

Stimuli-responsive hydrogels based on cascade reactions: a novel strategy to promote the efficient repair of diabetic wounds

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Abstract

The impaired healing of diabetic wounds is caused by complex multifactorial pathologies and conventional therapeutic approaches often show limited efficacy. In recent years, stimulus-responsive hydrogels based on cascade reactions have become a promising approach in the management of diabetic wounds. These hydrogels are designed to react to particular characteristics of the wound microenvironment, such as glucose concentration, pH, reactive oxygen species (ROS) and enzyme activity, allowing spatiotemporally controlled drug release and synergistic multi-target control. This review focuses on the recent development in understanding of the pathophysiology of diabetic wounds, immune microenvironment modulation, and the development of stimuli-responsive cascade hydrogels, as well as the challenges. By integrating responsive moieties, these hydrogels dynamically control the polarization of immune cells and scavenging of ROS. Furthermore, cascade systems, from single-step to multistep design, enable precise spatiotemporal activation and coordinate antibacterial, antioxidant and pro-regenerative effects. Additionally, emerging technologies such as AI-assisted modeling, biosensing-guided feedback, and organ-on-a-chip platforms have great potential to improve the rational design and predictive validation of cascade hydrogel systems, paving the way for intelligent and personalized diabetic wound therapies.

Keywords: cascade reaction; hydrogel; responsiveness; diabetic wound

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder that is spreading across the globe at an unprecedented rate. According to the international diabetes federation, the number of people suffering from diabetes is rapidly rising and is expected to reach almost 1.31 billion by 2050 [1]. Beyond greatly affecting the quality of life of patients, diabetes leads to many complications, such as cardiovascular and cerebrovascular diseases, nephropathy, retinopathy and neuropathy, that impose a significant burden on the healthcare systems worldwide [2,3]. Among these complications, the wound healing of diabetics is a particularly formidable challenge, with a long healing process, risk of infection and a high rate of recurrence [4]. In severe cases, wounds may become chronic and non-healing and may lead to amputation.

The diabetic wound healing process is hindered by several interrelated factors including persistent inflammation, hyperglycemia, excessive reactive oxygen species (ROS), bacterial infections, hypoxia and other complex microenvironmental disturbances [5]. These obstacles hinder the normal repair cascade, thus highlighting the urgent need for efficacious therapeutic strategies against diabetic wounds. Wound dressings play an integral part in treatment and create an essential barrier and healing [6]. However, conventional dressings, such as gauze and foam, mostly maintain moisture and prevent bacterial contamination but are limited in their functional capabilities. They do not adequately address the multifaceted and dynamic microenvironmental alterations that are characteristic of diabetic wounds,

and therefore do not adequately address the diverse and evolving needs of this patient population [5].

In the last few years, hydrogels have become a promising new class of wound dressings with a great potential in treating diabetic wounds. Hydrogels are composed of hydrophilic polymer networks that can absorb and hold large volumes of water, which in turn provides a moist environment that can enhance healing while minimizing bacterial colonization. Compared to traditional dressings, hydrogels more closely replicate the structure of the extracellular matrix (ECM) providing better cell adhesion and migration, which increases wound repair. Moreover, the high tunability of the hydrogels enables customization depending on the specific circumstances of the wound, which enables tailored treatment strategies to address diverse treatment requirements [7-9]. Stimuli-responsive hydrogels have attracted broad attention because of their intelligent, adaptive characteristics [10]. These hydrogels can react to external stimuli, such as pH, temperature, enzyme activity, or biomolecular signals, by changing their physical and chemical properties to adapt to the changing wound microenvironment. For example, pH-responsive hydrogels can respond to the acidic environment common to the inflammatory phase and release anti-inflammatory agents to reduce inflammation. Similarly, temperature-responsive hydrogels change their hardness or shape depending on the body temperature and hence can better conform to the wound contour [11-13]. These smart, stimuli-responsive behaviors facilitate active and enhanced hydrogel involvement in the wound healing process and provide novel strategies to handle diabetic wounds.

Cascade reactions are frequently found in biology as a series of consecutive chemical reactions, in which the product of one reaction is a catalyst for the next [14-15]. In tissue repair this concept has been exploited to design smart materials that can mimic these complex biological processes [16-18]. By integrating the responsive units into the hydrogel networks, the cascade reactions can be induced to experience a sequence of orderly transformations in response to specific stimuli, thus allowing the wound microenvironment to be precisely regulated.

This review focuses on giving a comprehensive summary of diabetic wound pathology and wound therapeutic strategies, especially focusing on the recent progress of stimulus-responsive hydrogels based on cascade reactions. First, the pathophysiological process in diabetic wounds is explained and divided into four different stages: hemostasis, inflammation, proliferation, and

remodeling. Emphasis is placed on the important roles of macrophages and neutrophils in modulating the immune microenvironment during each stage as well as the relevant cell signaling pathways. Next, combining these cellular and molecular knowledge, several types of microenvironment-responsive hydrogels, such as glucose-, pH-, enzyme-, and ROS-responsive systems are discussed for their ability to enhance the local microenvironment by facilitating neovascularization, tissue repair, and immune regulation (Figure 1). Based on the source of stimulation, various cascade hydrogel systems have been developed, with most of the current models based on the principle of enzymatic cascade. Increasingly, dual or multi-step modules are used to improve the spatiotemporal precision. These approaches have a lot of benefits including enhanced catalytic efficiency and stability, especially in nanzyme mimicking systems, as well as enabling synergistic cascades to promote diabetic wound therapy towards complete and dynamic regulation. Finally, the review emphasizes outstanding challenges such as the development of intelligent materials that are able to dynamically adapt to different healing stages, the coordination of multiple simultaneous response signals, and the achievement of an optimal balance between biosafety and therapeutic functionality. Future research directions may include organ-on-a-chip (OoC) platforms to simulate wound microenvironments, minimizing off-target effects in biomimetic systems, and creating multiscale frameworks for evaluating biocompatibility. A more integrated approach that combines mechanistic understanding, materials innovation and clinical validation is critical for the advancement of precision and personalized management of diabetic wounds.

2. Pathophysiology of Diabetic Wound Healing

2.1 Characteristics of diabetic wounds and their impact on each stage of wound healing

Diabetic wounds are defined by their chronicity and resistance to healing [1]. The pathophysiology behind this is chronic inflammation, poor angiogenesis and susceptibility to bacterial infection. The hyperglycemic microenvironment enhances excessive accumulation of ROS, which induces sustained expression of pro-inflammatory factors, thus continuing a vicious cycle of inflammation [4, 6]. Additionally, hyperglycemia causes damage to the vascular endothelial cells, resulting in impaired neovascularization and chronic local hypoxia in the wound [4]. Elevated glucose levels also support the

growth of pathogenic bacteria, which greatly raises the risk of infection [10]. Moreover, peripheral neuropathy has been shown to interfere with the tissue repair process, further complicating wound healing in diabetic patients [19, 20].

Abnormally prolonged inflammatory phase: In normal wound healing, the inflammatory phase is normally short. However, in diabetic wounds this response is unable to resolve on time, as a result of macrophage dysfunction [21, 22]. Notably, the expression of netrin-1 protein is significantly reduced in diabetic wounds, which affects the polarization of macrophages into the anti-inflammatory M2 phenotype. Concurrently, pro-inflammatory cytokines like TNF- α and IL-6 are continuously secreted and create a pathological inflammatory microenvironment [21, 23].

Impaired proliferative phase function: Persistent hyperglycemia has been demonstrated to suppress fibroblast activity, leading to decreased synthesis and disordered structure of the ECM [24]. Oxidative stress, which is associated with excessive production of ROS, further impair keratinocyte migration and slows epithelialization [25]. The vascular endothelial

growth factor (VEGF) signaling pathway is inhibited, worsening the hypoxia in the tissues with the lack of blood vessel formation [26]. Moreover, impaired expression of pro-angiogenic factors such as Cu²⁺ and netrin-1 affects the proliferation of endothelial cells in diabetic wounds [27, 28].

Structural defects during remodeling: An imbalance in collagen cross-linking causes reduced scar strength [25]. The prolonged action of matrix metalloproteinases (MMPs) leads to the breakdown of newly formed tissue in excess, making wounds prone to recurrence or deterioration [29].

The diabetic wound microenvironment is defined by a complex interplay of pathological factors. Hypoxia and oxidative stress are reciprocally related: hypoxia leads to increased ROS generation, which further accumulates and suppresses the activity of hypoxia-inducible factor-1 alpha (HIF-1 α), leading to a vicious cycle [30, 31]. Likewise, infection and inflammation act in a synergistic manner to increase tissue damage with bacterial biofilms enhancing the inflammatory response whereas proteases released by inflammatory cells degrade the antimicrobial barrier [5, 32].

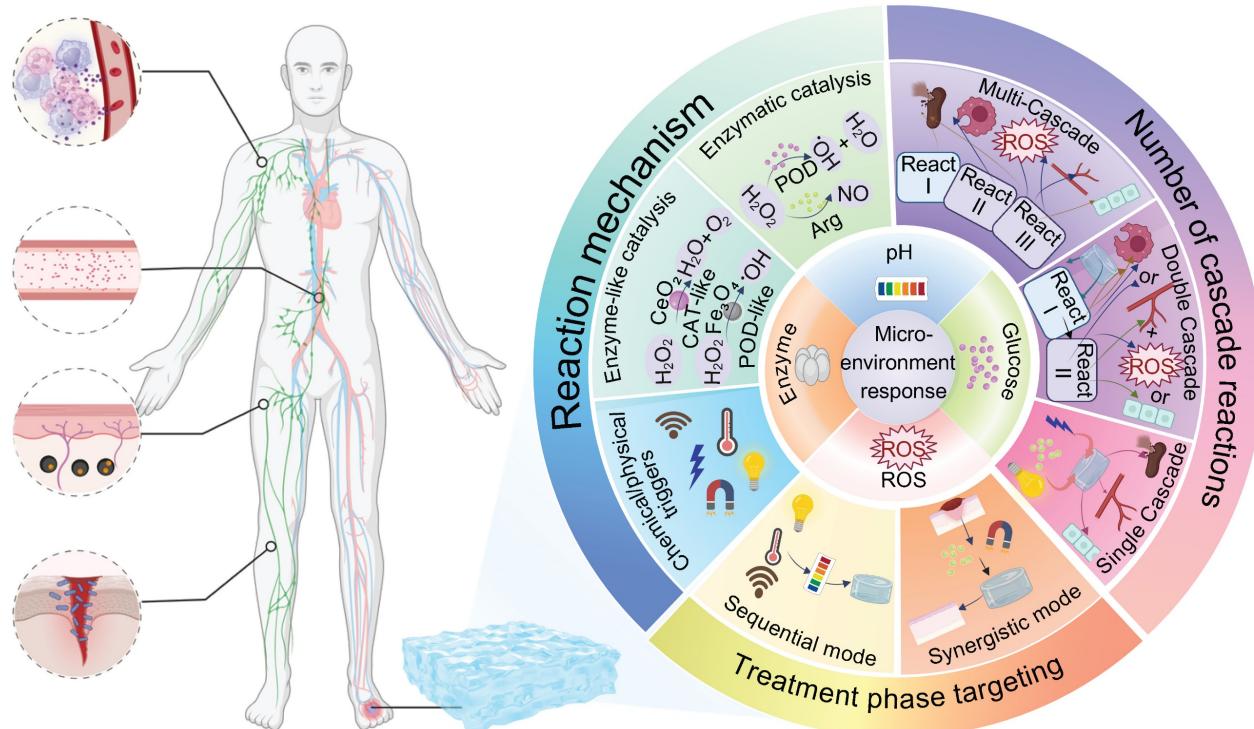


Figure 1. Schematic representation of the pathological characteristics of diabetic wound healing and the types and classification criteria of the cascade reactions contained in microenvironment-responsive hydrogels. Created in BioRender. Jia, J. (2025) <https://BioRender.com/b8q7n94>.

Conventional therapeutic modalities often have difficulty modulating these multifaceted factors simultaneously [33]. Recent advances have revealed novel strategies that target macrophage phenotype switching, for example, topical administration of exosomes (Exos) has been demonstrated to promote macrophage polarization towards the M2 phenotype [34]. In addition, the dual control of oxidative stress and angiogenesis by nano-enzymatic materials has proven to be promising [35]. Metal-organic framework (MOF)-based catalysts have shown the potential of scavenging ROS and facilitating vascular regeneration [36]. Furthermore, smart-responsive dressings, such as glucose-sensitive hydrogels allow dynamic drug release based on microenvironment changes in the wound [6, 10].

Given the multifactorial and interactive nature of diabetic wounds, pathological deviations occur in the various phases of the inflammatory, proliferative and remodeling phases of healing. Future studies should focus on the development of multi-target synergistic intervention strategies designed to restore and restructure the wound microenvironment in order to promote effective healing.

2.2 The important regulatory role of the immune microenvironment (macrophages, neutrophils) in each stage of diabetic wound repair

The skin immune microenvironment is a complex network of cells including neutrophils, macrophages, T cells, B cells and natural killer (NK) cells that interact closely with keratinocytes and fibroblasts to maintain tissue homeostasis and defend against pathogens [37-39]. These immune cells communicate mainly via cytokines, orchestrating processes that are important for wound healing. Neutrophils are responsible for clearing debris and pathogens, macrophages for guiding tissue repair by dynamic M1 to M2 polarization, and T cells for regulating adaptive immunity. Upon injury of the skin, transforming growth factor-beta (TGF- β), a multifunctional cytokine implicated in the regulation of inflammation and tissue regeneration, is released by platelets to recruit neutrophils. Afterward, the macrophages change from the pro-inflammatory M1 phenotype to the reparative M2 phenotype, while fibroblasts participate in ECM reconstruction [39-41]. Macrophages release the growth factors, VEGF and platelet-derived growth factor, which play a key role in angiogenesis and epithelial regeneration.

In the case of diabetic wounds, this finely tuned repair program is broken. Hyperglycemia inhibits M2 macrophage polarization through ROS/NF- κ B signaling axis, which sustains a predominance of the

pro-inflammatory M1 phenotype and perpetuates chronic inflammation [42-45]. Additionally, the ECM altered by advanced glycation end products (AGEs) negatively affects healing by impairing TGF- β signaling, blocking fibroblast migration and reducing the response of endothelial cells to the growth factor VEG during the inflammatory phase. Emerging therapeutic approaches are aimed at "restarting" the impaired repair process. These include delivery of anti-inflammatory cytokines such as IL-10 or TGF- β using nanocarriers to induce M2 macrophage activation, as well as modulation of ROS/NF- κ B signaling pathways using MOFs. Tumor necrosis factor-stimulated gene-6 (TSG-6), an anti-inflammatory glycoprotein released by mesenchymal stem cells, plays a very important role in immune balance restoration and ECM remodeling, acting as a key mediator in the use of stem cell-based therapies in the reshaping of the immune niche [44-50]. Functional hydrogels also play a role by relieving hypoxia and improving angiogenesis. Collectively, these strategies address the intertwined triad of inflammation, hypoxia, and infection that is the basis for impaired diabetic wound healing.

2.2.1 Inflammation phase

Hyperglycemia disrupts the skin barrier, promotes bacterial colonization, and increases inflammatory responses. Under high glucose conditions, mitochondrial dysfunction and activation of the enzyme NADPH oxidase cause increased ROS production, which causes damage to vascular endothelial cells and collagen, and inhibits macrophage polarization toward the anti-inflammatory M2 phenotype and secretion of IL-10 and TGF- β [51-54]. This metabolic imbalance traps macrophages in the pro-inflammatory state called M1, and creates a vicious cycle of inflammation, oxidative stress, and infection. Diabetic wounds are associated with significant immune dysfunction, including a M1/M2 macrophage ratio more than three-fold higher than in healthy tissue, elevated levels of pro-inflammatory cytokines IL-6 and IL-12, impaired angiogenesis, and excessive neutrophil extracellular traps (NETs), DNA-protein complexes secreted by neutrophils that trap microbes but also contribute to persistent tissue damage [55-59]. Additionally, T cells and dendritic cells become skewed to pro-inflammatory phenotypes accompanied by decreases of regulatory T cells (Tregs) and Th2 cells as well as increases in chemokine expression that inhibit fibroblast and endothelial cell functions [60-62]. Targeted therapeutic interventions aimed at promoting M2 macrophage polarization, collagen synthesis and re-epithelialization are showing

considerable promise. Engineered hydrogels and nanomaterials carrying IL-4, IL-13 or small interfering RNA (siRNA), which induces sequence-specific gene silencing through RNA interference, have shown promise in the modulation of the wound immune microenvironment [63-65] (Figure 2). Future research should be aimed at understanding the complex interactions between immune and matrix cells in order to develop precision strategies for chronic wound repair.

2.2.2 Proliferation phase

During the proliferative phase of diabetic wound healing, the regulation of the immune system is severely affected by hyperglycemia. Unlike the normal healing process, which promotes faster resolution by apoptosis of neutrophils and the activity of pro-resolving mediators, AGEs interact with their receptor (RAGE) in diabetic wounds, inhibiting macrophage autophagy by ~60%, which delays the important switch between the pro-inflammatory M1 and the reparative M2 phenotype [66, 67]. This impairment results in delayed clearance of cellular debris, increased ROS generation, impaired dendritic cell antigen presentation, and diminished phagocytic function of neutrophils and together leads to disruption of immune homeostasis. Normally, M2 macrophages make up some 70% of the immune cell

population in wound tissue. However, there is an association between diabetes and a higher number of Treg cells and a reduced number of functional NK cells, which contribute to suppressed immune surveillance [68-70]. Pro-inflammatory Th17 and $\gamma\delta$ T cells further increase the inflammation, and dendritic cells are unable to sufficiently support epidermal proliferation (Figure 3A). The polarization of M2 macrophages mediated by IL-4/IL-13-STAT6 signaling, adenosine-A2a receptor activation and miR-21-5p/PI3K-Akt pathway is suppressed under hyperglycemic conditions [71, 72]. Impaired clearance of NETs leads to oxidative stress "storms" that result in damage to the endothelium. Therapeutic interventions include IL-10 loaded hydrogels which have shown enhanced healing effects [73]. Toll-like receptor 7/8 agonists have been shown to induce M2 macrophage polarization, and peptidylarginine deaminase 4 inhibitors inhibit ROS accumulation. In addition, Sema4D-miR-21 scaffolds are also being investigated for their angiogenic potential [74]. Gene editing on ROR γ t and PD-1 pathways is a promising approach to precise immune modulation [75-77]. Ultimately, the translation of these findings into clinical practice requires a multifaceted approach to harmonize resolution and regeneration through spatiotemporal, multi-omics-based interventions.

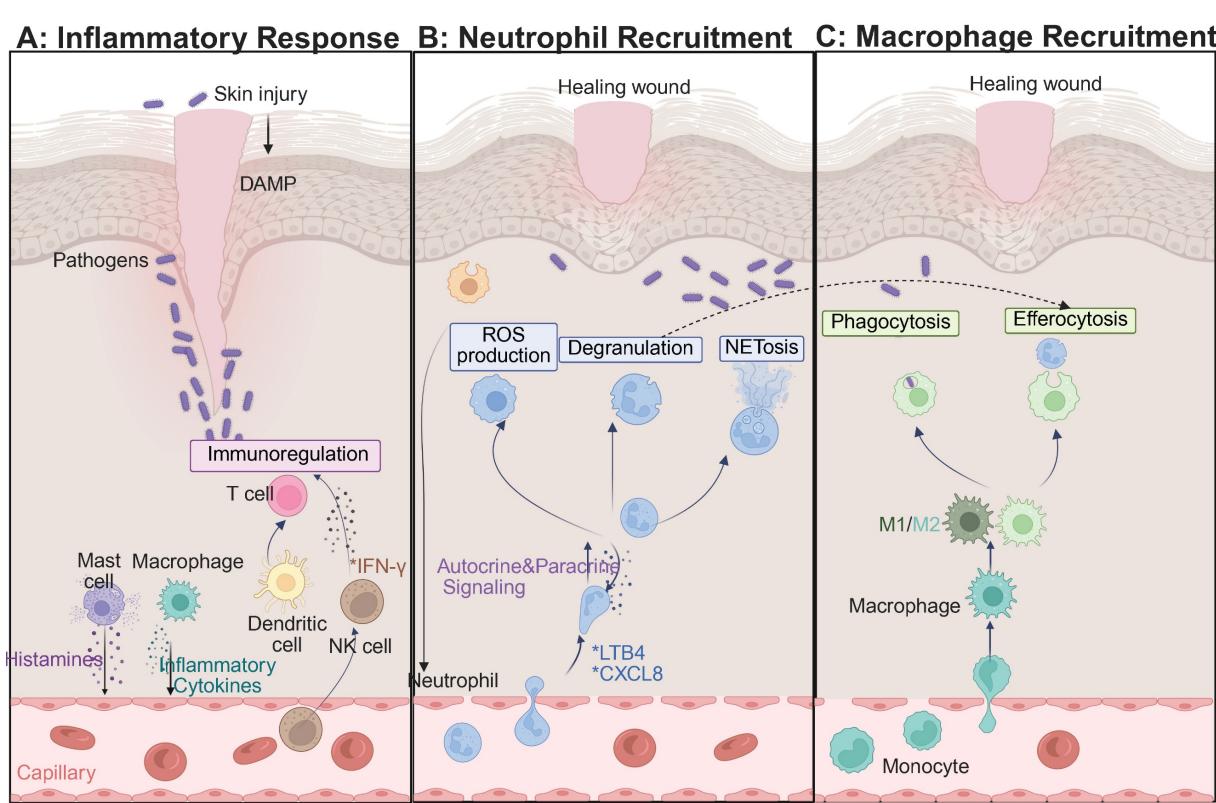


Figure 2. Dynamic evolution of immune microenvironment in the inflammatory phase of diabetic wound healing (A: inflammatory; B: neutrophil recruitment; C: macrophage recruitment). Created in BioRender. Jia, J. (2025) <https://Biorender.com/lcu92wa>.

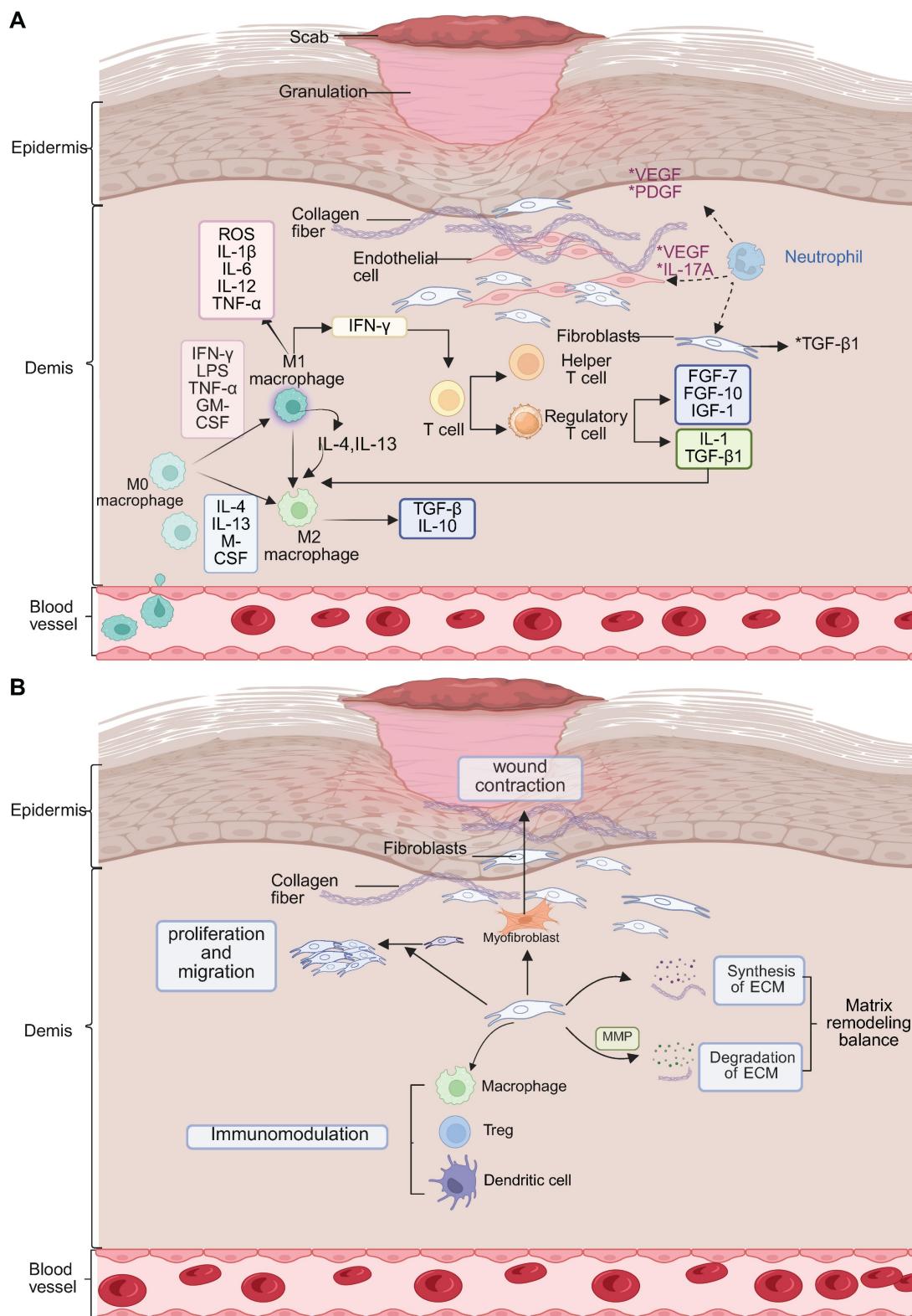


Figure 3. (A) Dynamic evolution of immune microenvironment in the proliferative phase and **(B)** Reshaping phase of diabetic wound healing. Created in BioRender. Jia, J. (2025) <https://BioRender.com/f8nmo43>.

2.2.3 Reshaping phase

In the remodeling phase of diabetic wound healing, AGEs have been shown to destroy collagen

cross-linking by covalent modification, leading to a reduction in tensile strength of more than 60% [11, 78]. Concurrently, the ratio of MMP-9 to its tissue inhibitor TIMP-1 changes dramatically to 5:1, favoring

excessive and disorganized degradation of ECMs. Macrophage-derived lysyl oxidase (LOX), an extracellular enzyme important in the crosslinking of collagen and elastin, shows a 40% reduction in activity [79, 80]. The HIF-1 α -mediated glycolytic pathway favors pro-inflammatory M1 macrophages over M2 phenotypes, disrupting fibroblast contraction through elevated IL-6 and TNF- α levels and inhibiting apoptosis of myofibroblasts [81]. Treatment with metformin, which acts through AMP-activated protein kinase, has been seen to restore M2 macrophage polarization by 50%, and normalizes LOX activity by 70%. Neutrophils have a significantly extended half-life, ~12-fold, and contribute to chronic NETosis and M2c macrophage polarization via histone H3 signaling. DNase I therapy has been shown to decrease the thickness of scars by 50% [82, 83]. Additionally, apoptosis of Tregs cells and IL-10 deficiency cause impairment in antifibrotic functions, while NK cells have a 50% impairment in their ability to clear senescent fibroblasts due to NKG2D glycosylation alterations [84-86]. The pathological basis of diabetic wound remodeling thus involves disruption of the AGEs-RAGE-MMP-9 axis, dysfunction in metabolism-mechanics signaling, and hypoxia marked by a 40% reduction in blood flow. Therapeutic interventions such as HIF-1 α inhibitors, pH-responsive DNase I, and copper oxide (CuO)-loaded biomimetic scaffolds have shown promise, enhancing healing rates by twofold (Figure 3B) [87, 88]. Multiscale regulation of the interconnected "matrix-immunity-metabolism" triad is essential for reversing chronic fibrosis and promoting effective wound remodeling.

3. Types of Microenvironment-Responsive Hydrogels

Chronic diabetic wounds constitute a highly dynamic and pathologically complex microenvironment, often characterized by persistent hyperglycemia, chronic inflammation, excessive oxidative stress and abnormal MMP activity all of which severely impair tissue regeneration [89, 90]. Although conventional hydrogel dressings offer advantages such as moisture retention and physical protection, they are usually not able to actively sense and respond to pathological cues. As a result, they fail to meet the stage-specific and multi-target and changing needs in the management of a diabetic wound [25, 90-92]. In this regard, microenvironment-responsive hydrogels have become an advanced class of functional biomaterials that can sense pathological stimuli, such as glucose, pH, ROS, and MMPs, and then induce spatiotemporally controlled drug release and wound

microenvironment modulation. By adding dynamic covalent bonds, enzyme sensitive peptide linkers or redox responsive moieties, these hydrogels exhibit smart responsiveness, which allows for simultaneous control of inflammation, stimulation of angiogenesis, and decrease of oxidative damage [93-100]. Based on their stimulus recognition mechanism, these systems are broadly categorized as glucose-responsive, pH-responsive, enzyme-responsive and ROS-responsive hydrogels [101-104]. The following sections systematically review their design principles, therapeutic mechanisms, and recent advancements in the remodeling of the diabetic wound microenvironment to give both theoretical insight and practical guidance for the development of next-generation multi-responsive platforms.

3.1 Glucose-responsive hydrogel

Chronic diabetic wounds are closely associated with the hyperglycemic microenvironment. Prolonged hyperglycemia not only provides a nutrient-rich substrate for bacterial proliferation, which increases the infection risk of pathogens such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* by over threefold [105], but also persistently activates the M1 polarization of macrophages. This activation results in excessive release of proinflammatory cytokines (e.g. IL-6, TNF- α) and increased oxidative stress [106]. Additionally, deposition of AGEs inhibits the expression of VEGF, leading to tissue hypoxia and failure of vascular regeneration. Together these factors form a vicious cycle of hyperglycemia, infection, inflammation, and vascular damage [107].

In order to break this harmful cycle, researchers have developed smart hydrogel systems based on multi-responsive mechanisms. Among these, catalytic systems driven by glucose oxidase (GOx) have shown excellent but condition-dependent performance. For example, a boronic ester-crosslinked hydrogel based on modified quaternized chitosan and polyvinyl alcohol (PVA), which reacts with high glucose levels and hydrogen peroxide (H₂O₂), breaks dynamic boronic ester bonds, thus reducing oxidative stress and releasing deferoxamine-loaded gelatin microspheres (DFO@G). The activation level for this glucose triggered reaction (\approx 15 mM) is very close to the pathological blood glucose range found in diabetic wounds (10-25 mM), ensuring physiological relevance. Subsequently, MMPs promote the long-term release of DFO, which promotes the expression of HIF-1 α and angiogenesis, promoting the healing of diabetic wounds (Figure 4A) [101]. More innovative self-regulating systems, such as MN-GOx/Arg microneedles, are responsive to

MMP-9 overexpression in the wound microenvironment and trigger arginine release via cascade reactions. This facilitates collagen deposition and angiogenesis which enhances the wound healing rate in diabetic rats by 2.3 times [108, 109]. Similarly, Li *et al.* developed a quaternized chitosan/salvianolic acid B (QF/SAB) hydrogel with dynamic boronic ester and imine bonds, which are sensitive to both glucose and ROS. This allows on-demand drug release, ROS scavenging, and improved angiogenesis with more than 90% wound closure in diabetic models [110]. A triple-responsive hydrogel that quickly releases insulin in the acidic (pH 5.5-6.5) and high temperature (40-42 °C) environments characteristic of wound surfaces through the synergistic effect of the Schiff base, boronic acid ester and hydrogen bond interactions. In addition, it has a photothermal antibacterial effect and inhibits over 95% of methicillin-resistant *Staphylococcus aureus* (MRSA) under near-infrared (NIR) irradiation [111]. Photoresponsive hydrogels are a new method of deep-tissue repair. For example, a Rh/AgMoO nanzyme composite hydrogel produces ROS ($\cdot\text{OH}$ and O_2^-) and hydrogen under visible light excitation. This process inhibits bacterial glycolysis by disrupting

the phosphotransferase system and downregulates the expression of the RAGE improving the wound healing rate of diabetic mice by 78% [112]. Experiments have demonstrated that such hydrogels can simultaneously control macrophage M2 polarization and promote angiogenesis to achieve multidimensional microenvironmental repair. Comparative studies have shown that glucose responsive systems are more specific for their substrates than pH or ROS responsive hydrogels, but are more sensitive to variations in oxygen concentration and enzyme stability. Despite these promising results, the clinical translation of glucose-responsive hydrogels is faced with several challenges. The stability and catalytic efficiency of GOx are affected by variations in pH and local hypoxia conditions, which results in inconsistent performance *in vivo*. Moreover, the overaccumulative byproduct of the oxidation of glucose, H_2O_2 , may cause oxidative stress and tissue irritation. Future studies should be designed to combine biomimetic enzyme mimics and oxygen-controlled cascade systems to enhance long-term catalytic efficiency, biosafety, and clinical reliability.

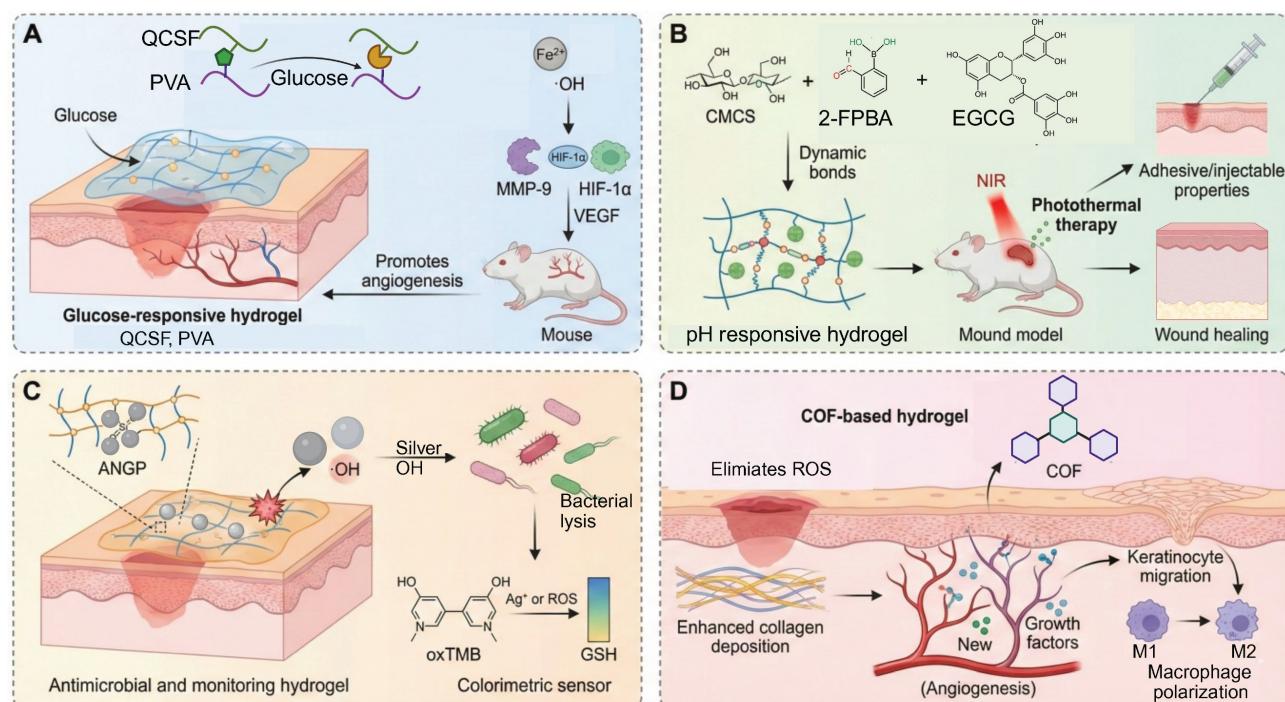


Figure 4. Types of microenvironmental responsive hydrogel. **(A)** Glucose-responsive hydrogel. **(B)** pH-responsive hydrogel. **(C)** Enzyme-responsive hydrogel. **(D)** ROS-responsive hydrogel. Created in BioRender. jia, J. (2025) <https://BioRender.com/4spcrm7>.

3.2 pH-responsive hydrogels

The pH of diabetic wounds is not static but changes dynamically throughout the healing process. The wound environment during the inflammatory stage is generally mildly alkaline, which is thought to be due to chronic exudation and increased protease activity [113]. As infection progresses, the metabolism of bacteria and tissue necrosis lead to the accumulation of lactic and fatty acids, which creates a microenvironment that is more acidic [114]. These dynamic pH changes represent the pathological changes that occur at various stages of healing in chronic, non-healing diabetic wounds, underscoring the complex interplay between inflammation, tissue necrosis and bacterial colonization [115]. Accordingly, the design of pH-responsive hydrogels that can adapt to these fluctuations is crucial in order to ensure efficient drug delivery during the healing process. Such responsiveness is mainly accomplished by reversible ionization and or dynamic covalent bonding mechanisms that are sensitive to pH variations.

In material design, natural polysaccharides like chitosan and gelatin are commonly used because of their good biocompatibility and cell proliferation. For example, modified gelatin/chitosan composite systems significantly increase the pH responsiveness and antibacterial activity under laboratory conditions due to dopamine coating and quaternization treatments [116]. On the other hand, synthetic polymers such as PVA and polyacrylic acid (PAA) are frequently used. PVA/CS-BA systems that are formed by dynamic covalent cross-linking, e.g., borate and hydrogen bonds, can intelligently release pro-angiogenic drugs in response to the acidic environment induced by infection and metabolic byproducts such as lactic acid, while retaining a moist wound environment [117]. This pH-triggered drug release, which is effective in a pH range of 5.5 to 7.0, is quite compatible with the pH variations that typically occur in diabetic wounds (pH 5.4-8.9), thus highlighting its physiological relevance [118]. Recent studies highlight that the pH-dependent assembly or disassembly of the phytochemical-based hydrogels based on tannic acid, gallic acid, and epigallocatechin gallate (EGCG) occurs via hydrogen bonding and π - π stacking. This allows acidity induced softening and accelerated release of intrinsic bioactive components without need for additional carriers [119]. Notably, a recently developed EGCG-based adhesive hydrogel based on carboxymethyl chitosan and 2-formylphenylboronic acid via dual dynamic covalent bonds with favorable mechanical strength, antioxidant capacity, and pH-controlled EGCG

release. This design also provides on-demand dissolvability to reduce secondary damage during dressing removal (**Figure 4B**) [102].

Furthermore, multi-component composite hydrogels incorporating PAA and natural cellulose along with modified carbon quantum dots, exhibit both self-healing properties and real-time pH monitoring [120]. When wound pH is reduced from 7.4 to 5.8 by bacterial infection, carbon quantum dots induce controlled drug release, and antimicrobial peptides release rate is 3.8-fold higher. Simultaneously, the addition of zinc oxide nanoparticles results in improved mechanical properties (compressive strength up to 45 kPa) as well as antioxidant efficiency (the 2,2-diphenyl-1-picryl-hydrazyl radical scavenging rate is more than 90%). This pH-responsive and graded release mechanism not only enhances insulin release in acidic conditions (4.2-fold increase in release rate) but also burst release of antimicrobial drugs in alkaline conditions, which reduces inflammatory factors and enhances the process of angiogenesis. Moreover, phytochemical alkaloids such as berberine and flavonoids such as curcumin show increased solubility and intermolecular mobility in mildly acidic microenvironments, which allows self-controlled release kinetics to complement conventional polymeric pH-responsive platforms.

In summary, pH-responsive hydrogels, with their ability to perform precise drug delivery, intelligent monitoring, and multifunctional integration, are a versatile platform for the management of diabetic wounds. However, the dynamic pH range in chronic wounds is relatively small and spatially heterogeneous, which often restricts the full activation of these systems. Localized infection and necrosis can create conflicting micro-pH gradients and buffering capacity of the wound exudate may further reduce responsiveness. Compared to glucose or enzyme responsive systems, pH responsive hydrogels provide a faster but less specific regulatory response. These limitations indicate that future designs should combine pH sensitivity and biochemical recognition mechanisms to provide more precise and sustained therapeutic control.

3.3 Enzyme-responsive hydrogels

In human tissues, enzymes are ubiquitous natural biocatalysts. Their high specificity and rapid response enable them to be known to play key roles in ECM remodeling, cell migration, and signal transduction [29, 121]. During normal wound healing, enzymes participate in inflammation regulation, angiogenesis, and collagen deposition, thereby

promoting tissue regeneration. However, due to persistent hyperglycemia and oxidative stress, the local microenvironment of diabetic wounds is significantly disturbed, accompanied by chronic inflammation and abnormally elevated MMPs and cyclooxygenase-2 activities[122]. These abnormal enzymes not only disrupt the normal secretion of growth factors such as VEGF and EGF, but also inhibit the formation of granulation tissue by excessively degrading ECM components such as collagen, ultimately leading to stagnation of wound repair. In addition, iron ion overload and ROS accumulation further aggravate tissue damage forming a vicious cycle [123].

Enzyme-responsive hydrogels have a three-dimensional network structure similar to that of ECM, and are self-repairing and highly permeable, and can dynamically respond to the complex microenvironment of diabetic wounds [31, 108, 124]. A POD-mimetic lysozyme-hemin nanozyme-anchored Gelatin/PVA hydrogel (ANGP) exploits bacterial GSH-mediated catalysis for rapid colorimetric detection and •OH-based sterilization, though long-term hemin release remains to be optimized (Figure 4C) [103]. Compared with traditional dressings that passively release drugs, this type of hydrogel responds to abnormal enzyme activity through dynamic covalent bonds (such as phenylboronic acid ester bonds) or breakable connections composed of MMP-sensitive peptides, thereby achieving precise on-demand release of drugs and regulation of the microenvironment [125]. For example, in wound areas where MMP-9 is overexpressed, hydrogels can simultaneously release anti-inflammatory drugs or iron chelators after enzymatic degradation, maintaining the structural stability of the ECM while exerting anti-inflammatory and oxidative stress-reducing effects [126]. This dual function gives it significant advantages in scavenging ROS, inhibiting inflammation, and promoting angiogenesis.

In response to the challenges of MMP overexpression and iron ion imbalance in diabetic wounds, researchers designed a composite hydrogel system based on modified alginate and polyethylene glycol diacrylate (PEGDA). This system introduces MMP-sensitive peptides as crosslinkers and loads microspheres containing the iron chelator deferoxamine (DFO) to achieve a dual response to abnormal enzyme activity and iron ion overload [126]. In an acidic environment or in areas with high MMP expression, the hydrogel releases DFO through enzymatic degradation, effectively chelating free iron, reducing ROS levels, improving the microenvironment, and promoting vascular

endothelial cell migration. Animal experiments have shown that this system was reported to increase the expression of VEGF and CD31 and to promote collagen deposition and granulation tissue formation, and thus shortens the healing cycle.

In order to overcome the problems of low drug release efficiency and insufficient biological activity of traditional hydrogels, researchers further integrated mesenchymal stem cell-derived Exos (MSC-exos) into enzyme-responsive hydrogels. For example, the "MSC-exo@MMP-PEGDA" hydrogel embeds Exos into the MMP-sensitive cross-linking network through electrostatic adsorption [127, 128]. In the area where MMP-9 is highly expressed, the hydrogel gradually degrades and continuously releases Exos. Exos can activate the PI3K/Akt/eNOS signaling pathway to promote endothelial cell proliferation, while inhibiting NF-κB-mediated inflammatory response. The miRNAs they carry can also regulate ECM synthesis-related genes, reduce excessive collagen deposition and inhibit scar formation. This composite system showed a sustained release effect of up to four weeks in a diabetic rat model, significantly improving re-epithelialization and angiogenesis.

In summary, enzyme-responsive hydrogels have unique merits in the controlled drug release and adaptive microenvironment regulation via biologically specific degradation [108, 129]. However, their performance remains highly dependent on the fluctuating enzyme activities present in chronic diabetic wounds, which can result in inconsistent release profiles. The synthesis of enzyme-cleavable linkers and incorporation of bioactive cargos also increase manufacturing complexity and limit large-scale production. Compared with pH- or ROS-responsive systems, enzyme-responsive hydrogels exhibit superior specificity but slower response kinetics and reduced structural stability [12, 113, 130]. Therefore, future research should focus on designing hybrid hydrogels that integrate enzyme-responsive degradation with other stimuli-sensing elements to enhance precision and translational feasibility.

3.4 ROS-responsive hydrogel

ROS are a class of highly oxidative molecules, including O_2 , H_2O_2 and OH , which are inevitable byproducts of cellular metabolism. Diabetic wounds fall into a vicious cycle of "difficult to heal-infected-necrotic" due to the imbalance of oxidative stress caused by persistent hyperglycemia. ROS have a biphasic regulatory effect in wound repair. At physiological concentrations, ROS promote angiogenesis by activating the VEGF signaling pathway and drive the bactericidal function of

neutrophils [131]. However, in the diabetic wound microenvironment, abnormal mitochondrial electron transport chain leads to a surge in ROS ($>100 \mu\text{M H}_2\text{O}_2$), breaking through the redox homeostasis threshold, triggering overactivation of the NF- κ B signaling pathway, prompting macrophages to polarize to the pro-inflammatory M1 type, inhibiting collagen deposition and exacerbating ECM degradation [25, 132]. Studies have shown that ROS levels in diabetic wounds are 3-5 times higher than those in normal tissues, forming a positive feedback loop with pro-inflammatory factors such as TNF- α and IL-6, further aggravating hypoxia and vascular regeneration disorders [133]. Although traditional hydrogel dressings can provide a physical barrier and local moisturizing, they lack dynamic response capabilities: single antioxidant components (such as vitamin C) are easily exhausted in the early stage and cannot cope with continuous ROS generation; the separation of antibacterial and healing functions leads to insufficient control of deep tissue infection, and the hypoxic microenvironment hinders late epithelial regeneration [134]. For example, although ordinary chitosan hydrogels have antibacterial properties, they cannot target the removal of intracellular ROS or regulate macrophage phenotypic transformation [135].

In view of the limitations of traditional materials, smart responsive hydrogels have attracted increasing attention due to their dynamic molecular design and technological integration. Among them, the "ROS threshold trigger" mechanism based on dynamic covalent bonds has emerged as a key approach: the thiolketone bond (-SS-) and the phenylboronic acid bond are selectively broken under pathological ROS levels (Among them, the -SS- and the phenylboronic acid bond are selectively broken under pathological ROS levels (typically $\approx 100 \mu\text{M H}_2\text{O}_2$, within the physiological ROS range of 50-200 μM in diabetic wounds)) to achieve spatiotemporal controllable drug release. For example, CMCS-PBA/OXD hydrogel preferentially releases α -lipoic acid in the high ROS area of the wound through ROS-sensitive Schiff base bonds to modulate ROS levels and inhibit biofilm formation of *Staphylococcus aureus* [12]. In addition to the ROS responsive dynamic linkages commonly used in synthetic hydrogels, several traditional Chinese medicine (TCM) derived phytochemicals such as baicalein, quercetin, and resveratrol have been reported to undergo ROS mediated oxidation or structural softening [136-142]. This behavior increases molecular mobility and promotes the release of their intrinsic antioxidant components. These TCM related antioxidant frameworks thus offer a biodegradable and biocompatible supplementary mechanism for

ROS responsive modulation in chronic diabetic wounds, while avoiding the long term biosafety issues associated with metal based catalytic systems. For the improvement of the hypoxic microenvironment, the bionic cascade strategy of oxygen self-supply and antioxidant system shows significant advantages. For instance, a dynamic oxygen-releasing hydrogel constructed by encapsulating basic fibroblast growth factor (bFGF), microalgae, and COF-1 into a self-assembled network demonstrates synergistic effects in alleviating oxidative stress and promoting angiogenesis. The borate-based covalent organic framework (COF) achieves ROS scavenging and glucose-responsive degradation, while the microalgae continuously provide the dissolved oxygen to alleviate the hypoxia. In addition, the B-N coordination bonds assist in pH-sensitive drug release. This multifunctional hydrogel has a favorable biocompatibility and can promote re-epithelialization and collagen remodeling in diabetic wounds, which is a promising strategy for wound management in chronic wounds (Figure 4D) [104].

In summary, ROS-responsive hydrogels can effectively modulate oxidative stress, angiogenesis enhancement, and immune remodeling via threshold-triggered and cascade catalytic mechanisms. However, the concentration and distribution of ROS in chronic wounds is highly variable and this makes precise activation control difficult. Excessive scavenging of ROS may impair normal redox signaling, whereas insufficient response could fail to alleviate oxidative damage. In addition, the long-term biosafety of metal-based nanozymes and quantum dots remains uncertain, and their mechanical stability is often inadequate for deep wound support. Compared with enzyme- or glucose-responsive systems, ROS-responsive hydrogels provide faster responses but lower selectivity and reduced structural integrity. Therefore, future research should aim to establish quantitative redox regulation and develop biodegradable, metal-free catalytic systems to achieve safe, tunable, and clinically reliable wound therapies.

To provide a concise summary of the single-stimulus systems discussed above, Table 1 compiles representative examples of glucose-, pH-, enzyme-, and ROS-responsive hydrogels reported in 2024-2025, along with their key physical parameters. This comparative overview highlights how each stimulus type influences the mechanical, adhesive, and degradation behaviors of the hydrogels, offering a foundation for the development of multi-responsive platforms discussed in the next section.

Table 1. Representative single-stimulus microenvironment-responsive hydrogels for diabetic wound healing and their key physical properties (2024-2025). All values represent typical ranges reported in the cited literature, and may vary substantially depending on formulation composition and testing conditions.

Hydrogel type	Representative system	Core mechanism	Compressive strength (kPa)	Adhesive strength (N cm ⁻²)	Swelling Ratio (%)	Degradation rate (% mass loss, days)	Ref. (Year)
Glucose-responsive	Zn-MOF-GOx cascade nanoreactor	GOx-catalyzed glucose oxidation triggers NO generation and microenvironment modulation	65 ± 5	1.8 ± 0.2	370 ± 25	45 ± 3 (7 d)	[101] (2024)
Glucose-responsive	Multienzyme "nanoflower" hydrogel (GOx-activated NO)	Glucose-triggered NO release from multienzyme composite	72 ± 6	2.0 ± 0.3	380 ± 20	50 ± 4 (7 d)	[109] (2025)
pH-responsive	TA/QCMC/OSA injectable hydrogel	Acid-base reversible dynamic bonds enabling pH-triggered release	60 ± 4	1.6 ± 0.2	350 ± 15	40 ± 5 (5 d)	[102] (2024)
pH-responsive	Acid-responsive CST@NPs system	Acidic wound milieu triggers drug release from acid-labile construct	45 ± 3	1.2 ± 0.2	390 ± 30	42 ± 6 (7 d)	[116] (2024)
Enzyme-responsive	MMP-9-responsive hydrogel (ferroptosis suppression)	MMP-cleavable crosslinks enable on-demand release; protects endothelial cells from ferroptosis	70 ± 5	1.7 ± 0.2	380 ± 25	55 ± 4 (10 d)	[126] (2024)
Enzyme-responsive	MMP-9-responsive exosome-releasing hydrogel	MMP-sensitive network degrades to release MSC-derived exosomes	68 ± 5	1.5 ± 0.3	370 ± 20	50 ± 5 (10 d)	[127] (2025)
ROS-responsive	HA-based ROS-responsive injectable hydrogel (HA@Cur@Ag)	ROS-cleavable/disulfide chemistry enables on-demand release and ROS scavenging	68 ± 6	1.9 ± 0.2	400 ± 30	45 ± 5 (7 d)	[12] (2024)
ROS-responsive	GelMA/PVA-UIO-66-NH ₂ @Quercetin nanocomposite hydrogel	MOF-assisted ROS-responsive release; modulation of inflammatory microenvironment	75 ± 7	2.1 ± 0.2	390 ± 20	48 ± 4 (10 d)	[104] (2025)

As summarized in **Table 1**, single-stimulus microenvironment-responsive hydrogels show different physical behaviors mainly due to the differences in their molecular crosslinking mechanisms. Glucose- and enzyme-responsive systems typically employ covalent or enzyme cleavable linkages that yield denser polymer networks, providing higher mechanical strength and slower and more controlled rates of degradation. In contrast, pH- and ROS-responsive hydrogels are typically formed by reversible dynamic bonds, such as imine, borate, or disulfide bonds, that are easily cleaved under acidic or oxidative conditions. These structural characteristics encourage higher network relaxation, swelling ratios, and faster disassembly, which aids in on-demand release of drugs.

Overall, these distinctions emphasize the specific benefits and drawbacks of each stimulus type in striking the right balance between stability and responsiveness. Such insights offer a structural basis for the design of multi-responsive hydrogels with complementary properties, which will be discussed in the next section.

3.6 Multi-responsive hydrogels

Diabetic wounds are defined by a vicious cycle, including hyperglycemic microenvironment, constant oxidative stress (ROS), overexpression of MMP-9 and the imbalance of inflammatory mediators (especially the IL-10/TNF- α ratio). This complex and dynamically intertwined pathology poses great challenges to conventional single-responsive hydrogels. For instance, strategy that is focused only on scavenging ROS may result in excessive ROS

depletion, impairing their physiological pro-angiogenic functions. Similarly, a hydrogel that can only respond to pH changes has difficulty responding to the multi-stage requirements of diabetic wounds, which include anti-infection, anti-inflammation, and tissue regeneration [148]. In this context, multi-stimulus responsive systems are on the verge of integrating signals of glucose, ROS, pH, enzymatic activity and temperature to achieve temporally and spatially adaptive, precisely synergistic therapeutic effects. During the first inflammatory phase, a dual pH/ROS-responsive module can release antimicrobial agents to inhibit infection (**Figure 5A**) [143]. In the following phase, the regulation of redox balance and immune microenvironment is accomplished by the action of enzymes or temperature-sensitive mechanisms. Finally, in the remodeling phase, the sensitivity of glucose may be used to stimulate angiogenesis and the ECM remodeling process to aid in the entire wound healing process [121]. This development of dynamic sensing and multi-modal responsiveness highlights the potential of multi-responsive hydrogels as a transformative technology to overcome the persistent challenges in diabetic wound healing.

To meet the complex requirements in diabetic wound treatment, a hierarchical and progressive design paradigm has been proposed by researchers [144-151]. For instance, a COF-modified microalgae hydrogel system was created that combines glucose, ROS and NIR light responsiveness in one therapeutic system [144]. The boronic ester-based COF-1 scavenges ROS and allows glucose-triggered release of bFGF and embedded microalgae continuously

generate oxygen to relieve hypoxia (**Figure 5B**). Upon 808 nm NIR irradiation, localized heating promotes the permeability of the gel and increases the speed of cargo release. This synergistic system enhances angiogenesis, inhibits inflammation and restores redox balance, which greatly enhances diabetic wound closure and tissue regeneration through a cascade-responsive mechanism. The combination of boronic ester-linked COFs and microalgae enables glucose- and ROS-responsive drug release, and NIR-induced oxygenation. This spatiotemporal synergy counteracts oxidative damage caused by hyperglycemia and re-establishes redox homeostasis, promoting angiogenesis, improving cell proliferation and accelerating chronic diabetic wound repair without interfering with physiological ROS signaling. Another innovative approach is through the adaptation of the healing process through a chronological sequential release strategy (**Figure 5C**). For example, a glucose/ROS/MMP-9 multi-responsive hydrogel (OE-G@D system) is sensitive to hyperglycemia in the early stage of inflammation by breaking phenylboronate bonds to release EGCG, which scavenges ROS and inhibits the accumulation of AGEs. This is followed by MMP-9-mediated release of DFO to stimulate angiogenesis [145]. During the repair phase, dissolution of a polysaccharide called chitosan under acidic conditions releases manganese-based nano-enzymes, which improves ROS scavenging efficiency and the rate of collagen

deposition is increased by 50%. Cutting edge research is also being conducted on adaptive closed-loop systems, such as a dual-responsive electric field/temperature dressing that activates precise insulin delivery via a polyaniline conductive network that senses changes in wound potential (with sensitivity of 0.1 mV/mm²). This system integrates coupling temperature-sensitive polymer segments to mediate controlled release of VEGF, in addition to real-time biomarker monitoring using flexible microelectrodes, to create a dynamic "sense-respond-regulate" closed-loop treatment platform [147].

Despite the great progress, clinical translation of multi-stimulus-responsive hydrogels is still hindered by three key challenges: (1) material incompatibility, e.g. the tendency of uncontrolled cross-linking between ROS-sensitive thioether bonds and enzyme-sensitive peptide chains [148, 149]; (2) poor dynamic adaptability, i.e. delayed response to rapid pH fluctuation or pulsed bursts of ROS [150]; and (3) heterogeneity in large-scale production, such as AuNRs/chitosan complexes, which are suffering from batch-to-batch variability due to nanoparticle aggregation [151]. Specifically, chitosan-based complexes are prone to inconsistencies due to clustering of nanoparticles which affects reproducibility. To overcome these obstacles, future research is increasingly focusing on interdisciplinary and synergistic innovations. These include programming biomimetic topologies using DNA

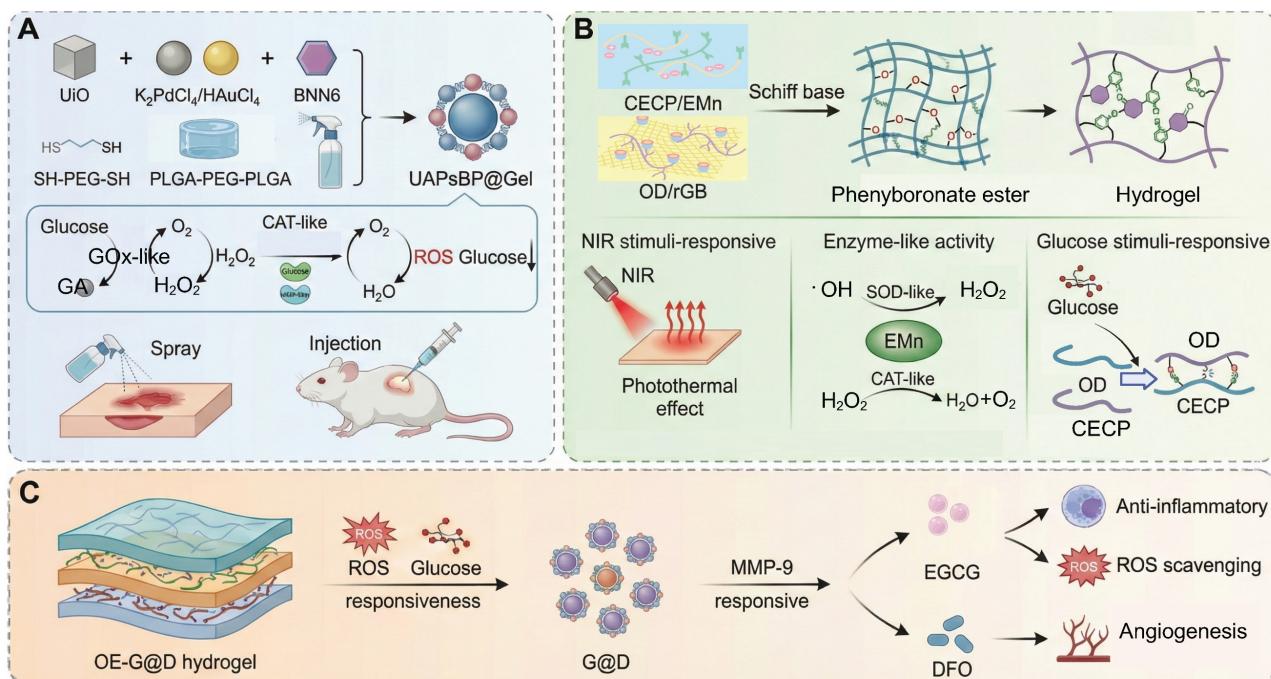


Figure 5. Types of multi-responsive hydrogel. **(A)** pH/ROS responsive hydrogel. **(B)** NIR/Glu/ROS responsive hydrogel. **(C)** ROS/Glu/MMP responsive hydrogel. Created in BioRender. Jia, J. (2025) <https://BioRender.com/f9f93g2>.

origami technology to build smart materials that can dynamically respond to multiple biomarkers such as MMP-9, IL-6 and VEGF; using genetically engineered cyanobacteria implanted into wounds to achieve simultaneous photosynthetic oxygenation and necrotic tissue degradation; and developing 3D-printed gradient drug-release hydrogels that incorporate macrogenomic data of the patients microbiota for personalized microbial modulation [152-155].

4. Designation of Cascade Reaction in the Responsive Hydrogels Combine with Treatment of Diabetic Wounds

Diabetic wound healing is a complex pathophysiological network, where the main difficulty of wound healing is caused by the spatiotemporal interaction of several pathological factors, such as bursts of ROS, protease imbalances, chronic inflammation, and impaired vascular regeneration in a hyperglycemic microenvironment. Traditional single target therapies have difficulty interrupting this multidimensional vicious cycle because of limited targets and mismatched therapeutic time windows. In recent years, cascade reaction strategies have been able to achieve temporal adaptation of multi-target synergistic intervention and therapeutic effects through the use of a trigger-response-amplification regulatory logic. Smart responsive hydrogels are suitable carriers for these strategies, allowing controlled delivery of cascade signals induced by pathological microenvironmental cues (such as pH, ROS levels or enzyme activity) to reshape the regenerative microenvironment in both spatial and temporal dimensions [12, 155]. Building on this concept, combined therapies not only improve the accuracy of the treatment, but also increase the biological effect of cascade reactions. Examples include the ability to simultaneously control angiogenesis and anti-inflammatory response through cascade release of nitric oxide (NO), or the use of cascade enzymatic reactions to selectively target and destroy excessive inflammatory mediators [19]. To systematically explore these mechanisms, this study uses a three-tier classification system according to reaction chain length, molecular mechanism, and treatment stage targeting to give a comprehensive analysis of the adaptation logic and translational potential of cascade reaction strategies for diabetic wound therapy [156].

4.1 Classification based on the number of cascade reactions

Given the complex pathological characteristics of

diabetic wounds, including persistence of hyperglycemic microenvironment, drug-resistant bacterial infections, oxidative stress and inflammatory storms, traditional monotherapies often struggle to achieve effective dynamic intervention. In recent years, cascade-based stimulus-responsive hydrogel systems have become a cutting-edge approach to address these multifaceted challenges by a hierarchical and progressive treatment logic.

To gain a better understanding from a conceptual point of view, we use a more rigorous definition of a true cascade reaction: one in which the intermediate or product formed at one step directly drives or catalyzes the next step, leading to a self-propagating or sequentially amplified reaction. By contrast, systems which are triggered by a single stimulus are categorized as single-stimulus-responsive systems and do not, strictly speaking, constitute cascade reactions.

Accordingly, the systems reviewed in this section are classified according to the number of cascade levels, i.e. single-stimulus responsive systems, dual-layer cascades, and multi-layer cascade systems (Table 2). This classification reflects the different levels of coupling of reactions and functional complexity. It is important to emphasize that this framework is conceptual rather than a strict chemical-step definition and is used to clearly distinguish between simple stimulus-response systems and true multistep cascades while retaining internal consistency in the current discussion.

4.1.1 Single-stimulus responsive system

During the acute infection phase of diabetic wounds (within 48 hours), rapid acidification of the local microenvironment (pH=5.5 - 6.5) and the formation of biofilms by drug-resistant bacteria such as MRSA and *Pseudomonas aeruginosa* represent the main threats [179]. In these scenarios, single stimulus responsive systems, which work through a single signal trigger mechanism, are often preferred because they are fast acting. Although these systems are not true cascade reactions, they are fast, targeted responses. For example, hyaluronic acid-based pH-responsive silver gel (HA-Ag) releases Ag⁺ ions via Schiff base bond cleavage in the acidic microenvironment with a peak concentration of 2.8 µg/mL in 24 hours and clears 99.3% of MRSA. However, residual Ag⁺ suppresses the migration of fibroblasts and retards the regeneration of the epidermis [180]. Similarly, the Gel-FCHO/Mg-motor GCM hydrogel decomposes the Schiff bases at wound pH 5.5-6.5, while releasing curcumin-containing micelles and H₂ produced by Mg micromotors. Yet, rapid Mg corrosion threatens to cause an alkaline shift

($\text{pH} > 8$), which results in loss of peptide stability and requires buffering of microdomains to keep local pH (**Figure 6A**) [157]. Another interesting design, a thermosensitive chitosan-tobramycin gel, induces a hydrophobic-hydrophilic transition at body temperature, which slowly releases tobramycin that penetrates biofilms with a 92% clearance rate and decreases local glucose concentration by 19% [181]. The major benefits of these single-stimulus systems are their ease of synthesis and speed of response, which make them especially useful in the outpatient setting for acute treatment of superficial ulcers. However, their linear release kinetics can lead to sudden release of the drug, which could potentially cause local oxidative stress, and they cannot control the release of inflammatory factors, which limits their efficacy in chronic wounds. As a complementary strategy, the PEG-DA/HA-PBA/MY hydrogel takes advantage of the glucose-induced borate cleavage to release myricetin selectively under hyperglycemic conditions ($\geq 15 \text{ mM}$) to reduce ROS without stopping physiological H_2O_2 bursts. Nevertheless, its release drops dramatically below 8mM glucose, requiring secondary triggers during normoglycemic phases

(**Figure 6B**) [158]. Meanwhile, the G/D-CuP hydrogel is based on dimeric CuP connected through ROS-cleavable bonds, where CuP is released only when H_2O_2 concentration is over 100 μM , hence coupling the anti-inflammatory and angiogenic effects. Dimerization provides increased protease resistance but can inhibit rapid diffusion in deep wound fissures (**Figure 6C**) [92]. Other single-layer systems have been based on thermal or enzyme-mediated cascade activation, e.g. temperature-triggered release of antibiotics, which maintains ROS production and wound closure [181, 182]. Compared to multilayer designs, these single-stimulus systems have simpler synthesis and quicker responses, and therefore are well-suited for early infection control. However, their linear release profiles and single level of activation limit their capacity to control inflammation and tissue regeneration over the long-term. Therefore, future research should be focused on the incorporation of secondary triggers or self-feedback mechanisms to increase the temporal adaptability and therapeutic precision of single-stimulus responsive systems.

Table 2. Various types of cascade reaction-based stimuli-responsive hydrogels for promoting efficient repair of diabetic wounds and their therapeutic effects on wound healing.

Classification	Hydrogel dressing	Triggers	Reaction unit	Therapeutic properties	Ref.
single-stimulus responsive system	GMPE hydrogel	Glu	• Boronic ester bonds	• ROS scavenging • Inhibition of inflammation • Angiogenesis stimulation	[161]
	HMPG hydrogel	Glu	• Boronic ester bonds	• Scavenges excessive ROS • Enhances angiogenesis	[162]
	TA/QCMCS/OSA@CQD hydrogel	pH	• Schiff-base bonds	• Anti-inflammatory activity • Antibacterial • Enhanced angiogenesis	[163]
	CF Gel @ Ber-F127 micelles	ROS	• CD-Fc host-guest interaction	• Anti-inflammatory • Promotes M2 polarization	[24]
	HA-Gel hydrogel	MMP-9	• MMP-9 cleaves gelatin network	• ROS scavenging • Promotion of angiogenesis • MMP-9-responsive controlled release	[164]
	LIN@PG@PDA hydrogel	Near-infrared light (NIR)	• NIR triggers photothermal effect via PDA • PNIPAM undergoes thermal-induced volume shrinkage	• Promotion of angiogenesis • Acceleration of epithelial regeneration • Enhanced wound closure	[165]
	NNH patch	Heat	• PNIPAM responds to heat • Inverse opal structure	• Promotion of angiogenesis • Collagen remodeling and epithelial regeneration	[166]
Dual Cascade System	Gel(CaO ₂ /alg/Gox/Glu/NB/CAT-Ce ₆)	Glu 660 nm laser	• Gox • CAT	• Antibacterial • Analgesic • Oxygen Supply • Enhance Photodynamic Therapy • Reduce Inflammation	[167]
	BGL-interactive dynamic hydrogel	Glu pH	• Gox • Schiff-base bonds	• Maintain homeostasis • Promote wound healing • Antibacterial • Prevent continuous decline of BGL and pH • Adaptive behavior	[168]
	PBA/Cs hydrogel	Glu ROS	• Boronate ester bonds formed by PBA and diol-rich polymers	• Enhanced epidermal and dermal reconstruction • Promotion of angiogenesis	[169]
	Bi/Bi ₂ WO ₆ /H-TiO ₂ -gel	Visible light Glu	• Photocatalytic Z-scheme heterojunction • Glucose	• Continuous H ₂ generation • ROS scavenging and macrophage M1→M2 polarization	[170]

Classification	Hydrogel dressing	Triggers	Reaction unit	Therapeutic properties	Ref.
				<ul style="list-style-type: none"> Inhibition of advanced AGEs Promotion of angiogenesis, collagen remodeling, and cell proliferation 	
Multilayer cascade reaction system	EGC Hydrogel (LYZ-GOx-CAT)	Glu pH	<ul style="list-style-type: none"> •GOx: •Schiff base imine bonds 	<ul style="list-style-type: none"> Self-healing and shape adaptability Glucose and ROS regulation Promotion of angiogenesis and tissue repair pH-responsive controlled release 	[171]
	GDHPC hydrogel	pH Glu ROS	<ul style="list-style-type: none"> •Borate ester bonds •Schiff base bonds 	<ul style="list-style-type: none"> Antioxidant Anti-inflammatory Antibacterial Pro-angiogenic 	[11]
	PLPT hydrogel	Glu pH NIR	<ul style="list-style-type: none"> •Borate ester bonds •PPy 	<ul style="list-style-type: none"> Antimicrobial Antioxidant Anti-inflammatory Pro-angiogenic 	[172]
	DFO/ENZ@CPP hydrogel	Glu pH NIR	<ul style="list-style-type: none"> •Phenylboric ester bonds •Schiff base bonds 	<ul style="list-style-type: none"> Antimicrobial, antioxidant Anti-inflammatory Pro-angiogenic pH regulation Oxygen supply 	[173]
	GOx@ZIF-90-Arg-loaded hydrogel	Glu pH	<ul style="list-style-type: none"> •GOx •ZIF-90 •L-Arg 	<ul style="list-style-type: none"> Broad-spectrum antibacterial Biofilm disruption Anti-inflammatory Neurovascular regeneration Improved glucose tolerance Promotion of collagen synthesis and cell proliferation Controlled NO delivery avoiding oxidative stress Hemostasis and tissue adhesion enhancement 	[174]
	Cu-MOF/GOX-Gel hydrogel	Glu H ₂ O ₂ Heat	<ul style="list-style-type: none"> •GOX •L-Arg 	<ul style="list-style-type: none"> Antibacterial via cascade catalytic ROS generation Local glucose depletion Controlled NO release Angiogenesis promotion Collagen deposition Enhanced epithelial cell migration Biocompatible and thermosensitive scaffold 	[6]
	DPH3@INS@ZIF-8@PEG-TK hydrogel	Glu ROS pH	<ul style="list-style-type: none"> •Boronate ester bonds •PEG-TK •DA 	<ul style="list-style-type: none"> Insulin-mediated glucose regulation ROS scavenging Anti-inflammatory Promotion of angiogenesis and collagen remodeling M1-to-M2 macrophage polarization Antibacterial activity Hemostatic effect 	[175]
	HPCG/PFD hydrogel	Glu pH NIR (808 nm)	<ul style="list-style-type: none"> •Schiff base •Phenylboronate ester bond •GPC 	<ul style="list-style-type: none"> Photothermal antibacterial activity Photodynamic antibacterial activity Anti-inflammatory Promotion of angiogenesis Antioxidant activity 	[176]
	Cu-TCPP(Fe)@Au@BSA hydrogel	Glu H ₂ O ₂ pH	<ul style="list-style-type: none"> •Au@BSA •Cu-TCPP(Fe) 	<ul style="list-style-type: none"> Glucose consumption and pH reduction Local •OH production for CDT-based antibacterial effects Epithelialization and collagen regeneration Antioxidant effect 	[177]
	CRMs-hydrogel composite	MMP-9 enzyme Heat	•PVGLIG peptid	<ul style="list-style-type: none"> Targeted antibacterial activity MMP-9-responsive controlled release Promotion of cell migration Promotion of angiogenesis Thermosensitive adhesion 	[178]

4.1.2 Dual cascade system

When the wound enters the subacute inflammatory phase, the vicious cycle of hyperglycemia, ROS overload, and hypoxia continues to be a critical limitation to wound healing. Dual cascade systems provide a major advance by allowing the modules of treatment to be activated in stages,

which allows for energy self-supply and functional synergy. For example, the copper peroxide-GOx (CP@GOD) system uses GOx to catalyse glucose into H₂O₂, which is then decomposed by the CP nanozymes into hydroxyl radicals (•OH) and Cu²⁺ ions. The •OH result in a sterilization rate of over 99% against *Staphylococcus aureus* whereas Cu²⁺ ions trigger the HIF-1 α pathway, which results in an 180%

increase in the expression of the growth factor "VEGF" and, consequently, in the process of angiogenesis. In diabetic mouse models, this approach reduced the wound healing time to 14 days and greatly improved the vascular density [183]. Another innovative design, the photodynamic ROS-responsive nanogel (Ce6@ZIF-8), takes advantage of the acidic microenvironment in the wound to release the photosensitizer Ce6. When activated by NIR light, Ce6 produces oxygen and can be used to target eradication of MRSA. At the same time, the photothermal effect promotes the orderly deposition of collagen, thereby reducing the formation of scars [184]. The main benefit of these systems is the temporal control: the first infection control is performed by the antibacterial module, then the regeneration of factors to prevent interference with the therapeutic effect. However, synchronization of the kinetics of dual reactions is a technical challenge. For example, the injectable nanoreactor hydrogel Arg@Zn-MOF-GOx Gel (AZG-Gel) orchestrates two consecutive cascades: (1) GOx converts the hyperglycemic glucose into gluconic acid and H₂O₂, rapidly lowering local pH; (2) disassembly of Zn-MOF, triggered by the acid, releases arginine which consumes H₂O₂ to produce NO, thus ablating biofilms and inducing angiogenesis without the need

for exogenous ROS. Although this all-in-one platform has a wound closure rate of 98.7% within 14 days, premature Zn-MOF degradation below pH 5.0 poses the risk of an NO burst that may induce transient cytotoxicity, underscoring the necessity of buffering microenvironments for clinical translation (Figure 6D) [159]. Similarly, the rate of H₂O₂ generation in the CP@GOD system should be carefully balanced with the release of Cu²⁺ to avoid excessive free radical damage to surrounding tissues. Moreover, endogenous catalase activity is in competition during the decomposition of H₂O₂, which could decrease the efficiency of the cascade [183].

Dual-layer cascade hydrogels are made of different functional domains that act synergistically to spatially organize antibacterial, anti-inflammatory and regenerative effects. Compared to single layer systems, which provide fast response but mainly local action, these dual layer architectures can provide sequential therapeutic regulation and prolonged drug release. However, the fabrication of heterogeneous material layers of different swelling and degradation characteristics can cause interfacial instability and inconsistent cascade activation. Achieving synchronization of biochemical reactions within layers poses serious challenges in control, which raises processing complexity and hinders

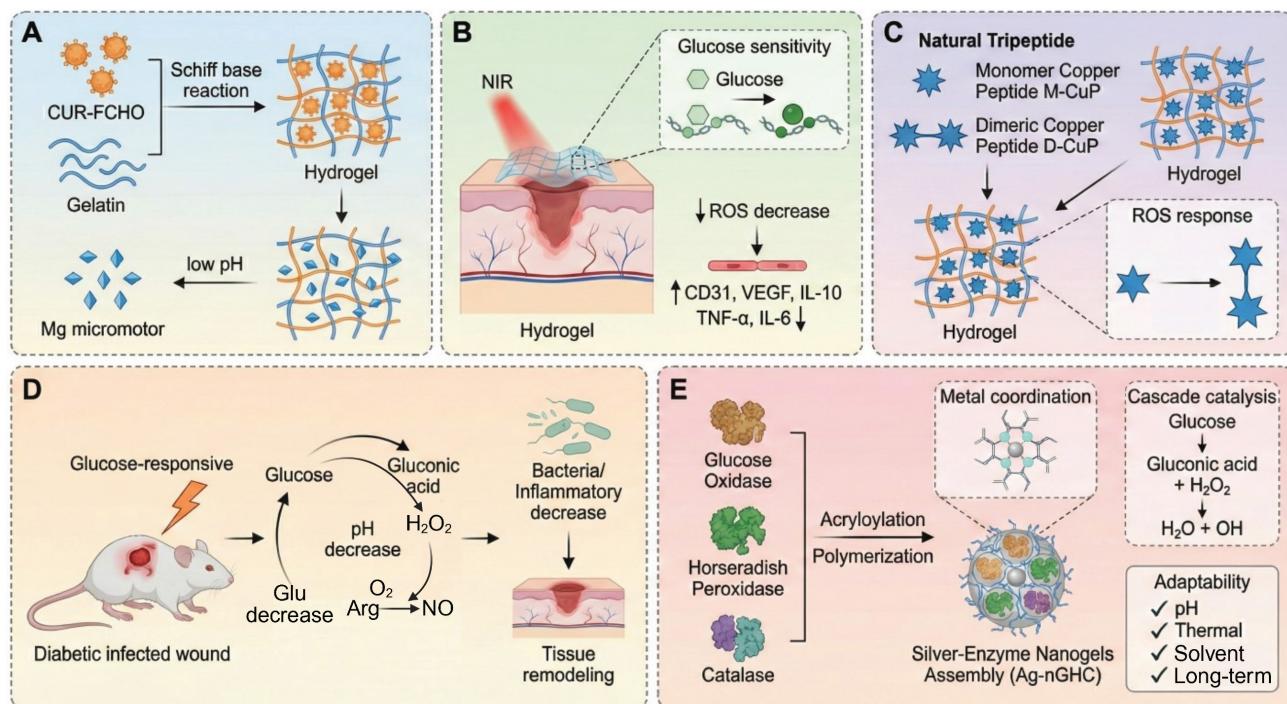


Figure 6. Classification based on the number of cascade reactions. (A-C) Single-layer cascade reaction system. (A) pH-responsive hydrogel enabling Mg micromotor disintegration and therapeutic release under acidic diabetic wound conditions. (B) The glucose-responsive antioxidant hydrogel for diabetic wound healing. HA-PBA provides glucose sensitivity, enabling dynamic binding with myricetin. (C) ROS-responsive hydrogel. (D) Dual cascade system of a dual-responsive AZG-Gel hydrogel that responds to hyperglycemia and high pH by GOx-mediated glucose oxidation. (E) Multilayer cascade reaction system of a multi-responsive Ag-nGHC nanogel system, responding to hyperglycemia, hypoxia, and bacterial infection via a cascade of GOX/HRP/CAT enzyme reactions. Created in BioRender. Jia, J. (2025) <https://BioRender.com/f9fv3g2>.

reproducibility. Despite promising therapeutic outcomes shown in preclinical studies, dual-layer cascade systems still suffer from challenges in structural optimization and scalable manufacturing. Therefore, future studies should aim to increase interfacial bonding, coordinate permeability between layers, and standardize production processes to increase stability and promote clinical translation.

4.1.3 Multilayer cascade reaction system

The multiple cascade reaction system is a biomimetic catalytic network, which incorporates multiple enzymes or enzyme-like catalysts (e.g., nanozymes) in confined domains to build a multi-step, self-sufficient biochemical reaction chain for synchronous regulation of the diabetic wound microenvironment. Its main characteristics are: (1) multifunctional coupling, realized by synergistic enzyme catalysis (e.g., GOx/hydrogen peroxidase), nanomaterial catalysis (e.g., Pt/CeO₂), and controlled release of bioactive molecules, which can achieve time-sequenced intervention, including glucose reduction, antioxidation, anti-inflammation, and tissue regeneration; (2) pathological responsiveness, induced by disease-specific signals such as hyperglycemia and ROS to achieve targeted metabolic regulation.

Given the multidimensional pathological characteristics of diabetic wounds such as hyperglycemia, inflammation, infection, and impaired angiogenesis, therapeutic systems need to have dynamic and synergistic intervention capabilities depending on wound stages. Single-layer cascade systems (e.g., glucose-activated antibacterial gels) consume glucose quickly and release Ag⁺ through enzymatic reactions, killing 99% of MRSA within 48 hours, but are not multifunctional enough for later stages of repair [112]. Dual cascade systems (e.g., pH/ROS-responsive hydrogels) that allow synergistic ROS clearance and sustained exosome release with temporal control to facilitate orderly anti-inflammatory and pro-angiogenic responses with a 40% increase in healing rate in animal models. Multi-layer cascade systems combine glucose response, antioxidation and epithelial regeneration, reducing wound closure to 8 days in diabetic mouse models, a good example of whole chain management [168]. The Ag-nGHC platform demonstrates a multilayer cascade with stage-adaptive responsiveness (Figure 6E) [160]. Its triple-enzyme nanogel structure allows for sequential glucose depletion, oxidative sterilization and oxygen regeneration, matching therapeutic activities to the wound healing process timeline, from infection control to tissue regeneration. Importantly, the high

biocompatibility of the system stems from the incorporation of native enzymes, without the immunogenicity that is common with inorganic nanozymes. However, the inherent fragility of native proteins requires encapsulation strategies for *in vivo* sustained activity. This approach offers a new blueprint for enzyme-based therapeutics in diabetic wound care with potential applications beyond diabetic foot ulcers in burns and ischemic ulcers.

Hydrogel cascades multi-layer cascade hydrogels have emerged as a new advancement in regenerative medicine, in which the multiple layers with functional specifications permit hierarchical coordination of therapy because of spatially and temporally discrete responses [168]. These hydrogels are more functionally complex and allow sequential delivery of various biochemical signals than dual-layer systems. The increased structural hierarchy however causes problems including kinetic imbalances, diffusion mismatch across layer and buildup of intermediate byproducts all of which may cause incomplete or slow cascade activation [165]. Also, mechanical discrepancies and fabrication issues do not allow reproducibility and stability.

Moreover, excessive combination of various stimuli, catalytic modules and signaling pathways is dangerous to biological incoherence. The responsive units can interfere with each other, leading to kinetic interference or overlapping signals, which can disrupt the redox balance or result in immune overactivation. These unintended interactions may backfire on the therapeutic benefits and may augment the biosafety issues. Although multi-layer hydrogels are promising as programmable wound therapies, inter-module interference and the complexity of the system have inhibited their clinical translation. Thus, the functional simplification, decoupling of reaction pathways, and rational coordination of response modules should be made in the future to maintain controllability and biological harmony.

4.2 Classification based on cascade reaction mechanism

The pathological complexity of diabetic wounds demands systems of treatment capable of dynamically and multidimensionally controlling the underlying mechanisms [25, 105]. Depending on the principle of their triggering, the cascade reaction mechanism can be classified into three groups namely natural enzyme driven, biomimetic catalytic, and physicochemical response. Biocatalysis, material biomimetics and non-enzymatic cascade processes are precise interventions. The concerted integration of these mechanisms not only is commensurate to the pathological features stage-specific for the wound, but

also overcomes the inherent limitations of single-modality treatments.

4.2.1 Enzymatic cascade reaction: precise activation of endogenous substrates in wounds

The cascade system based on natural enzymes has shown significant biocompatibility in acute phase applications. For example, the dual enzyme system of GOx and HRP converts high-concentration glucose into antibacterial reactive oxygen (OH) through two-step catalysis, reducing the bacterial load on the wound surface by 98% in a diabetic mouse model (only 58% in the control group), while promoting collagen deposition to accelerate healing [186]. In this process, GOD first catalyzes glucose to produce H₂O₂, and then HRP decomposes it into OH with a broad-spectrum bactericidal effect, which not only achieves the goal of anti-infection, but also alleviates high glucose toxicity by reducing local glucose. Complementing the above GOD-HRP platform, an α -amylase/GOx-coupled chemodynamic patch has been engineered to sequentially degrade EPS polysaccharides and hyperglycaemic glucose. α -amylase first liquefies the biofilm matrix, liberating glucose that is immediately oxidised by GOx-immobilised MOF nanoneedles to generate local H₂O₂; subsequent Fenton-like chemistry converts H₂O₂ into cytotoxic •OH without exogenous H₂O₂, achieving 99.9 % MRSA eradication while lowering ambient glucose by 45 %. Nevertheless, the burst release of •OH at pH 5.5-6.0 transiently elevates oxidative stress, demanding ROS-quenching back-up layers to protect nascent granulation tissue (Figure 7A) [185]. Alternatively, a pH-driven NO-releasing cascade was recently constructed by co-encapsulating GOx and L-arginine within acid-labile ZIF-90 (GOx@ZIF-90-Arg) [158]. GOx-mediated glucose oxidation simultaneously consumes glucose and acidifies the microenvironment, triggering ZIF-90 disintegration to release Zn²⁺ and H₂O₂; the latter drives arginine oxidation to produce NO, which disperses 96% of pre-formed biofilms and enhances angiogenesis via cGMP signalling. The system attains 98.7% wound closure within 14 days, yet the rapid ZIF dissolution below pH 5.0 risks premature payload exhaustion, necessitating pH-buffering hydrogels or core-shell architectures to prolong therapeutic windows (Figure 7B) [174]. Enzymatic cascade reactions are considered to be one of the most biologically compatible strategies for wound regulation. These reactions use endogenous substrates to trigger sequential biochemical reactions with high spatial selectivity. In the setting of diabetic wounds, multi-enzyme systems, such as GOx/peroxidase or superoxide dismutase (SOD)/catalase cascades, have

been shown to convert excessive glucose or ROS into controlled signals [158]. This process allows the modulation of oxidative stress, oxygen supply, and inflammation *in situ*. The efficacy of these designs in promoting self-sustaining biochemical feedback has been demonstrated, especially in promoting angiogenesis and tissue regeneration under conditions of hyperglycemia and hypoxia. However, the use of enzymatic cascade hydrogels is frequently limited by their complex kinetic processes and sensitivity to environmental variations. The activity and stability of natural enzymes can be affected by variation of pH, changes in temperature and by proteolytic degradation, resulting in unpredictable catalytic efficiency *in vivo*. Moreover, the over-integrated cascade networks with multiple catalytic modules can be affected by issues like kinetic crosstalk, substrate competition or imbalanced reaction rate. These issues may result in a reduction of controllability and potentially the production of unwanted intermediates. These effects can lead to local redox homeostasis or oxidative and immune stress which can reverse the desired therapeutic effects.

Multi-enzyme reactions are more specific to substrates compared to single-enzyme or photo/ROS-driven cascade systems, but they require strict stoichiometric control and local cofactor balance, which is a challenge to their standardization in clinical application. To address these issues, subsequent research should aim at stabilizing enzymes, either through biomimetic confinement or nanozymatic replacement, and rational pathway decoupling to guarantee catalytic precision and biological harmony in general.

4.2.2 Enzyme-mimetic cascade reaction: an engineering revolution in biomimetic catalysis

To overcome the instability and limited catalytic turnover of natural enzymes, biomimetic cascade systems employ engineered materials to reproduce and enhance enzymatic redox activity through spatial confinement and controlled electron transfer. MoS₂@Au@BSA nanozyme-hydrogel conjugates integrate GOx-, POD-, CAT- and SOD-like activities in one scaffold, consuming glucose, releasing •OH and O₂ while adapting to pH shifts; ultrasmall Au domains boost catalysis but the multi-step synthesis elevates cost and batch variability (Figure 8A-B) [188]. The ultrafine Au domains act as electron relays between Mo and S centers, accelerating charge transfer and enhancing peroxidase-like activity. The injectable genipin-chitosan hydrogel is cross-linked and activated by CaO₂ *in situ*, establishing a self-sustaining O₂/Ca²⁺ release network. The confined

gel matrix with nanoscale channels localizes oxygen and facilitates ion diffusion, enhancing gelation kinetics and mechanical integrity while accelerating coagulation; the resulting hyperoxia and Ca^{2+} further promote rapid hemostasis and macrophage M2-driven angiogenesis. However, optimization of CaO_2 dosage and control of alkaline by-products are still required to balance the catalytic efficiency and biocompatibility (Figure 8C) [189]. The iron single-atom nanzyme (Fe-SAzyme) gel is a remarkable advance in the world of catalyst speed. Within the acid microenvironment of diabetic wounds (pH 5.5-6.5), it has been found to mimic the activity of CAT, thus degrading H_2O_2 to O_2 , and reversing hypoxia. Additionally, at a neutral pH, it has POD mode, which results in the generation of ROS. The Fe-SAzyme shows a quantitative tendency of H_2O_2 decomposition with a turnover frequency of about $1.8 \times 10^4 \text{ s}^{-1}$. This is almost four times the rate of conventional Fe_3O_4 nanozymes under similar conditions. As a result, it has an MRSA inhibition rate of 99.99%, indicating its remarkable efficiency in antibacterial applications [191]. The metastable nanocube-based hydrogel makes use of a biofilm environment-responsive cascade. In this cascade,

Cu-Fe dual sites catalyze Fenton-like reactions to produce the formation of the reactive oxygen species (ROS) $\cdot\text{OH}$ that degrade DNA and disrupt biofilm structures. Electron redistribution between copper (Cu) and iron (Fe) centers creates a redox-relay network for speeding up the Fenton reaction rate constant to about $1.2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$, which is about 2.8 times faster than that of Fe^{2+} alone [192]. Meanwhile, the mild hydroxyl flux at the biofilm periphery reprograms macrophages toward a pro-inflammatory phenotype. This reprogramming eliminates residual bacteria and achieves a complete clearance of implant infections. Recent advances have also focused on constructing cascade catalytic hydrogels that regulate the diabetic wound microenvironment through glucose-triggered NO generation. For instance, a GOx/hemoglobin artificial multienzyme nanoflower integrated CMCS/OSA hydrogel (COH-GB) converts excess glucose into gluconic acid and H_2O_2 , and subsequently drives H_2O_2 -mediated NO release from hydroxyurea under hemoglobin catalysis, achieving synchronized glucose consumption, ROS scavenging, antibacterial activity, and angiogenesis promotion in MRSA-infected diabetic wounds.

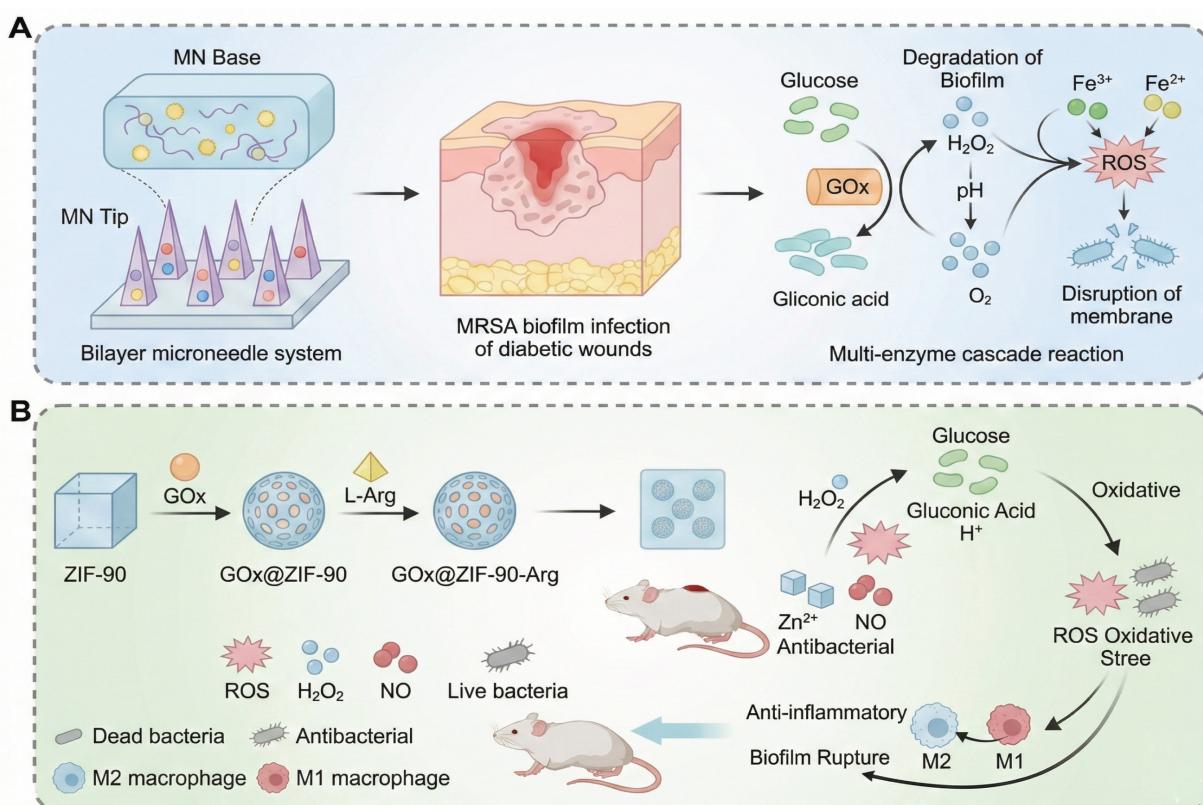


Figure 7. Enzymatic cascade reaction: precise activation of endogenous substrates in wounds. **(A)** Schematic illustration of the multi-enzyme cascade microneedle system for chronic wound treatment. **(B)** Schematic representation of the enzyme cascade reaction-based hydrogel (Hyd-GZA) for treating diabetic wounds infected with bacterial biofilms. Created in BioRender. Jia, J. (2025) <https://BioRender.com/iizi4ou>.

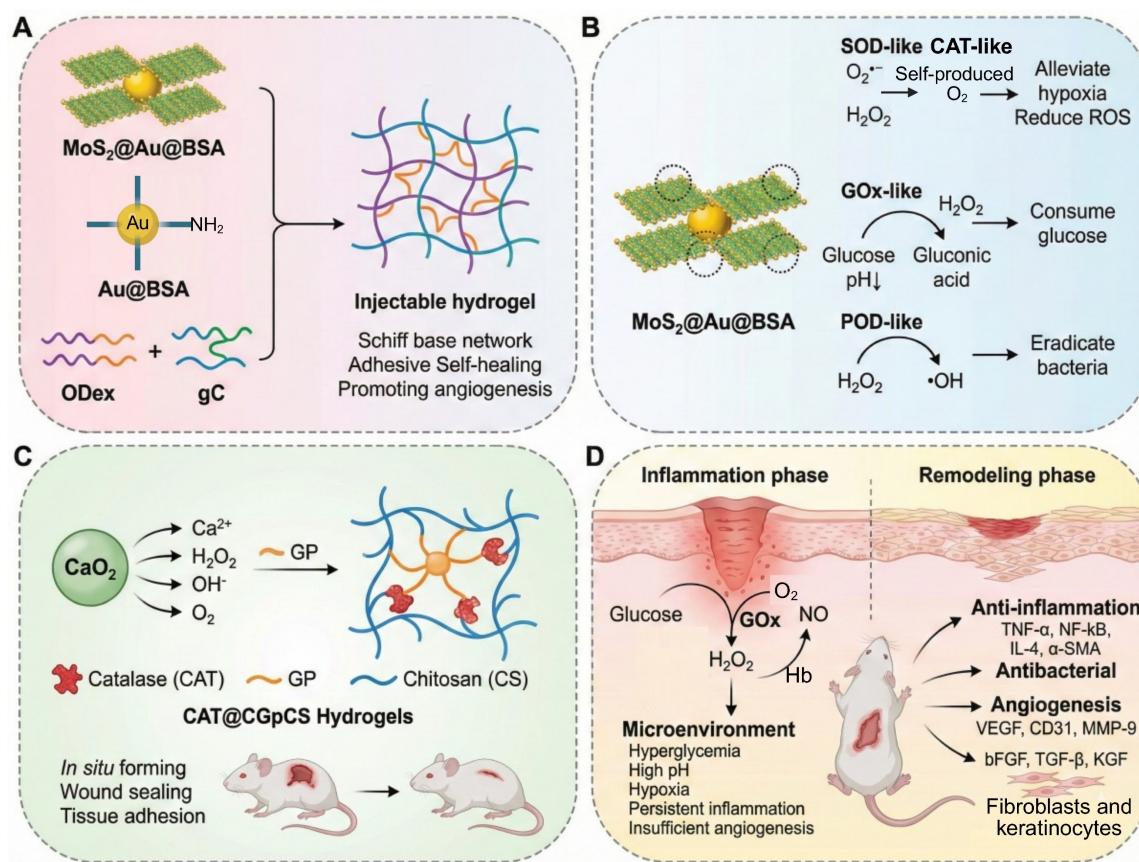


Figure 8. Enzyme-mimetic cascade reaction: an engineering revolution in biomimetic catalysis. **(A-B)** Schematic representation of the enzyme-mimicking cascade reaction: Au nanoparticles mimic glucose oxidase to catalyze glucose into gluconic acid and H₂O₂, while MoS₂@Au@BSA mimics peroxidase to convert H₂O₂ into •OH for bacterial eradication. **(C)** Schematic illustration of the enzyme-mimicking cascade reaction: CaO₂ mimics catalase to convert H₂O₂ into O₂, enhancing oxygen supply for rapid hemostasis and wound healing. **(D)** Schematic diagram of the enzyme-mimicking cascade reaction: Hb mimics peroxidase to catalyze H₂O₂ into NO, while GOx converts glucose into H₂O₂, enabling glucose-activated NO release and microenvironment regulation. Created in BioRender. Jia, J. (2025) <https://BioRender.com/ofjnlrk>.

The hierarchical nanoflower structure enhances enzyme stability and cascade efficiency, providing a model for multienzyme confinement strategies in biomimetic catalysis (Figure 8D) [190]. Recent studies employ MOFs as confined catalytic scaffolds that enhance active-site accessibility and facilitate charge transfer via spatial confinement and defect modulation. For instance, Co₃O₄ nanozymes confined within MOF channels have been shown to enhance the utilization rate of H₂O₂ from 21% to 68%, thereby achieving a 3.2-fold improvement in catalytic efficiency through defect-induced electronic redistribution [193].

A comparison between enzyme-mimetic systems and natural enzyme cascades shows better mechanical robustness, long-term catalytic stability and denaturation resistance in the former. However, an expansion in substrate range often leads to a diminution in substrate specificity and fine kinetic coordination between reaction modules. Despite the improvements mentioned above that are measurable in quantifiable terms, the majority of biomimetic cascade based on hydrogel lacks any standard kinetic parameters that can be used to measure cascade

efficiency. The turnover rate, ratios of catalytic constants (k_{cat}/k_m), reaction half-life ($t_{1/2}$) and synchronization coefficients are rarely reported, which makes it challenging to compare systems across and to rationally optimize them. The present gap in the knowledge can be sealed by the future research that will involve the quantitative modeling of the electron transfer kinetics together with the rational design of the defects and spatial confinement. This combined methodology will guarantee the catalytic specificity without leakage of electrons or cross reaction. At the same time, the creation of bio-degradable or self-limiting nanozymes, as well as the creation of integrated evaluation standards, will be essential to sustaining biological coordination and advancing to clinically viable, safe and intelligently controlled biomimetic therapies.

4.2.3 Chemical/physical trigger cascades: non-enzyme-dependent responses

Compared to biocatalysis-based systems, physicochemically triggered cascades have unique benefits in complicated surroundings by exploiting non-enzymatic mechanisms. For example, a

pH/temperature dual-responsive PVA hydrogel takes advantage of the natural microenvironmental fluctuations of the wound: the tertiary amine groups are protonated in the acidic exudate (pH 5.5), allowing for the rapid release of 90% of chlorhexidine within 6 hours to control infection. When the temperature reaches 37 °C, the lysozyme is activated for the cleavage of pathogen peptidoglycan, which increases biofilm penetration [194]. This design ingeniously integrates the antibacterial and anti-biofilm effects by synergistic environmental cues. A more sophisticated light controlled, three-level system, provides temporally precise intervention through multi-wavelength illumination. NIR (808 nm) light causes the photothermal phase transition of the gold nanorods, releasing NO, which causes vasodilation and enhances blood flow by 40% [195]. The concomitant temperature increase causes secondary cross-linking of the hydrogel that allows slow release of insulin-like growth factor 1 to promote tissue regeneration. Subsequently, 650 nm blue light is used to excite conjugated polymers to produce reactive nitrogen species that effectively kill residual biofilms. Preclinical studies indicated this approach shortened wound closure time to 14 days without causing the bacterial imbalances that are commonly associated with traditional antibiotics. However, clinical translation is still limited by the device dependency: accurate light control necessitates specialized laser sources, and photothermal material efficiency is reduced after repeated cycles of use [196, 197].

In summary, these three types of cascade reaction-based systems have different characteristics: enzymatic cascade systems use the endogenous biomolecules to achieve highly specific reactions, which are suitable for early acute wound intervention; quasi-enzymatic systems use biomimetic catalysts to provide stable and controllable reaction pathways, which are suitable for continuous treatment of chronic wounds; chemical/physical trigger systems use multiple stimuli to comprehensively regulate the reactions from antibacterial and anti-inflammatory effects to tissue remodeling. Future developments should focus on optimizing the coordination of the timing and precision of responses across cascade steps, optimizing the long-term biocompatibility and safety of materials and incorporating embedded sensors with artificial intelligence (AI) to allow real-time monitoring of wound dynamics. Such advancements will lead to a more accurate and efficient multidimensional intervention platform in the care of diabetic wounds. This multi-level, intelligent cascade reaction strategy shows great promise for the further development of the

widespread clinical application of responsive hydrogels, which will ultimately bring significant therapeutic benefits and improve the quality of life of patients.

4.3 Classification based on therapeutic phase targeting: chronological cascade response and synergistic cascade response

The process of chronic diabetic wound healing is dynamic, staged and proceeds through initial infection and sustained inflammation to chronic regenerative impairment. As a consequence, it has become important to develop treatment systems which can react to particular stages to be able to target and intervene in the chronic wounds of the diabetic foot [198]. Intelligent systems with temporal responsiveness and synergistic mechanism coupling have become a promising approach, and is known as cascade therapy, enabling dual-dimensional accuracy in time and space. This strategy has contributed to a great enhancement in the effectiveness and safety of clinical interventions. An example of such a system is the glucose/pH dual-responsive hydrogel system (PBA-PCL/Chitosan) which enables drug release on a stage-by-stage basis (Figure 9A). It preferentially responds to high levels of glucose in infection by releasing metformin nanoparticles to inhibit the formation of AGEs, reducing oxidative stress before moving into tissue repair phases [199]. Another interesting system is a multifunctional nanzyme hydrogel based on MnO₂-Au-mSiO₂ Janus nanoparticles encapsulated with acidic fibroblast growth factor (aFGF), which synergistically neutralizes ROS, releases oxygen, and promotes angiogenesis, macrophage modulation, and fibroblast proliferation, providing both antimicrobial and pro-regenerative actions for diabetic wound therapy at the same time (Figure 9B) [200].

4.3.1 Chronological cascade response: dynamic adaptation of pathological processes

The pathological course of diabetic wounds is generally acidification and infection, oxidative stress explosion, and poor regeneration, which correspond to the characteristic stages of diabetic wounds, such as the early stage of acidic microenvironment, the middle stage of high ROS, and the late stage of the lack of angiogenesis. Therefore, the design of sequential cascade systems demands high sensitivity to identify precisely the markers of wound progression, such as pH and enzyme activity, and selectively to switch on the functional modules according to the therapeutic sequence of "anti-infection → anti-inflammation → regeneration promotion," to avoid cross-stage interference.

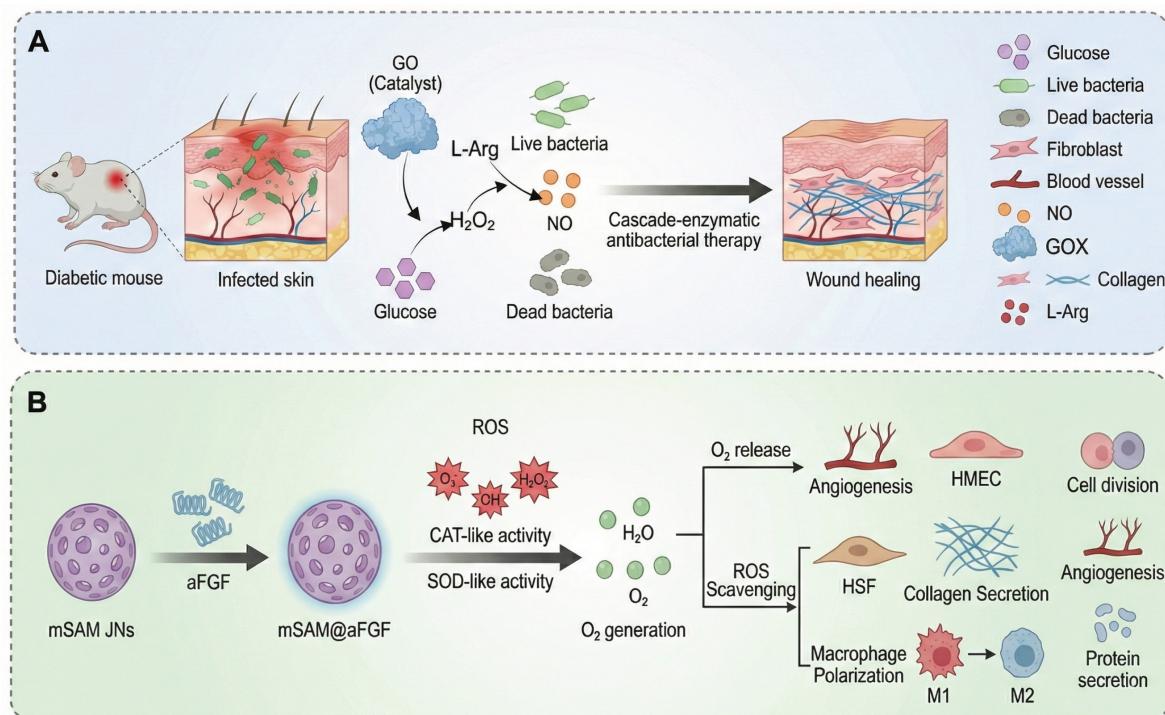


Figure 9. Classification based on therapeutic phase targeting: (A) Chronological cascade response of the time-sequential cascade reaction in the GOA@HG cryogel system: Glucose oxidase (GO) first catalyzes glucose to produce H_2O_2 , which subsequently reacts with L-Arginine (L-Arg) to generate nitric oxide (NO). (B) Synergistic cascades mechanisms of the mSAM@aFGF hydrogel system in promoting diabetic wound healing. Created in BioRender. Jia, J. (2025) <https://BioRender.com/pc6ij5>

A representative example is the temperature-directed spatiotemporal cascade system, which makes use of the synergistic responses of a PNIPAM thermosensitive layer and drug loaded nanofibers [27]. In the acute phase, the thermosensitive layer quickly shrinks and releases ciprofloxacin to inhibit deep infections. During the repair phase at 37 °C, nanofibers degrade to release EGCG which scavenges ROS and stimulates fibroblast migration. Preclinical studies showed that this system is highly effective in reducing the recurrence of infection in diabetic rabbit models.

Another interesting example is the enzyme-triggered bioorthogonal system, which uses the β -lactamase secreted by pathogens to activate a two-stage drug release [201]. First, the cleavage of the β -lactam bond produces ceftazidime acting against Gram negative bacteria. Thereafter, a catechol intermediate is formed, causing acidification of the microenvironment to pH 5.2, leading to controlled release of salicylic acid, which is effective in penetrating and eradicating resistant bacterial biofilms to depths of up to 200 μm . This approach resulted in an 84% biofilm removal rate and a significant reduction of systemic antibiotic use.

Sequential cascade systems provide smooth switching between modules based on the correct detection of microenvironmental changes, such as pH and enzyme concentrations, which prevents the

functional overlap and the adverse side effects [87, 113]. Although environmental marker-based stage switching minimises mutual interference between therapeutic modules, there are still translation issues: multi-stage material engineering raises concerns about cost, scale and reproducibility. The next generation should be simplified and adaptive architectures with the ability to provide temporal feedback in order that the materials can automatically adapt to the natural healing rhythm of the wound yet provide biological coordination.

4.3.2 Synergistic cascades: mechanism coupling in the spatial dimension

In order to address the above challenges, synergistic cascade systems are used to combine spatial coupling and functional complementarity strategies to realize multi-target and complementary interventions on the time and space dimensions. The most common one is the gas-synergistic hydrogel system, which relies on copper peroxide nanozymes (CuO_2) to decompose endogenous H_2O_2 to generate $\cdot\text{OH}$ and oxygen, and further catalyze nitrate to generate NO [202]. The direct effect of the $\cdot\text{OH}$ radicals is to disrupt the bacterial membranes, which inhibits the growth of the MRSA (inhibition zone of 18 mm), whereas NO induces the vasodilation, increasing the velocity of the blood flow by three times and suppressing the inflammatory action,

reducing IL-6 levels by 72%. In animal models, this system has been demonstrated to have 95% wound closure rate in 28 days in diabetic animals and 2.3-fold increase in blood vessel density of CD31⁺.

Although synergistic cascade systems have a huge potential in the simultaneous multi-target control of diseases, they also face new challenges, which are caused by the rise of structural and functional complexity. Redox, gas, and immune pathways crosstalk may lead to non-linear feedback loops that may cause oscillatory or competing biological signals, which can impair therapeutic efficacy or safety. Moreover, the energy and co-ordination requirements required to attain multi-modal activation may exceed physiological limits, raising concerns on long-term biosafety. The way forward in research is in the development of minimalist, but collaborative architectures that can be multifunctional by means of intrinsic material coupling rather than overly stacked modularly. In addition, the quantitative models to align the cascade kinetics with the physiological schedule of the wound are essential. Such design principles will enable a shift in the empirical assembly to the real intelligent integration in wound therapeutics.

5. Critical Challenges and Future Outlook

Despite great efforts on the development of microenvironment-responsive hydrogels for diabetic wound therapy, their clinical translation is at an early stage. While many of these systems show encouraging efficacy in rodent models, few have been advanced beyond preclinical validation. Bridging the gap between success in the laboratory and in the clinic involves solving a number of important challenges, including the translational divide, scalability of manufacture processes, developing standardized evaluation models, and finding the right balance between multifunctionality and biocompatibility.

5.1 The “Valley of Death” between preclinical success and clinical application

Although there have been many studies showing accelerated wound closure, enhanced angiogenesis, and modulated immune responses in small-animal models, few have been translated to clinical trials. This gap commonly known as the “valley of death” can be attributed to some underlying differences between the controlled conditions of laboratory experiments and the heterogeneous and multifactorial nature of chronic human wounds. The ulcers of diabetics in patients are typically typified by fluctuating infection patterns, intricate exudate formulations and intricate immune reactions which cannot be completely reproduced in rodent models. In

addition, numerous high-technology hydrogels include other substances like enzymes, MOFs or nanozymes, the long-term metabolic behavior and immunogenicity of which are not known. The lack of complete toxicological information and a lack of uniformity in reporting biodegradation pathways further complicate regulatory approval. To address this translational gap, it is necessary not only to understand the mechanisms that are involved in a better way, but also to collaborate on an interdisciplinary level between materials scientists, clinicians and regulatory experts to come up with hydrogels that are compatible with clinical manufacturing and safety assessment standards. It is worth noting that recent preclinical trials seldom use comorbidity models that are more representative of clinical conditions of diabetic patients (concurrent cardiovascular disease, obesity, immune dysregulation or peripheral neuropathy). The lack of these complex systemic conditions is a major limitation to the predictive power of current models and a major hurdle in bridging the translational “valley of death.”

5.2 Manufacturing and scalability: cost and complexity barriers

The second big problem is the cost and manufacturability of such highly engineered systems. Multi-responsive and cascade-reaction hydrogels often require complex synthetic methods, multiple purification processes and addition of costly catalysts, enzymes or nanoparticles. These contribute to the cost of production much higher than in the case of conventional wound dressings and are a considerable obstacle to scalability in the circumstances of good manufacturing practice (GMP). Also, the batch-to-batch difference of natural polymers or biologically-derived components contributes to the problems of reproducibility and quality control. The way forward must be based on more direct and simplified methods of fabrication, including click chemistry, microfluidic fabrication and 3D bioprinting where composition and spatial patterning can be precisely controlled. The advent of printable hydrogel inks and self-healing dynamic crosslinking chemistries promises to provide the ability to scale up production with less variability. Coupling these process innovations with automated quality control and continuous manufacturing systems will be critical for successfully taking these advanced materials from the laboratory to clinical application.

5.3 Need for standardized large-animal model testing

Preclinical testing of diabetic wound dressings is still largely based on streptozotocin-induced rodent

models which do not adequately recapitulate the complex pathophysiology of human chronic ulcers. Significant anatomical and physiological differences, including skin thickness, vascular density and immune cell composition, between rodent and human tissue often result in overestimated healing rates in these models. To better close this translational gap, standardized large animal models, such as diabetic minipigs and canines, are urgently needed. These models better resemble the size, biomechanics and inflammatory responses of human wounds and, therefore, provide more reliable predictions of clinical efficacy and safety. In addition, more meaningful cross-study comparisons will be made possible through the development of coherent evaluation criteria, which will include quantitative criteria, such as wound closure kinetics, neovascularization indices, and inflammatory cytokine profiling. The collaboration between countries and compliance with the regulatory standards, i. e., ISO 10993 on biological testing and NIH translational studies, are mandatory to align the preclinical testing and fast track regulatory approval. In addition to conventional wound closure outcome measures, functional outcomes (e.g. nerve regeneration, loss of tactile sensation, long-term scar quality and biomechanical strength) should be also measured in large animal studies, which are relevant to the long-term clinical outcome of diabetic wound therapies.

5.4 Balancing multifunctionality and biocompatibility

With the development of hydrogel designs towards multifunctional and cascade-based systems, the significance of a delicate balance between enhanced functionality and biocompatibility gains significance. Although photothermal agents, transition metal nanozymes, or conductive fillers can significantly improve antibacterial, antioxidant and pro-angiogenic properties, these components can also lead to cytotoxicity or chronic inflammatory reactions. Problems like overproduction of ROS, retention of residual metal ions and uncontrolled byproducts of degradation pose a threat to the tissues around. To achieve a perfect balance between therapeutic efficacy and biosafety, therefore, it is necessary to select materials rationally and control release kinetics. The use of biodegradable enzyme mimics, natural polysaccharides and bioinspired dynamic covalent bonds are some of the possible approaches to reduce the toxicity and maintain responsiveness. Moreover, adaptive degradation profiles coupled with "on-demand" activation mechanisms guarantee that hydrogels perform their therapeutic functions effectively without long-term accumulation and

disruption to the immune system.

5.5 Outlook: toward intelligent and personalized wound management

Future generations of responsive hydrogels can be expected to develop into intelligent, self-regulating therapeutic systems. The integration of AI, specifically predictive modeling, allows large datasets of the material compositions, reaction kinetics, and biological outcomes to be analyzed. This makes it easy to determine the best cascade parameters, including enzyme ratios, diffusion coefficients, and activation thresholds. By using machine learning algorithms in combination with extensive experimental databases, researchers can predict cascade dynamics and screen formulation candidates in an efficient way, substantially lowering the need for labor-intensive *in vivo* studies. However, the current application of AI-assisted modeling has been hampered by the lack of standardised and high-quality datasets as heterogeneity in experimental designs, data annotation and reporting format is a huge challenge.

Simultaneously, OoC platforms that can mimic the microenvironment of the diabetic wound, with its dynamic fluctuations of glucose, pH, and ROS, provide real-time evaluation of hydrogel functionality under physiologically relevant conditions. These microphysiological systems bridge the gap between traditional *in vitro* assays and animal models and offer a dynamic, human-relevant interface to monitor drug release, angiogenesis and immune responses *in situ*. Despite their promise, building multi-tissue OoC models that faithfully recapitulate the chronic wound milieu remains technically difficult, particularly in terms of keeping vascular, immune, neural, and epithelial components in concert.

The integration of the models driven by AI and the assessment of the models by oOC promises to speed up the transfer of complex cascade hydrogel systems between the conceptual phase and the clinic. Also, biosensing modules incorporated in hydrogels will allow feedback-based control to provide autonomous drug delivery and control the microenvironment. Hydrogel designs customized on patient-specific omics information, microbial flora profiling and wound metabolic signatures offer further refinement in accordance with individual healing patterns. With these approaches coupled with the development of three-dimensional bioprinting and microfluidic systems, heterogeneous and gradient-structured hydrogels will be produced that are more akin to the native tissue architecture.

Finally, the success of this undertaking in the long run is the establishment of methodologies of production that will be regulatory-compliant,

cost-effective, and environmentally sustainable. In order to effectively cross the valley of death between preclinical innovation and clinical implementation, multidisciplinary cooperation between materials scientists, bioengineers, clinicians and policy makers is necessary. It is only through this type of combined approach that microenvironment-responsive hydrogels can leave behind the experimental prototype stage to become standardized, intelligent wound care products that can transform chronic diabetic wound care.

6. Conclusion

Although current studies show the superior performance of responsive hydrogels in controlled experimental conditions, the environment of diabetic wounds is highly heterogeneous and dynamic. These wounds have varying pH, oxygen gradients, enzyme activities and distributions of immune cells, all of which can have a significant effect on hydrogel responsiveness, diffusion, and degradation behavior. Such complexities frequently cause discrepancies in *in vitro* and *in vivo* outcomes. Therefore, future research should include more bio-relevant wound models, such as microfluidic chips, OoC systems, or large-animal chronic wound models, to better mimic the spatiotemporal heterogeneity of real wounds and to assess the adaptive responses of materials in physiologically realistic settings. Microenvironment-responsive hydrogels have become a promising approach for the treatment of chronic diabetic wounds. By sensing pathological cues, such as glucose, pH, ROS, and enzyme activity, these intelligent materials allow for spatiotemporally controlled drug delivery and the coordinated modulation of inflammation, angiogenesis, and oxidative stress. Over the past few years, progress in dynamic covalent chemistry, enzyme-mimetic catalysis and cascade reaction design has led to significant improvement in the therapeutic precision and performance of hydrogel dressings. Particularly, multi-responsive and cascade-reactive systems have started to mimic the complex feedback loops of the wound microenvironment, with the potential of comprehensive and adaptive repair across the healing process.

Nevertheless, there are still important challenges to overcome on the way to clinical translation, as discussed in Section 6. Bridging the translational gap, scalable and cost-effective manufacturing, large-animal testing standardization, and balancing multifunctionality and biocompatibility are important prerequisites for real-world application. Future progress will require interdisciplinary collaboration between materials science, biomedical engineering

and clinical medicine to bring conceptual prototypes to the clinic. The combination of biosensing technologies, AI-driven modeling, and OoC evaluation has the potential to transform responsive hydrogels into personalized and self-regulating therapeutic platforms.

In summary, the development of microenvironment-responsive hydrogels represents a paradigm shift from the passive wound covering to a more dynamic, intelligent and precision-guided therapy. With further innovation and stringent translational validation, these materials are expected to become the next generation of bioactive dressings that will significantly enhance the management of diabetic wounds.

Abbreviations

- AGEs: Advanced glycation end products
- AI: Artificial intelligence
- bFGF: Basic fibroblast growth factor
- CAT: Catalase
- CD31: Cluster of differentiation 31
- COF: Covalent organic framework
- DFO: Deferoxamine
- ECM: Extracellular matrix
- EGCG: Epigallocatechin gallate
- ELISA: Enzyme-linked immunosorbent assay
- EMT: Epithelial-to-mesenchymal transition
- EXOs: Exosomes
- GMP: Good manufacturing practice
- GOx: Glucose oxidase
- H₂O₂: Hydrogen peroxide
- HA: Hyaluronic acid
- HIF-1 α : Hypoxia-inducible factor-1 α
- IL-6: Interleukin-6
- IL-10: Interleukin-10
- TNF- α : Tumor necrosis factor- α
- MMPs: Matrix metalloproteinases
- MMP-9: Matrix metalloproteinase-9
- MOF: Metal-organic framework
- MRSA: Methicillin-resistant *Staphylococcus aureus*
- MSCs: Mesenchymal stem cells
- NETs: Neutrophil extracellular traps
- NO: Nitric oxide
- NIR: Near-infrared light
- PAA: Poly(acrylic acid)
- PBA: Phenylboronic acid
- PEG/PEGDA: Poly(ethylene glycol) / Poly(ethylene glycol) diacrylate
- PVA: Poly(vinyl alcohol)
- ROS: Reactive oxygen species
- SOD: Superoxide dismutase
- STZ: Streptozotocin
- TA: Tannic acid
- TCM: Traditional Chinese medicine

VEGF: Vascular endothelial growth factor

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Author contributions

Jialin Jia conceived the review, designed the overall framework, and drafted the manuscript. Xiaosu Wang participated in literature collection and data analysis. Tao Zhang assisted in manuscript editing and contributed to content refinement. Qingxia Sun participated in literature screening and assisted in manuscript editing. Shude Yang* and Wennu Wu* supervised the study, provided critical revisions and essential suggestions throughout writing and revision, and approved the final version for publication. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

Competing Interests

The authors have declared that no competing interest exists.

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