REVIEW

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The integration of wound treatment and detection based on biological macromolecules

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Several factors can impede the wound healing process, and the non-healing and formation of chronic wounds pose a threat to patient health and a burden to society. With the discovery of various biomaterials (*e.g.*, hydrogels and nanomaterials), new treatment options have been developed to improve wound healing. Hydrogels and nanomaterials exhibit good biocompatibility and are often used in wound healing as carriers for drug delivery. However, the wound environment during the wound healing process is often complex, making it difficult to achieve precisely controlled drug release. Changes in various wound response factors have been found to control drug release. Therefore, it is important to develop wound response factors as a switch for drug release. This review describes the healing process of wounds and the factors affecting wound healing; materials with self-repairing ability and their application as drug delivery systems for the treatment of wounds; biomarkers that can be used to detect the recovery of wounds; and monitoring of wound healing based on the environmental response to achieve the detection of wound detection and treatment. Lastly, this review highlights the difficulties and future prospects of the integration of wound treatment and detection.

1. Introduction

The skin is the body's largest organ; it acts as a protective barrier, regulates temperature, retains body fluids, and prevents environmental, chemical, and pathogenic damage.[1] Additionally, it acts as a soft elastic membrane between the inside and outside of the body, performing several important functions. The skin is vulnerable to various external factors, resulting in surface wounds. When the wound dressing is frequently changed, the wound is vulnerable to bacterial invasion, long-term inflammation, and other factors that may negatively affect wound repair. Prolonged wound healing can lead to increased morbidity and mortality; thus, to reduce patient suffering and reduce the burden on the healthcare system, a certain approach is required for wound treatment.

After skin wounds occur, dressings are chosen to cover the affected area and promote wound healing. Although there are many types of wound dressings,[2] owing to the complexity of the wound microenvironment, it is still challenging for several wound dressings to fully adapt to the wound-healing process; thus, a single dressing may not be effective for wound treatment. Traditional wound-care methods based on the use of passive bandages cannot be used to accurately assess wounds and may result in secondary injuries during the frequent replacement of dressings.[3]

With the development of new technologies in the field of biomedicine, various materials have been developed that are beneficial to wound treatment and have broad applications. Several researchers have used physical or chemical cross-linking methods to produce hydrogel dressings with multiple functions that can play anti-infection, anti-oxidation, and anti-inflammatory roles in wound healing.[4] In addition, some researchers have added "sensors" in the hydrogel that can respond to changes in the wound environment. For example, environmental changes, including those to pH, glucose, and reactive oxygen species, can be used as a switch to release drugs, creating an intelligent drug delivery system that can be used to treat deep wounds with high efficiency.[5] Additionally, NO-based strategies have valuable applications in the wound-healing process, which have been limited owing to chemical instability and disordered release at the affected area;[6] consequently, researchers have used various stimuli such as pH, light, and heat to trigger and achieve accurate release of NO. In the study by Zhong, MOF-derived FeO@PLGA microspheres were designed and applied to bacterial infectious wounds through

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magnetic release of NO.[7,8] Zhang *et al.* used Prussian blue nanoparticles combined with sodium nitroprusside to control the release of NO under light and heat stimulation. They also designed a multi-functional chitosan/alginate brine gel and bioactive glass nanocomposite material, which can realize the active release of light, heat, and NO and promote the healing of bacterial infected wounds.[9] MOFs consist of both organic and inorganic components and possess antiviral and bactericidal properties, which make them have great potential for clinical applications.[10] Currently, many studies focus on adjusting the functions of MOFs by regulating metal bonds. Metals such as Au, Ag, Zn, Fe, and Mg have been widely used in the construction of antibacterial MOFs.[11] Due to the relatively stable structure and persistent composition of MOFs, they are considered a promising treatment platform.[12] For example, in terms of anti-inflammatory effects, MOFs can serve as drug delivery carriers, and titanium-based MOFs can effectively solve the problems of drug loading and controlled release of anti-inflammatory drugs.[13] To obtain harmless and economically efficient biomaterials, scientists have discovered that the mucus present in persimmon seeds contains a large amount of hydrogel. By properly utilizing this mucus, it can not only serve as a drug delivery carrier but also adsorb various organic/inorganic pollutants and heavy metals, which is not only environmentally friendly but also serves as a renewable resource, playing an important role in biomedical fields such as drug delivery.[14,15]

Wound repair involves four stages: hemostasis, inflammation, proliferation, and remodeling, which are closely related and thus influence each other. The body's immune system plays a crucial role in promoting the development of these four stages. When the immune system is impaired, the wound will remain in the inflammatory stage without entering the proliferation stage, hampering wound healing. Moreover, microbial infection can affect wound healing; specifically, *Staphylococcus aureus* is a threat to human health owing to its strong virulence and resistance. Zhu *et al.*[16] designed a new supramolecular hydrogel based on the manufacture of hydroxypropyl chitosan (HPCS) and poly (*n*-isopropylacrylamide) (PNIPAM), which are heat-sensitive, self-healing, and have excellent biocompatibility. This injection of dipotassium glycyrrhizinate also results in antibacterial properties against *Staphylococcus aureus*. However, with the use of antibiotics, bacterial resistance is gradually becoming more common.[17] Drugs used to treat bacterial infection have begun to fail to achieve the expected effects, and the development of alternatives for antibiotics is urgently needed. A multi-functional single-component palladium nanosheet (PdNS) has been found to have efficient bactericidal properties against multi-drug-resistant bacteria.[18] The PdNS can produce a certain amount of heat in the near infrared region through the photothermal effect; this substance utilizes the nanoknife effect and the synergistic combination of peroxide/peroxidase catalytic activity, photothermal effects and photodynamic effects to achieve a bactericidal effect.[19]

Previously, during clinical diagnosis and treatment, doctors generally judged the healing process by observing the state of the wound or confirmed the diagnosis by culturing the wound surface; however, these methods may cause secondary damage to the wound. There are negative consequences for inaccurate diagnosis; therefore, it is necessary to develop biomarkers as indicators to detect wound recovery. Certain progress has been made in evaluating wound healing by using biomarkers and imaging methods.[20] Biomarkers, including temperature, pH, glucose, and lactic acid, which can reflect chronic wound infection and inflammation, have been used as indicators for wound detection. In practical applications, pH and temperature are the most commonly used and effective biomarkers to provide information about the wound condition. Furthermore, computed tomography, magnetic resonance imaging, thermal imaging and other imaging methods have potential for use in wound diagnosis. Although traditional methods can provide some information on the wound, owing to the complexity of clinical practical applications, there is a need for fast, accurate, and highly specific therapeutic materials.

Clinical debridement is an important part of wound treatment. Debridement is the main step in which necrotic tissue and infection sources are removed. In addition to commonly used surgical debridement methods (such as mechanical debridement and surgical sharp instrument debridement), enzymatic debridement is a novel surgical tool. For example, bromelain-based debridement can be used to remove eschar in burn patients, thereby improving the efficiency of wound treatment.[21] Additionally, modern debridement techniques combine precision medicine with new tools. Ultrasonic debridement, an effective alternative to traditional debridement, is preferred when there are contraindications to surgical debridement, such as poor vascular status. Compared with traditional methods that require frequent changes of the wound dressing and increase infection risk, negative pressure wound treatment reduces the infection risk by closing the environment and can accelerate healing by promoting blood circulation and granulation tissue growth. However, despite its many advantages, negative pressure wound treatment should not be used in patients with active bleeding.

In summation, environmentally sensitive and self-repairing hydrogels (along with other materials, such as nanoparticles) can be combined with various drugs and supplemented by various detection methods to construct a composite material, which can assist clinical treatment. On the one hand, such materials can monitor changes in the wound-surface environment; on the other hand, these materials can be good drug-delivery systems. Further methods that combine wound detection with wound treatment can help achieve the integration of wound detection and treatment. Compared with the traditional wound treatment, such combined methods can not only provide a moist and antibacterial environment for the wound but also avoid secondary injuries caused by multiple dressing changes. Although there have been many achievements in the integration of wound detection and treatment, the manufacturing costs of various integrated platforms are high and the actual clinical applications are limited.

This review introduces the basic healing process of acute and chronic wounds and the factors affecting wound healing and summarizes the application of certain biomaterials in wound treatment, focusing on various environmental factors
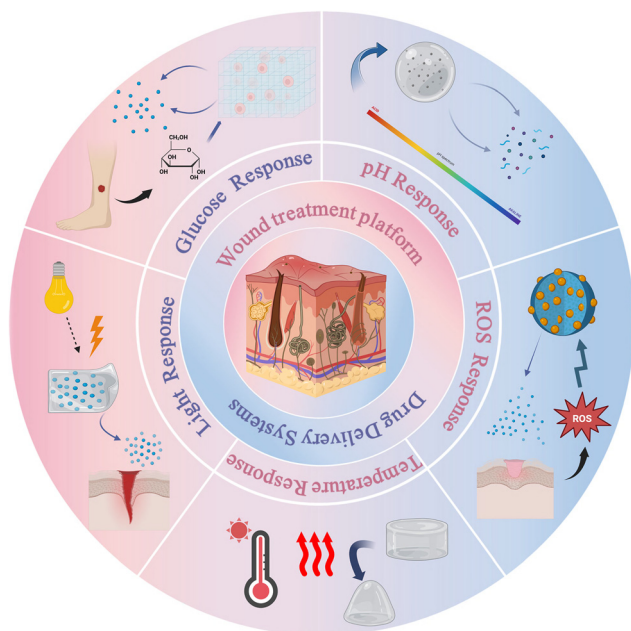
Fig. 1 Mechanism of wound detection and treatment integration.

and biomarkers that can be used in wound detection (Fig. 1). Furthermore, to address the gap in the literature regarding wound detection and wound treatment on the same platform, this review summarizes the advantages and difficulties of integrated wound treatment as well as future prospects.

2. Mechanisms of acute and chronic wound healing

2.1. Classification of trauma

Wounds that heal quickly and effectively under normal circumstances are considered acute wounds. However, some wounds do not heal quickly due to factors such as age and diabetes.[22] Wounds that do not heal after 12 weeks are considered chronic wounds.

2.2. The healing process of acute wounds

Wound healing refers to the stage-by-stage regeneration of damaged tissues through the regeneration of connective tissues and capillaries, which leads to wound recovery and generally involves a series of changes in the activity of damaged cells and tissues. The healing of acute wounds generally consists of four processes: hemostasis, inflammation, proliferation, and dermal remodeling.[23]

2.2.1. **Hemostasis.** The complete hemostatic process generally includes three stages. In the early stage of injury, the blood vessels in the tissues rapidly contract, and the platelets adhere, aggregate, and form the initial hemostatic thrombus on the surface of the damaged blood vessels.[24] Bleeding occurs in the early stages of wound injury. Therefore, inorganic mineral materials (*e.g.*, nanomaterials) with loose mesoporous properties can be used for hemostasis. These materials promote blood coagulation to form

hemostatic plugs by absorbing large amounts of blood and concentrating platelets.[25] In contrast, phase II hemostasis results in the formation of a fibrin clot, which involves the activation of thrombin and the formation of fibrin.[26] Protein-based hemostatic materials can be used to control bleeding by accelerating natural coagulation reactions to achieve hemostasis. Phase III hemostasis is mainly a process of clot contraction. A loose mesh composed of platelet polymers, fibrin filaments, and trapped red blood cells forms a firm clot.[27] Polysaccharide hemostatic materials are often used as reliable hemostatic materials because of their non-immunogenicity, non-toxicity, and biocompatibility. For example, chitosan (CS) binds with anionic electrostatic interactions on the surface of erythrocytes,[28] which ultimately leads to the aggregation of erythrocytes on the surface of the wound and the formation of a clot.[29]

2.2.2. **Inflammation.** After the hemostatic phase, the body produces an inflammatory response through autoimmune reactions and bacterial invasion.[30] The inflammatory process promotes cell expansion and recruitment, which is an important phase in the body's defense against bacterial attack and the digestion of foreign bodies.

Cytokines act as signaling substances that trigger the entire inflammatory cascade, after which endothelial cells continuously produce vasodilators, proteins that allow leukocytes to pass through the vessel wall, and tissue factors that activate the coagulation pathway.[31] Subsequently, granulocyte colony-stimulating factor (G-CSF) and CXC chemokines are transported through the incoming bloodstream and circulation to the bone marrow; thus, mature neutrophils from the bone marrow are transported through the bloodstream to the wound, and the number of neutrophils in the wound increases significantly.[32,33] After successful accumulation at the site of injury, neutrophils recognize the infected microorganisms and necrotic tissues through a variety of receptors, further exerting cytotoxic and scavenging effects. This action is mainly realized through phagocytosis by neutrophils, and the phagocytosed bacteria are rapidly killed by protein hydrolases, antimicrobial proteins, and ROS.[34] Therefore, cytokines related to inflammation can be detected and wound recovery can be observed in real time.

Macrophages are the main cells involved in tissue injury repair and have a high degree of plasticity.[35] However, they tend to form two different phenotypes during the wound healing process. In the early stage of repair, the pro-inflammatory M1 phenotype is observed.[36] Rebapatide-loaded chitosan nanoparticles have been found to inhibit pro-inflammatory M1 macrophage activity *via* the NF-κB signaling pathway, thereby blocking the inflammatory response and facilitating wound healing.[37] In contrast, the anti-inflammatory M2 phenotype usually manifests in the later stages of healing during repair and vascular remodeling.[38] Scar tissue forms gradually during the period of inflammatory regression, and normal scar tissue includes the regression of the neovascular system and reconstruction of the extracellular matrix (ECM).[39] However, when the abnormal proliferation of adult fibers leads to excessive redundancy of the ECM,[40] it can result in the evolution of the wound to a state of excessive scarring, hyperplastic keloids, and

keloids. Scar tissue formation is often regulated by macrophages, whose numbers and phenotypes influence fibroblast proliferation, myofibroblast differentiation, and collagen deposition. Thus, macrophages can determine the level of scar formation.[41]

The body also produces inflammatory mediators and inducible synthases (*e.g.*, cyclooxygenase, NO, and arachidonic acid-like synthase). These substances play an important role in the inflammatory pathway. Therefore, interference with the action of inflammatory mediators can be used as an anti-inflammatory approach.[42] Natural terpenoids are widely available, have a wide variety of derivatives with diverse bioactivities and anti-inflammatory properties, and are promising biomaterials.[43]

2.2.3. Proliferation. During the proliferation phase, the main processes consist of the formation of new stroma by fibroblasts (re-epithelialization), regeneration of new blood vessels, formation of granulation tissue, and synthesis of collagen.[44,45]

Re-epithelialization is an important step in wound healing during proliferation.[46] Re-epithelialization depends on the migration and proliferation of epithelial keratin-forming cells.[47] The process of re-coverage of the entire wound surface by keratin-forming cells is known as re-epithelialization.[48,49] MMP-1 and MMP-9 are essential for the migration of keratin-forming cells.[50,51] They degrade components at the junction of the dermis and epidermis, which further contribute to the migration of keratin-forming cells.[52] By understanding the sensitivity of keratinocytes to epidermal growth factors, we can further control the rate of wound re-epithelialization. Growth factors affecting keratinocytes include TGF-β, KGF, HB-EGF, FGF, and EGF. KGF and FGF2 are crucial because they upregulate the expression of keratins 6, 16, and 17,[53] thereby promoting cell migration. An antioxidant polyurethane (PUAO), OxOB, was identified and encapsulated in adipose-derived stem cell exosomes, and a significant increase in the rate of keratinocyte migration was observed after phagocytosis of the exosomes by keratinocytes.[54] After skin injury, the potential of epithelial cells is disrupted, which creates a potential difference from intact tissue, further inducing cell migration.[55] Based on this information, electroactive dressings for wound treatment can be developed.

Angiogenesis is the process by which new blood vessels grow from previously existing vessels and is mainly mediated by vascular endothelial growth factor (VEGF).[56] Tip cells can use their filamentous pseudopods to guide blood vessel sprouting when induced by VEGF-A;[57] thus, VEGF is an important substance for angiogenesis during the wound healing stage. Du *et al.*[58] utilized metformin and mesenchymal stromal cells and found that activation of Akt/mTOR to promote VEGF-mediated angiogenesis in diabetic wounds can improve the expression of VEGF-A during diabetic wound healing and indirectly help wound healing. The stalk cell phenotype was observed following Dll4/Notch-mediated lateral inhibition.[59] Notch signaling inhibits the transformation of stalk cells into tip cells.[60] This led to the discovery of novel biocompatible nanomaterials, tetrahedral DNA nanostructures, which enhance angiogenesis by upregulating Notch signaling. Alternatively, γ-secretase inhibitors can be used to inhibit Notch signaling to increase the number of tip cells and form more vascular branches,[61] thereby

controlling vessel growth. Adding growth factors such as VEGF, PDGF, and TGF to bioactive materials is one of the available methods to modulate angiogenesis in endothelial cells.

Granulation tissue appears within 2–3 days after tissue injury and grows from the bottom up (such as surface wounds) or from the periphery to the center (such as intra-tissue necrosis), filling the wound or organizing foreign bodies. Fibroblasts are key cells in the formation of granulation tissue, and generally proliferate and migrate under the action of different growth factors. They can be derived from mesenchymal stem cells; therefore, the properties of fibroblasts can be used to design bioactive materials to control cell behavior. A double-drug-loaded double-layer nano-fiber sponge 3D scaffold made of a keratin–fibrin–gelatin–mupirocin 3D sponge with a poly(3-hydroxybutyric acid) electrospun fiber and curcumin-supported gelatin,[62] mimicking the properties of ECMs, promoted fibroblast migration and enhanced Col synthesis (Fig. 2A). The main component of the secreted Col is hydroxyproline, which plays an important role in ECM deposition during wound healing. In addition to the 3D scaffolds, Yang *et al.*[63] combined various mesenchymal stem cell-derived exosomes (hUCMSC-exos) from the human umbilical cord with heat-sensitive Pluronic F-127 (PF-127, also known as poloxam 407). hUCMSC-exos are continuously released into the wound through temperature changes, which can attract fibroblasts and endothelial cells to promote the formation of granulation tissue, whereas PF-127 has mild inflammatory properties and the ability to absorb wound secretions, providing a good environment for the healing of diabetic wounds (Fig. 2B). At present, gold nanoparticle (AuNP)-coated scaffolds for photothermal therapy (PTT) can be used to treat the abnormal formation of granulation tissue[64] (Fig. 2C).

2.2.4. Remodeling period. The remodeling stage of wound healing is generally the end of the proliferation stage, which involves the proliferation and differentiation of fibroblasts, including ECM deposition and remodeling.[65] Fibroblasts can be transformed into myofibroblasts under the influence of some signals and GF (such as TGF-β),[66] and in the dermal remodeling stage, the action of fibroblasts and myofibroblasts can cause wound contraction and closure.[67] Therefore, it is necessary to study the effects of these biomaterials on fibroblasts and myofibroblasts. Watarai *et al.*[68] designed a StarPEg-heparin hydrogel with the introduction of a RGD peptide to achieve sustained release of TGF-β and induce fibroblasts to differentiate into myofibroblasts, thereby improving the expression of ED-A fibronectin and Col I. α-SMA and palladin were incorporated into F-actin stress fibers. One study showed that SF hydrogels had higher potential to promote wound healing and induce the expression of TNF-α and CD163 compared with Col gels, indicating that the healing process shifted from inflammation to a proliferative remodeling stage.[69]

2.3. Chronic wounds and pathological mechanisms

2.3.1. Overview of chronic wounds. After the above four consecutive overlapping stages, the wound heals; however, when the wound is affected by certain factors, wound healing is delayed or the wound does not heal. Since chronic wounds
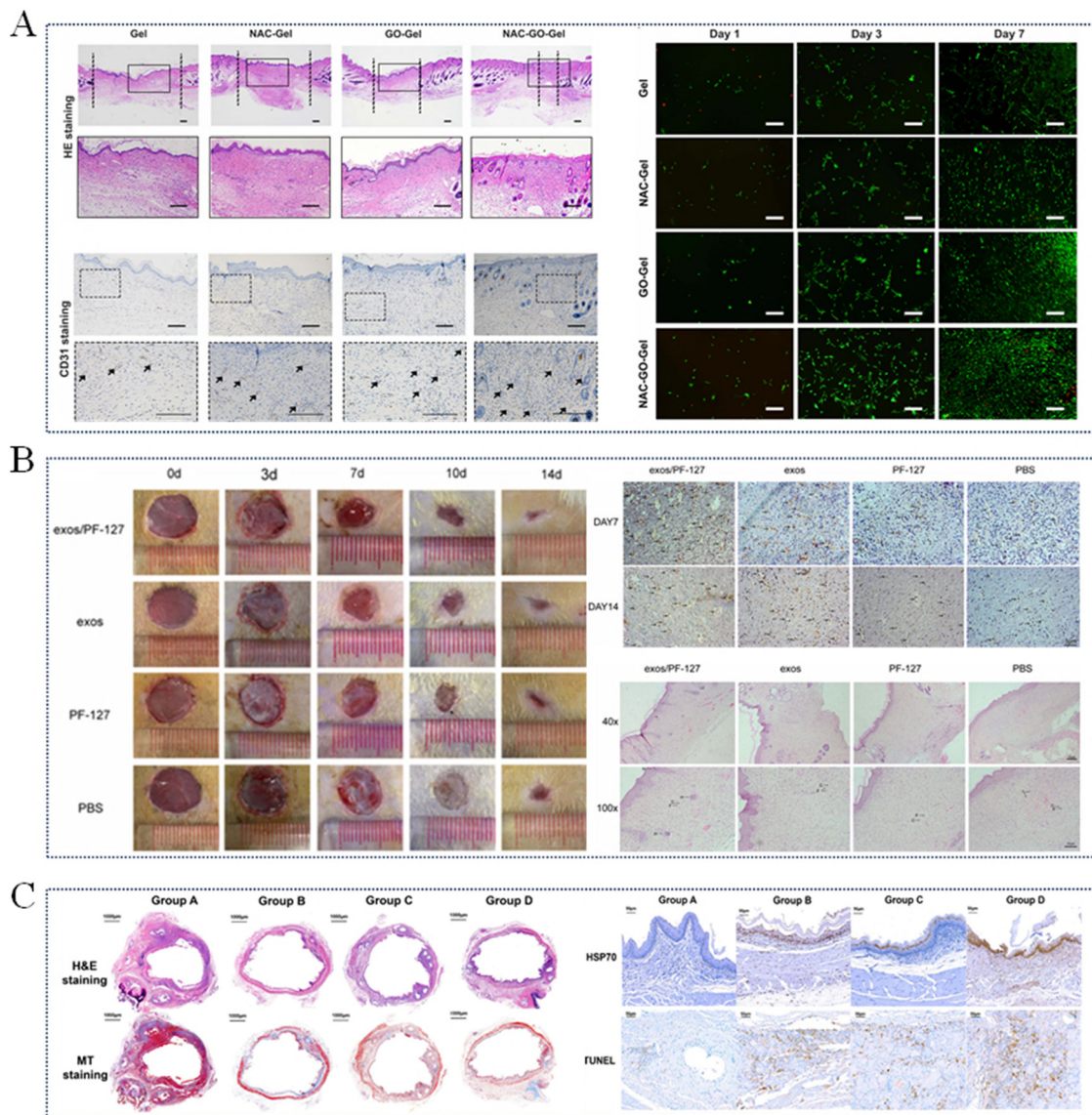
Fig. 2 Composite promoting cell proliferation and accelerating wound repair through enhanced wound detection and healing capabilities. (A) NAC–GO-Gel was placed on the wound surface; the regeneration of collagen can be observed, thereby reducing the formation of a scar. The cell viability was significantly increased, as demonstrated by the good biocompatibility of the scaffold. Reproduced from ref. 62 with permission from Dove Medical Press, copyright 2023. (B) After treatment with hUCMSC-exos/PF-127, the wound area was significantly reduced compared with other groups. Additionally, the number of neovessels increased significantly, new hair follicles were formed, and fibroblasts proliferated under the epidermis. Reproduced from ref. 63 with permission from Dove Medical Press, copyright 2020. (C) After stent placement, the formation of granulation tissue can be observed, which promoted wound repair. Reproduced from ref. 64 with permission from Springer Nature, copyright 2021.

are a type of long-term wasting disease that is difficult to cure and has a long healing time, it is important to understand the main influencing factors and treatment targets of chronic wounds.

The formation of diabetic wounds is mainly due to the inability to complete the repair of the function and structure of the wound, which makes it difficult to enter the proliferative stage owing to prolonged inflammation.[70,71] Second, the decrease in angiogenic ability in the proliferative stage is also one of the reasons for the difficulty in healing diabetic wounds,[72] infiltration of immune cells, and continuous immune response.[73] The proinflammatory phenotype of macrophages in a high-glucose

environment[74,75] and the weakened ability of the immune system to clear bacteria[76] lead to a long-term inflammatory phase in the wound. The aging of fibroblasts[77–79] and cessation of re-epithelialization due to increased MMP expression make it difficult for the wound to enter the proliferation stage. Therefore, promoting wound proliferation is important for the healing of chronic wounds. Zhu et al.[80] combined Met@1CuPDA NPs/HG with NIR photothermal therapy for diabetes treatment, which alleviated inflammation and lead to the wound entering the proliferation stage and later healing (Fig. 3A). In Deng et al.'s article, it is elaborated that metal–organic frameworks (MOFs) can promote fibroblasts to transform into myofibroblasts during
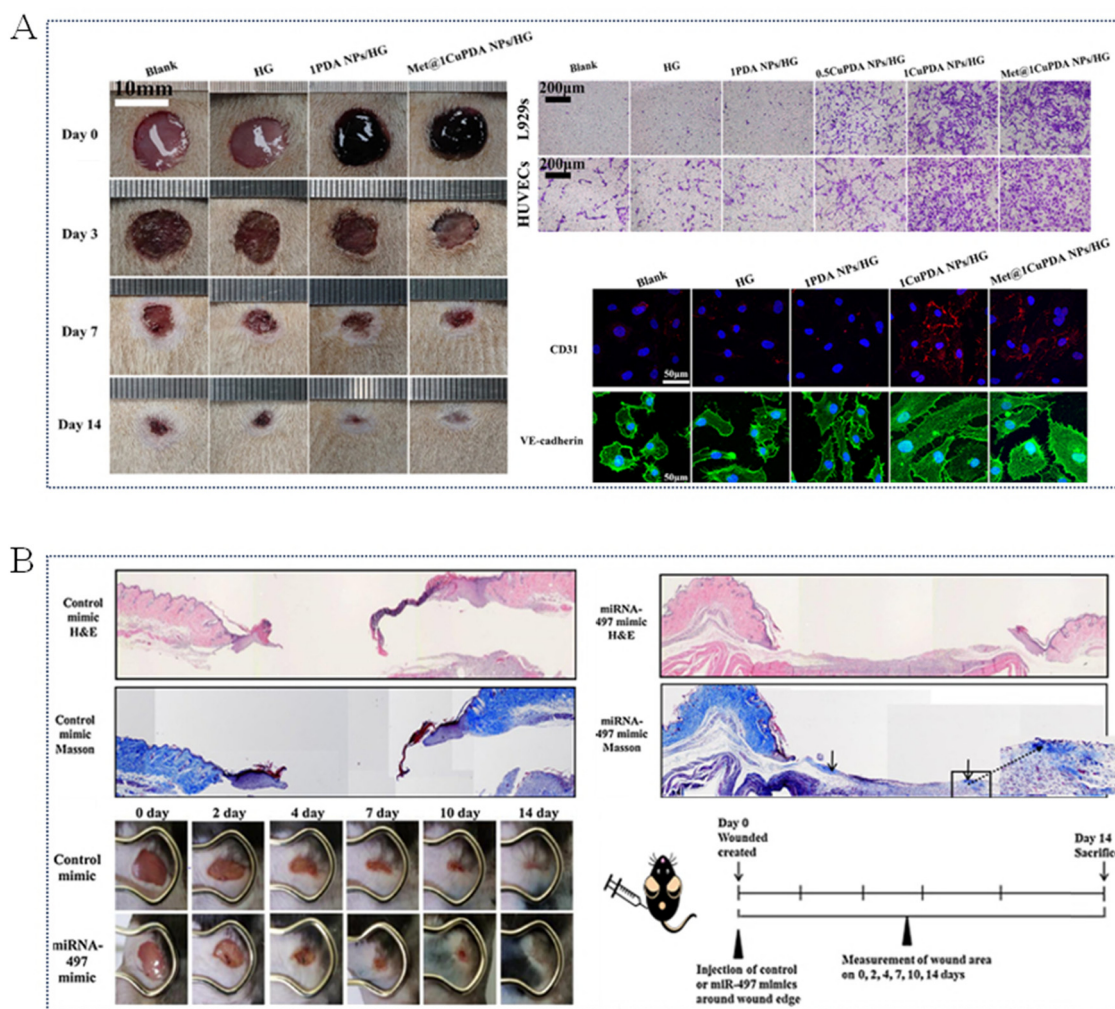
Fig. 3 Integrated wound detection and treatment materials used for the treatment of chronic wounds. (A) The intervention of Met@1CuPDA NPs/HG in wound healing can avoid bacterial infections, promote the formation of blood vessels, enhance the ability of cell recruitment, and contribute to wound recovery. Reproduced from ref. 80 with permission from Elsevier, copyright 2023. (B) The treatment with miRNA-497 inhibits inflammation in diabetic wounds, thereby promoting the healing of chronic wounds. Reproduced from ref. 85 with permission from Elsevier, copyright 2019.

the degradation process, and accelerate the regeneration of blood vessels.[81] In Huang and his team's article, it is suggested that MOFs not only can achieve antibacterial effects by releasing metal ions such as zinc and copper, but also can be used as an intelligent carrier to deliver bioactive agents locally for wound repair and skin regeneration, providing a new idea for the wound repair of diabetic patients.[82] While Liu *et al.* used MOFs as a dual-function nanoplatform for precise diabetes wound management, they pointed out that by detecting acetone gas as a new method for diagnosing diabetes, and using MOFs as drug carriers to achieve targeted drug delivery and controlled release, they innovatively provided a scheme for managing and treating the wounds of diabetic patients.[83]

Existing studies inhibited inflammation by influencing the phenotype of macrophages in the wound. For example, they inhibited the activity and quantity of inflammatory M1 macrophages and promoted the proliferation and function of M2 macrophages.[84] Additionally, Ban *et al.*[85] screened miRNA candidates, including mirNA-497, in the injured skin of type 1 diabetic mice induced by streptozotocin and found that, compared with normal mice, the expression of mirNA-497 in diabetic mice was reduced. Further experiments showed that mirNA-497 could reduce the content of pro-inflammatory molecules. Therefore, we conclude that miRNA-497 has anti-inflammatory and therapeutic effects on diabetic wounds (Fig. 3B).

2.3.2. Pathological mechanism of chronic wounds. Many factors affect wound healing and resolving these factors often promotes wound healing. The main factors inhibiting wound healing are microbial infections, ROS, hypoxia, and nutrition.

In the process of wound healing, the most common bacteria are generally *Pseudomonas aeruginosa* and *Staphylococcus aureus*,[86] which express special virulence factors that promote adhesion and invasion, cause the chemotactic of white blood cells, secrete inflammatory factors and ROS, and cause the wound to be in an inflammatory response.[87] Due to the action of inflammatory factors and proteases, growth factors and the ECM are degraded, cell migration is hindered, wound healing is delayed, and bacteria are wrapped in the protective matrix of

the extracellular polymer.[88] Bacteria usually form biofilms, resulting in long-term inflammation of wounds that are difficult to heal, and eventually chronic wounds.[89] Therefore, it is necessary to develop new wound dressings that efficiently remove bacterial contaminants during wound healing. If growth factors conducive to wound healing can be added to the wound microenvironment, they may have a positive effect on infected wounds.[90] In existing research, the realization of antibacterial functions by the destruction of bacterial biofilms has become the focus of anti-microbial infection research.

High concentrations of ROS promote inflammation in the body; however, low concentrations of ROS can affect cell proliferation, differentiation, and migration. With an appropriate ROS concentration,[91] the expression level of the transcription factor NF-κB can be increased, and it can bind to the promoter of MMP to induce the formation of blood vessels.[92,93] After M1 macrophages are co-cultured and activated by the MAPK signaling pathway, ROS levels in stromal cells increase rapidly, affecting their proliferation, differentiation, and migration, thereby affecting wound healing.[94] Based on this mechanism, U0126, an inhibitor of the MAPK signaling pathway,[95] can effectively reduce ROS levels. Its addition to drugs for wound treatment is expected to promote wound healing. Several studies have shown that both metallic and non-metallic nanoparticles, such as zinc oxide, titanium dioxide,[96] metallized lanthanides,[97] silver, gold,[98] graphene oxide, and carbon nanotubes, can reduce ROS formation and promote EC migration and initial tube formation.

Oxygen plays an important role in wound healing. When the wound is deeply damaged, the oxygen content of the wound is low, which inhibits angiogenesis and re-epithelialization as well as extracellular matrix (ECM) synthesis.[99] Oxygen is also important for the synthesis of collagen, the basic scaffold of the skin. If the oxygen supply is insufficient, it will inevitably lead to failure of the skin scaffold construction. Some materials can achieve a wound oxygen concentration that reaches or slightly exceeds the physiological level to achieve chronic wound healing. Oxygen-releasing materials are mainly calcium peroxide-based dressings and oxygen-supplying hydrogels. Yang *et al.* fabricated an oxygen-supplying 3D-printed bioactive hydrogel scaffold, which can release oxygen sustainably and increase the oxygen content of wound surface. This scaffold, as expected, promoted cell proliferation.

Nutritional factors play key roles in wound healing. Studies have shown that insufficient protein intake significantly reduces the rate of collagen synthesis and delays epithelial cell formation. Furthermore, vitamin C deficiency leads to decreased hydroxyproline production and impaired extracellular matrix stability.[100] Supplementation with omega-3 fatty acids can improve the healing rate of chronic wounds, and docosahexaenoic acid (DHA) and eicosapentaenoic acids (EPA) can contribute to cell proliferation. Experiments have shown that the metabolic activity of keratinocytes and fibroblasts significantly increases after 72 h of treatment with DHA and EPA, which has a positive effect on wound healing.[101] Furthermore, studies have shown that honey has antioxidant and anti-inflammatory properties owing to its

flavonoid and phenolic acid contents, and the local application of honey can effectively prevent infection and heal the wound faster by reducing inflammation and wound epithelialization.[102]

Hormones have a certain impact on wound healing. For instance, growth hormone (hGH) can stimulate the production of insulin-like factor 1 (IGF-1), thereby promoting the proliferation of keratinocytes and fibroblasts and accelerating wound healing. Based on the characteristics of these hormones, some researchers have linked cell-penetrating peptide TAT with hGH through cross-linking agents. Experimental results have shown that TAT-hGH significantly accelerates wound healing, demonstrating its potential for use in wound treatment.[103] Additionally, estrogen causes abnormalities in the extracellular matrix and leads to scar formation, resulting in adverse effects on wound healing; when androgen levels increase, it may prolong the inflammatory phase of the wound, prevent it from entering the proliferative stage, and form chronic non-healing wounds.[104]

The immune system is indispensable during the wound healing process. The immune response to tissue damage has a significant impact on the speed and outcome of wound healing. By activating the innate immune system and the adaptive immune system, it promotes the recruitment and activation of immune cells, completing the process of tissue repair and regeneration. Therefore, many researchers aim to accelerate wound healing by regulating the immune system. In Geng's study, it was demonstrated that activating the TGF-β/Smad pathway can increase the expression of M2 macrophage markers and reduce the expression of M1 macrophage markers, thereby promoting the generation of the ECM in the wound and wound closure.[105] In Li's study, a self-assembled LA peptide hydrogel was developed. This hydrogel can release LA peptides in a controlled manner, dynamically regulate the TGF-β level, maintain the homeostasis of the wound microenvironment, and promote scarless wound healing.[106]

3. Overview of the integration of wound detection and wound treatment

There are considerable difficulties in wound healing owing to differences in the biochemical and cellular processes occurring in different types of wounds.[107] Environmentally sensitive hydrogels are smart materials that can respond to external stimuli, including pH and temperature, in the wound environment.[108] Changes in light intensity can also be used to detect wound healing and release the loaded drugs to treat the wounds. Overall, the response functions of biological materials can be combined with drugs to integrate wound treatment and detection.

3.1. Main ideas for the integration of wound detection and wound treatment

An integrated wound detection and treatment platform aims to detect changes in various factors on the wound surface, diagnose wound healing using these changes, and then release drugs accurately under the stimulation of various environmental

responses to promote wound healing. Wound detection includes assessments of biomarkers, infection, blood supply, and pain.

3.1.1. Biomarkers for wound detection. Biomarkers for wound healing include cytokines, growth factors, and proteases.[109] Gelatinase and procalcitonin are produced during the infection stage; uric acid expression in patients with gout can be used as a biomarker for wound detection.

Wound exudate is produced by damaged skin, and the status of the wound can be detected by collecting and analyzing a sample of the wound exudate. Compared with traditional wound detection methods, the detection of wound exudates is not only rapid, but also a non-invasive collection method that provides convenient bedside detection. Nucleic acid lateral tomography immunoassays can be used for rapid detection of pathogens in wounds. Because opportunistic pathogens colonizing the wound site are detrimental to wound compounds, a simplified assessment scheme can aid in initially identify pathogens. This method has great potential for bedside detection and targeted treatment.[110] In the stage of wound infection, gelatinase, a biomolecule that is mainly expressed, can be used as a biomarker to detect wound recovery, which can enable clinical medical staff to detect wound infection in a timely manner and effectively treat it.[111] When the wound is infected, if not treated in time, it can lead to sepsis, infectious shock, and even death. Li et al.[112] designed a soft, wearable wound dressing system that can detect biomarkers (procalcitonin) in wound exudates in real time, continuously monitor the wound status, and accurately detect the pH and temperature of the wound for diagnosis. For wounds that are difficult to heal, it is important to frequently monitor the wound over a long period of time to facilitate the application of more targeted treatment regimens. Recently, a new textile chemical sensor based on poly(3,4-ethylenedioxythiophene):polystyrene sulfonate (PEDOT: PSS) has been developed to detect uric acid (UA) in wound exudates.[113] This sensor targets wound management by preventing gout-associated UA crystals from delaying wound healing.[114]

C-reactive protein is widely regarded as a biomarker of infection and can generally be used as an early detection indicator for infection. However, due to its low specificity and the tendency to cause clinical misdiagnosis at low concentrations, C-reactive protein velocity (CRPv) has been introduced as a new biomarker to enhance the diagnostic ability of CRP. This new biomarker may have certain value in guiding the use of antibiotics in clinical practice.[115,116] Lactate dehydrogenase (LDH) shows a significant increase in deep activity in burn skin, and the areas with increased activity often exhibit cell infiltration. At this time, the wound area may be in an inflammatory disorder or metabolic hyperactivity. Therefore, lactate dehydrogenase can be used as one of the biomarkers for detecting wounds; although LDH has metabolic and inflammatory indication values, its non-specificity suggests that it should be combined with other indicators for comprehensive judgment in clinical applications. Future research can focus on the application of LDH isoenzymes in wound detection.[117] Detection of biomarkers can be done through various methods and platforms, but the fluorescence detection of MOFs has high

sensitivity, strong selectivity, and is more convenient. In the future, MOF fluorescence detection can be integrated with wound detection and treatment to provide more accurate detection results for clinical practice.[118]

3.1.2. Detection of the wound infection status. The diagnosis of clinical infection is mainly based on the clinician's judgment and assisted by microbiological outcome data (e.g., using biopsy and swab collection to quantify microorganisms). However, this approach is often inaccurate, invasive, and time-consuming. In general, an increase in skin temperature can be detected in the first three days of surgery and a gradual decrease can be detected in the fourth to eighth days, which corresponds to the stage of inflammation in the healing process. Therefore, many scientists use temperature as an indicator of infection. In addition to temperature as an indicator of wound infection, changes in pH and ROS levels have been widely used to detect infections. For example, Su et al.[119] designed a highly stretchable smart dressing for wound infection detection and treatment, and experimental results showed that the smart dressing could detect bacterial infections through temperature and pH biomarkers. Furthermore, the electrically controlled release of antibiotics significantly improved wound infection factors. The accumulation of bacteria was noted in all wound types, especially in chronic wounds. Gram-positive bacteria were more abundant in acute wounds than Gram-negative bacteria, and the population of Staphylococcus was more than that of Pseudomonas.

3.1.3. Wound blood supply detection. Wound blood supply assessment is a key indicator of wound healing potential, particularly in patients with diabetes and vascular diseases. Blood circulation disorders (such as arteriosclerosis and microangiopathy) are the main causes of chronic wound healing difficulty. Insufficient blood supply leads to tissue hypoxia, insufficient nutrient supply, and the accumulation of metabolic waste, which in turn inhibits cell proliferation and repair processes. Therefore, an accurate assessment of wound blood supply is essential for the development of personalized treatment. The blood supply status of a wound can be reflected by vascular assessment, which can assist in clinical decision-making. Fluorescence angiography (FA) can be used in wound care, especially for evaluating the healing of chronic wounds.[120] Continuous inflammation may cause the vessels around the wound bed to become highly permeable owing to the overexpression of VEGF. Angiography can be used to monitor wound healing and identify diabetic ulcers and traumatic wound reperfusion.

3.1.4. Pain assessment. Scales are often used to assess the level of pain the patient is experiencing. For example, with the visual analog scale (VAS),[121] patients are asked to rate their level of pain on a 10-centimeter line according to the level of pain, with 0 indicating no pain and 10 indicating the most intense pain. The numerical scale (NRS) refers to pain intensity on a scale of 0 to 10, with 0 indicating no pain and 10 indicating the most intense pain.[122] The Facial Expression Pain Scale (FPS-R), which is used for children and patients with communication difficulties, uses facial expressions that represent pain levels.[123] The McGill Pain Questionnaire (MPQ) is used to assess the nature, intensity, and duration of pain.[124] A better analgesic

plan can be developed after pain assessment. Drug analgesics are the most commonly used analgesics. Based on the assessed degree of pain, NSAID and opioids can be reasonably selected to relieve discomfort.[125] Pain can also be alleviated by cold compresses and muscle relaxation.

3.2. Integrated application of wound treatment and wound detection

3.2.1. Drug release to treat wounds. A dressing that integrates wound detection and treatment can be used as a carrier to transport drugs and achieve sustainable drug release, thus overcoming the shortcomings of traditional drug delivery methods, such as drug property changes, early drug release, and explosive drug release. To avoid explosive drug release, Bostanci et al.[126]

constructed a pH-responsive release step for curcumin. Through stepwise release, curcumin is released more accurately, which can enhance epithelial regeneration and fibroblast proliferation, and it exerts a positive effect on wound healing. Owing to the constant oxidative stress microenvironment and inflammation present in chronic wounds, drugs often fail to have a therapeutic effect on the wound. Therefore, Zhu et al.[127] designed a compound hydrogel dressing with an appropriate swelling rate, GelMA/SFMA composite hydrogel, to avoid the efficacy and delivery limitations of single-drug treatment and achieve continuous drug release (Fig. 4A). To overcome the limitations of non-specific distribution and insufficient accumulation of therapeutic drugs in drug delivery systems,[128] resveratrol with anti-inflammatory properties was added to mesoporous silica nanoparticles to enhance the
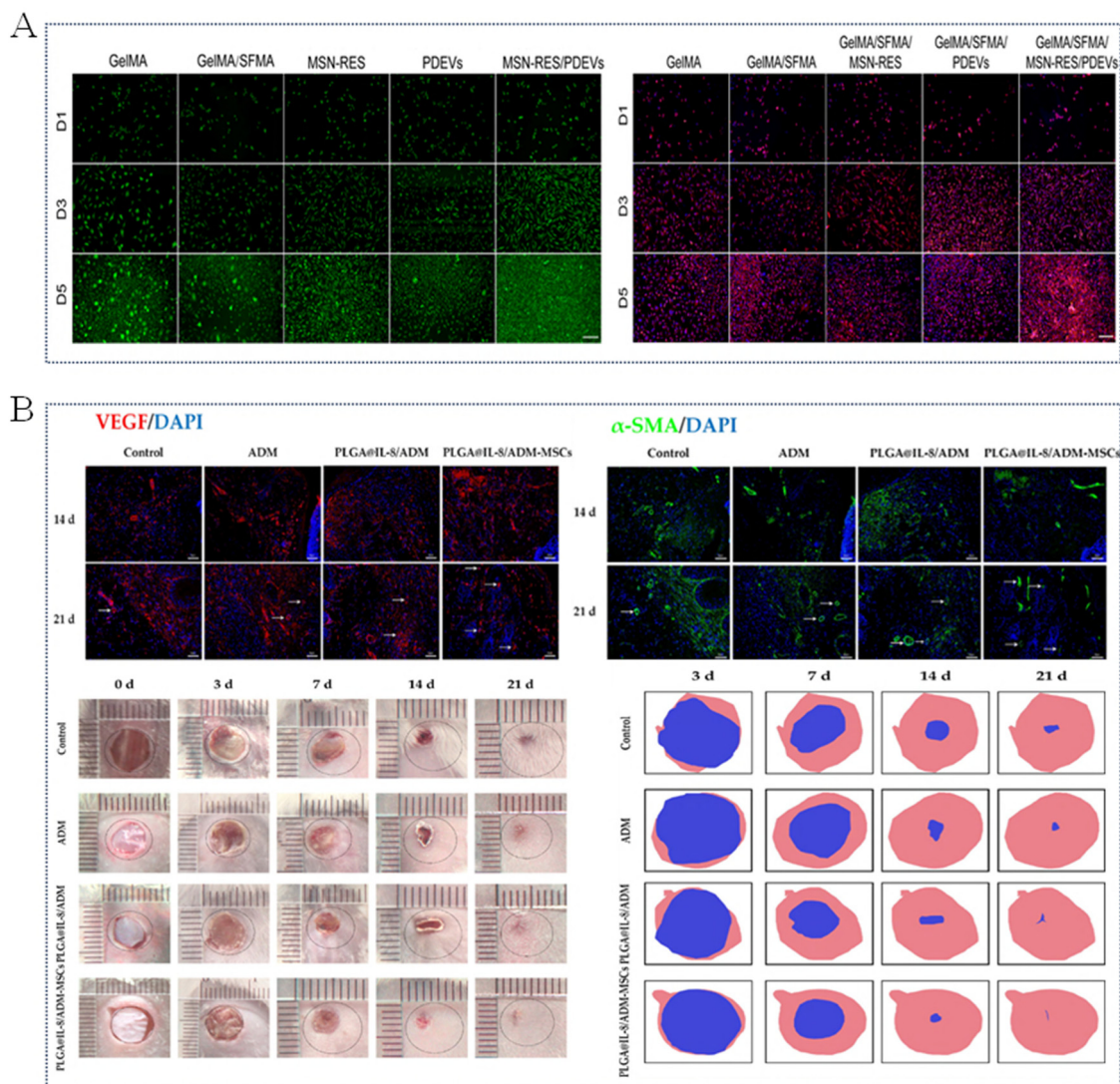

Fig. 4 Illustrations showing wound healing and the excellent performance of integrated materials in promoting enhanced wound healing. (A) After testing GelMA/SFMA/MSN-RES/PDEVs, the cells exhibited normal proliferation and morphology, indicating that the composite was non-toxic and had good biocompatibility. Reproduced from ref. 127 with permission from Elsevier, copyright 2022. (B) The application of the PLGA@IL-8/ADM-MSC complex to diabetic wounds resulted in smaller wound areas and less inflammatory reactions compared with the control group. In addition, the number of newly formed blood vessels significantly increased, contributing to enhanced wound healing. Reproduced from ref. 130 with permission from Elsevier, copyright 2022.

release kinetics and improve drug utilization. In many studies, mesenchymal cells (MSC) have been found to play an important role in skin tissue repair;[129] however, owing to their low transplantation efficiency, poor cell viability, and poor tolerance, their tissue repair ability is weak. Zhang et al.[130] considered this a breakthrough point. They used acellular dermal matrix containing PLGA@IL-8 nanoparticles as a delivery system for exogenous MSCS for diabetic wound healing (Fig. 4B). The acellular dermal matrix (ADM) has excellent biocompatibility and bioactivity,[131–133] which can provide the MSC with a niche similar to their internal microenvironment,[134] thereby improving the proliferation and migration ability of exogenous MSC and greatly improving the skin regeneration rate of diabetic wounds. As IL-8 is a pro-inflammatory molecule that acts as a strong angiogenic factor that can accelerate capillary regeneration,[135] the team developed a PLGA@IL-8/ADM-MSC complex. This complex can help capillary reconstruction and collagen deposition in skin wounds and has potential for clinical application in wound healing of cases of chronic diabetes. Nowadays, micelles, exosomes, inorganic NPs, and MOFs can all serve as nanoscale materials for drug delivery, and they have played significant roles in cancer treatment.[136,137] In the future, with the continuous advancement of nanomedicine, more personalized solutions for wound treatment may be brought about. The high water content and maximum pore size of most hydrogels lead to accelerated drug release.[138] Therefore, to avoid the explosive release of drugs many hydrogels are combined with nanoparticles. Chitosan can enhance the loading capacity of nanoparticles through functionalization with various molecules;[139] when MOFs are used as a nanomedicine delivery system, it is beneficial for prolonging the drug's duration in the body, increasing the circulation time of the drug in the body, and helping to save clinical drug resources.[140]

Owing to poor pH reactivity, it is difficult for general self-healing injectable hydrogels to release substances freely after implantation. In the strategy proposed by Chen et al.,[141] the biological macromolecule skeleton is cross-linked through double pH-sensitive dynamic double bonds, thus endowing hydrogels with self-healing ability and pH-responsiveness for injection and improving the bioavailability of protein drugs. This represents a new method for wound repair. Nanoparticles are also widely used as therapeutic vectors in many diseases and they can achieve controlled or sustainable drug release. Shetty et al.[142] found that, through the combination of the drug–nanoparticle and the nanofiber, the drug could ooze from the nanoparticle during use, and the nanoparticle could also be protected by the nanofiber to ensure that the drug would not be released in advance during transportation. Future studies should focus on composite wound dressings based on nanomaterials and hydrogels. Both materials have good wound treatment capabilities and have commonalities in many aspects, making them a good platform for carrying drugs.

3.2.2. Reduction of the wound reaction.
In the treatment of chronic wounds, owing to the longer healing time and more difficult treatment, it is often necessary to replace dressings in clinical treatment. Compared to traditional dressings, which are not firmly fixed, disassembly further aggravates the condition of

the wound. Hydrogel materials prevent these problems and reduce wound reactions. Acidic pH and high blood sugar levels inhibit wound recovery; therefore, scientists are committed to researching special wound dressings that can respond to the environmental pH and glucose concentration. In a study by Zhang et al.,[143] a thermo-inducing adhesive and removable hydrogel were designed to treat wounds. The hyaluronic acid (HA)/Gel-R-Ag hybrid Gel was prepared by incorporating a silver ion cross-linked HA ester/gelatine-based polymer gel network into a supramolecular rhein gel network, thereby significantly enhancing its mechanical properties. The temperature-responsive gelatin chain enables the hybrid gel to exhibit reversible tissue adhesion and separation, thus avoiding secondary injury to the wound when the hydrogel is replaced, while exhibiting excellent antibacterial properties and providing a promising dressing for wound treatment.

Bacterial invasion also complicates wound healing. In addition to the change in pH value in response to wound changes, photothermal changes can also be used as stimuli. Zheng et al.[144] manufactured a multifunctional photo-hot water gel dressing based on sodium alginate. Cerium dioxide nanoparticles with antioxidant and angiogenic properties were added to heat-sensitive gelatin for embedding, and the nanoparticles were integrated into a sodium alginate hydrogel network to exert their antibacterial and antioxidant properties. To promote wound healing in chronic diabetes, the composite material can maintain a soft gel form under near-infrared light to adapt to wounds of different sizes and shapes, rather than becoming a liquid which would cause problems. After basic healing is completed, an ice pack can be placed on the surface of the hydrogel to reduce the temperature, achieve painless molting, and avoid secondary damage.

3.2.3. Reduction of wound inflammation and promotion of cell proliferation.
Many studies have found that H_2S can regulate hemostasis, promote cell migration and adhesion, help ameliorate inflammation, and reshape the extracellular matrix, all of which have positive effects on the treatment of chronic wounds. Initially, H_2S was considered a toxic gas.[145] Zhang et al.[146] developed a nano-disinfectant (ICG-ZNS NPs) using zinc sulfide (ZnS) as the core to generate H_2S and indocyanine green (ICG) as the photosensitizing agent. This nano-disinfectant is sensitive to changes in the environmental temperature (Fig. 5A). Furthermore, zinc has antibacterial and anti-inflammatory properties and can help to accelerate the regeneration of blood vessels. Thus, it is conducive to wound healing and has great potential for future applications.

A hyperglycemic environment promotes bacterial proliferation and inhibits immune cell function. It also leads to the occlusion of microvessels and reduces the arrival of essential materials for wound healing, thus prolonging wound healing. Yang et al.[147] developed a glucose-responsive multifunctional metal–organic liquid carrier gel to address these adverse healing factors (Fig. 5B). This metal–organic hydrogel provides a fulcrum for the design of multifunctional materials owing to its good drug-loading performance and pH-response. First, it provides a basic protective barrier for the wound through its adhesion and covering effects. Second, zinc has antibacterial properties that can inhibit persistent infection of the wound
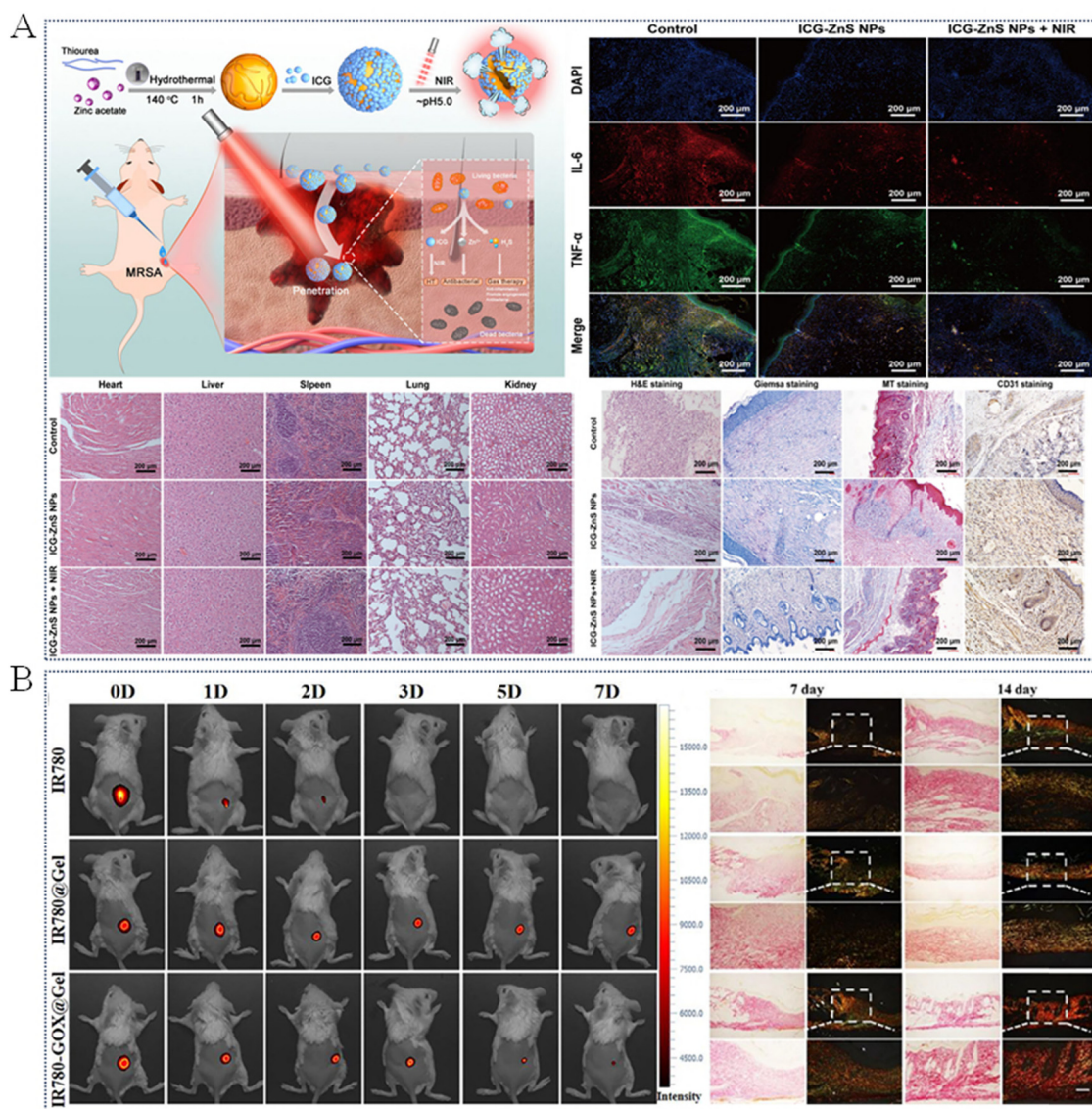
Fig. 5 Different composites promoting cell proliferation. (A) Schematic illustration of the composition and the antibacterial mechanism of a biofilm-responsive hierarchical H$_2$S-releasing nano-disinfectant. After the application of ICGZnS NPs + NIR on the wound, the degree of neutrophil infiltration was significantly reduced, collagen deposition was accelerated, new blood vessel formation was observed, and inflammation was decreased, demonstrating excellent biological safety. Reproduced under terms of the CC-BY license.[146] Copyright 2022, Springer Nature. (B) Compared with other groups, the treatment with IR780-GOX@Gel showed a sustained therapeutic effect and the best biodegradation rate. The collagen content in the wound was also increased, which accelerated the wound repair. Reproduced from ref. 147 with permission from Elsevier, copyright 2021.

and avoid resistance caused by traditional antibiotics. This type of metal–organic hydrogel has been shown to exhibit good antibacterial activity and promote cell proliferation, migration, and tube formation.

Because chronic inflammation can make diabetic wounds difficult to heal, Zhou et al.[148] developed a temperature-sensitive adaptive hydrogel with a dual response to glucose and MMP-9 (CBP/GMs@Cel&INS), which can release drugs on demand at high glucose levels while downregulating MMP-9. This hydrogel promotes cell proliferation, migration, and glucose consumption and provides good conditions for wound healing.

Excessive ROS can aggravate oxidative stress, obstruct vascular remodeling of diabetic wounds, and thus prolong the inflammatory period. Therefore, He et al.[149] designed a wound dressing with effective ROS clearance and antibacterial properties for chronic diabetic wound management. This multifunctional hydrogel material is based on the dynamic double crosslinking of Schefky and metal coordination bonds. It can induce an NIR photothermal response, resulting in protein denaturation and bacterial death, thus achieving antibacterial effects and the ability to remove ROS. Furthermore, Wu et al.[150] constructed a chitosan-based photocurable hydrogel dressing (LCPN), which can be used to accelerate the healing of infected wounds and can also enhance cell proliferation, migration, and antioxidant capacity, which is conducive to accelerating wound healing.

In a treatment scheme for arthritis, owing to the need for targeted distribution and accurate drug release, He et al.[151] designed a PEGyl-phenylborate-glycerol monostearate triester (polyethylene glycol [PEG]-phenylboric acid [PBA]-triglycerol monostearate [TGMS]; PPT). The PPT conjugate assembles double stimulus-response polymer micelles to deliver dexamethasone specifically to the site of arthritis and improve the release rate of dexamethasone based on the response to acidic pH and over-expression of matrix metalloproteinases, thus achieving effective treatment of arthritis. This study provides directions for new research, in addition to the traditional stimulus response factors, based on the wound secretion of different substances targeting the stimulus response. The findings highlight the potential of dual response factors to effectively treat inflammatory diseases or wounds.

Biocompatibility is a common feature of many biological materials that enables them to exist normally in the body. For example, biocompatible hydrogel dressings are considered as ideal materials for wound dressings due to their good flexibility, but the adhesion, mechanical, and antibacterial properties of ordinary hydrogel dressings cannot meet clinical needs.[152] Xue et al.[153] developed a polysaccharide based hydrogel, which, by referencing quaternary ammonium chitosan (QCS), imparts antibacterial properties to the hydrogel, and the antibacterial effect can be further improved under near-infrared light. The hydrogel exhibited self-healing properties through the reversible Schiff base bond between QCS and oxidized HA (OHA), which showed photothermal antibacterial activity and sustained drug release, even when the wound was slightly acidic. In a study by Li et al.,[154] a functional hydrogel was directly designed to respond to the acidic environment of the wound surface using a convertible nanoparticle composed of a hydrophobic Ph-responsive cyclodextrin host material and a polytropic hydrophilic guest macromolecule. When triggered by protons in the environment, the nanoparticles are transformed into hydrogels. These nanoparticles enable the triggering and continuous delivery of drugs, which in turn can achieve anti-inflammatory effects and improve and accelerate wound healing.

3.3. Significance of the integration of wound treatment and wound detection

3.3.1. Precision treatment. Relying on advanced wound detection technology, a wound-integrated platform can perform comprehensive and real-time detection of various physiological states of the wound. In the detection process, the platform uses highly sensitive sensors and professional detection algorithms to accurately analyze key indicators, such as temperature, humidity, pH, and tissue fluid composition of the wound surface. Once signs of bacterial infection appear in the wound, such as abnormally elevated concentrations of metabolites from specific bacteria, or large fluctuations in the levels of certain inflammatory factors resulting from an inflammatory response, the platform quickly captures these changes and provides intuitive feedback to clinicians.

This feedback mechanism provides strong support for doctors' clinical judgment. With this detailed information, doctors can implement targeted interventions based on the specific conditions of the wound. For example, for mild infections and small wounds, doctors can use mild irrigation debridement.[155] For severely infected wounds with a large amount of necrotic tissue, doctors can perform more thorough surgical debridement. Furthermore, highly absorbable dressings can be selected if there is more exudation of the wound. In contrast, in wounds that require tissue growth, functional dressings containing growth factors are more appropriate. In terms of drug selection, antibiotics can be used accurately according to the type of infectious bacteria and the results of drug sensitivity tests, thereby avoiding ineffective treatment caused by blind drug use.

3.3.2. Improvement of treatment efficiency. In the early stages of wound treatment, complications can be detected through the continuous detection of various wound indices. For example, when the local temperature of a wound is abnormally elevated and tissue color changes are detected, combined with changes in inflammatory indicators, infection can be identified.[156] If the texture of the wound tissue is hard, and blood perfusion is reduced, necrosis may have occurred. Once these potential risks are detected, physicians can quickly implement effective interventions.

After infection is detected, the antibiotic use regimen should be adjusted in a timely manner or local antimicrobial therapy should be strengthened. Potentially necrotic areas should be given nutritional support in advance to improve blood circulation and avoid further aggravation of the disease. Consequently, the difficulty and cost of follow-up treatments will be greatly reduced. During the course of treatment, doctors can dynamically adjust drug treatment with the aid of real-time detection of wound status data. According to the different stages of wound healing, a timely increase or decrease in the drug dose and change in the drug type ensure the effectiveness and safety of the drug treatment.

Real-time detection of the wound status, such as observing the healing speed of the wound and the growth of new tissue, can aid in the timely detection of any problems. This process can greatly reduce the wound healing time, enable the patient to recover faster, reduce patient pain and economic burden, and improve the utilization efficiency of medical resources.

4. Available materials that integrate wound treatment and detection

4.1. Hydrogels

Hydrogels exhibit good histocompatibility, biodegradability, and excellent physical and chemical properties. These biological materials have broad application prospects and functions. When a wound is injured, dressings are typically used to absorb osmotic fluid and isolate external pathogens to prevent infection. In traditional treatments, materials such as gauze and bandages are used for hemostasis. Although they absorb exudates and protect the wound from external stimulation, they may lead to wound crusting and adhesion,[157] thereby hindering wound healing. Hydrogels are multifunctional wound dressings that can act as ordinary materials and simultaneously treat and monitor wound conditions.

Common natural polymer materials include chitosan, alginate, and HA.

Chitosan (CS) is a polycationic bidimer that originates from a wide range of sources and has superior histocompatibility, biodegradability, adhesion, and antibacterial activity.[158] Therefore, it has become a hot topic in wound dressings. CS can stimulate platelet coagulation and promotes the release of vascular endothelial factors that promote angiogenesis. In addition, CS is characterized by a stable structure, easy transformation, strong water absorption, and is easy to prepare into hydrogels. Deng et al.[159] reported that chitosan has antibacterial properties and can be used to isolate wounds from the external environment. The process of wound healing is accelerated; therefore, chitosan hydrogels have potential value as wound treatment materials.

Chitosan hydrogel dressings can combine bioactive factors, such as growth factors and antibacterial substances.[160] Functional hydrogels with bioactive factors or drugs conducive to wound healing can be designed to deliver these bioactive factors and therapeutic drugs to the wound in a targeted and lasting manner, which can improve chronic wound treatment. In a study by Sarmah et al.,[161] functionalized starch was designed as an aggregation cross-linking agent to help stabilize the structure of the hydrogel, and chitosan was introduced to make a self-cross-linking starch/chitosan hydrogel a biocompatible carrier for controlled drug release. The longest sustained release period for the hydrogel carrier loaded with ampicillin sodium was 29 h. This drug-loaded hydrogel accelerated the healing of chronic wounds by prolonging the duration of drug action. Li et al.[162] emphasized that chitosan hydrogels could achieve rapid repair and prepared a novel chitosan-polyethylene glycol-hydrocaffeic acid (CS-PEG-HA) hybrid hydrogel. Compared to traditional hydrogels, this new hydrogel material can enhance mucosal adhesion and improve hemostatic performance. They demonstrated that the CS-PEG-HA hydrogel could achieve rapid repair of the skin defect model in the circle, thus helping to rebuild the complete skin epidermis within 14 days.

Alginate is a non-toxic natural linear polysaccharide widely derived from brown algae or bacteria that have good biocompatibility and high water absorption;[163] it has become a popular wound dressing material. When alginate acts on wounds, it can activate macrophages and stimulate monocytes to produce cytokines (IL-6 and TNF-α) and promote the healing of chronic wounds.[164] Chemical and physical crosslinking are typical production methods for alginate-based hydrogels. Sun et al.[165] used the crosslinking of Ca^{2+} ions and glutaraldehyde to propose a sulfonamine-supported alginate hydrogel supported by ions and chemical crosslinking. Their research showed that the mechanical properties of alginate hydrogels could be enhanced and the swelling degree could be reduced through the cross-linking of glutaraldehyde. Thus, it is beneficial for hydrogels to have an adjustable fluid adsorption capacity. Simultaneously, sulfanilamide is accurately applied to local wounds to achieve the combination of antibacterial and anti-inflammatory effects and promote wound healing. Timely hemostasis is important when a wound continues to bleed. Ma et al.[166] synthesized

quaternary ammonium salt oxidized sodium alginate (QOSA) by grafting sodium alginate with quaternary ammonium salt. By adding quaternary ammonium groups, QOSA has antibacterial and hemostatic effects. Furthermore, antler blood polypeptide (DABP) was added to the hydrogel (QOSA & CMCS & DABP) to confer antibacterial, hemostatic and antioxidant abilities and help wound healing.

HA is a major component of the skin extracellular matrix (ECM) and participates in inflammation, angiogenesis, and tissue regeneration.[167] Due to its histocompatibility and hydrophilicity, HA is widely used in wound dressings. Thones et al.[168] designed an HA/collagen hydrogel containing sulfated HA to improve the wound healing status; the sulfation of HA increased the binding capacity of HB-EGF. Through molecular modeling and surface plasmon resonance (SPR) analysis, researchers showed that hydrogels containing HA and collagen or a mixture with sHA were shown to bind and release bioactive HB-EGF over at least 72 h, which could induce keratinocyte migration in fibroblasts and accelerate skin healing. Xu et al.[169] developed a glucose-reactive HA derivative (HAMA–PBA) by modifying methacrylate hyaluronic acid (HAMA) with phenylboric acid (PBA). Next, a glucose-responsive HAMA–PBA/catechin (HMPC) hydrogel platform was constructed by forming a borate ester bond between HAMA–PBA and catechin. After in vitro and in vivo experiments, HMP hydrogels were compared with the untreated group; this antioxidant HA-based hydrogel was found to have an initial effect on diabetic wound repair, indicating that this multifunctional hydrogel has great potential for application in diabetic wounds.

PEG is a multifunctional polymer that is often used as a carrier. Although PEG is often considered weak or even non-immunogenic,[170] it can be immunogenic when combined with other materials (such as proteins and nanomaterials).[171] Several PEG-based hydrogel wound dressings have been developed. For example, Zhou et al.[172] developed a hydrogel dressing that facilitated antibacterial hemostasis. The multifunctional PEG–CMC–THB–PRTM hydrogel was prepared using carboxymethyl chitosan (CMC), 2,3, 4-trihydroxybenzaldehyde (THB), protamine (PRTM), and 4-arm pegylaldehyde (PEG) using the one-pot method. These hydrogels exhibited excellent mechanical properties. The hydrogel promoted the formation of the extracellular matrix, accelerated wound closure, and was effective in water. PF127 is a copolymer that forms a heat-sensitive hydrogel, which contains both hydrophilic and hydrophobic chains, showing a superior thermal response. However, PF127 also has the disadvantages of poor mechanical properties and rapid drug release. Therefore, different polymers are often added to change specific properties and optimize various properties. Zhang et al.[173] studied patients with periarthritis of the shoulder and found that the sustainable drug release and wound healing detection provided a platform for the generation of injectable thermosensitive hydrogels, which flow freely in a liquid form at specific temperatures. However, when the temperature exceeds a certain value, these hydrogels lose their moisture and become solid hydrogels that squeeze out the drug load to treat the disease.

4.2. Adhesives

In recent decades, the discovery of various phenomena and mechanisms has led to the continuous development of adhesives. In a recent study, Gao et al.[174] found that a natural bioadhesive derived from snail mucus gel had excellent biocompatibility, biodegradability, and anti-bleeding properties. This bioadhesive is mainly composed of positively charged proteins and polyanionic glycosaminoglycan, which has a malleable adhesive matrix and covers the wound through different interactions; it can not only accelerate the normal wound healing process but can also effectively heal the wound in diabetic patients. In addition to natural biological adhesives, synthetic adhesives play an important role in wound healing. Sun et al.[175] designed a multi-functional medical adhesive that was injectable, was self-healing, and had strong viscosity. A self-healing injection adhesive was prepared via the physical interaction of polyphenol tannic acid (TA) and an octo-brach polyethylene glycol end cap with succinimide glutarate active ester (PEG–SG). This adhesive had the characteristics of repeatable adhesion unlike other wound-healing materials; in vitro experiments, this adhesive was proven to self-heal wounds, and thus, it can be used as a dressing to promote wound healing.

4.3. Nanoparticles

Nanomaterials have become a popular research topic in recent years. Nanomaterials usually have large surface areas and small particle sizes and can carry more substances.[176] The functions of these materials are being explored in the biomedical field. A study by Zheng et al.[177] on starch-based nanoporous particles emphasized that powdery hemostatic particles have many application prospects in large open wounds (Fig. 6A). In their study, nanoscale mesoporous and macroporous silica (MMSN), nanoscale mesoporous and macroporous bioactive glass (MBG), micron-scale cross-linked porous corn starch microspheres (CMS), MMSN@CMS, and MBG@CMS starch-based microporous nanoparticles were synthesized. The water absorption of the composite particles was improved, internal and external coagulation pathways were activated, and the concentration of platelets increased the efficiency of wound hemostasis. Therefore, these starch-based nanoparticles can be used as a hemostatic material, which is likely to be important in cases of excessive bleeding from external wounds or sudden bleeding during surgery. Research has shown that inorganic nanoparticle can adhere to wound tissues based on their nanobridging effect. Zeng et al.[178] described a type of nanoparticle that can not only automatically degrade in a short time, but also has intact biocompatibility, which can quickly close the wound and promote the regeneration of blood vessels and the epidermis (Fig. 6B). Therefore, this type of porous silicon nanoparticle has great potential for wound healing.

5. Integrated classification of wound treatment and wound detection

Wound detection indices can be divided into pH, temperature, glucose, active oxygen, and photosensitive response types.

5.1. pH responsive hydrogels

The normal skin pH tends to be slightly acidic (generally between 5.0 and 6.0). Studies have found that in acute wounds, the skin pH changes due to exposure to interstitial fluid with a pH of 7.4.[179] However, with the evolution of wound healing, the skin pH often returns to a weakly acidic state,[180] whereas chronic wounds are affected by the presence of blood, interstitial fluid, ammonia, and other substances. Generally, the pH increases to approximately 7–9,[181] which affects wound healing. However, during wound healing, keratinocytes generally secrete amino and fatty acid metabolites that form a slightly acidic environment that inhibits bacterial proliferation.[182] In addition to the body's own factors, bacteria prolifically produce acidic metabolic wastes, such as lactic acid and carbonic acid,[183] resulting in a decrease in the wound pH.[184] Therefore, pH can be used as an indicator of wound healing status.

Hydrogels related to the pH response have been widely manufactured; for example, hydrogels targeting the release of tannic acid (TA) have been widely used.[185,186] TA is not only an antioxidant, but also an antioxidant. It can reduce oxidative damage at the wound site, promote the formation of blood vessels, regulate macrophages, block the inflammatory pathway to prevent inflammation, and create a favorable environment for wound recovery. Therefore, Yang et al.[187] constructed a pH-responsive tannic acid/carboxymethyl chitosan/sodium alginate oxyhydrogel that could effectively treat diabetic wounds and detect wound healing status. Liang et al.[188] designed a metformin hydrogel dressing with pH and glucose responses for chronic foot wounds in patients with type II diabetes. They observed that this hydrogel stimulated the response to metformin. When administered locally, metformin effectively reduces blood glucose levels in this region.[189] When the pH was reduced, the drug release of this wound dressing significantly increased, mainly owing to the biocompatibility and strong double dynamic bond release ability of the Schiff base and phenylborate added by the hydrogel. Schiff bases easily dissociate under acidic conditions, whereas glucose competitively binds with phenylboric acid. Therefore, this versatile hydrogel dressing responds not only to pH but also to glucose.

Hydrogels released in neutral environments, even under alkaline conditions, are urgently needed. For example, alginate and some metal ions can cause charge removal, hydration, and swelling of hydrogels under alkaline conditions so that specific substances can be released under alkaline conditions to promote the healing of chronic wounds.[190] In the future, it will be necessary to study and develop a specific release system for chronic alkaline wounds.

5.2. Temperature responsive hydrogels

The temperatures of different types and stages of wounds are closely related to their healing states. Therefore, the wound temperature detection index is a reliable, rapid, and accurate method for evaluating wound healing.

Generally, low temperature affects the physiological state of the wound; therefore, maintaining the normal temperature of the wound and preventing it from entering the low-temperature
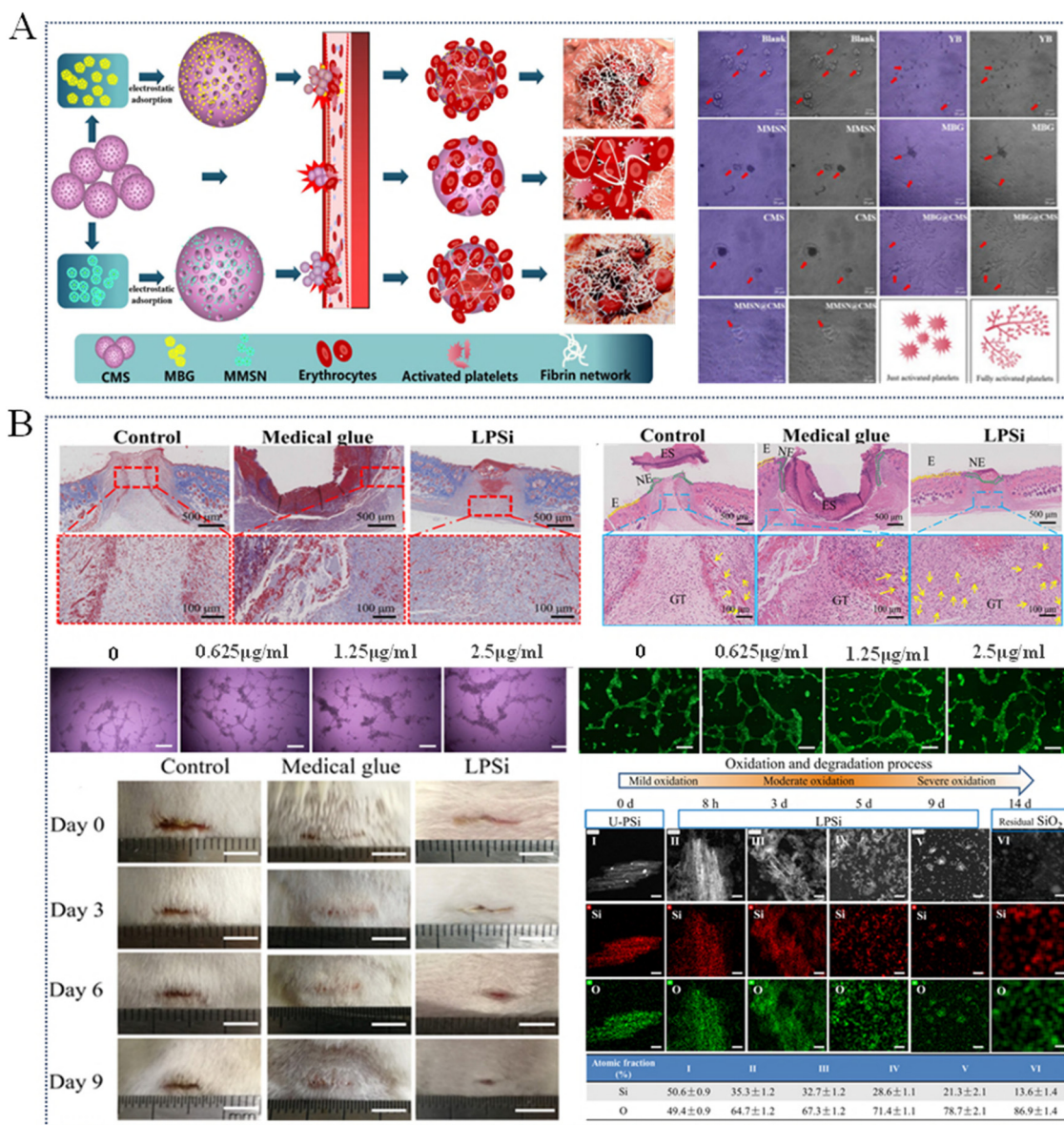
Fig. 6   The role of nanomaterials in wound healing. (A) Preparation and coagulation mechanism of starch-based nanomicroporous particles. These particles effectively activated the platelets, enhancing hemostatic efficacy and thereby promoting wound repair. Reproduced from ref. 177 with permission from Elsevier, copyright 2021. (B) LPSi treatment not only promoted the formation of blood vessels and regeneration of new tissues in the wound, but also effectively facilitated the wound closure. Reproduced from ref. 178 with permission from Elsevier, copyright 2021.

state is an effective means to promote wound healing.[191] In addition, when the inflammatory reaction occurs, the local temperature of the wound is often too high; thus, the temperature can reflect the healing process of the wound.[192,193]

Traditional dressings do not exhibit temperature detection characteristics. In a recent study, scientists considered promoting wound healing by managing temperature-responsive polymers that would release a substance once the exudate on the wound surface becomes warmer than normal for detection purposes.[194,195] Hydrogels change from a liquid to a solid state[196] when the temperature exceeds a certain value, which is generally considered the lower critical liquid temperature (LCST).[197] When the temperature is lower than LCST, the

polymers dissolve and they become hydrophobic and appear as liquids.[198] Thermosensitive hydrogels are highly sophisticated materials and scientists are working to develop materials that combine thermal responsiveness and mechanical properties.

Heat-responsive PNIPAM was anchored to a tough polymer skeleton of polyvinyl alcohol (PVA) and its methacrylate derivatives by irradiation with an ultraviolet lamp. After a pot of polymerization, the sample is immersed in a sodium sulfate salt solution to further enhance the hydrogel network in which, in these cases, PVA aggregates and crystallizes. Because of the single-network topology, this hardening process did not degrade the thermal response performance.[199] Yuan et al.[200] explored local administration to avoid the adverse effects of systemic

drug use in the treatment of osteomyelitis. Natural hydrogels are generally immunogenic; however, PEG hydrogels have high swelling rates. Thermal hydrogel-polymerized (D,L-lactide-*co*-ethyl ester)-poly (ethylene glycol)-poly (D,L-lactide-*co*-ethyl ester) (PLGA–PEG–PLGA) has attracted wide attention. The polymer usually exists in a liquid state at room temperature, where therapeutic drugs can be incorporated. If injected into the human body (37 °C), it will rapidly gel. Owing to the regulation of human temperature, the hydrogel loses water, transforms into a gel state, and accelerates the release of loaded drugs, ensuring precise drug delivery. Jiang and his team[201] invented a flexible and temperature-sensitive hydrogel dressing with real-time and remote detection capabilities. The dressing has anti-bacterial properties and temperature response characteristics; it can wirelessly transmit temperature changes to a smart device to monitor wound temperature, which helps in the early diagnosis of wound infection and in aiding wound repair (Fig. 7A).

5.3. Glucose responsive hydrogels

Diabetes affects chronic wounds and seriously affects the wound healing process. Therefore, real-time detection of blood glucose dynamics and timely self-regulation of insulin release are effective means for controlling blood glucose. Glucose-sensitive biomaterials consist of three sensitive elements: glucose oxidase (GOD), ConA (ConA), and phenylboric acid (PBA).[203] Phenylboric acid (PBA) has become a popular material for the glucose response owing to its excellent stability, good adaptability to the environment, and lack of an immune reaction. Zhao *et al.*[202] designed a
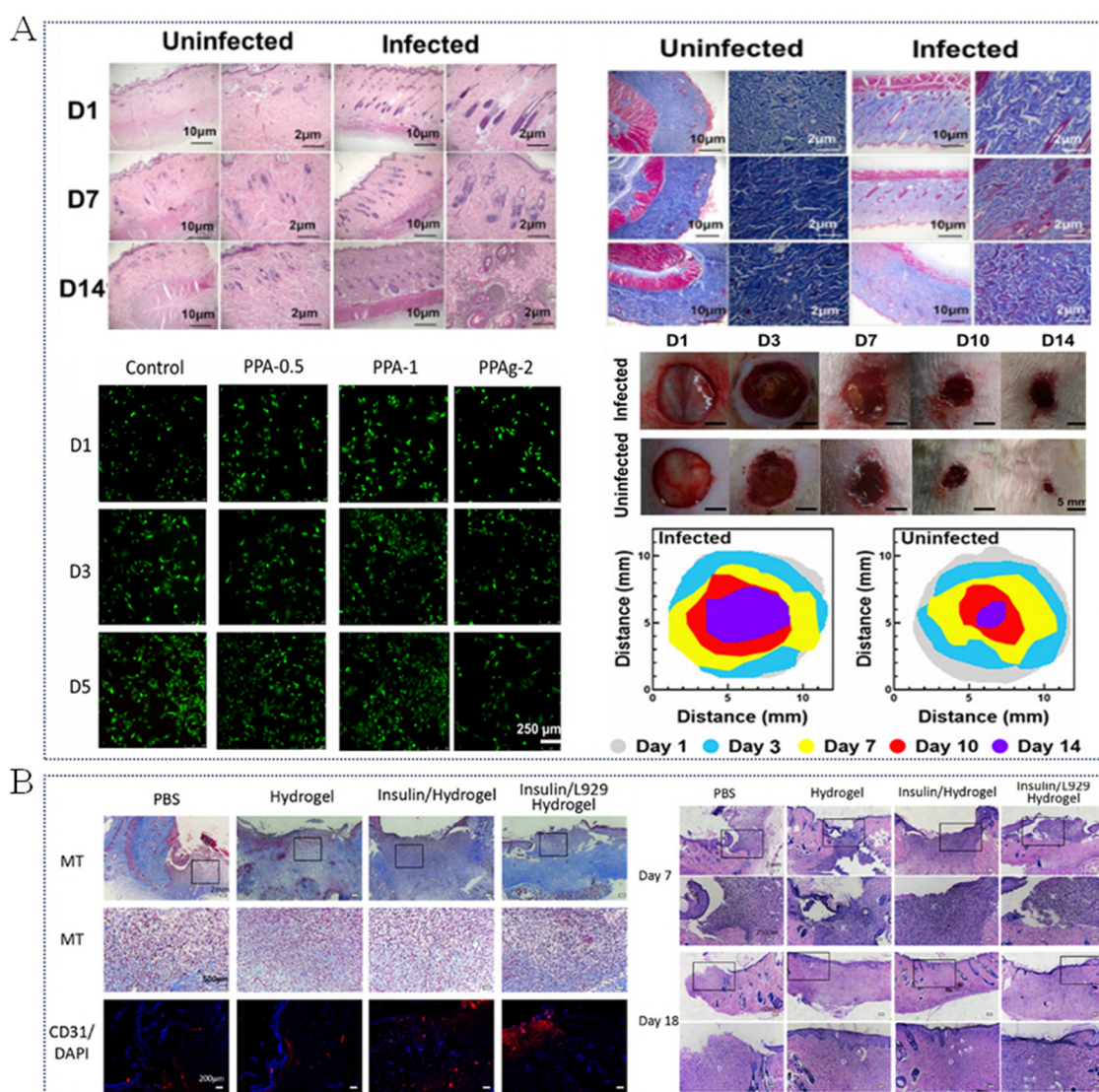

Fig. 7 Temperature-responsive composites effectively promote cell recovery and wound healing. (A) Application of the hydrogel increased cell viability, promoted well formation of granulation tissue, and effectively contracted the wound, all of which significantly benefited wound healing. Reproduced from ref. 201 with permission from Royal Society of Chemistry, copyright 2023. (B) After treatment with the hydrogel dressing, the number of inflammatory cells in the wound decreased dramatically, while neovascularization increased, both of which are important for wound healing. Reproduced from ref. 202 with permission from American Chemical Society, copyright 2017.

multifunctional hydrogel dressing with dual pH and glucose responses. Chitosan, polyvinyl alcohol, and benzyl alcohol were modified with phenylboric acid to seal the polyethylene glycol, and then the Schiff base and phenylborate were crosslinked to prepare a pH and glucose dual-response injection hydrogel. Protein drugs and cells can also be added to this hydrogel, and experiments have shown that the addition of insulin and L929 to the hydrogel can promote the formation of new blood vessels, collagen deposition, and the wound healing process in diabetic wounds (Fig. 7B).

5.4. ROS responsive hydrogels

ROS is produced during wound healing.[204] When the concentration of ROS in the wound is too high, wound inflammation is aggravated, the effect of endogenous stem cells and macrophages is inhibited, and the formation of blood vessels is inhibited,[205] thus affecting wound healing. Therefore, clearing or reducing ROS levels is a potential strategy for treating chronic wounds. Huang et al.[206] developed an ROS-scavenging hydrogel using polyvinyl glycol (PVA) to cross-link through ROS-responsive linkers; the hydrogel was composed of N1, N1, N3, N3, N3, N3, N3, and N3. The ROS response linder N1-(4-borobenzene)-N3-(4-borobenzene)-N1,N1,N3,N3-tetramethylpropane-1,3-diamine (TPA) was synthesized by the quaternization of N3-tetramethylpropane-1,3-diamine (TPA) with N3-tetramethylpropane-1,3-diamine and 4-(bromoethyl) phenylboric acid as raw materials. When the ROS reacts with the joint cracks, the administered hydrogel gradually degrades, releasing loaded mupirocin and GM-CSF to act on the wound. When PVA and TPA were mixed, ROS-responsive hydrogels with cross-linked phenylboric acid and alcohol hydroxyl groups were formed rapidly. With an increase in the hydrogen peroxide concentration at the wound site, the degradation of the hydrogels accelerated, indicating that the hydrogels had ROS-responsive ability (Fig. 8A). Furthermore, Kulkarni et al.[207] designed a multifunctional hydrogel that automatically activates the drug platform when ROS levels increase on the wound surface and couples ROS-reactive linkers for on-demand drug delivery. Using ROS-responsive thiooxaldehyde (Tk) linkers and the nucleobase thymine (Thy) coupled with CS, the dressing was placed on the wound, and the release of loaded drugs at high levels of ROS was studied. In addition to using ROS as a stimulus response factor, Wu et al.[208] also used pH as another stimulus response factor. They constructed a pH/ROS double response injectable glycopeptide hydrogel based on phenylboric acid grafted oxidative glucan and caffeic acid grafted ε-polylysine, which showed inherent antibacterial and antioxidant ability (Fig. 8B). It also had a positive effect on the treatment of chronic diabetic wounds. During the treatment process, many drugs and other organic pollutants resist natural degradation and biodegradation processes. The long-term presence of these substances can lead to endocrine disorders and genetic toxicity. Based on silver halide photocatalysts, under the promotion of light, they can guide the degradation of pollutants;[209,210] therefore, photocatalysis can be used as an effective alternative to water treatment method, ultimately converting into non-toxic CO_2 and water.[211,212]

5.5. Photoresponsive hydrogels

In addition to pH, glucose, temperature, and ROS, light is a response factor. Light, as an easily accessible and harmless external stimulus, has a wide range of abilities; therefore, researchers are interested in using light responses to achieve accurate drug delivery.

Photoresponsive hydrogels are clinical dressings based on the light response and are mainly fabricated by incorporating photosensitive materials (such as photosensitizers) into hydrogels and other materials. Drug release is generally achieved through three mechanisms: photoisomerization, photochemical reactions, and photothermal reactions.[213] For instance, in the study by Wei et al., a series of photo-induced Schiff base cross-linked adhesive hydrogels were prepared by using the Diels-Alder (DA) reaction between functional group grafted carboxymethyl chitosan (CMCS) and the photoresponsive polyethylene glycol (PEG) crosslinking agent. The quaternary ammonium groups and phenolic groups in the modified CMCS enabled the hydrogels to possess antibacterial and antioxidant properties. Through ultraviolet irradiation, the hydrogels exhibited good adhesion. Experimental results in mice demonstrated that this multifunctional hydrogel could be used as an effective dressing for improving wound healing.[214] In the management of chronic wounds, Li et al. considered the secondary damage caused to the wound by frequent dressing changes; they proposed a fully photonic hydrogel dressing. This hydrogel can achieve rapid and remotely controllable replacement of the dressing through light irradiation, and can also promote wound re-epithelialization and angiogenesis. It holds significant importance in the treatment of chronic wounds.[215] In addition to hydrogels as carriers of the photoresponse, scientists have found that many nanoparticles can also achieve photoresponse, solving the dilemma of relying solely on hydrogel materials and providing insight into the development of multi-response multifunctional dressings. Wound repair is a major clinical challenge and many factors affect the healing process.[216] Photosensitizer-based PDT mainly stimulates photosensitizers to produce ROS by irradiation with appropriate excitation sources, thus killing wound microorganisms and inhibiting their reproduction. In addition, it promotes wound re-epithelialization, angiogenesis, tissue remodeling, and other processes. Therefore, photodynamic therapy based on photosensitizer-based PDT plays an important role in wound sterilization and regeneration.

Cheng et al.[217] designed a photoresponsive multifunctional nanoparticle conjugated with quaternary ammonium chitosan and the photosensitizing agent chlorin e6 (Ce6) (Fig. 9A). This nanoparticle combined photodynamic therapy with chemotherapy to achieve an effective antibacterial effect, avoiding the problem of low efficiency of a single antibacterial agent. Molybdenum disulfide (MoS_2) nanomaterials are promising biomaterials that are photoresponsive to near infrared light. Carrow et al.[218] found that this 2D nanomaterial regulates human stem cells and plays a role in cell migration and wound healing. Therefore, this molybdenum disulfide nanomaterial combined with near-infrared wavelength treatment can be used for wound regeneration.To address the invasion of Staphylococcus aureus and Escherichia coli into the damaged skin and their adverse
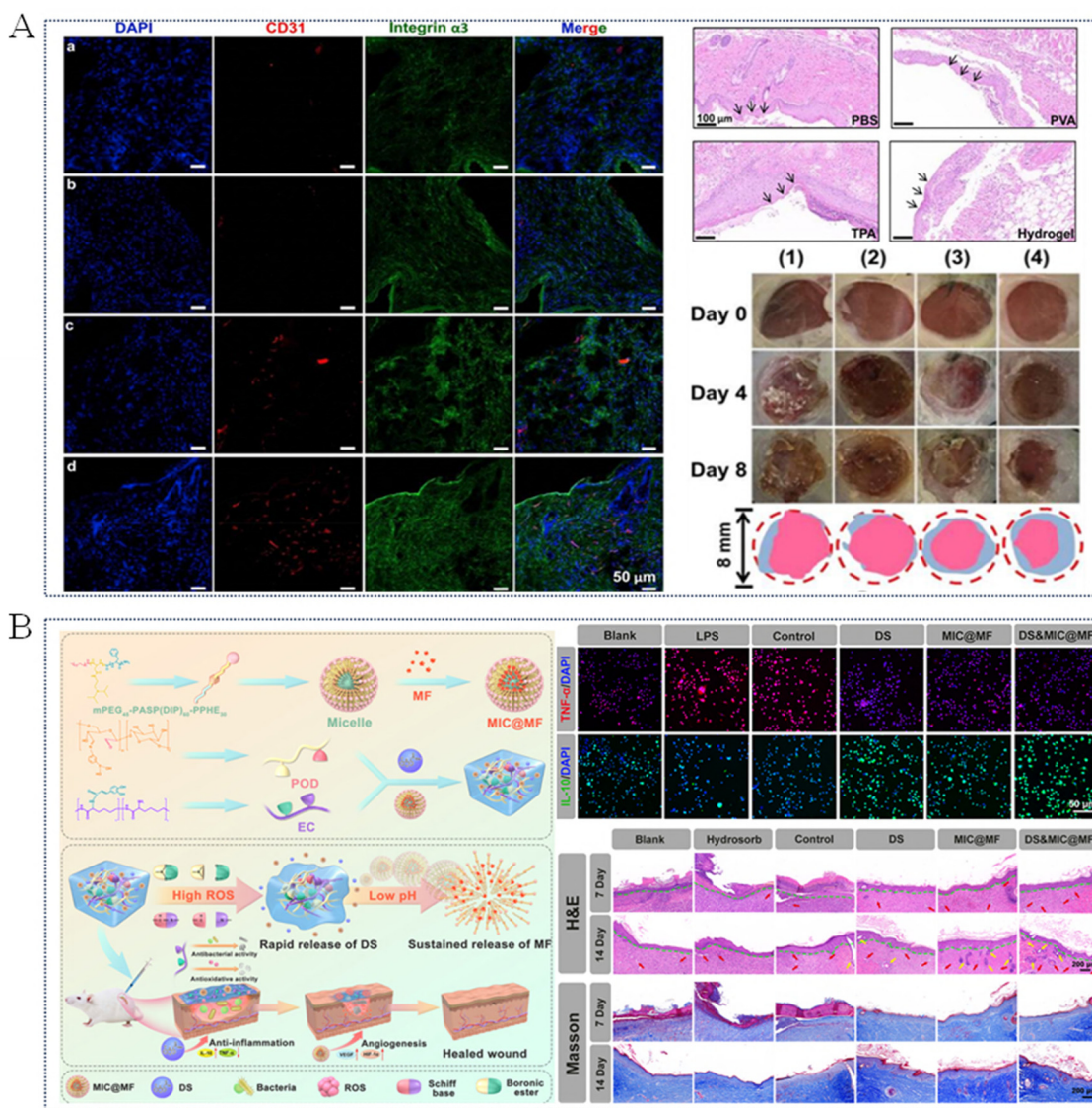
Fig. 8 Accurate drug release through the ROS response can achieve wound healing. (A) In the wounds treated with hydrogels, the regenerated wound tissue was thicker, there was neovascularization, and the S.a.u. accelerated wound healing *in vivo* under infections. Reproduced from ref. 206 with permission from Elsevier, copyright 2020. (B) Schematic diagram of DS&MIC@MF embedded POD/CE hydrogel fabrication, the drug release process and the mechanism of accelerated wound recovery. After the application of the DS&MIC@MF hydrogel, the expression of IL–10 was enhanced, which achieved the purpose of anti-inflammation. A large amount of granulation tissue was also observed in the wound. Reproduced from ref. 208 with permission from Elsevier, copyright 2021.

effects on wound healing, a multifunctional EGCG@ZIF-8 nano-platform was developed by Gu *et al.*[219] This platform combines epigallocatechin-3-gallate (EGCG) with zeolitic imidazolate framework-8 (ZIF-8), photodynamic therapy, and chemotherapy to achieve antibacterial synergies that also promote collagen fiber regeneration and accelerates wound healing (Fig. 9B).

6. Summary of the difficulties and limitations of integrated wound detection and treatment

Although many materials have excellent biocompatibility and degradability, some materials have shortcomings that are not

conducive to wound healing. For example, nanomaterials can promote wound healing and provide sufficient space for drug loading. These materials are ideal for designing wound dressings, and their application prospects and research potential are significant. However, in recent studies, nanomaterials have been found to cause allergic reactions in some patients when applied directly to the open wound.

Second, because they are small, nanomaterials may enter the blood circulation through broken blood vessels after contact with the wound surface. Some reports have shown that metal nanoparticles used to treat wounds can cause hemolysis in patients. Although nanomaterials have certain limitations, their role in wound healing should not be overlooked. Many researchers have applied nanomaterials to promote wound
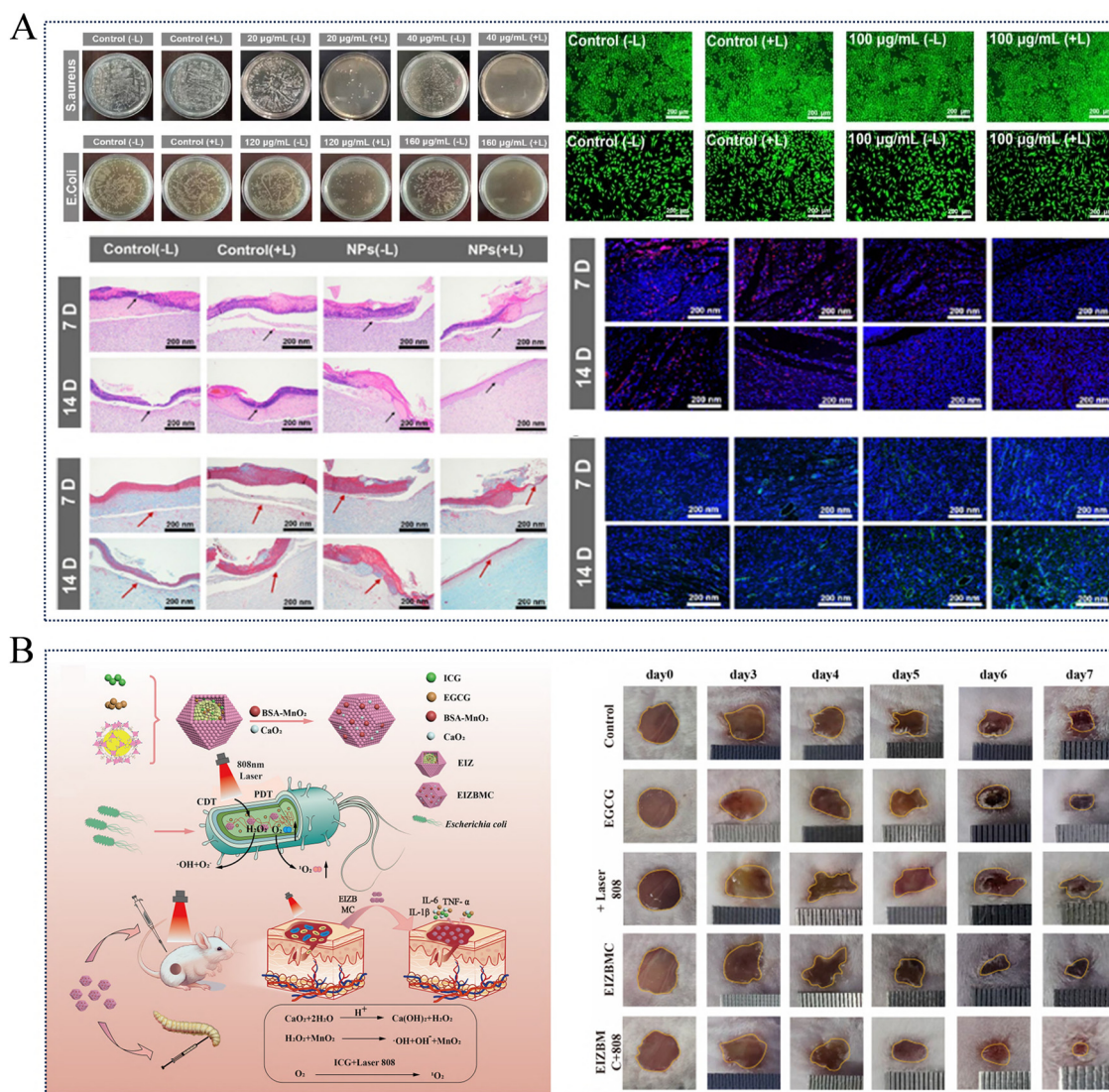
Fig. 9 Wound healing by accurate drug release *via* the light responsive mechanism. (A) NPs showed strong antibacterial activity under photodynamic therapy, and promoted continuous and orderly production of collagen fibers in the wound, facilitating reconstruction of blood vessels and further accelerated wound regeneration and healing. Reproduced from ref. 217 with permission from American Chemical Society, copyright 2019. (B) Mechanism of EIZBMC in combating bacterial infection and promoting wound healing. Treatment with the multifunctional nanoplatform resulted in faster wound healing compared with all other groups. Reproduced from ref. 219 with permission from American Chemical Society, copyright 2024.

healing, and their potential for promoting hair follicle growth and avoiding sensory loss is significant. Nanoparticles provide a platform for the combination of nanotechnology and electronic technology, and also provide a way to repair perceptual disturbances after wound injury. There are an increasing number of drugs and methods for wound treatment, and nanomaterials are widely used in wound treatment. However, knowledge of the mechanisms of wound healing using nanomaterials is limited and requires further examination.

Hydrogels are good materials for wound treatment. Many researchers have designed different materials that can be combined with hydrogels to prepare composite materials with improved effects. However, this process generally requires a large number of chemical crosslinking agents and chemically modified response molecules, which inevitably results in biological toxicity.

Degradability is also an important property of hydrogels. The degradation products of hydrogels should be non-toxic and harmless and be able to be metabolized normally in the body. Future studies should aim to develop multifunctional hydrogel dressings with low toxicity and biodegradability.

In wound treatment, excessive use of antibiotics or other drugs will eventually be excreted through the human urinary system into the surrounding environment. Moreover, many antibiotics are non-biodegradable and traditional biological and chemical treatments are ineffective.[220] Eventually, this will impose a certain burden on the environment.[221,222] Therefore, finding appropriate and harmless drug delivery systems is of great significance for reducing urban pollution. In recent studies, researchers have sought to develop drug delivery systems that can achieve pollutant degradation through various catalysts.

A coupled CuO–SnO$_2$ catalyst, under the action of photocatalysis, can degrade piperidine (PP) and reduce the impact of this drug on the aquatic world.[223] In clinical treatment, problems such as drug abuse still need to be addressed to reduce environmental damage.

Most of the current studies were conducted *in vitro*, and mouse models were often used. The wound healing process and skin conditions of rodents are different from those of humans, and it is difficult to obtain data consistent with human wound healing. Compared with that of rodents, the skin structure of pigs is similar to that of humans. However, owing to the high purchase cost and cumbersome maintenance of large animals, pig models have not been widely used in the experimental verification of wound healing. Additionally, many experiments lack standardization of wounds; therefore, the verification process must be improved.

7. Outlook

Previously, wound treatment mainly focused on the application of drugs to the affected area to accelerate healing. However, hydrogels have gained interest due to their histocompatibility, degradability, non-toxicity, and hydrophilicity. Hydrogels have been mainly used as drug delivery systems, and researchers have found that stimulus-responsive injectable hydrogels can be designed by chemical or physical cross-linking. The basic idea of the hydrogel is to sense changes in the wound environment (changes in pH, temperature, glucose, and active oxygen levels) and release the drug into the wound in a certain period of time based on such changes. In addition to hydrogels, composite wound dressings involving nanomaterials have shown potential in wound healing and cancer treatment. Nowadays, cancer has become one of the major diseases threatening human life. Anti-cancer drugs are the main treatment methods for cancer, but the side effects, drug resistance, and dosage effects of anti-cancer drugs are important factors in clinical research.[224] In recent years, researchers have discovered that platinum-based drugs (Pt) can effectively solve the problem of tumor resistance when they exist in the form of metal complexes. By combining MOFs with high porosity to Pt, they can target and kill tumor cells' mitochondria to achieve the goal of eradicating drug-resistant cancer.[225] Nanoparticles are widely used in cancer treatment. Tamoxifen (TAM) is an effective drug for preventing and treating breast cancer.[226] When it is at a lower dose, it can reduce the side effects on other body organs. Researchers found that the complex has a high drug loading capacity, a long release time, good permeability to breast cancer cells, and can be used as an important method for treating cancer.[227]

Traditionally, the pursuit of material biocompatibility is "inert", meaning to minimize host reactions as much as possible. However, such materials impose certain limitations on research. In the future, we should not aim for complete non-reaction but instead guide the host reaction towards a beneficial and controllable direction. This enables the material to respond promptly to environmental changes, such as releasing antibacterial agents during infection or rapidly degrading in the later stage of wound healing, which is beneficial for protecting the environment. Secondly, regarding the mutual influence of various detection indicators during the wound detection process, such as temperature, pH, glucose levels, and biomarkers, for example, local temperature and pH changes in the infected area make it difficult to determine the condition of the wound. In the future, distinguishing and accurately judging various interfering signals is the key to implementing precise detection. By combining multiple technologies with different materials, a more perfect wound assessment system can be constructed. For instance, through artificial intelligence, integrating massive data for dynamic detection and wound infection warning, it can assist in clinical medication. To reduce the final clinical treatment cost, researchers are constantly seeking high-performance and low-cost materials through technological innovation. Many scientists have improved treatment efficiency by developing new composite materials and reducing the frequency of dressing changes to indirectly reduce costs. Secondly, natural materials with relatively wide sources, such as chitosan and silk fibroin, can also be developed. During the manufacturer's production process, optimizing production processes and improving production efficiency are the key to breaking through the bottleneck of large-scale production. In the future, automated and more intelligent production lines can be introduced, and key parameters in the production process can be monitored in real time through the network to ensure the stability of product quality and, to a certain extent, control costs.

In addition to environmental response factors such as temperature, pH and glucose, which can be used as indicators for wound detection, many potential biomarkers can be used for trauma detection (such as procalcitonin and C-reactive protein). Furthermore, research to develop an integrated platform for trauma detection and treatment, which can provide signals for the precise treatment and healing of wounds, needs to be expanded. The wound-related information derived from such integrated platforms can be transmitted to clinicians to improve diagnosis. Additionally, an integrated platform for trauma testing and treatment can provide bedside testing, which is convenient for emergency and intensive care scenarios that require rapid testing. This would help reduce the patients' pain and improve resource utilization.

Author contributions

Weiwei Yang (first author): conceptualization, visualization, writing – original draft, and writing – review and editing. Ning Liang: conceptualization, writing – review and editing, and supervision. Lan Liu: writing – original draft and writing – review and editing. Zhaojun Jian: writing – review and editing and supervision. Jiani Kong: conceptualization and writing – review and editing. Weifang Liao (corresponding author): conceptualization, supervision and funding acquisition.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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