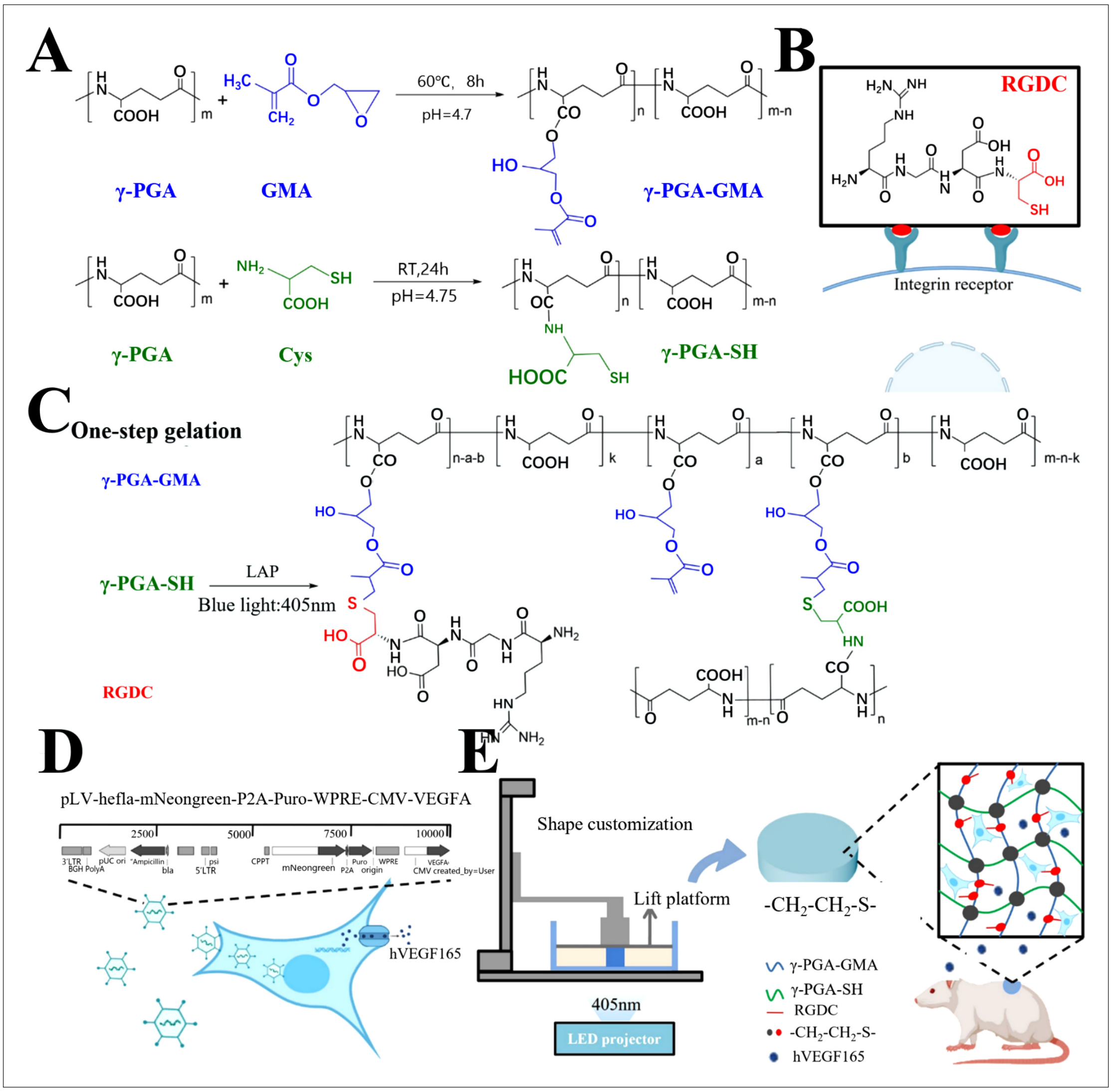

Figure 3. Design of cell-printable peptide hydrogel platform to produce self-renewable VEGF165 for diabetic wound healing. (A) Synthetic routes of γ-PGA-GMA and γ-PGA-SH. (B) Chemical structure of RGDC, which presents additional thiol groups compared to RGD. (C) One-step generation of all-peptide hydrogels using the thiol-ene click reaction of γ-PGA-GMA with γ-PGA-SH and RGDC. LAP is a type of photoinitiator that is stimulated by blue light. (D) Transfection of VEGF165 transcript-carried lentivirus in HUVECs for overexpressing VEGF165. (E) Printing the HUVEC$^{vegf165+}$-laden peptide hydrogels for diabetic wound healing using sustained-release VEGF165. Adapted from Huang *et al.*[51] Abbreviations: γ-PGA-GMA, glycidyl methacrylate-conjugated γ-polyglutamic acid; γ-PGA-SH, thiolated γ-polyglutamic acid; HUVEC, human umbilical vein endothelial cell; LAP, lithium phenyl-2,4,6-trimethylbenzoylphosphinate; RGDC, thiolated arginine-glycine-aspartate; RT, room temperature; VEGF, vascular endothelial growth factor.

of high-performance biomaterials. With the use of 3D printing technology, the 3D structure of hydrogels can be accurately designed, while the enzymatic cross-linking method enables rapid and mild stabilization of structures during the printing process, ensuring optimal mechanical properties and biocompatibility in the final hydrogel constructs.

Zhang *et al.*[53] prepared an injectable hydrogel system that contained type collagen tyramine (Col-TA) and HA tyramine (HA-TA) using horseradish peroxidase (HRP) and H_2O_2. HRP rapidly catalyzes the oxidation of phenolic hydroxyl groups in Col-TA and HA-TA to generate ROS intermediates within 10 s under physiological conditions, and promotes the formation of covalent diamine cross-links between tyramine molecules. Likewise, Mahran *et al.*[54] prepared a 3D-printed biocatalytic scaffold consisting of mesoporous SiO_2 hydrogels suitable for the immobilization of enzymes with different properties (Figure 4). Sakai *et al.*[55] prepared 3D-printed hydrogel wound dressings using a precursor ink containing phenolated CS and CS nanofibers, which underwent HRP-mediated gelation. By adjusting the content of phenolated CS and CS nanofibers, the viscosity of the ink, the gelation time, and the mechanical performance of the 3D-printed hydrogels could be precisely controlled. While this process enabled the fabrication of hydrogels with enhanced mechanical robustness, its reliance on H_2O_2 as an oxidizing agent introduced oxidative by-products that may compromise biocompatibility and pose cytotoxicity risks.

Huang *et al.*[56] utilized transglutaminase, an enzyme with broad substrate specificity and high catalytic efficiency, to covalently cross-link gel with recombinant human type III collagen. This enzymatic approach facilitated the formation of ε-(γ-glutamyl)lysine isopeptide bonds between protein molecules under mild reaction conditions, thereby circumventing the cytotoxicity associated with chemical cross-linking agents. Meanwhile, this approach also preserved both the biocompatibility and 3D printability, offering an efficient strategy for fabricating whole-protein hydrogel scaffolds with excellent mechanical stability and cell-adhesive properties.

Jafari *et al.*[57] fabricated biocompatible Gel-chito-oligosaccharides (COS) hydrogels through a dual cross-linking strategy, including co-enzyme-mediated cross-linking via glucose oxidase (GOx)/HRP and a phenolated polyelectrolyte complex. The cross-linking was initiated through spontaneous electrostatic interaction between positively charged CS and COS and negatively charged phenolated alginate, followed by mild co-enzymatic cross-linking triggered by H_2O_2 gradually released from the GOx reaction. This hydrogel showed strong potential in treating diabetic foot and venous leg ulcers through its combined protective, healing, and antimicrobial properties. Zhou *et al.*[58] developed a 3D-printed GelMA hydrogel with adjustable flow properties, shear-thinning behavior, and dual-stage cross-linking. The hydrogel maintained cell viability while providing long-lasting structures for tissue engineering applications.

2.4. Optimization of 3D printing parameters

In addition to cross-linking methods, the optimization of 3D printing parameters is also crucial for the performance of hydrogels. In recent years, artificial intelligence (AI) technology has been introduced to efficiently optimize the printing process. Optimization of 3D bioprinting parameters, including temperature, extrusion pressure, and cross-linking kinetics, is essential for fabricating hydrogel scaffolds with high structural fidelity and uniform material properties.[59] Traditional parameter optimization in 3D bioprinting depends heavily on operators' experience and numerous time-consuming experiments, resulting in inefficient processes that are challenging to standardize.

Mohammad *et al.*[60] accurately predicted the rheological properties of 3D-printed polyacrylamide hydrogels using

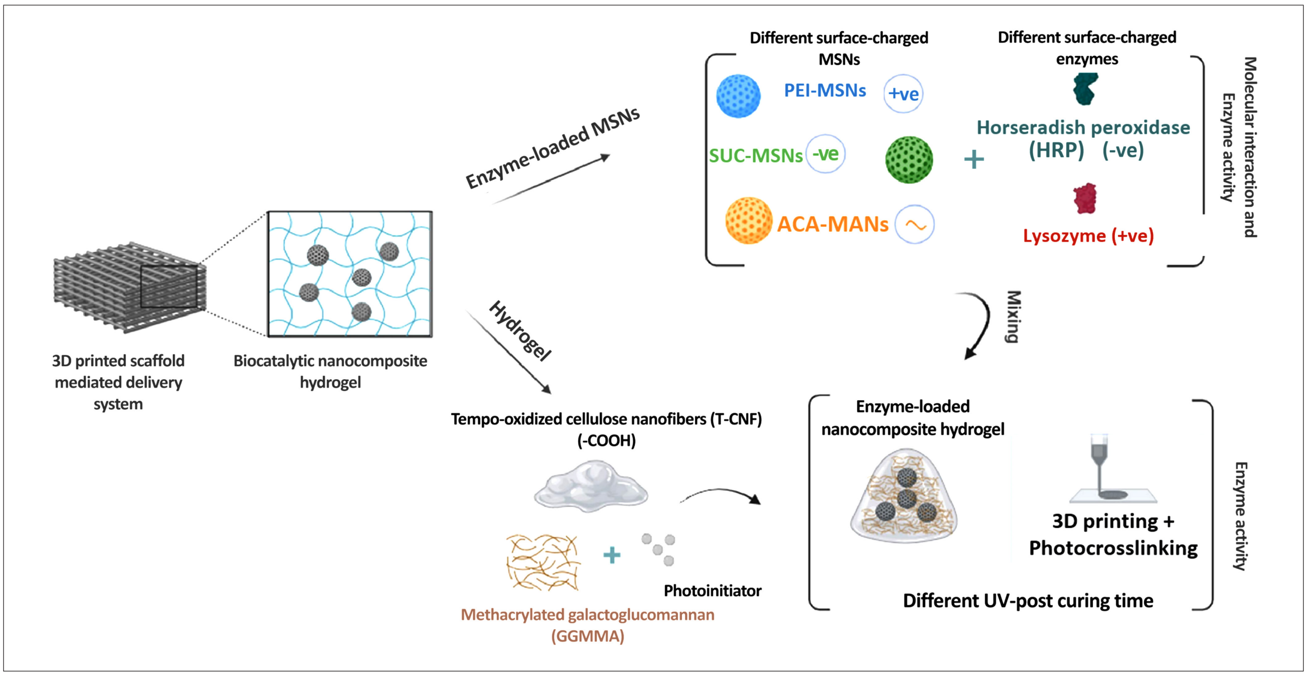

Figure 4. Schematic process of the biocatalytic mesoporous silica nanocomposite hydrogels. Adapted from Mahran *et al.*[54] Abbreviations: ACA, acetic anhydride; MSN, mesoporous silica nanoparticle; PEI, polyethylene imine; SUC, succinic anhydride.

Table 1. Comparative analysis of cross-linking methods for 3D-bioprinted hydrogels

Cross-linking method	Cross-linking agent/ condition	Printability and gelation kinetics	Advantages	Limitations	References
Physical cross-linking	Temperature	Moderate; requires precise environmental control; reversible gelation	Biocompatible, avoids chemical cross-linkers and potential cytotoxicity, allows for reversible sol–gel transitions	Poor mechanical strength, weak structural stability, rapid degradation, high sensitivity to environmental conditions	24,27
Chemical cross-linking	Photoinitiators, Schiff base reaction, click chemical reaction	High; rapid, irreversible curing; enables high-resolution printing and complex architectures	Excellent mechanical properties, high structural fidelity and stability, tunable degradation profiles	Risk of cytotoxicity from unreacted photoinitiators/ cross-linkers, potential for damaging biomolecules/ cells (UV light), irreversible process	36,37,44,49
Enzymatic cross-linking	Horseradish peroxidase, microbial transglutaminase	Low to moderate; slower gelation kinetics; requires careful optimization to prevent nozzle clogging	High bio-orthogonality and specificity, occurs under physiological conditions (e.g., mild pH and temperature), and excellent cytocompatibility	Enzyme activity can be sensitive to printing parameters (e.g., shear stress and temperature), high cost of enzymes, and potential for immunogenicity	52

deep learning models and inferred multiple feasible material composition and printing parameter combinations from the target modulus values through generative AI models. These AI methods have significantly reduced the cost of experimental trial-and-error, achieving a forward mapping from material formulation to performance prediction and a reverse design from performance requirements to formula generation.

Furthermore, the advancement in 3D printing and AI technologies has enhanced material precision and adaptability, suggesting that traditional diabetes treatment strategies may soon become insufficient to meet emerging therapeutic demands. Chen *et al.*[61] developed an AI-assisted high-throughput system combining a pneumatic extrusion 3D bioprinter with AI-based image analysis to rapidly optimize 3D printing parameters for tissue engineering applications. Based on the system, the printing conditions of the hydrogel architecture with uniform structures are screened in a high-throughput manner. Similarly, Kim *et al.*[62] developed a functional 3D printing ink composed of salmon sperm DNA and sponge-inspired DNA-induced biosilica for the machine learning-based 3D printing of wound dressings (Figure 5). These biomimetic 3D-printed hydrogels provided excellent functional platforms in diabetic wound healing, demonstrating the broad prospects of the combination of 3D printing and AI in the field of diabetic wound healing.

3. Mechanisms of 3D-printed hydrogel in diabetic wound healing

Diabetic wound healing is hindered by a pathological microenvironment characterized by persistent hyperglycemia, chronic inflammation, and cellular dysfunction. The inherent design flexibility of 3D printing technology enables hydrogels to combine multifunctional components with spatially controlled structures, thereby simultaneously addressing interrelated pathological barriers at the molecular, cellular, and tissue levels. 3D-printed hydrogels can overcome these obstacles through multi-level mechanism interventions:

(i) Dynamic microenvironment regulation achieved by modulating water and oxygen permeability, promoting ROS clearance, and preventing infection.

(ii) Targeted cell behavior regulation to restore fibroblast migration, macrophage polarization, and ECM remodeling.

(iii) Accelerated angiogenesis and tissue regeneration through continuous growth factor delivery and dynamic ECM remodeling.

3.1. Regulation of microenvironment

The microenvironment is important for the biological behavior of cells, affecting cellular adhesion, migration, differentiation, proliferation, and intercellular

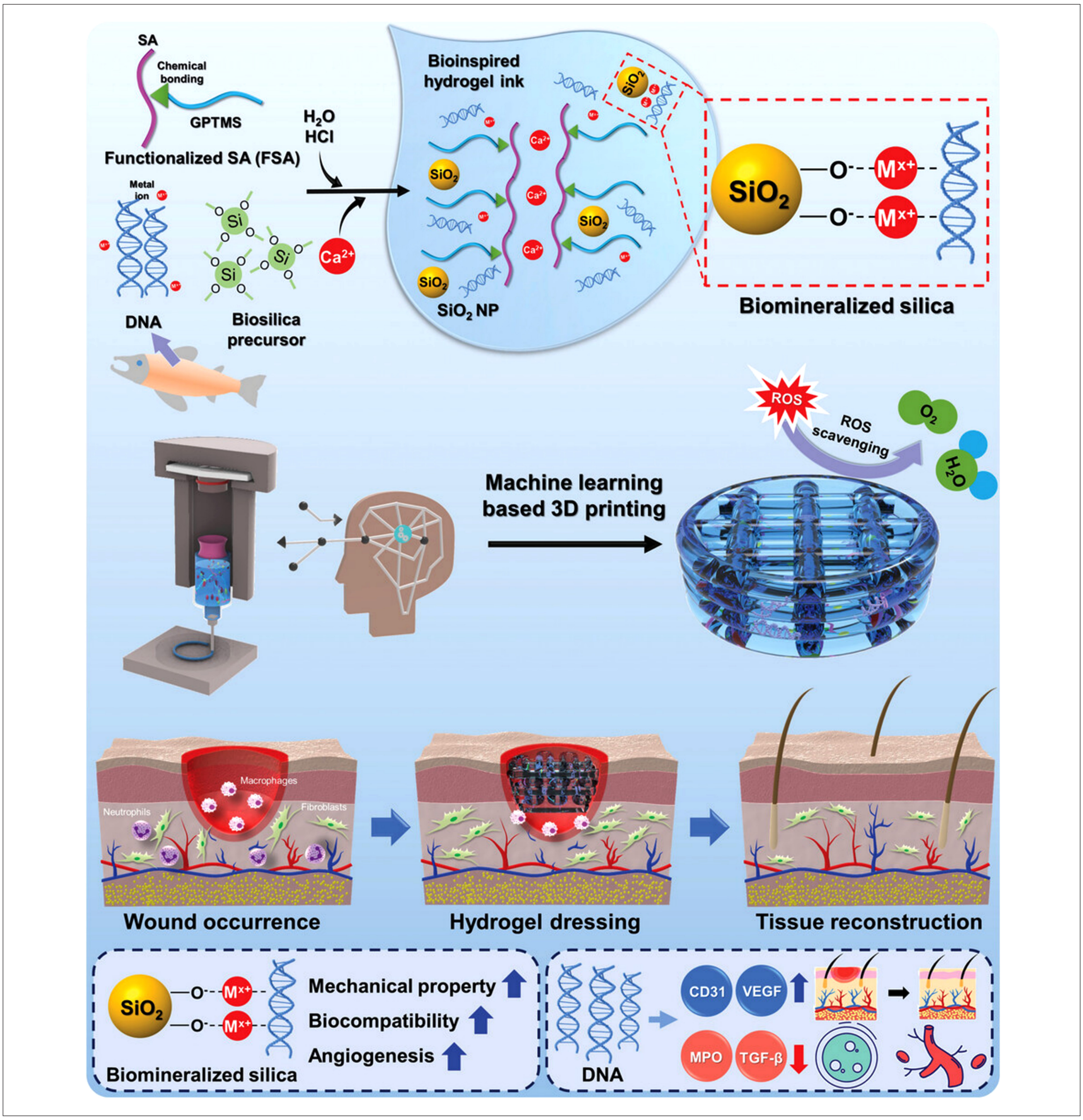

Figure 5. Schematic process of 3D-printed hydrogels by DNA-induced biomineralization. Adapted from Kim *et al.*[62] Abbreviations: CD31, cluster of differentiation 31; GPTMS, 3-Glycidoxypropyl trimethoxysilane; MPO, myeloperoxidase; NP, nanoparticle; ROS, reactive oxygen species; SA, sodium alginate; TGF-β, transforming growth factor-beta; VEGF, vascular endothelial growth factor.

communication between cells and the ECM or biomaterial surfaces. As a finely regulated "command center," the microenvironment guides cells to complete a series of life activities through a variety of signaling molecules, as well as physical and chemical factors. In addition, chemical composition, sizes, biomaterial microstructures, and cellular geometries also influence the microenvironment.[63] In diabetic wound healing, hydrogels regulate the water content of wounds, promote O_2 permeability, facilitate ROS clearance, and reduce oxidative stress responses, representing a new therapeutic strategy.

Hydrogels for diabetic wound healing must be able to absorb a large amount of wound exudates and maintain a moist microenvironment.[64] A moist wound microenvironment enhances cell survival rates, sustains growth factor release, and significantly accelerates wound healing by optimizing key healing processes, including re-epithelialization, angiogenesis, and ECM remodeling.[65] 3D printing technology, especially the extruding-based bioprinting strategy, has achieved multi-level precise control of the macroscopic structure and microscopic pores of hydrogel scaffolds by programming the rheological properties, printing parameters, and the model structure of hydrogel inks.[66] This control ability enables researchers to design and fabricate complex 3D porous architectures with customized pore size, porosity, connectivity, and spatial gradient distribution, thereby significantly optimizing the mechanical properties, swelling behaviors, and material transport characteristics of hydrogels.[67] More importantly, through multi-print head systems or functionalized inks, it is possible to achieve on-demand distribution and targeted release of bioactive molecules.[68] This synergistic regulation ability of physical structure and chemical microenvironment has greatly enhanced the comprehensive performance of hydrogel scaffolds in managing exudate at wound sites, maintaining appropriate moisture, promoting oxygen exchange, guiding directional cell migration and infiltration, and sequentially releasing bioactive factors. Thus, it creates a controlled, dynamic, and tissue regenerative microenvironment for the healing of diabetic wounds.

Kim *et al.*[62] developed a 3D-printed hydrogel by integrating marine-derived and marine-inspired materials, and found that this material rapidly absorbed wound exudates while maintaining mechanical stability during AI-assisted printing, protecting healing tissues from deformation and promoting vascularized regeneration. Likewise, Jin *et al.*[69] developed a lemon-derived GelMA/dialdehyde starch/exosome hydrogel dressing targeting the diabetic wound microenvironment and demonstrated that this hydrogel participated in immunomodulation and promoted the regeneration of vascular and fibrous tissues on macrophages. Li *et al.*[65] developed a 3D nanofiber/hydrogel core-shell scaffold that promoted diabetic wound healing by enhancing angiogenesis (Figure 6). Compared to 2D poly(*D*,*L*-lactic acid) nanofiber scaffolds, the 3D scaffold showed 1.6-times higher porosity, 21-times longer water retention, and 1.9-times greater water vapor permeability, significantly improving wound healing conditions. *In vivo* results showed that the 3D scaffold not only effectively managed wound exudates but also significantly promoted the formation of 3D capillary networks. Meanwhile, Huang *et al.*[70] loaded epinecidin-1–chitosan nanoparticles into electrospun poly(lactid acid-co-trimethylene carbonate) nanofibers and GelMa hydrogel to fabricate a thermoresponsive self-shrinking nanofiber/hydrogel composite dressing. The dressing regulated the microenvironment of diabetic wounds by enhancing collagen deposition, promoting angiogenesis, and reducing inflammation, thereby accelerating chronic wound healing.

The hyperglycemic microenvironment of diabetic wounds induces inhibitory angiogenesis and excessive ROS, leading to oxidative stress damage of biomolecules, such as lipids, nucleic acids, and proteins, and cells, such as endothelial cells, keratinocytes, and fibroblasts, thereby impeding wound healing.[71,72] Therefore, there is an urgent need to develop a novel strategy that provides continuous O_2 supply while controlling excessive ROS accumulation. At present, the primary strategy is to load bioactive compounds, such as antioxidants and enzymes, into hydrogels, thereby eliminating ROS and alleviating oxidative stress.

The combination of 3D printing technology and hydrogels provides customizable services for diabetic wound patients. Wei *et al.*[73] grafted gallic acid and methacrylic acid onto gelatin, respectively, endowing the hydrogel with ROS scavenging and ultraviolet polymerization properties. More importantly, the addition of gallic acid significantly improved the rheological properties of GelGA–GelMA bio-inks, ensuring the printability of customizable hydrogel scaffolds. Likewise, Fellin *et al.*[74] employed a high-precision 3D printing through DLP technology to construct complex bionic structures. Tannic acid (TA) treatment post-printing provided efficient ROS scavenging capacity through phenolic hydroxyl groups and significantly enhanced the mechanical properties of the hydrogel, offering a scaffold solution that combines antioxidant protection and customizable shapes for diabetic wound healing.

Studies have shown that excessive ROS accumulation disrupts macrophage polarization by transforming M1 into M2 macrophages while inducing oxidative stress, collectively leading to impaired phagocytosis and tissue necrosis. To address this issue, researchers have explored enzyme-based ROS scavenging strategies and nanoenzymatic catalysts, such as manganese dioxide,[75] Prussian blue,[76] manganese–cobalt oxide,[77] and black phosphorus,[78,79] as well as catalases that degrade H_2O_2 while simultaneously generating oxygen. Meanwhile, black phosphorus, MOFs, and DNA-based nanostructures can enhance the spatiotemporal control of 3D-printed hydrogels in therapeutic release and microenvironment regulation, improve their mechanical properties, ROS

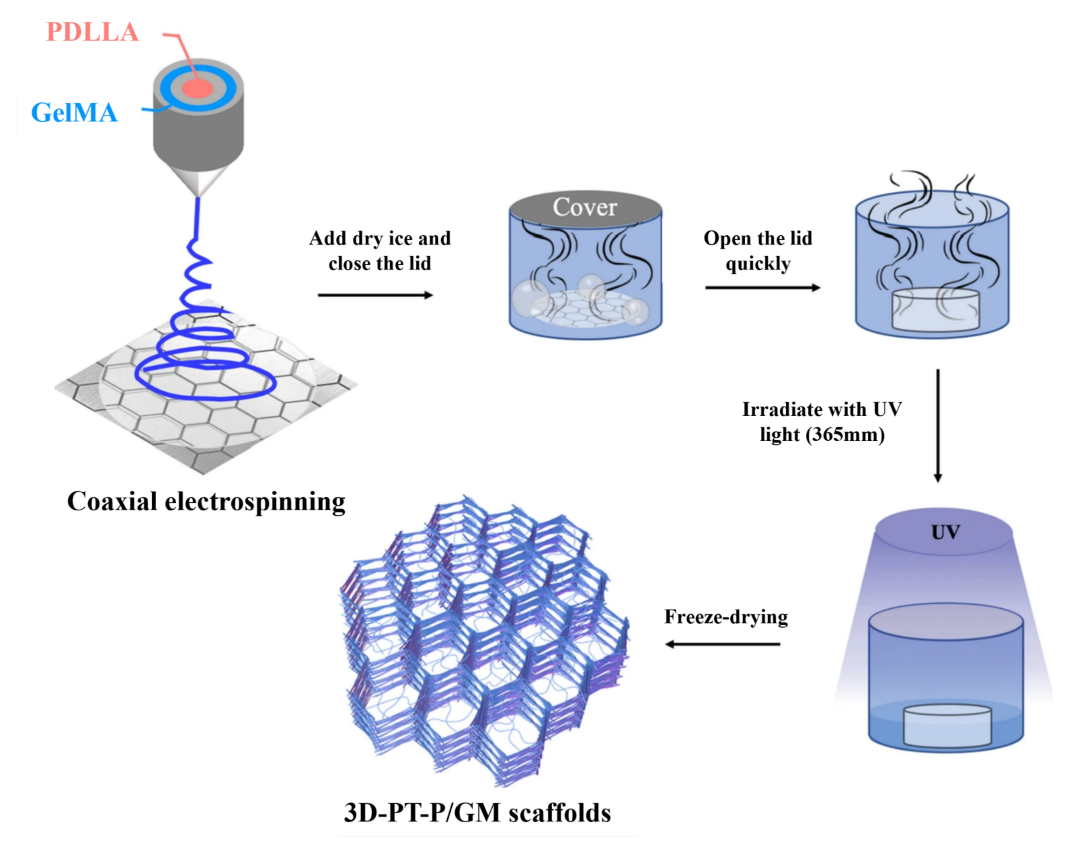

Figure 6. Fabrication illustration of a nanofiber/hydrogel core–shell scaffold with 3D multilayer patterned structure (3D-PT-P/GM) scaffolds. Adapted from Li *et al.*[65] Abbreviations: GelMA, gelatin methacrylate; PDLLA: poly(*D*,*L*-lactic acid).

scavenging capacity, and antibacterial activity, and further expand the functions of 3D-printed hydrogels.[80]

The healing of large-scale bone defects and incisions from gastrointestinal surgeries remains a clinical challenge. Chen *et al.*[81] innovatively developed a 3D-bioprinted, antioxidant M–Mn_3O_4@Gel by integrating M–Mn_3O_4 nanozyme into photo–cross-linked GelMA. The incorporation of M–Mn_3O_4 enhanced the mechanical properties of the nanocomposite hydrogels, with a compressive modulus 141.79% higher than that of pure GelMA. The hydrogels maintained excellent 3D printing adaptability and exhibited an efficient function of ROS clearance.

Similarly, gastrointestinal surgical incisions often face an acidic environment-induced ROS burst. Muñoz *et al.*[82] proposed a new idea for alleviating oxidative stress in diabetic wounds by blocking 95% of protease permeation through modified polyethylene imine with buffering capacity and a micelle-dense structure. The damage to skin barriers and poor vascularization in diabetic patients increases the risk of bacterial infection, while local hyperglycemia also creates a fertile environment for bacterial proliferation.[83,84] This interplay between hypoxia and infection transforms diabetic wounds into a complex inflammatory state that impedes the healing process.[85,86] Recent advances in hydrogel wound dressings have yielded improved mechanical barrier function, histocompatibility, and antimicrobial properties, making them a promising option for diabetic wound care. This microenvironment regulation strategy can avoid direct interference with host cell behaviors, especially in the high-risk environment of chronic wound infection. Liu *et al.*[87] designed a lichen-inspired, 3D-bioprinted bioderived hydrogel with a customizable structure to accelerate the healing of chronic diabetic wounds. These hydrogels exhibited superior performance both *in vitro* and *in vivo*, including enhanced dissolved oxygen production by microalgae and effective probiotic anti-infection activity. Similarly, Kumi *et al.*[34] proposed a 3D-printable APFE that combined electrical stimulation therapy targeting infected diabetic wound healing. APFE demonstrated excellent cell activity, with antibacterial rates of 85.71% against methicillin-resistant *Staphylococcus aureus* and 93.65% against *Escherichia coli*.

Collectively, these innovative strategies orchestrate a multifaceted therapeutic outcome in diabetic wound healing, concurrently addressing oxidative stress via ROS scavenging, inhibiting inflammation, and promoting tissue healing through macrophage phenotype modulation.

3.2. Regulation of cellular behavior

Three-dimensional printing technology plays a significant role in regulating cell behavior. It can guide the directional migration, proliferation, and differentiation of cells by constructing scaffolds with bionic multi-level channels, customized mechanical properties, and heterogeneous structures.[88] The multi-nozzle system can precisely target immunomodulatory and growth factors to different regions of the scaffold, collaboratively regulating the polarization of macrophages to the M2 type to alleviate chronic inflammation, promote ECM secretion by fibroblasts, and stimulate neovascularization by vascular endothelial cells.[89] Not only that, 3D printing supports direct loading of mesenchymal stem cells and the construction of bionic co-culture systems, continuously releasing nutrient factors and further optimizing the microenvironment.[90]

Guo *et al.*[91] loaded the inherent bioactive components of egg white into hydrogels, thereby providing cell recognition sites, simulating the ECM environment, promoting cell adhesion, proliferation, and migration. At the same time, with the help of 3D printing technology, they constructed the porous structure of hydrogels, enhancing the ability of nutrient penetration and the regulation of cell spatial distribution. Ultimately, this scaffold significantly accelerated the recovery of cellular function and tissue regeneration in diabetic wounds. Similarly, Rybak *et al.*[92] embedded electrowoven short fibers loaded with gold nanorods and dexamethasone into GelMA/sodium alginate hydrogels and constructed photothermal responsive scaffolds through 3D printing. These scaffolds can locally heat up and trigger drug-controlled release under near-infrared irradiation, significantly enhancing the antibacterial and anti-inflammatory effects, and promoting the adhesion, extension, and proliferation of L929 fibroblasts.

The promoting effects of hydrogel on diabetic wound healing have multidimensional biological mechanisms. Its core advantages are reflected not only in the precise regulation of the wound microenvironment but also in the synergistic healing effects by targeting the key behaviors of cells.[87,93,94] In the healing process of normal skin injury, fibroblasts, as the core effector cells, rapidly respond to the injury signal and migrate to the wound site to construct a temporary repair hydrogel scaffold by synthesizing and secreting type I collagen and other ECM components. In this process, the balance between dynamic synthesis and the degradation of collagen is the key to drive orderly tissue healing: matrix metalloproteinases (MMPs) secreted by fibroblasts and tissue inhibitors cooperate to regulate collagen turnover, ensuring that newly generated tissues have sufficient mechanical strength and providing space for subsequent cell infiltration and angiogenesis.[95,96]

However, chronic hyperglycemia in diabetic patients directly damages the functions of fibroblasts by activating the polyol pathway and accumulating advanced glycation end products, characterized by a significant decrease in migration ability, VEGF secretion, and hypoxia-inducible factor 1α (HIF-1α) stability, leading to angiogenesis disorders. Moreover, reactive aldehydes produced by lipid peroxidation can covalently modify collagen molecules to form cross-linked structures, not only reducing the bioavailability of collagen but also disrupting ECM homeostasis by activating the overexpression of MMPs. This double hit further impairs the migration ability of keratinocytes and delays the re-epithelialization process.[97]

Liang *et al.*[98] used recombinant human collagen methacrylate and HA to construct a 3D network using ultraviolet light cross-linking and loaded with gold nanoparticles. The porous structure of the network mimicked the ECM, promoting fibroblast adhesion and migration, while collagen components directly induced collagen deposition. Together with its antibacterial properties, this hydrogel established a healing-conducive microenvironment and accelerated wound healing. Similarly, Huang *et al.*[99] constructed a bovine dermal type I collagen bionic scaffold loaded with overexpressed fibroblast growth factor (bFGF). This biomimetic scaffold activated the HIF-1 signaling pathway through continuous release of bFGF, promoting endothelial tube formation and fibroblast migration, and accelerating diabetic wound healing by enhancing protein kinase B phosphorylation and collagen deposition. The scaffolds were similar to hydrogels in terms of their porous structure, biocompatibility, and controllable release characteristics.

Gastrointestinal surgical incisions are often affected by an acidic environment, which delays the formation of blood clots and granulation tissues. Therefore, fibroblast growth factor can be added to hydrogels to address this issue.[100] Wang *et al.*[101] used the chemical ligation method of Spy to efficiently integrate interferon-alpha (IFN-α) into hydrogels, preserving its biological activity. This design enhanced fibroblast migration and upregulated the expression of ECM proteins, such as type I collagen alpha chain and α-smooth muscle actin.

Macrophages are tissue-resident immune cells with dual roles: M1 subtype addresses infections via ROS and pro-inflammatory cytokines, while M2 subtype promotes tissue healing through anti-inflammatory factors and ECM remodeling, making them key targets for treating chronic inflammation and cancers.[102] In diabetic wounds, the abnormal polarization of macrophages has become an important barrier to wound healing. This issue arises from the chronic inflammatory environment induced by hyperglycemia and obesity, perpetuating the activation of M1 macrophages and hindering tissue regeneration.[103] Reduced expressions of macrophage-secreted growth factors (e.g., transforming growth factor-β1 and platelet-derived growth factor-BB) and pro-inflammatory cytokines (e.g., interleukin-6 and tumor necrosis factor-α) create an optimal healing environment: keratinocytes differentiate properly, fibroblasts deposit balanced collagen, and new blood vessels form without leakage, resulting in faster wound closure with minimal scarring.

Macrophages are highly heterogeneous and exhibit a variety of functions and phenotypes.[104–107] Diabetic wounds are characterized by a prolonged inflammatory phase and difficulty in healing due to the accumulation of M1 macrophages in the wound. Therefore, dressings with macrophage heterogeneity regulation ability have great potential in treating diabetic wound healing. However, the conversion of M1 into M2 macrophages through simple and biosafe methods remains a significant challenge. Chen *et al.*[108] developed an ROS/glucose-responsive hydrogel coupled to a chemokine aptamer encapsulating mannose-modified lipid nanoparticles (mLNPs) loaded with ADAM17 small interfering RNA (siRNA). This hydrogel enhanced macrophage recruitment by enriching endogenous chemokines. In addition, it was responsive to the pathological microenvironment with dynamic release of mLNPs to deliver targeted siRNAs to macrophages. ADAM17 siR@mLNPs treatment significantly enhanced hyperphagia through the tyrosine kinase Mer–Ras-related C3 botulinum toxin substrate 1 pathway and glycolytic reprogramming, thereby initiating the resolution of inflammation and tissue healing. Likewise, Fu *et al.*[109] developed a natural hydrogel capable of modulating macrophage heterogeneity to promote angiogenesis and diabetic wound healing. This hydrogel exhibited excellent bio-adhesion, antibacterial performance, and ROS scavenging ability. Notably, the hydrogel could transform M1 macrophages into M2 macrophages without any additional components.

Hypoxic bone marrow mesenchymal stem cell-derived exosomes are important in regulating cellular functions through their microRNAs. Shi *et al.*[110] developed a multifunctional hydrogel based on gallic acid-coupled CS and partially oxidized HA. The hydrogels significantly promoted diabetic wound healing by modulating macrophage polarization to the M2 phase. It can be ascribed to the fact that the extracellular vesicle miR-4645-5p and the antioxidant properties of the hydrogel work together to inhibit the activity of sterol regulatory element-binding protein 2 in macrophages. Shu *et al.*[111] designed a GelMA hydrogel for sustained release at the wound site and evaluated its potential for promoting wound healing in diabetic patients. Mechanistic studies showed that the wound liner regulated macrophage heterogeneity through the adenosine A2b receptor/signal transducer and activator of transcription/peroxisome proliferator-activated receptor gamma signaling pathway and promoted endothelial cell function, thereby accelerating wound healing in diabetic patients. Similarly, Wang *et al.*[112] developed a silk fibroin/gelatin (SG) hydrogel for chronic diabetic wounds and incorporated mitochondrial division inhibitor-1 (SG/M). Compared with the pure SG hydrogel, the SG/M hydrogel significantly accelerated wound healing in diabetic patients. The therapeutic effect of mitochondrial division inhibitor-1 was attributed to its ability to enhance macrophage polarization toward the M2 phenotype and to alleviate high glucose-induced mitochondrial dysfunction in both macrophages and human umbilical vein endothelial cells (HUVECs). Su *et al.*[113] prepared an asymmetric bilayer hydrogel through ultraviolet polymerization of chemically modified CS (TA@CS) combined with a deamidated and pyrogallol-derivatized form of marine collagen. The resulting asymmetric hydrogel exhibited unique directional adhesion properties, which are critical for healing diabetic and gastrointestinal wounds. This feature simplifies surgical application by reducing handling complexity and minimizing associated risk.[114]

3.3. Promotion of angiogenesis and tissue regeneration

In diabetic wound healing, angiogenesis and tissue regeneration are the key biological links that determine the healing effects. They complement each other and jointly affect the quality and speed of wound healing. Studies have shown that the expression of VEGF in diabetic wounds is significantly lower than that in normal wounds. This reduction impairs the migration ability of endothelial cells and the formation of tubular structures, thereby blocking angiogenesis. As a result, blood supply to the wound becomes insufficient, limiting the delivery of nutrients and oxygen while hindering the discharge of metabolic waste, thereby delaying the healing process.[115,116]

Three-dimensional printing technology primarily builds hydrogel scaffolds with bionic multi-level channels and fully interconnected micro-networks. This is achieved by manipulating the spatial structure of biomaterials to simulate the structural and functional characteristics of the natural vascular system from both physical topology and cellular microenvironment levels, thereby promoting angiogenesis and tissue regeneration. Luo *et al.*[117] utilized 3D printing technology to construct a hydrogel scaffold with a fully interconnected microchannel network that mimics the structure of natural blood vessels, guiding the directional arrangement of endothelial cells and angiogenesis. This approach enabled the integrated and precise manufacturing of macropores and microchannels, enhancing nutrient transport and cell survival capabilities. The hydrogel scaffold promoted blood vessel growth toward the central region both *in vivo* and *in vitro*, addressing the challenge of insufficient vascularization in traditional tissue engineering. The 3D-printed hydrogel prepared by Mujawar *et al.*[118] represented an ideal physical scaffold for cell migration and vascular growth through its precisely fabricated interconnected porous structure. The incorporation of aloe vera extract enabled sustained release of bioactive factors, which promoted angiogenesis, effectively reduced inflammation and oxidative stress, and synergistically optimized the wound microenvironment. Ultimately, it efficiently enhanced vascularization and facilitated high-quality tissue healing by accelerating granulation tissue formation, collagen deposition, and epithelial regeneration while reducing scar formation.

Hydrogels can provide physical topological guidance and support for endothelial cell migration and tubular structure formation by simulating the 3D porous structure and mechanical properties of ECM. Their high-water content characteristic can maintain the moisture of the wound surface and provide a favorable pathway for cell metabolism and communication.[119] Han *et al.*[120] constructed an injectable self-healing HA hydrogel via a Schiff base cross-linking method and incorporated GOx–MnO_2 nanoenzymes, synthesized through condensation reactions, and VEGF nanobubbles produced prepared through double emulsification. This design established a novel US@GOx@VEGF (UGV) hydrogel system for diagnosis and treatment. The results showed that VEGF could be precisely released through *ex vivo* ultrasound to enhance the vascularization and accelerate diabetic wound healing. Huang *et al.*[121] prepared VEGF plasmid-loaded macrophage exosomes and encapsulated them in injectable self-healing hydrogels prepared through dynamic Schiff base cross-linking. This system enhanced VEGF binding to VEGF receptor 2 through VEGF production and release from exosomes, secretion by M2 macrophages, and the high affinity of the 2-N,6-O-sulfated chitosan (SCS) hydrogel, creating an intrinsic immunomodulatory environment that effectively promoted angiogenesis. Kim *et al.*[122] prepared an anisotropic nanofiber hydrogel using fibrin electrospinning and self-assembling peptide modification. By leveraging the triangular synergy of the immuno-angiogenic neurogenesis microenvironment, this hydrogel exhibited an ideal directional arrangement of nanoscale fibers and significant pro-angiogenic bioactivity, thereby improving diabetic wound healing.

The abnormal expression of MMPs in diabetic wounds is also an important factor affecting wound healing. Overexpression of MMPs disrupts the dynamic balance of the ECM, leading to excessive degradation of key ECM components, such as collagen and fibronectin. This degradation compromises tissue integrity and impairs the formation of stable granulation tissue, further delaying the wound healing process.[123] Specifically, overexpression of MMP-9 is involved in this process. Therefore, wound dressings that validly inhibit the expression of MMP-9 have significant translational potential in clinical practice. Lan *et al.*[124] developed a composite hydrogel dressing for the locally sustained delivery of MMP-9 siRNA (siMMP9). After forming a complex with glycogen–triethylenetetramine, siMMP-9 was loaded into a thermosensitive hydrogel based on Pluronic F-127 and hydroxypropyl methylcellulose. The hydrogel released the encapsulated GT/siMMP9 into wound tissues through heat-sensitive controlled release over seven days, inhibiting MMP-9 expression and significantly accelerating diabetic wound healing. Similarly, Lei and Fan[125] prepared TA-siRNA nanogels for the first time, based on the self-assembled interaction between TA and siRNA. This highly efficient and biodegradable nanogel was incorporated into polyvinyl alcohol–human-like collagen–TA–borax hydrogels. Electrical stimulation improved the *in vivo* release of the hydrogels and the endocytosis of the nanogels. Combination therapy using electrical stimulation and TA-siRNA hydrogels accelerated diabetic wound healing by lowering ROS and MMP-9 levels, as well as promoting macrophage polarization, collagen production, and angiogenesis. Meanwhile, Wu *et al.*[126] developed a supramolecular peptide hydrogel doped with nanoparticles for the local delivery of siMMP9. siMMP9 was encapsulated within nanoparticles fabricated from amphiphilic cationic lipid-like compounds, subsequently embedded within a supramolecular peptide hydrogel formed through the self-assembly of amphiphilic peptides. The hydrogels significantly prolonged the retention time of siMMP9-loaded nanoparticles in wound tissues and their porous networks gradually released these nanoparticles to enhance siMMP9 uptake by keratinocytes, thereby achieving efficient MMP9 silencing and markedly accelerating diabetic wound healing. Zheng *et al.*[127] highlighted the critical role of m6A methylation in regulating MMP-9 expression during diabetic wound healing. They combined enhanced mRNA m6A modification with a ROS scavenging strategy by loading an FTO inhibitor into a nanocolloidal hydrogel, which showed excellent wound-healing effects in a diabetic model.

Diabetic wounds represent a complex pathological condition driven by the interplay of multiple systemic and local factors, where any single factor may exacerbate the healing process. Consequently, multifunctional hydrogels that simultaneously address infection, inflammation, and impaired angiogenesis are crucial for clinical efficacy.[128] For example, Huang *et al.*[51] developed a click chemistry-based all-peptide hydrogel platform, as discussed in the click chemical cross-linking section. Constructed through a one-step photo-curing reaction, this hydrogel featured high-precision 3D printing capabilities and was loaded with HUVECs overexpressing VEGF165, enabling the self-continuous release of growth factors. The hydrogel not only promoted cell adhesion and migration through the RGDS sequence but also significantly enhanced angiogenesis through continuous VEGF165 secretion. Meanwhile, it protected endothelial cells from high glucose-induced damage by inhibiting Bax-mediated mitochondrial membrane perforation, thereby reducing oxidative stress and inflammation levels. Moreover, this material demonstrated excellent biocompatibility and degradability both *in vivo* and *in vitro*, and can be customized to different wound morphologies through DLP printing technology.

4. Conclusion

Diabetic wound healing remains a major challenge in clinical medicine, as its complex pathological microenvironment imposes multidimensional functional requirements on treatment strategies. With precise structural control enabled by CAD and additive manufacturing, combined with strong biocompatibility and dynamic microenvironment regulation, 3D-printed hydrogels have demonstrated significant advantages for diabetic wound healing. However, current studies often rely on single functional modules, exhibit imperfect dynamic response mechanisms, and face major barriers to clinical translation. The long-term biocompatibility and potential immunogenicity of synthetic polymers and cross-linking agents remain insufficiently explored. In addition, sterilization methods, such as those using gamma radiation and ethylene oxide, may alter hydrogel structure and biological activity, while the high cost of bio-inks and specialized 3D printers limits widespread adoption. Future research should focus on multifunctional and synergistic intelligent 3D-printed hydrogel systems that integrate treatment strategies across three stages: infection control, inflammation regulation, and tissue remodeling. Incorporating living cells, extracellular vesicles, or gene editing technologies into hydrogel design could enable targeted cell differentiation and on-demand synthesis of ECM components, creating a “material–cell–gene” trinity treatment system. Meanwhile, AI-assisted material platforms could accelerate hydrogel optimization by analyzing high-throughput experimental data with machine learning algorithms, guiding the formulation of bio-inks and printing parameters to speed up the development of personalized hydrogel dressings. It is also worth noting that while gastrointestinal surgical incisions and diabetic wounds share pathological characteristics, their microenvironments differ and require tailored design. For example, multifunctional 3D-printed hydrogels could adopt modular strategies, such as coating gastrointestinal wound scaffolds with acid-resistant layers, to establish cross-indication treatment strategies.

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Conflict of interest

The authors declare they have no competing interests.

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Availability of data

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