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REVIEW

Functional Hydrogels as Wound Dressing to Enhance Wound Healing

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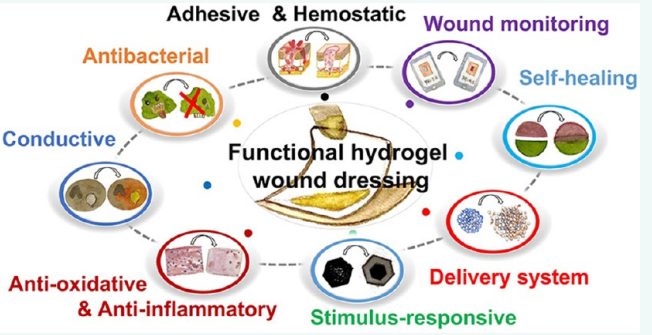
ABSTRACT: Hydrogels, due to their excellent biochemical and mechnical property, have shown attractive advantages in the field of wound dressings. However, a comprehensive review of the functional hydrogel as a wound dressing is still lacking. This work first summarizes the skin wound healing process and relates evaluation parameters and then reviews the advanced functions of hydrogel dressings such as antimicrobial property, adhesion and hemostasis, anti-inflammatory and anti-oxidation, substance delivery, self-healing, stimulus response, conductivity, and the recently emerged wound monitoring feature, and the strategies adopted to achieve these functions are all classified and discussed. Furthermore, applications of hydrogel wound dressing for the treatment of different types of wounds such as incisional wound and the excisional wound are summarized. Chronic wounds are also mentioned, and the focus of attention on infected wounds, burn wounds, and diabetic wounds is discussed. Finally, the future directions of hydrogel wound dressings for wound healing are further proposed.



KEYWORDS: *multifunctional hydrogel, bioactive wound dressing, wound healing, tissue engineering, bioactive biomaterials, wound regeneration, skin repair, wound closure, collagen deposition*

The skin is a very important organ that covers the surface of the human body and directly contacts the external environment, and it has the effects of feeling external stimuli and regulating body temperature, protecting the human body from external damage.[1−3] Due to the characteristics of direct contact with the outside world, the skin has also become one of the most vulnerable tissues. Although most of the common injuries of skin can be basically restored to their original appearance within a period, it is difficult for adult skin damage to restore 100% of skin functions like babies.[4,5] This is often accompanied by the formation of scar tissue and the critical absence of skin appendages such as hair, sweat glands, and sebaceous glands.[6] The repair of skin wounds is divided into four continuous and coordinated processes, including hemostasis, inflammation, proliferation, and remodeling.[5,7] However, the process of wound healing generally cannot be followed perfectly and orderly. The impact of various factors at any stage may cause abnormal wound repair,[8] such as excessive inflammation,[9] burns,[10] or an accident caused by large area skin tissue loss,[11] infection,[12] diabetes,[13] and others.

Wound dressings can cover the wound and provide a temporary barrier against external infections[14] and serves as an induction template to guide the reorganization of skin cells and subsequent infiltration and integration of host tissues, showing a significant effect on wound healing. An ideal skin wound dressing needs to meet the following requirements: (1) good tissue compatibility, without causing toxicity or inflammation; (2) good moisture retention, which can maintain the moist environment of the wound and promote cell hydration and have certain absorption for wound exudate; (3) sufficient physical and mechanical strength to ensure its integrity and avoid the intrusion of external bacteria caused by materials' breakage; and (4) appropriate surface microstructure and biochemical properties to promote cell adhesion, proliferation, and differentiation.[15] Many wound dressings have been developed to promote wound repairs, such as semipermeable membranes, semipermeable foams, hydrocolloids, and hydrogels.[16,17] Among them, hydrogels have become the most competitive candidates for wound dressings due to their good hydrophilicity, biocompatibility, and three-dimensional (3D) porous structure like extracellular matrix (ECM), and it also has aroused the

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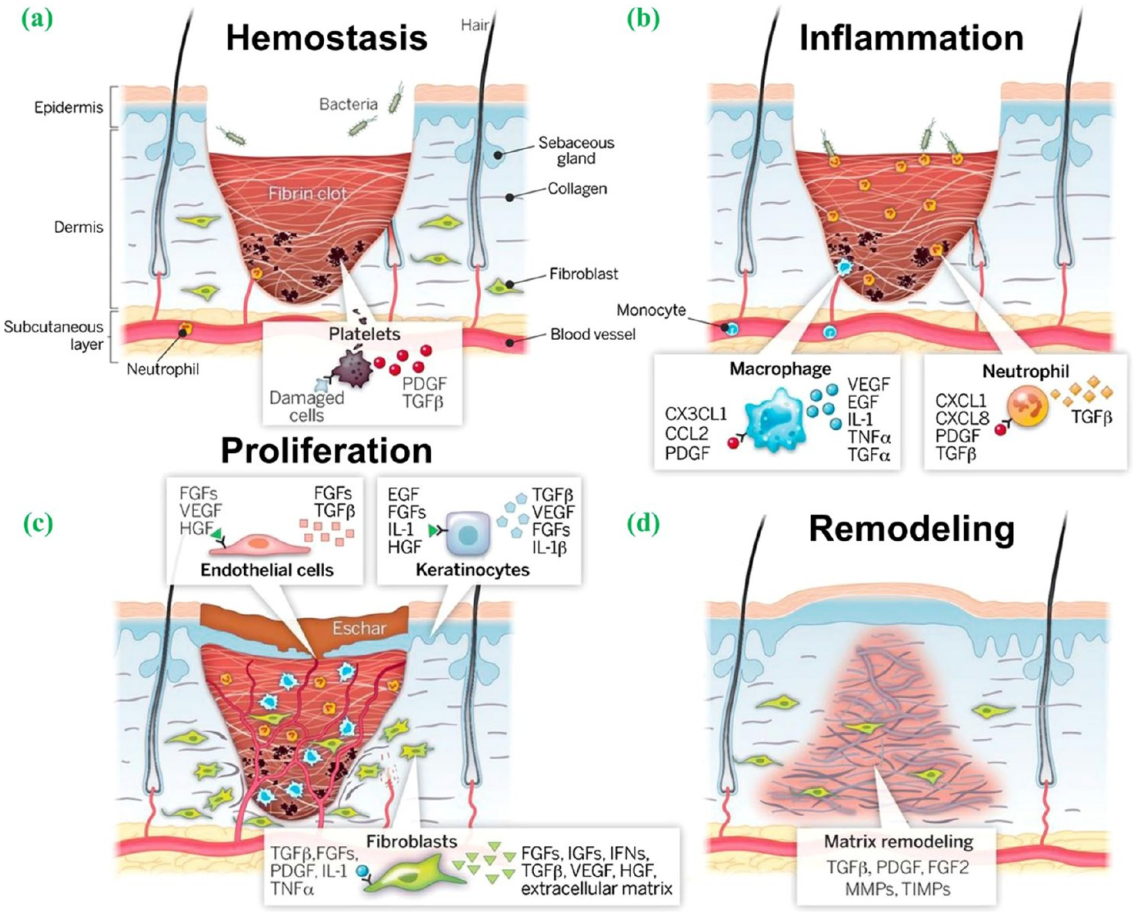

Figure 1. Four stages in wound healing: (a) hemostasis, (b) inflammation, (c) proliferation, and (d) remodeling. Reprinted with permission from ref 20. Copyright 2018 Elsevier.

interest of many researchers.[18] The research on hydrogels as wound dressings also shows a trend of increasing especially in the past decade. Many hydrophilic polymers, including natural ones such as chitosan,[19] gelatin, hyaluronic acid, alginate, and dextran as well as synthetic hydrophilic polymers such as poly(ethylene glycol) (PEG) and poloxamer, poly(vinyl alcohol), olefin-containing polymerized monomers such as polyacrylamide (PAM), poly(acrylic acid), and polypeptides have been used to construct hydrogels through various chemical or physical cross-links.[20,21] Among them, dynamic chemical bonding, photo-cross-linking *in situ* polymerization, dual network, semi-interpenetrating network, and 3D printing all show good advantages.[22] In addition, the function of hydrogel has also changed from a single physical coverage or a single function to a combination of multiple functions now and shows a trend toward further intelligence. However, a comprehensive review of the functional hydrogel as wound dressing still has not been reported.

In this review, the process of skin wound healing and parameters to evaluate the process are first discussed. Second, the advanced functions of hydrogel dressings including antimicrobial activity, adhesion and hemostasis, anti-inflammatory and anti-oxidation, substance delivery, self-healing, stimulus response, conductivity, and wound monitoring feature are all classified and discussed. Third, the applications of these functional hydrogel wound dressings in various wounds, such as incisional wound and excisional wound as well as chronic wounds like infection, burn, and diabetic wounds, are elaborated. Finally, the future development trends are also further prospected.

THE PROCESS OF SKIN REPAIR AND EVALUATION PARAMETERS

Before discussing the process of skin repair, we must understand the structure of normal skin at first. It involves the physiological structure of the skin, which is usually divided into an epidermal layer and a dermal layer. The epidermal layer directly relates to the outside world, mainly including the keratinocyte layer and the germinal layer, which can prevent the outflow of tissue fluid, antifriction, and anti-infection. Therefore, the reconstruction of the integrity of the epidermal layer is critical to the repair of skin tissue, and it is generally possible. The dermis layer is composed of dense connective tissue, and from shallow to deep is the papillary layer and the reticular layer, respectively. The papillary layer is rich in capillaries, lymphatic vessels, nerve endings, and tactile corpuscles, and other receptors. The reticular layer enriches in collagen fibers, elastic fibers, and reticular fibers, which mainly provide mechanical strength to the skin.[23]

The regeneration of wounds is divided into four continuous processes, that is, hemostasis, inflammation, proliferation, and remodeling[7] (Figure 1). Almost within a few minutes after trauma, platelet aggregation and fibrin clot formation will produce a hemostatic effect, and the process of wound healing is rapidly transferred into the inflammatory stage. At this stage, inflammatory cells such as neutrophils (a kind of white blood cell) and monocytes are recruited to the wound site and

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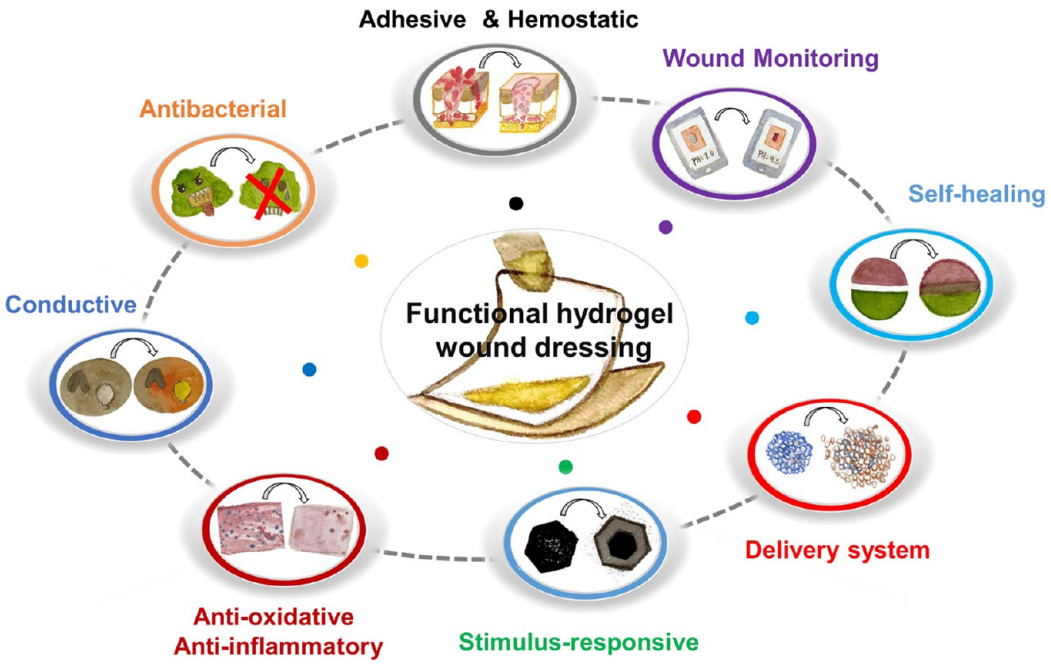

Figure 2. Advanced functions appeared in hydrogel wound dressing.

differentiate into macrophages.[24] The resulting inflammatory response can not only remove foreign bodies, bacteria, and damaged endogenous tissues but also secrete chemokines and growth factors (GFs) to further attract cells. The number of neutrophils usually reaches a peak within 24 to 48 h after injury and decreases significantly after 3 days. As white blood cells leave, macrophages continue to clear debris and secrete GFs and proteins, attracting immune system cells to the wound to promote tissue repair,[25] thereby guiding the healing process into the proliferation phase. In the proliferation phase (within 2 to 3 days after the wound generated), fibroblasts and keratinocytes at the wound surface generate some light pink tissue to fill the defect, which is called granulation tissue because its shape is similar to granulation. The granulation tissue mainly contains inflammatory cells, fibroblasts, and some new capillaries. Simultaneously with the formation of granulation tissue, the basal cells around the defected tissue continue to proliferate and migrate to the wound surface to form new epithelial cells. When the whole wound was covered with the epithelial cells, it marked the completion of re-epithelialization, while the scar epithelium will be formed if the epithelialization is completed after the granulation tissue completely fills the defect. On the other hand, collagen will be deposited because the production of collagen (mainly type III collagen) at the wound site is higher than the decomposition. Meanwhile, the endothelial cells of the vascular wall break through the basement membrane to split into vascular buds and further develop into microvessels or capillaries, which exist in the granulation tissue. Subsequently, the wound repair process turns to the final remodeling stage, collagen production and decomposition gradually tend to balance, and gradually changes from type III collagen to type I collagen. The arrangement of collagen also tends to be more consistent, resulting in increased strength of the new tissue. The number of capillaries also reduced, and a few capillaries are converted into small arteries and veins. Some skin appendages such as hair, sweat glands, and sebaceous glands may regenerate. The previously formed matrix slowly shifts toward the formation of functional skin or semi/nonfunctional scar tissue.

Given the complexity of the wound healing process and the number of cells and cytokines involved, there are many factors affecting wound healing. Therefore, evaluation parameters in wound healing are also numerous. At first, the wound closure rate is the most intuitive parameter to show the speed of wound healing.

In the inflammatory stage, appropriate inflammation is conducive to the recruitment of inflammatory cells.[26] There are also some studies to further confirm the anti-inflammatory properties of hydrogel dressings in promoting wound healing through some inflammation-related cytokines such as TNF-α,[27−30] TGF-β, IL-1,[27] IL-6,[31,32] and CD 68.[33]

The formation of granulation tissue is also used as an indicator to evaluate wound healing. Most literature believes that thicker granulation tissue will transport more nutrients and build a larger volume frame for subsequent repair,[34−37] but some reports state that the thicker granulation tissue shows the precursor of partial scar healing. However, granulation tissue changes dynamically during wound healing, and different thicknesses may exist at different times, so proper thickening should be beneficial, but excessive thickening may lead to poor healing.

Since the completion of re-epithelialization means that wound healing enters the next stage, the remodeling phase, it is also a particularly important indicator in the healing process. A large number of studies have revealed that the hydrogel dressing achieves a better healing effect by promoting re-epithelialization.[34,38,39] Some cytokines such as epidermal growth factor (EGF) are also used to further evaluate epidermal production.[28]

The metabolism of collagen participates in the whole process of wound repair and the regenerated collagen constitutes an important part of the repaired wound, so its importance is obvious. On the other hand, the strength of the repaired tissue mainly depends on the orientation of the regenerated collagen. Therefore, a large number of reports suggest that more collagen deposition[35,40−42] during the proliferative phase, and a more consistent collagen trend[43] in the remodeling phase indicates better wound healing efficiency.

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Table 1. Functional Classification of Hydrogel Wound Dressings

function		functional components
antibacterial property	antibiotics and other antibacterial drugs	amoxicillin,[30,51] ampicillin,[52,276,277] tetracycline,[53−55,278−280] doxycycline,[35,56,57] gentamicin,[58,59,281−283] neomycin,[284] ciprofloxacin,[60−62] moxifloxacin,[63,64] chloramphenicol,[65] sulfadiazine,[66] linezolid,[67] povidone-iodine,[68,285] chlorhexidine acetate,[42,69,70] triclosan,[71] simvastatin,[72] salicylate[73]
	inorganic metals and metal oxides	Ag,[92−101] Au,[80,81] zinc,[82−86,104] copper,[87−89] Ag/curcumin,[102] Ag/graphene,[103] Ag/sulfadiazine,[66] Ag/Au,[81] Ag/zinc,[85] Ag/iron,[84] ZnO/CS,[86] Zn-penicillin,[52] ZnO/mesoporous silica,[53] ZnO/GO,[83] CuS/CuO,[105] Cu/metal organic framework,[88] CuS/mesoporous silicon[88]
	photothermal antibacterial	CNTs,[57,107] GO,[35,49,108] PDA,[60] grape seed extract,[45] cypate[106]
	photodynamic antibacterial	MoS_2,[111] g-C_3N_4@AuNPs,[110] Fe_3O_4@MoS_2-Ag,[112] tannic acid/Ag,[116] selenoviologen/polythiophene[286]
	cationic polymer	CS/gelatin,[118] CS/konjac glucomannan,[119] CS/lignin/PVA,[120] CS/PVP/agar,[121] CS/carbon dots,[122] CS/PF127,[123] CS/PEG,[125] poly(aminoethyl),[127] antimicrobial peptides[106,128−131]
adhesion	cationic polymer	CS,[50,119,137] quaternized CS,[36,125] EPL[138]
	aldehyde group	oxidized dextran,[137] aldehyde-terminated PF-127[50] and PEG[139]
	polymers containing carboxyl groups	SA,[136] *N*-acryloyl 2-glycine,[150] HA[147]
	polyphenol	dopamine,[35,49,57,74,143,144,104,148,149] 3,4-dihydroxybenzaldehyde,[144] dihydrocaffeic acid,[51] pyrogallol[147]
	others	sulfydryl,[140] long-chain alkyl groups,[124,137,141] gum arabic,[58,151] hydrogen bonding[287]
hemostasis	cationic polymer	CS,[86,152] cationic polypeptides,[132] quaternization CS,[155] quaternized hydroxyethyl cellulose/mesoporous silicon foam[153]
	anion	SA,[136] hyaluronic acid,[288] montmorillonite[289]
	metal	Ca^{2+},[159] Fe_2O_3,[290] ZnO,[291] Ag NPs[292]
	silicon-based materials	zeolite,[293] mesoporous silicon foam,[153] montmorillonite,[289] kaolinite[290]
antioxidant, anti-inflamm-atory	natural polyphenols	tea polyphenols,[161] resveratrol,[162] anthocyanins,[163] flavonoids[164]
	curcumin	curcumin/2-hydroxypropyl-γ-cyclodextrin,[175] nanocurcumin,[176] curcumin NPs/gelatin microspheres,[177] curcumin/PF127 micelles[50]
	DA	gelatin-DA/CS/CNT,[57] HA-DA/GO,[35] gallic acid[43]
	others	honey,[165] aloe vera,[166,167] acacia gum,[168] sericin,[169,170] ferulic acid,[38] quercetin,[171] bletilla striata polysaccharide,[28,172] astragaloside IV,[173] *Hippophae rahmnoides* L. extract,[174] Polyaniline,[36] aniline tetramer,[30] SOD,[179] prostaglandin E2,[26] thrombin-derived peptide TCP-25,[131] citrate,[89] povidone-iodine[180]
controlled delivery	cells	ADSCs,[147,167,183−186] BMSCs,[187−190] umbilical cord mesenchymal stem cells,[27] L929 fibroblast,[191] keratinocytes/fibroblasts,[192−194] endothelial progenitor cells,[195,196] human microvascular endothelial cells[48]
	cytokines	FGF,[32,198−202] FGF-2,[37,204,205] FGF/EGF,[203] EGF,[39,67,206,207] EGF/VEGF,[208] VEGF,[124,147,162] KGF,[210] platelet-derived GF BB,[90] interleukin-8/macrophage inflammatory protein-3α,[211] SDF-1,[212] rhGM-CSF[213]
	gas	NO,[44,214−216] O_2[217−219]
	others	miR-223-microRNAs,[31] feather keratin,[220] neurotensin,[221] laminin mimetic peptide SIKVAV,[41] boron,[223] proline hydroxylase inhibitor[224]
self-healing	hydrogen bond	tannic acid,[230] COOH[294]
	Schiff base	carboxymethyl CS/oxidized cellulose nanocrystal,[236] hydrazide-modified HA/benzaldehyde terminated F127,[237] quaternized CS/benzaldehyde-terminated PF127[50]
	metal coordination	phosphate/Ag,[238] Ag-SH coordination,[77] Fe^{3+}/COOH,[90] Fe^{3+}/DA[29,295]
	host−guest interaction	tripeptide Phe-Gly-Gly ester derivative (FGG-EA)/cucurbit[8]uril,[232] cyclodextrin/amantadine,[234] cyclodextrin/silk fibroin[235]
	others	electrostatic interaction,[231] acylhydrazone bonds,[42] phenylboronate ester,[191] dopamine[35,74]
stimulus response	thermoresponse	NIPAM,[32,61,89,189,190,204,212,240] NIPAM/Ag@rGO,[79] PEG-PCL-PEG,[243,244] PLGA-PEG-PLGA,[245] PEG-PLGA-PEG,[246] PF127,[50,80,177,202,210] polyisocyanopeptide,[247] ethylcellulose,[95] hydroxybutyl CS[67]
	pH response	tannic acid/metal ions,[251,252] schiff base,[191,253] electrostatic interaction, hydrogen bonds and π−π stacking,[106] carboxyl/metal ions[133,254]
	photoresponse	photothermal and photodynamics antibacterial, GO/malachite green carbinol base[255]
	multiresponse	PDA/glycol chitosan (photo/thermoresponse),[60] PDA/cellulose (photo/pH-response),[55] Schiff base/phenylboronate ester (pH/glucose response)[191]
conductivity	organic polymer	polyaniline,[36] aniline tetramer,[30,269] polypyrrole,[270,296] polythiophene,[271] Ag/polyaniline[74]
	inorganic nanomaterials	CNT,[57,107] GO[35,108,178]
wound monitoring		pH responsive color-changing mesoporous resin beads (pH monitoring),[272] temperature sensor (infection diagnosis),[273,274] phenol red/glucose oxidas/horseradish peroxidase (pH/glucose monitoring)[275]

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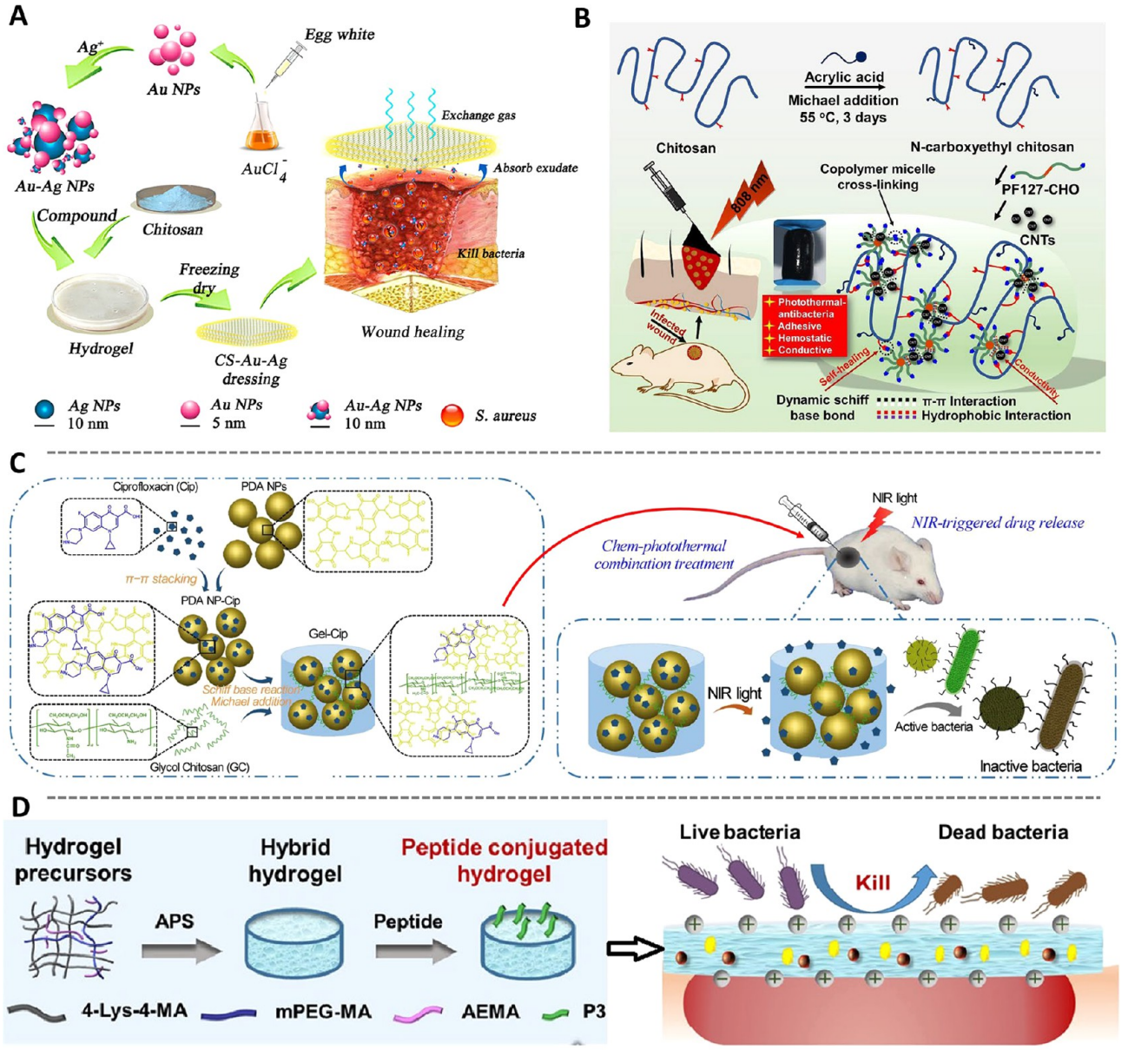

Figure 3. Antibacterial hydrogel in wound healing application. (A) Ag-Au NPs composite chitosan-based hydrogel for bacteria-infected wound repair. Reprinted with permission from ref 81. Copyright 2017 American Chemical Society. (B) A conductive self-healing adhesive nanocomposite hydrogel dressing based on Schiff base of *N*-carboxyethyl chitosan and PF127 and CNTs was encapsulated for photothermal antibacterial. Reprinted with permission from ref 107. Copyright 2020 Elsevier. (C) A hydrogel dressing containing PDA nanoparticles loaded with ciprofloxacin not only exerts near-infrared-induced photothermal effect of PDA but also realizes the synergistic antibacterial effect by photothermal response release of drugs. Reprinted and modified with permission from ref 60. Copyright 2019 Elsevier. (D) Cationic short peptides-functionalized amino acid-derived pseudoprotein-based hydrogel for antibacterial wound repair. Reprinted and modified with permission from ref 132. Copyright 2019 American Chemical Society.

The regeneration of blood vessels mainly involves the proliferation and remodeling stage of wound healing. When granulation tissue is produced, the microvessels or capillaries present in it were responsible for transporting oxygen and nutrients to the wound site. On the other hand, local blood supply also plays an important role in the absorption of necrotic substances and the control of local infection. It can be stated that the regeneration of blood vessels is essential for wound healing. Among most wound healing research, blood vessel regeneration is mentioned.[26,44−47] There are also some studies to further confirm the properties of materials to promote angiogenesis through some cytokines related to angiogenesis such as vascular endothelial growth factor (VEGF)[48−50] and CD31.[29,30,33]

Besides, perfect wound healing often involves the regeneration of some dermal appendages during the remodeling phase. In addition to blood vessels, the regeneration of hair follicles is also an indicator of better repair.[27,43]

ADVANCED FUNCTIONS IN HYDROGEL WOUND DRESSINGS

As a wound dressing, hydrogels initially only play a role of simple physical isolation and creating a moist environment, but with the increasing clinical requirements for wound repair, more and more requirements for material performance were proposed, and with the deepening of basic research, more hydrogel

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dressings with enhanced single/multiple biological functions are beginning to appear (Figure 2). In this section, we discuss the recent advances in hydrogel wound dressings from the perspective of functional modification, and the related content is summarized in Table 1.

Antibacterial Hydrogel Wound Dressing. Bacterial infections are the most common and inevitable challenge to wound healing. When a wound becomes infected, the bacteria may cause a continuous inflammatory response in the infected site, which will further delay the healing process during the inflammatory phase. For severe inflammation, it often leads to unsuccessful wound healing and can even result in complications, including sepsis. Although antibiotics can be used clinically to achieve good infection control, the problem of bacterial resistance is becoming increasingly serious. Therefore, the search for better antibacterial strategies has become a topic of great concern. Thus, the following section will focus on describing the research progress of various antibacterial hydrogel dressings on wound healing by category.

So far, antimicrobial drugs remain the preferred strategy for clinical treatment of infected wound, and a large number of drugs have been reported to be encapsulated into hydrogels for preparing antimicrobial wound dressing, including antibiotics like amoxicillin,[30,51] ampicillin,[52] tetracycline,[53−55] doxycycline,[35,56,57] gentamicin,[58,59] ciprofloxacin,[60−62] moxifloxacin,[63,64] chloramphenicol,[65] sulfadiazine,[66] linezolid[67] and some other antibacterial drugs such as povidone-iodine,[68] chlorhexidine acetate,[42,69,70] triclosan,[71] simvastatin,[72] and salicylate.[73]

Inorganic metal NPs, including silver (Ag),[74−79] gold,[80,81] zinc,[82−86] copper,[87−89] and other metal-containing NPs,[90,91] have been widely explored for potential antibacterial applications. Although some of the biotoxicity problems associated with the use of metal as biomaterials and some of the potential risks of long-term retention have not been addressed, it still cannot stop them from being one of the most used antimicrobials agents except for antibiotics. Ag has been known for many years to be a useful antimicrobial agent with broad-spectrum activity and compatibility with mammalian tissues, and numerous proposals have been made to incorporate Ag into wound dressings to obtain bactericidal properties. Early Ag wound dressings were mostly physical coating hydrogel systems of silver nanoparticle (Ag NPs), which was based on a range of natural or synthetic polymers such as chitosan (CS),[92,93] gelatin,[94] cellulose,[95] xylitol,[96] κ-carrageenan,[97] poly(vinyl alcohol) (PVA),[98] poly(vinyl pyrrolidone) (PVP),[99] PAM,[100] and 2-acrylamide-2-methylpropanesulfonic acid sodium salt,[101] and others. In addition to exerting antibacterial properties alone, Ag is also used in combination/synergy with various substances such as curcumin,[102] graphene,[103] sulfadiazine,[66] and other metal such as gold,[81] zinc,[85] or iron[84] to achieve better antibacterial effects. For example, Li *et al.* prepared a CS-based hydrogel encapsulated with Ag−Au composite NPs, showing good antibacterial activity (Figure 3A).[81] After Ag, zinc is the most widely studied metal particle used in antibacterial wound dressings. Kumar *et al.*, respectively, applied zinc oxide in CS and chitin to obtain a series of freeze-dried hydrogels with antibacterial properties.[86,104] Then, Ag/Ag@AgCl/ZnO hybrid nanostructures,[85] Zn-penicillin complex, ($[Zn(pin−G)(Cl)]\cdot 6H_2O$),[52] zinc oxide impregnated mesoporous silica (ZnO-MCM-41),[53] and zinc oxide quantum dots (ZnO QDs)-modified thin-layer graphene oxide (GO)[83] have all been extensively studied and demonstrated to have good antibacterial properties. Besides, some other metallic elements are also used in wound dressings as antimicrobial ingredients. Copper sulfate and copper oxide[105] have been shown to promote healing in healthy and diabetic BALB/c mice.[89] But at the same time, the toxicity level of copper ions is class 3 (moderately toxic), so some methods were developed to reduce the potential toxicity of copper ions, such as compounded copper into metal organic framework nanoparticles (HKUST-1 NPs) or use mesoporous silicon dioxide to modify CuS nanoparticles.[88]

The resistance of antibiotics and the biological toxicity or the potential for long-term retention of inorganic metal antimicrobials has prompted researchers to try to find better antimicrobial strategies. Photothermal therapy is a therapeutic method by converting light energy into heat. The common materials that can possess photothermal ability mainly include metal materials such as gold, Ag, tungsten, and copper[87,88] as well as carbon-based materials such as carbon nanotubes (CNTs) and GO.[35,49] Besides, photothermal agents such as polydopamine (PDA),[60] grape seed extract,[45] and cypate[106] have also been reported recently. Our research group has prepared a series of multifunctional hydrogels with photothermal antibacterial activity based on CNTs,[57,107] and GO,[35,108] respectively. And it is worth noting that the hydrogels in both systems also contain the photothermal component PDA. As shown in Figure 3B, we developed a multifunctional nanocomposite hydrogel with good photothermal antibacterial properties based on *N*-carboxyethyl chitosan (CEC), benzaldehyde-terminated Pluronic F-127 (PF127-CHO) and CNTs, which has been proved to have great potential as photothermal therapy for infected wounds through *in vivo* animal tests.[107] Furthermore, Gao *et al.* recently developed a strategy that combines near-infrared (NIR) light-induced antibiotic release with photothermal effects (Figure 3C).[60] In addition, by mimicking the way in which biological enzymes (such as peroxidase, oxidase) generate ROS to achieve sterilization, while avoiding the disadvantages of high cost and complex conditions in production and poor catalytic stability of biological enzymes, nanozymes have become promising alternatives to fight against bacteria. Metal-based compounds,[109] carbon-based nanomaterials,[110] transition-metal dichalcogenides/peroxides/oxides,[111,112] single-atom nanozymes (SAzymes),[113] and metal−organic frameworks (MOFs)-based compounds[114] have been widely developed.[115] Some of them have been applied to skin wound repair. For example, hydrogels containing MoS_2 nanoenzymes have been shown to convert H_2O_2 into ·OH with higher bactericidal efficiency, which can realize antibacterial and repair of infected wounds.[111] Besides, in addition to generating hydroxyl radicals, Au nanoparticles integrated ultrathin graphitic carbon nitride (g-C3N4@AuNPs),[110] Fe_3O_4@MoS_2-Ag,[112] tannic acid chelated Ag nanoparticles (TA-Ag NP),[116] and others also exert long-term antibacterial activity due to the release of Au, Ag and other particles. However, PDT and nanozymes antibacterials also have some problems such as low catalytic activity, limited specificity, and long clinical conversion time.

Some cationic substances have also been shown to have antibacterial activity, because the positive charges among them easily attract bacteria with surface negative charge and then kill it by damaging bacterial cell membrane.[117] As the only natural cationic polysaccharide, CS has been used to combine with gelatin,[118] konjac glucomannan,[119] lignin/PVA,[120] PVP/agar,[121] carbon dots,[122] PF127,[123] four-armed benzaldehyde-terminated PEG,[124] and other natural or synthetic polymers as antimicrobial excipients. There are also some methods to

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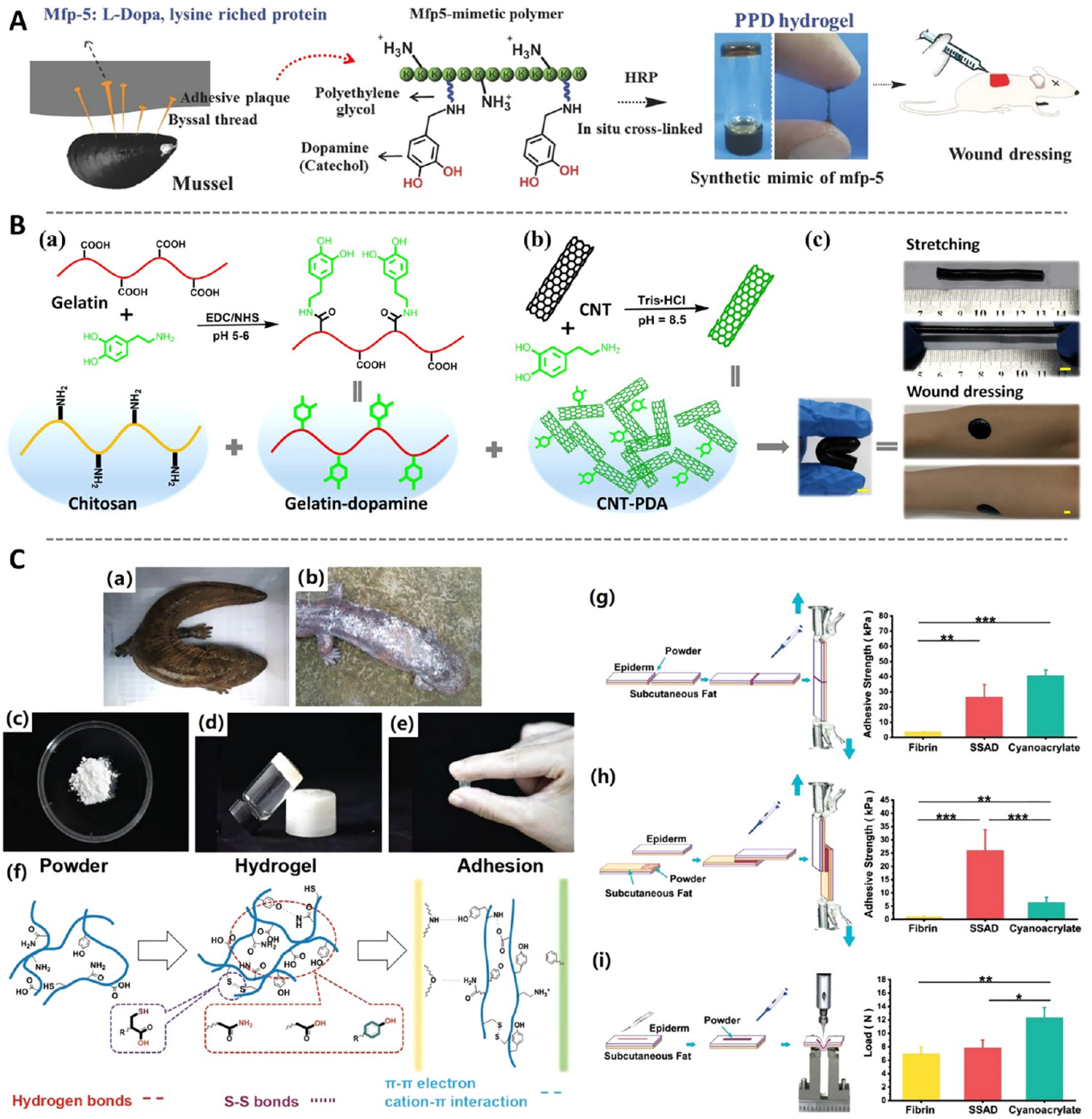

Figure 4. Hydrogel wound dressing with tissue adhesion function. (A) An Mfp5-mimetic polymer (dopamine-modified ε-poly-L-lysine-polyethylene glycol) hydrogel dressing prepared by the inspiration of Mfp-5, an important component of mussel adhesion protein in the plaque of mussel. Reprinted and modified with permission from ref 146. Copyright 2017 Wiley-VCH. (B) An adhesive hydrogel dressing based on gelatin-grafted dopamine *via* oxidative coupling of catechol groups with polydopamine coated CNTs. Reprinted and modified with permission from ref 57. Copyright 2019 Elsevier. (C) A bioadhesive hydrogel prepared by skin secretion of *Andrias davidianus* and the difference in adhesion between the hydrogel and cyanoacrylate and fibrin glue were studied by (g) edge-to-edge adhesion test, (h) standard lap shear test, and (i) three-point bending test. Reprinted and modified with permission from ref 141. Copyright 2019 Wiley-VCH.

enhance the antibacterial effect by further grafting cations such as quaternary ammonium,[125,126] and poly(aminoethyl)[127] onto the main chain of CS. In addition, for example, polyethylenimine (PEI), cationic peptides were also added into the hydrogel dressing to exert antibacterial effect.[106,128−131] Zhu *et al.* also developed an amino acid-derived pseudoprotein hydrogel dressing consisting of polyester amide and three cationic short peptides (RGDK, RRRFK, and RRRFRGDK) and confirmed that surface peptide modification can enhance the antibacterial ability of hydrogel (Figure 3D).[132] Beside, hydrogel dressings with protamine nanoparticles,[133] and silk sericin[134] have also been proved to possess antibacterial properties through the cationic role.

Adhesive and Hemostatic Hydrogel Wound Dressing. Hemostasis occurs at the earliest stage of wound healing. Therefore, hydrogel dressings with the hemostatic property have

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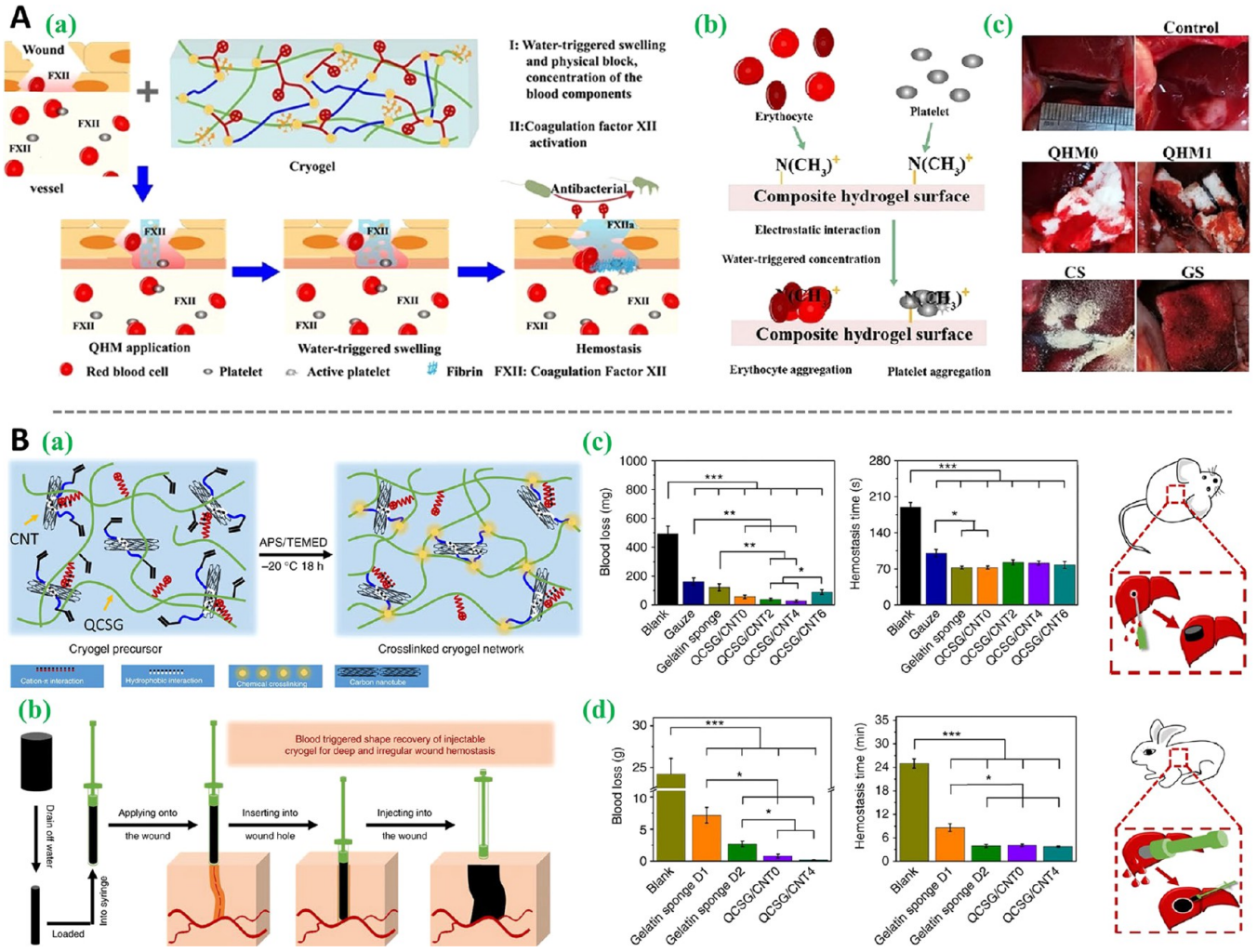

Figure 5. Hydrogel wound dressing with hemostatic function. (A) (a) Illustration of the hemostasis and antibacterial process of the quaternized hydroxyethyl cellulose/mesocellular silica foam hydrogel sponge (QHM); (b) composite hydrogels promotes adhesion and aggregation of blood components; and (c) schematic image of the hemostatic effect of this QHM hydrogel sponge in a model of fatal liver defect. Reprinted and modified with permission from ref 153. Copyright 2019 American Chemical Society. (B) An injectable antimicrobial conductive cryogel based on CNTs and glycidyl methacrylate functionalized quaternized CS for lethal noncompressible hemorrhage hemostasis and wound healing. (a) Schematic diagram of cryogel preparation; (b) schematic diagram of cryogel triggering hemostasis; (c) statistical chart of quantitative experimental data of hemostasis time and amount of bleeding in mice with liver injury; and (d) in rabbits with lethal incompressible hemorrhage. Reprinted with permission under a Creative Commons Attribution 4.0 International License from ref 155. Copyright 2018 Springer Nature.

positive significance in promoting wound healing. Studies have shown that the hemostatic property of hydrogels is not only supported by the physical sealing but also the enrichment of coagulation factors through the absorption of wound extract.[70,132] But as a basic function, hemostasis is often used in combination with other functions. For example, combining with the adhesiveness of bioadhesive hydrogels, the wound can be sealed to provide hemostasis, and the adhesive hydrogels can also be seamlessly attached to the wound site for a long time, avoiding the potential risk of infection caused by the contact between the wound and the external environment.[135] Therefore, adhesive hydrogels were first discussed. In the following section, a review of hydrogels that perform hemostatic effects by other means is summarized.

Adhesive hydrogels based on dextran,[125] sodium alginate (SA),[136] and CS[50,119,137] have been reported because biopolysaccharides show a certain adhesion. CS with a certain positive charge can enhance the adhesion to biological tissues through electrostatic interaction. Furthermore, the cationic quaternary ammonium group was grafted on the backbone of CS to achieve better adhesion.[36,125] ε-Polylysine (EPL) is also a cationic polymer at physiological pH value, showing excellent biological adhesion to various biological surfaces.[138] It has also been reported that free radical-induced covalent bonding during the formation of *in situ* hydrogels by photo-cross-linking can also provide a certain degree of tissue adhesion.[31,129]

In addition, a common method for preparing adhesive hydrogels is to incorporate functional groups with adhesive properties to their structures, which can interact and bind with the surrounding tissues. The aldehyde group can be cross-linked with the amino group on the tissue *via* a Schiff base reaction, resulting in strong tissue adhesion. A variety of adhesive hydrogels based on the oxidized SA and dextran, aldehyde-terminated PF-127 and PEG have been prepared.[50,137,139] The enhancement of tissue adhesion by mercapto-tissue reactions has also been reported.[140] Besides, grafting some long-chain

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alkyl groups on the main chains of macromolecules can produce hydrophobic interactions with the alkyl groups in subcutaneous adipose tissue, thus achieving adhesion effect.[124,137,141]

Inspired by the super adhesion of marine mussels in the humid environment, the underwater wet adhesion theory based on dopamine is widely known, and a large number of dopamine-based biological tissue adhesive hydrogels have been developed.[49,74,104,142−145] For example, an *in situ* formed biomimetic dopamine-modified EPL-PEG-based hydrogel (PPD hydrogel) was developed by using horseradish peroxidase (HRP) cross-linking. Due to the synergistic effect of catechol-Lys, the PPD hydrogel has a good wet tissue adhesion property (Figure 4A).[146] Shin *et al.* also prepared catechol/pyrogallol grafted hyaluronan (HA) hydrogel patches, serving as drug-loaded ready-made tissue tape for promoting wound healing.[147] In the past two years, our research group has also made progress in the direction of dopamine-based adhesive hydrogels.[35,51,57] For example, Figure 4B shows a gelatin-grafted dopamine-based CNT-loaded hydrogel, which not only possesses good adhesion performance but also has multiple functions such as injectable, antibacterial, conductive, hemostatic, and antioxidant, showing great potential to promote better healing of infected full-thickness skin wounds.[57] At the same time, Lu's group reported a series of adhesive hydrogels based on the adhesion properties of dopamine.[39,148,149] By comparison, the average shear adhesion of dopamine-enhanced tissue adhesive hydrogels can be increased by 10−30 kPa.

Besides, other bioinspired adhesive hydrogels were also prepared. For example, Deng *et al.* used the skin secretion of *Andrias davidianus* to prepare a bioadhesive hydrogel. The test results showed that the shear adhesion of the adhesive hydrogel (26.66 ± 8.22 kPa) was equivalent to cyanoacrylate synthetic glue (40.71 ± 3.71) and was significantly higher than fibrin glue (3.76 ± 0.16 kPa) (Figure 4C).[141] A kind of hydrogel based on poly(*N*-acryloyl 2-glycine) and hydroxyapatite showed adhesion strength that up to 105 kPa, which is because of the synergistic interactions between carboxyl and the substrate surface and the enhanced contraction of poly(*N*-acryloyl 2-glycine) chains to adherent surfaces facilitated by hydroxyapatite nanoparticles.[150] Inspired by the Sundew, a carnivorous plant, gum arabic was also used in the hydrogel to play a role of adhesion.[58,151]

In addition to relying on the adhesive properties of the hydrogels to seal the wound for hemostatic effect, several other hemostatic hydrogels have also been reported. In 2012, Kumar *et al.* prepared a series of nanocomposite hydrogel bandages based on CS or chitin, demonstrating that cationic CS interacts with negatively charged blood cells and activates platelets to promote clotting.[86] Subsequently, Fan *et al.* prepared CS/gelatin/PVA composite hydrogel and further elaborated on the hemostatic mechanism of the activation of platelet by CS to produce coagulation factor and physical sealing of hydrogel.[152] Further studies have shown that grafting positively charged components on the hydrogels can improve the interaction between hydrogels and platelets, blood cells, and plasma fibronectin through electrostatic attraction, induce platelet activation and blood cell aggregation, and thus achieve the effect of promoting coagulation. In addition to CS, such cationic constituents also include quaternary ammonium groups[153,154] and cationic polypeptides.[132] Wang *et al.* prepared a quaternized hydroxyethyl cellulose/mesoporous silicon foam hydrogel sponge (QHM) for hemostasis. QHM hydrogel with hydrophilic and high-water absorbability can induce blood cells to enter its network. In addition to electrostatic interaction between quaternary ammonium and blood cells that can trigger hemagglutination and platelet aggregation, a moderate amount of mesoporous silicon foam (9.82 w/w %) was testified to activate FXII further. Thus, QHM hydrogel can significantly reduce the *in vitro* plasma clotting time to 59 ± 4% by these synergistic effects (Figure 5A).[153] In response to the irregular shape and incompressible bleeding, our group reported an multifunctional cryogel based on glycidyl methacrylate functionalized quaternization CS enhanced by CNT. These cryogels have been proved to have good mechanical capacity, rapid blood trigger shape recovery, and high blood uptake ability. In addition, the cryogel showed excellent hemostatic performance in mouse liver injury and lethal incompressible hemorrhage model of rabbit liver (Figure 5B).[155] Furthermore, porous cryogels formed by low-temperature oxidative cross-linking of dopamine with chitosan,[156] quaternary ammonium chitosan,[157] and gelatin[158] have been proved not only to have an excellent hemostatic effect but also to promote the final tissue repair.

As a blood coagulation factor, calcium ion can promote blood clotting. Therefore, Zhou *et al.* prepared an acetate CS/CaCO3 hydrogel. The H^+ of acetate CS reacted with $CaCO_3$ to release Ca^{2+} after absorbing water, which not only enhanced the strength of the hydrogel but also participated in hemostasis.[159]

Anti-Oxidant and Anti-Inflammatory Hydrogel Wound Dressing. Inflammatory, the second stage of wound healing, focuses on the destruction of bacteria and the removal of debris. Proper inflammation is essential in wound repair, so controlling inflammation is an important feature of wound dressings. Excessive inflammation can lead to high oxidative stress, and a sharp increase in reactive oxygen species (ROS, including superoxide anions, hydrogen peroxide, hydroxyl radicals, and nitric oxide), will destroy cells by triggering chain reactions, such as lipid peroxidation, or the oxidation of DNA and proteins. Antioxidants are substances that help to trap and neutralize free radicals, thereby eliminating their damage to the body. Therefore, hydrogels with antioxidant properties can obviously promote wound healing.[160]

As the most widely used natural antioxidant, polyphenol antioxidants exhibit better stability and are better able to bear prolonged storage. Common natural polyphenols such as tea polyphenols,[161] resveratrol,[162] and anthocyanins,[163] and some flavonoids[164] have been loaded into hydrogels to exert an antioxidant role in promoting wound healing. In addition, honey,[165] aloe vera,[166,167] acacia gum,[168] sericin,[169,170] ferulic acid,[38] quercetin,[171] bletilla striata polysaccharide,[28,172] astragaloside IV,[173] and *Hippophae rahmnoides* L. extract[174] also showed an anti-inflammatory effect during wound healing.

Curcumin, a low molecular weight polyphenolic compound isolated from ginger plants, has been shown to possess anti-inflammatory activity comparable to steroid or nonsteroidal drugs. However, curcumin has poor water solubility and stability, which greatly limit its further application *in vivo*. A variety of strategies have been developed to overcome these shortcomings and to capsulate curcumin into hydrogel dressings in recent years.[33] For example, Wathoni *et al.* prepared curcumin composite 2-hydroxypropyl-γ-cyclodextrin hydrogel, which showed enhanced water solubility and stability of curcumin.[175] Li *et al.* prepared nanocurcumin and loaded it into carboxymethyl CS/SA hydrogel, which greatly improved the bioavailability of curcumin.[176] Liu *et al.* loaded curcumin NPs into gelatin microspheres and further develop an efficient and safe system for promoting skin wound healing in diabetic patients (Figure 6A).[177] Qu *et al.* prepared curcumin micelles

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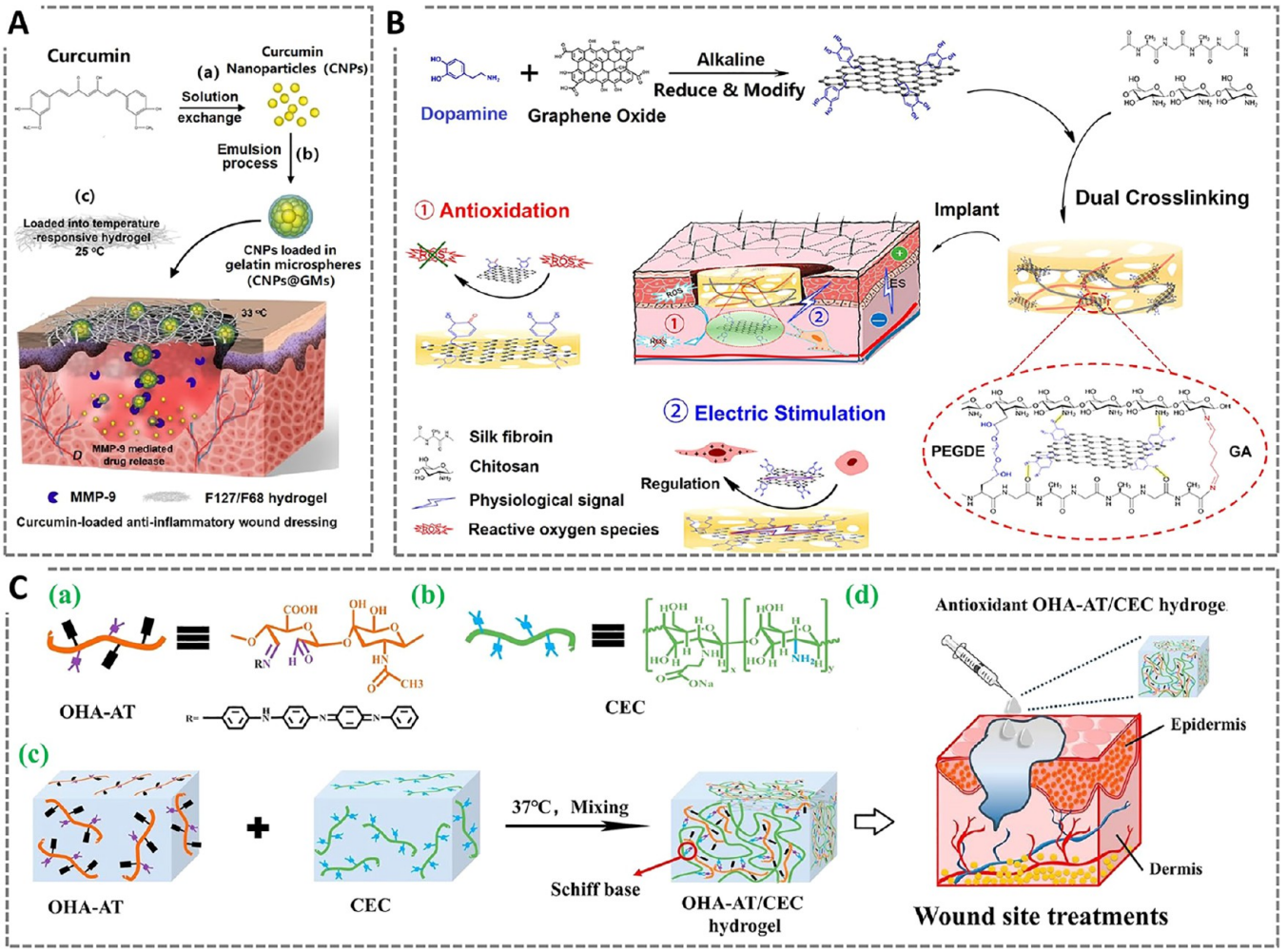

Figure 6. Antioxidant and anti-inflammatory hydrogel dressings. (A) Schematic representations of curcumin NPs/gelatin microspheres (CNPs@GMs) loaded hydrogel dressing for diabetic wound repair. Reprinted and modified with permission from ref 177. Copyright 2018 American Chemical Society. (B) Schematic diagram of the preparation of the electroactive and antioxidative PDA-reduced GO (rGO)-encapsulated chitosan and silk fibroin (SF) (rGO-CS/SF) scaffold. Reprinted with permission from ref 178. Copyright 2019 American Chemical Society. (C) Synthesis scheme of oxidized HA-grafted-aniline tetramer/CEC hydrogel and its application in full-thickness skin wound. Reprinted with permission from ref 30. Copyright 2019 Elsevier.

and combined them into hydrogels, which significantly improved the drug loading and encapsulation ratio of curcumin, while the sustained release effect also provided sustained antioxidant effect of curcumin *in vivo* (Figure 8C).[50]

Due to the presence of catechol structures, dopamine molecules show good antioxidant activity. Inspired by the self-polymerization of dopamine in the hydrogen peroxide/HRP system and the ability to form a coating on any surfaces under alkaline conditions, our research group prepared a series of multifunctional antioxidant hydrogel dressings based on gelatin/CS/CNT and HA/GO, respectively. Good antioxidant activity of hydrogel was verified by the usually used α,α-diphenyl-β-picrylhydrazyl (DPPH) free radical capture experiment. At a concentration of about 5 μg/mL of lyophilized hydrogels, a free radical scavenging ratio of more than 90% can be achieved.[35,57] At the same time, Tang and Gao *et al.* also prepared dopamine-based antioxidant hydrogels and verified the positive role of their antioxidant properties in wound repair (Figure 6B).[60,178] Dopamine-like phenolic compound gallic acid has also been shown to have a good antioxidant effect.[43] Moreover, based on polyaniline[36] (Figure 10A) and aniline tetramer,[30] our research group prepared different antioxidant hydrogel systems. The biocompatible polymer CEC and oxidized HA-grafted-aniline tetramer (OHA-AT) polymer are mixed and constructed the conductive antioxidant OHA-AT/CEC hydrogel through the Schiff base reaction between amino and aldehyde (Figure 6C). The hydrogel shows a suitable gelation time, stable rheological properties, high swelling ratio, and suitable *in vitro* biodegradation and electrical activity. When stable DPPH free radicals are used as compounds for testing the oxidation resistance of the dressings, aniline tetramer (AT) with good redox properties exhibits excellent DPPH scavenging ability.[30]

In addition, some endogenous factors were also added to the hydrogel to make the dressing have anti-inflammatory ability. For instance, SOD can catalyze the decomposition of superoxide free radicals into H_2O_2 that was then converted into water and oxygen. Therefore, Zhang *et al.* developed a SOD contained wound dressing that could remove excessive O_2^- and promote the healing process of chronic wounds.[179] Prostaglandin E2 is a lipid signaling molecule that acts as both an inflammatory mediator and a fibroblast regulator. So, Li *et al.* prepared a CS/prostaglandin E2 hydrogel, which prolonged the release of Prostaglandin E2, and demonstrated that the hydrogel achieved better repair by balancing inflammation, angiogenesis, and

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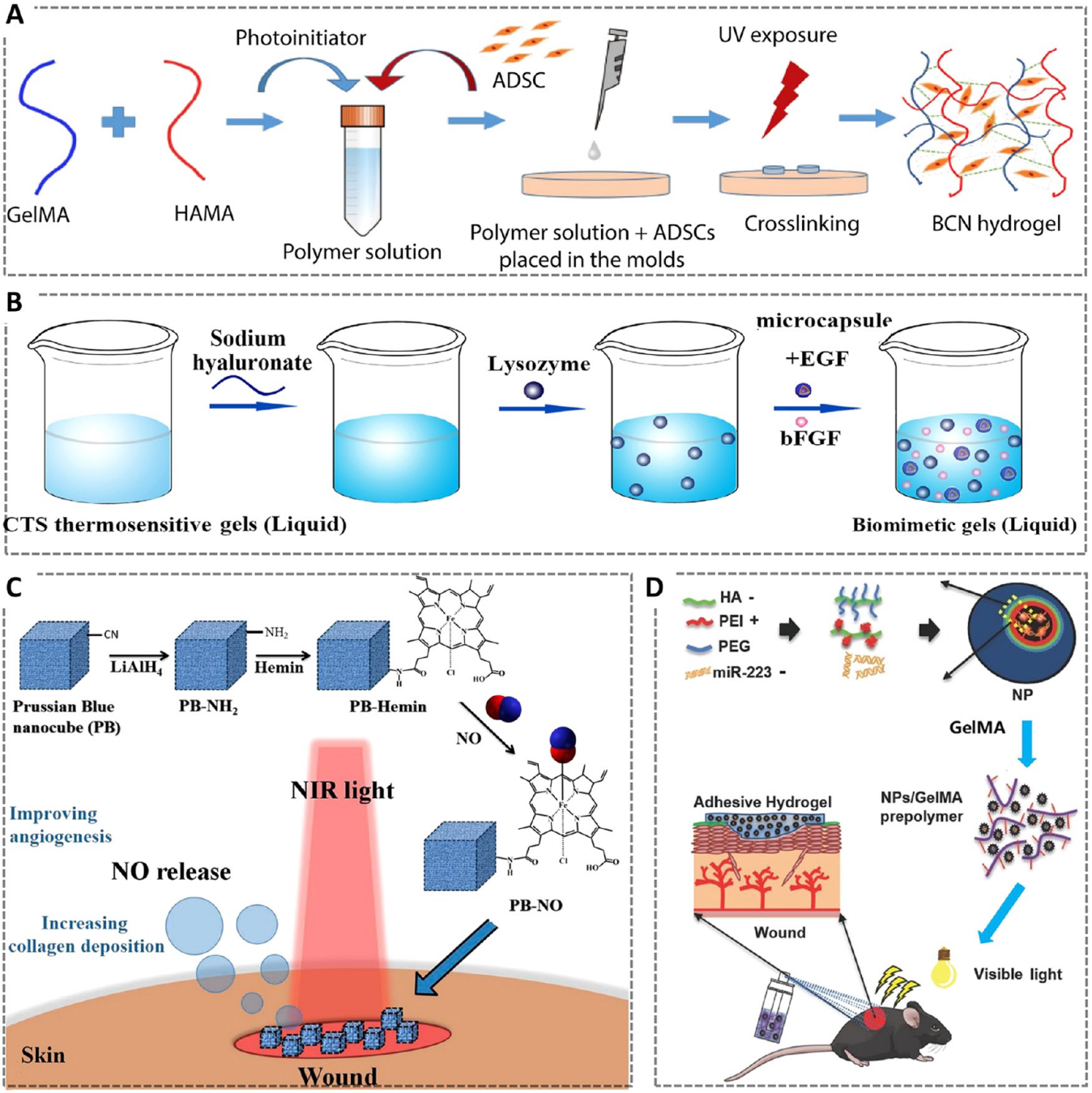

Figure 7. Hydrogel with controlled delivery property for wound dressing. (A) A schematic diagram of preparation for an ADSC-loaded ultravior-induced *in situ* forming hydrogel based on methacrylated gelatin and methacrylated HA. Reprinted and modified with permission from ref 184. Copyright 2017 Elsevier. (B) The preparation of a biomimetic CS/alginate (CS-SA) self-assembling microcapsule hydrogel encapsulated with bFGF and EGF. Reprinted and modified with permission from ref 203. Copyright 2019 Elsevier. (C) Illustration of the preparation process for NO-carried prussian blue nanocubes and the use of NIR responsive NO-release for wound healing. Reprinted and modified with permission from ref 44. Copyright 2019 American Chemical Society. (D) Schematic illustration of the formation for GelMA hydrogel contained miR-223 5p mimic and hyaluronic acid nanoparticles. Reprinted and modified with permission from ref 31. Copyright 2019 Wiley-VCH.

fibrosis remodeling during the healing process.[26] TCP-25 is a thrombin-derived peptide with antibacterial property, and it can lead to decreased downstream immune activation. Puthia *et al.* developed a TCP-25-based hydrogel scaffold that mimics the endogenous role of host defense peptides derived from trauma.[131]

Besides, Xiao *et al.* prepared a hydrogel containing poly-(polyethylene glycol citrate-*co*-*N*-isopropylacrylamide (NIPAM)), verifying the antioxidant properties of citrate by free radical scavenging experiments of 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid),[89] and also confirmed that povidone-iodine shows obvious anti-inflammatory effect due to the free radical scavenging effect.[180] Another study also demonstrated that WO_3 can achieve anti-inflammatory effects during wound healing by inhibiting tumor necrosis factor α (TNF-α).[181] The positively charged amino acid residues of

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chemokines can also bind to the negatively charged sulfate group of GAGs through electrostatic interaction, thereby reducing chronic wound inflammation during the treatment.[182]

Hydrogel with Controlled Delivery Property for Wound Dressing. The porous structure of hydrogels makes them naturally suitable for loading a wide variety of substances and releasing them slowly at specific locations. Of course, drug delivery should be the first one among the substances that hydrogels can support. But most of the drugs delivered are antibiotics, which we have covered in the antibacterial section. Wound healing also requires cellular interactions among various cell types, including keratinocytes, fibroblasts, endothelial cells, neutrophils, and macrophages, and is also regulated by the endogenous release of GFs, cytokines, and chemokines at the wound site. Therefore, local delivery of exogenous cells or cytokines showed a good advantage in promoting wound healing.

Among various types of stem cells, adipose-derived stem cells (ADSCs) are an effective source of cell therapy and have properties similar to mesenchymal stem cells. ADSCs can be performed through simple minimally invasive surgery and are less affected by the age of the donor. In addition, ADSCs can secrete some necessary factors conducive to wound repair to stimulate angiogenesis and re-epithelialization, so as to promote tissue regeneration. As a result, ADSCs have become the most commonly used hydrogel-loaded cells.[147,167,183] For example, Eke and coworks achieved *in situ* loading of ADSCs *via* photo-cross-linking between methacrylate anhydride functional gelatin (GelMA) and methacrylate HA, demonstrating that the vascular regeneration of the stem cells contained hydrogel group increased three times compared to the stem cells-free hydrogel group (Figure 7A).[184] Wang *et al.* prepared different ADSCs encapsulated hydrogels and detected significant increases in pro-angiogenic GF proteins such as PIGF, VEGF, and TGF-β.[185,186] Bone marrow mesenchymal stem cells (BMSCs) have also been shown to secrete TGF-β1 and bFGF, which can further differentiate into effector cells like keratinocytes, fibroblasts, and endothelial cells, to accelerate wound healing and strengthen vascularization,[187] granulation tissue formation[188] and re-epithelialization.[189] For example, Chen *et al.* prepared an BMSCs loaded *in situ* forming hydrogel composed of PNIPAM and poly(amidoamine).[190] Besides, hydrogel dressings loaded with human umbilical cord mesenchymal stem cells have also been reported.[27]

Fibroblasts play an important role in wound repair because they produce extracellular matrix molecules (such as collagen I) and secrete essential GFs (such as VEGF). These fibroblast-derived factors are necessary for endothelial cells to germinate, making the epithelium move toward the center of the wound and promote wound healing. Zhao *et al.* prepared an L929 fibroblast loaded self-healing hydrogel.[191] Hydrogels loaded with human epidermal keratinocytes and dermal fibroblasts were also reported to synergistically promote better wound repair.[192−194]

Skin-derived extracellular matrix bioinks have been used for 3D cell printing of simulated skin hydrogels, and it has been demonstrated that hydrogels combined with endothelial progenitor cells[195] can accelerate wound healing by accelerating hemostasis, epithelialization, and angiogenesis.[196] It was also found that the human microvascular endothelial cells (HMEC) loaded hydrogel possessed an obvious proliferative behavior. More importantly, certain levels of VEGF were observed in HMEC hydrogels, which led to the possibility of angiogenesis.[48]

Growth factors are a class of important bioactive proteins, which play an important role in regulating cell function and maintaining tissue homeostasis. Numerous studies have shown that topical treatments such as EGF, fibroblast growth factor (FGF), keratinocyte growth factor (KGF), and nerve growth factor enhance wound healing in primate models and clinical trials.[197] Conversely, the absence of relevant cytokines often results in delayed repair or even failure to heal the wound. Among all the GFs, EGF and FGF are the most commonly used factors that encapsulated in hydrogel dressings for wound healing. FGF plays an important role in angiogenesis, nerve regeneration, bone regeneration, anti-inflammatory, wound healing, and other aspects. However, a short half-life seriously limits its application. So, many FGF encapsulated hydrogel wound dressings have been reported.[32,198−200] For example, heparin-functionalized polymer hydrogel was prepared by combining positively charged bFGF with negatively charged heparin through electrostatic interaction. Test results also demonstrated that bFGF dose dependently accelerates wound healing (Figure 9B).[201,202] After loading bFGF with thermo-sensitive CS hydrogel, Kong *et al.* also double-loaded EGF with hydrogel and microsphere, which better simulated the differential release of bFGF and EGF, and achieved rapid healing while avoiding the scar hyperplasia due to fibroblast proliferation caused by bFGF overexpression in the later stage (Figure 7B).[203] Besides, FGF-2 is also loaded into different hydrogels and has been shown to promote wound healing by increasing the formation of dermal and granulation tissue, angiogenesis, and re-epithelialization.[37,204,205]

EGF is a polypeptide consisting of 53 amino acid residues that promote the proliferation of epithelial cells and the synthesis of ECM, which is the basis for accelerating wound healing. It has also been adopted by many reports.[39,67,206] For example, semi-interpenetrating network hydrogels were synthesized from PAM and CS by free radical polymerization, and EGF is embedded to increase the mitotic activity of hydrogels. The synthesized CS-PAM hydrogel shows a successfully sustained-release effect on EGF for more than 5 days.[207] There have also been studies that encapsulate VEGF at the same time as EGF loading, and the common control release of them can also improve the effect of angiogenesis and re-epithelialization compared with the control group or the group with a single GFs loading.[208] VEGF is a multifunctional molecule that has strong effects on the vascular system, including the ability to stimulate the growth of new blood vessels and increase vascular permeability and has been widely used in hydrogel dressings in recent years.[124] For example, by combination with resveratrol, VEGF can simultaneously inhibit the inflammatory response and promote microvascular formation in burn wounds.[162] Strong covalent interaction between catechol and various nucleophilic components in the protein resulted in the sustained release of VEGF from the hydrogel patch for 9 days and significantly increased microvascularization in the related tissues.[147] Cyclic adenosine phosphate has long been recognized as a second messenger and regulator of human keratinocyte proliferation. Therefore, one of its lipophilic analogues, which has been shown to promote wound healing, was also added to the hydrogels and showed significantly faster re-epithelialization.[209] In addition, in the process of wound healing, KGF,[210] platelet-derived GF BB,[90] interleukin-8 and macrophage inflammatory protein-3α,[211] stromal-derived factor-1 (SDF-1),[212] and recombinant human granulocyte/macrophage colony stimulating factor (rhGM-

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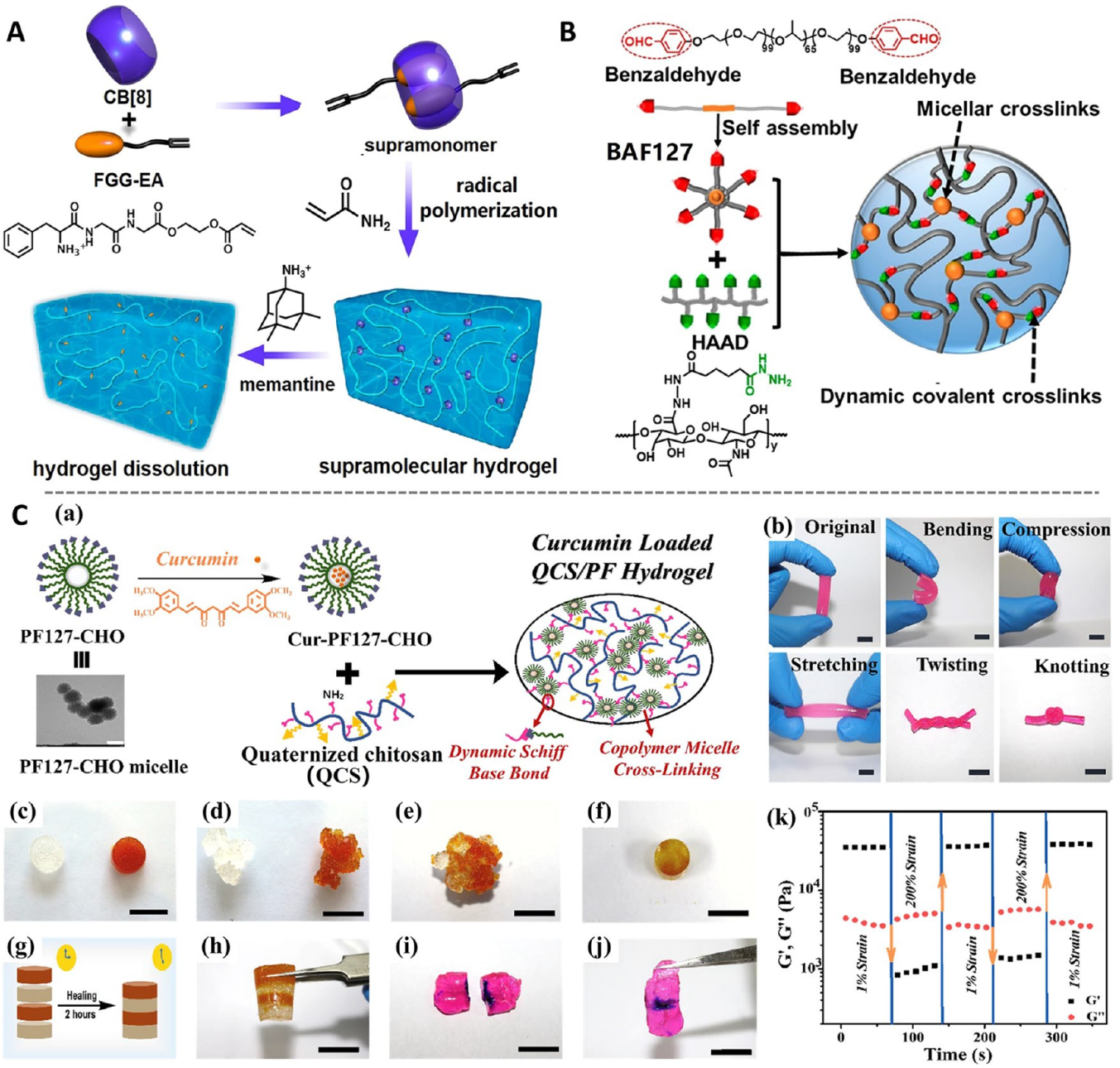

Figure 8. Self-healing hydrogel wound dressing. (A) A self-healing hydrogel based on host−guest interaction, and cross-linkable supramonomers. Reprinted and modified with permission from ref 232. Copyright 2017 American Chemical Society. (B) A double-cross-linked hydrazide-modified HA (HAAD) and benzaldehyde terminated F127 (BAF127) hydrogel with dynamic acylhydrazone bonding and micellization cross-linking. Reprinted and modified with permission from ref 237. Copyright 2018 American Chemical Society. (C) Self-healing properties of quaternized CS/benzaldehyde-terminated PF127 hydrogel: (a) Schematic illustration of Cur-QCS/PF hydrogel and TEM image of PF127-CHO micelles. Scale bar: 200 nm. (b) The mechanical property of QCS/PF hydrogel. Scale bar: 1 cm. (c−j) Self-healing property of the hydrogels and (k) the rheological properties of the hydrogel when alternate step strain switched from 1% to 200%. Reprinted and modified with permission from ref 50. Copyright 2018 Elsevier.

CSF)[213] *etc.* also showed promoting effects by angiogenesis and re-epithelialization.

Studies have long confirmed that the vasodilatory action of NO can increase the blood flow of microvessels in wound healing process, thus promoting the transport of nutrients and cells to the injured site. The production of NO by macrophages and other cell types can also promote wound healing by increasing the expression of VEGF. In addition to the antibacterial action we discussed above to promote wound healing, studies also demonstrated that NO released from the hydrogel dressings improves the quality of granulation tissue and increases the strength of healed wound by upregulating the deposition of the collagen.[214] Schanuel *et al.* also verified that when *s*-nitrosoglutathione (GSNO), the most commonly used NO carrier, was loaded into PVA/PF127 hydrogel, the release of NO increased the differentiation of myofibroblast.[215] In Champeau's study, more than 5 days' NO release from PAA:PF127/GSNO hydrogels in addition to leading the increased angiogenesis, also increased the expression of TGF-β, insulin-like GF-I, SDF-1, and IL-10 genes in damaged

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tissue.[216] In addition to GSNO, Su *et al.* successfully prepared a hemin-modified Prussian blue nanocubes recently, which possesses a strong affinity for NO gas. The thermal-induced release of NO was realized due to the photothermal properties of Prussian blue (Figure 7C).[44]

The availability of oxygen gets a profound effect on the repair process. In addition to the role of superoxide free radicals in preventing bacterial infections, oxygen also regulates angiogenesis, promotes cell proliferation and migration, and interacts with a variety of cytokines. It is also a prerequisite for the synthesis of hydroxyproline, which is a good component in collagen fibers that produced during wound repair. It is estimated that a wound requires at least 20 mmHg of tissue oxygen tension to heal, while the oxygen tension of a nonhealing wound is measured as low as 5 mmHg. Therefore, hyperbaric oxygen therapy is an effective method to treat chronic hypoxia wounds. Researchers have prepared a kind of oxygenated hydrogel dressing based on perfluorocarbon chain-modified methacrylamide CS, which can carry oxygen to the wound and maintain the enhanced local oxygen levels to improve local hypoxia environment, eliminating the use of complex oxygenating set-ups.[217,218] Besides, a light-responsive MoS_2 QDs integrated hemoglobin-GelMA inverse opal microcarriers was prepared. Due to the photothermal effect of MoS_2 QDs, larger and faster oxygen release could be achieved from hemoglobin-modified microcarriers after temperature increases.[219]

In addition to the delivery systems described above, other delivery systems are used to facilitate wound healing. For example, upregulation of miR-223-microRNAs (miRNAs) revealed macrophage polarization to an anti-inflammatory (M2) phenotype, so adhesive hydrogels of HA NPs containing miR-223 5p mimics were developed to control tissue-macrophage polarization during wound healing (Figure 7D).[31]

In addition, some other functional substances like peptides or protein are also used in hydrogel dressings to play a specific role in promoting wound healing. For example, a feather keratin hydrogel showed good histocompatibility.[220] A neurotensin loaded hydrogel plays the role of an inflammation regulator, reduces the expression of inflammatory cytokines TNF-α, and promotes wound healing.[221] By enhancing angiogenesis, re-epithelialization, and collagen deposition, a laminin mimetic peptide SIKVAV-conjugated hydrogel has also been shown to promote wound healing.[41]

In addition, organic-modified montmorillonite is used to enhance the physical strength of hydrogels.[222] Boron is involved in a variety of metabolic pathways, and it has also been shown to promote wound healing by increasing matrix metalloproteinase expression and keratinocyte migration.[223] A hydrophobic small molecule proline hydroxylase inhibitor is encapsulated in a supramolecular polymer hydrogels. This leads to a brief upregulation of hypoxia inducible factor-1α, which causes the deep tissue to regenerate in a manner similar to surface regeneration.[224]

Self-Healing Hydrogel Wound Dressing. In addition to *in situ* formation, adhesion, and other properties to achieve the rapid hemostasis, the physical barrier formed by the presence of hydrogels is also an important means to prevent the wound from external bacterial infection. However, general hydrogels are prone to breakage or fracture when exposed to external tension or tissue activity. In addition to causing deterioration of their own properties or even loss, breakage in hydrogels will further cause invasion of external bacteria and result in wound infection. So, it is also important to ensure the structural integrity of hydrogel dressings during wound healing. Therefore, the concept of self-healing hydrogels is proposed as a "smart" material that can repair its own functional and structural damage.[225,226] Most self-healing hydrogels are prepared based on the strategy of constitutional dynamic chemistry, which involves dynamic and reversible chemical bonds in the formation of a cross-linking network of hydrogels.[227−229] Although self-healing hydrogels have been reported in large numbers, their use in the repair of damaged skin tissue has only been developed in the last 5 years. Therefore, we will summarize the application of self-healing hydrogels in the repair of damaged tissues in this section.

Self-healing hydrogels can be divided into physical self-healing hydrogels and chemical self-healing hydrogels based on the healing mechanism. Physical self-healing hydrogels reconstruct networks by forming dynamically noncovalent interactions (including hydrophobic interactions, host−guest interactions, hydrogen bonds, crystallization, polymer−nanocomposite interactions, and multiple intermolecular interactions) between molecules, oligomers, or polymer chains. Liu *et al.* prepared a composite double-network hydrogel with gelatin methacrylate and tannic acid, and the dynamic hydrogen bonding of tannic acid provided hydrogel good self-healing function.[230] Bacterial cellulose modified by positive and negative fragments was prepared, respectively, and a self-healing hydrogel was prepared by forming an ionic interlocking system in the buffer solution with pH of 7.4.[231] Host−guest noncovalent interactions between the tripeptide Phe-Gly-Gly ester derivative (FGG-EA) and cucurbit[8]uril were also exploited to yield a supramolecular hydrogel. Benefiting from the dynamic nature of supramolecular hydrogels, it can dissolve after exposure to the FDA-approved drug memantine, making it easy to remove from wounds (Figure 8A).[232] Our group has also prepared some self-healing hydrogels based on host−guest interactions between cyclodextrins and NIPAM,[233] amantadine,[234] or silk fibroin.[235]

However, chemical self-healing hydrogels are now more widely reported, and they form reconstruction networks through dynamic covalent bonding, including phenylboronate ester, disulfide, imines, acylhydrazone, reversible radical reaction, and reversible Diels−Alder cycloaddition. Among the many chemical self-healing hydrogels, Schiff base (imines) structures account for a large proportion of the dynamic chemical bonds used in the reparation of self-healing hydrogel wound dressings.[34,36,50,51,119,124,137,139,143] In this section, common amino suppliers include modified/unmodified CS, various hydrazide-modified natural polymers, and common aldehyde group providers include benzaldehyde group-modified synthetic polymer chains and oxidized polysaccharide. For example, Huang *et al.* prepared a self-healing hydrogel based on the Schiff base bond between the amino of a water-soluble carboxymethyl chitosan (CMC) and the aldehyde of an oxidized cellulose nanocrystal (DACNC), which can quickly form after the injection to irregular and deep burn wound and completely fill the wound area. Finally, the dressing can be painlessly removed by on-demand dissolving using amino acid solution.[236] Hydrazide-modified HA (HAAD) and benzaldehyde terminated F127 triblock copolymers (BAF127) were developed and prepared a double-cross-linked hydrogel with dynamic covalent chemistry and physical micelle, which showed rapid gelation and shear thinning properties (Figure 8B).[237] Our group also prepared a self-healing hydrogel based on quaternized CS (QCS) and benzaldehyde-terminated PF127, which can still maintain good mechanical properties after bending, compres-

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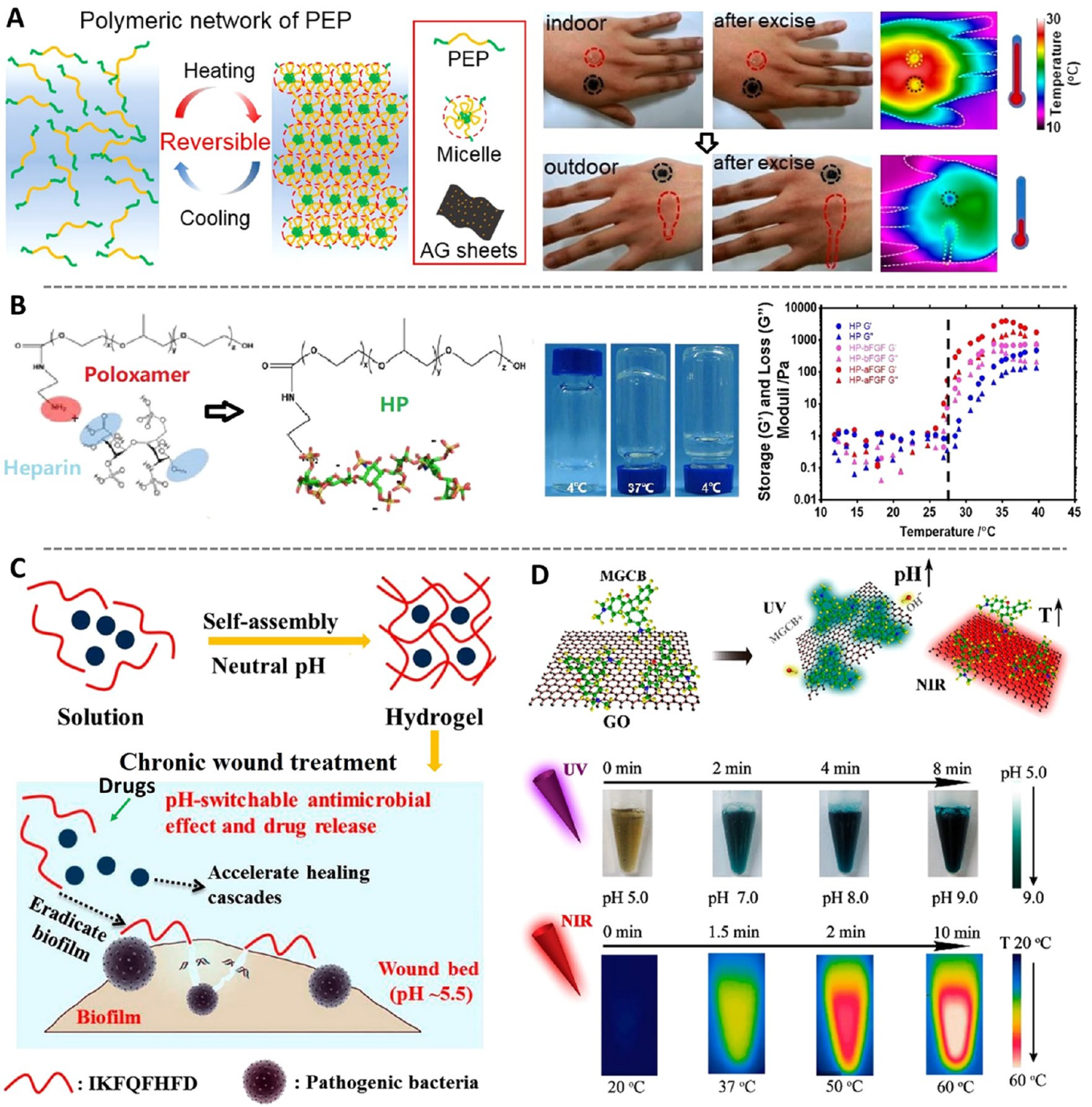

Figure 9. Stimulus-responsive hydrogel wound dressing. (A) A sprayable *in situ* forming skin temperature responsive hydrogel based on poly(NIPAM$_{166}$-*co*-*n*-butyl acrylate$_9$)-PEG-poly(NIPAM$_{166}$-*co*-*n*-butyl acrylate$_9$) copolymer (PEP) and Ag NPs-modified reduced GO (Ag@rGO, denoted as AG). The display pictures for the adjustable temperature sensitivity indoor (high temperature) and outdoor (low temperature). Reprinted and modified with permission from ref 79. Copyright 2019 American Chemical Society. (B) A GFs loaded thermosensitive heparin-PF127 hydrogel. The sol−gel transition allows aFGF and bFGF to be fully mixed with heparin-PF127 solution at 4 °C. Then, when the GFs-heparin-PF127 solution was applied to a live wound at 37 °C, gelation was allowed and GFs was successfully loaded into the heparin-PF127 hydrogel. Reprinted and modified with permission from ref 202. Copyright 2016 American Chemical Society. (C) A schematic diagram of antimicrobial peptide-based nanofiber network self-assembly at neutral pH and response to acidic conditions to release peptides for biofilm clearance and promote chronic wound healing. Reprinted and modified with permission from ref 106. Copyright 2019 American Chemical Society. (D) A dual photoresponsive hydrogel dressing containing both photothermal nanomaterial GO and photobase reagent MGCB. In addition to adjusting temperature in response to NIR light, ·OH can also be released by MGCB molecule in response to UV light, resulting in gradient of pH value. Reprinted and modified with permission from ref 255. Copyright 2017 American Chemical Society.

sion, stretching, twisting, and knotting. A rhodamine B stained hydrogel was cut into two pieces and was healed within 3 s. Self-healing behavior of hydrogel was also further demonstrated by rheological recovery test (Figure 8C).[50] Meanwhile, dynamic acylhydrazone bonds also exist in the hydrogel, and Chen *et al.* also reported self-healing hydrogels through the combination of

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dynamic Schiff base and acylhydrazone.[42] On the other hand, Zhao *et al.* also prepared a self-healing hydrogels based on phenylboronic-modified CS, PVA, and benzaldehyde-capped PFG, which combined the Schiff base and dynamic phenylboronate ester bonds.[191]

In addition, the strategy of achieving dynamic cross-linking through metal coordination has also been reported. For example, Shi *et al.* synthesized a phosphate-modified HA-based supramolecular hydrogel with self-healing properties by dynamic metal−ligand coordination between phosphate and Ag ions.[238] Chen *et al.* also prepared a hydrogel based on the dynamic properties of Ag−S coordination bond by cross-linking multiarm thiolated PEG (SH-PEG) with $AgNO_3$.[77] It has also been reported that self-healing hydrogels prepared using the synergistic effect between Fe^{3+} and COOH in HA with EDTA, as the ligand can repeatedly self-heal within a few minutes.[90]

Besides, there have been some reports of dopamine-based self-healing hydrogels in recent years. Due to the covalent/noncovalent bond coexisting characteristics of dopamine during self-cross-linking, dopamine-based cross-linking hydrogels have both structural strength and self-healing properties. Our research group prepared dynamic dopamine cross-linked hydrogels between dopamine-grafted HA and PDA-coated GO and proved the self-healing properties derived from coexistence of covalent/noncovalent bonds in dopamine cross-linked hydrogels.[35] Zhao *et al.* also demonstrated the self-healing properties of hydrogels assembled from PDA-modified Ag NPs (PDA@Ag-NPs). It is believed that the interfacial hydrogen bond and $\pi-\pi$ stacking mediated by catechol can be dynamically associated and dissociated, thus providing excellent self-healing performance of the hydrogels.[74]

In general, although the number of self-healing hydrogels for wound healing dressings have increased significantly in recent years, most of the self-healing properties are still derived from the dynamic Schiff base, and the macromolecular structure used to form Schiff base based self-healing hydrogels is still very limited. Therefore, self-healing hydrogel dressings based on more strategies need to be developed in the future. In addition, the current self-healing hydrogels generally have insufficient strength, which needs to be further improved.

Stimulus-Responsive Hydrogel Wound Dressing. Stimulation-responsive hydrogels are responsive to changes in the external environment (such as temperature, pH, light) and can make size or shape changes of different ranges under external environmental stimuli.[156,239] They have a good application prospect in the field of wound dressing hydrogels.

Based on the relatively common normal physiological temperature of the human body of 37 °C, the thermal sensitive materials used for hydrogel wound dressings generally exhibit lower critical solution temperature (LCST) around physiological temperature, which guarantees the gelation behavior at the normal human body temperature. The injectable low-temperature flowing hydrogel precursor solution can be rapidly transformed into a nonflowing hydrogel state after it was injected into a wound at a physiological temperature, which greatly simplifies the use of hydrogels, making the therapeutic process simple and easy to implement. Therefore, the research on thermoresponsive materials has aroused great interest.

NIPAM monomer is commonly used in the preparation of thermoresponsive hydrogels because its LCST is approximately 32 °C,[239] close to the physiological temperature. PNIPAM-based thermoresponsive hydrogels have also been widely reported.[32,61,89,189,190,212,233,240−242] Research by Mi *et al.* confirmed that when NIPAM is copolymerized with other monomers, the addition of hydrophilic monomers increases the LCST, while hydrophobic monomers lower the critical point.[73] Conversely, it has been reported that the stability of hydrogels can be enhanced at low temperatures by decreasing the temperature sensitivity. Yan *et al.* prepared a sprayable *in situ* hydrogel dressing based on poly($NIPAM_{166}$-*co*-*n*-butyl $acrylate_9$)-PEG-poly($NIPAM_{166}$-*co*-*n*-butyl $acrylate_9$) copolymer (denoted as PEP) and Ag NPs-decorated reduced GO nanosheets (Ag@rGO, denoted as AG) and confirmed that the addition of AG changed the reversible sol−gel change of original PEP hydrogel at low temperature, providing good outdoor low-temperature resistance for PEP-AG hydrogels (Figure 9A).[79] In addition, the hydrophobicity of PNIPAM hydrogel increased with the increase of temperature, resulting in the decrease of swelling ratio.[69] Thus, a thermally-sensitive drug release hydrogel dressing was prepared. In short, the hydrogel undergoes hydrophobic contraction at the physiological temperature that is higher than NIPAM's LCST, then squeezes out excess water and accelerates drug release, but no drug is released at room temperature.[204]

PEG is an interesting amphiphilic molecule. In addition to providing effective stealthing properties, it also exhibits a negative temperature response in water environments. Many PEG-based copolymer thermosensitive hydrogel wound dressings have been prepared, such as PEG-PCL-PEG,[243,244] poly(lactic-co-glycolic acid) (PLGA)-PEG-PLGA,[245] and PEG-PLGA-PEG,[246] which all showed good gelation properties at physiological temperature. Among all the PEG-based block copolymers, a popular system is commonly referred to as PF127, which contains both hydrophilic and hydrophobic segments, showing excellent thermal response. Many PF127-based thermosensitive hydrogel dressings have also been developed.[80,177,210] For example, Wu *et al.* prepared a GFs loaded thermosensitive heparin-PF127 hydrogel. The sol−gel transition allows aFGF and bFGF to be fully mixed with heparin-PF127 solution at 4 °C. Then, when the GFs-heparin-PF127 solution is applied to a live wound bed at 37 °C, heparin-PF127 gelation occurs, allowing GFs to be successfully loaded into the heparin-PF127 hydrogel (Figure 9B).[202] In 2018, our research group also developed a PF127-based thermosensitive hydrogel for curcumin sustained release (Figure 8C).[50] In addition, thermosensitive hydrogel wound dressings based on other molecules such as polyisocyanopeptide,[247] methylcellulose,[95] and hydroxybutyl CS[67] have also been reported.

The pH-responsive hydrogel is a subset of the stimulus-responsive system that can respond to pH changes in the wound. The pH of normal skin is maintained in the range of 4−6, which provides skin with a good resistance to external effects.[248] Once the skin is injured, after a short period of acute repair (hemostasis and inflammation phase) with a slight decrease in pH, normal wounds show a certain increase in pH in the proliferation phase, but eventually with the repair of the wound, the pH will return to normal levels (5.5−6.5).[249] However, for chronic wounds with abnormal continuous inflammation, such as infection, burns, bedsores, and diabetes, the pH value will always remain alkaline.[249,250] Among many pH-responsive hydrogel dressings, pH-responsive substance release accounts for a large proportion. In view of the lower pH in the acute phase of repair, some hydrogel dressings with enhanced release in acidic pH have been widely developed. For example, tannic acid-released antibacterial anti-inflammatory hydrogels were prepared by the reduction of coordination between tannic acid and

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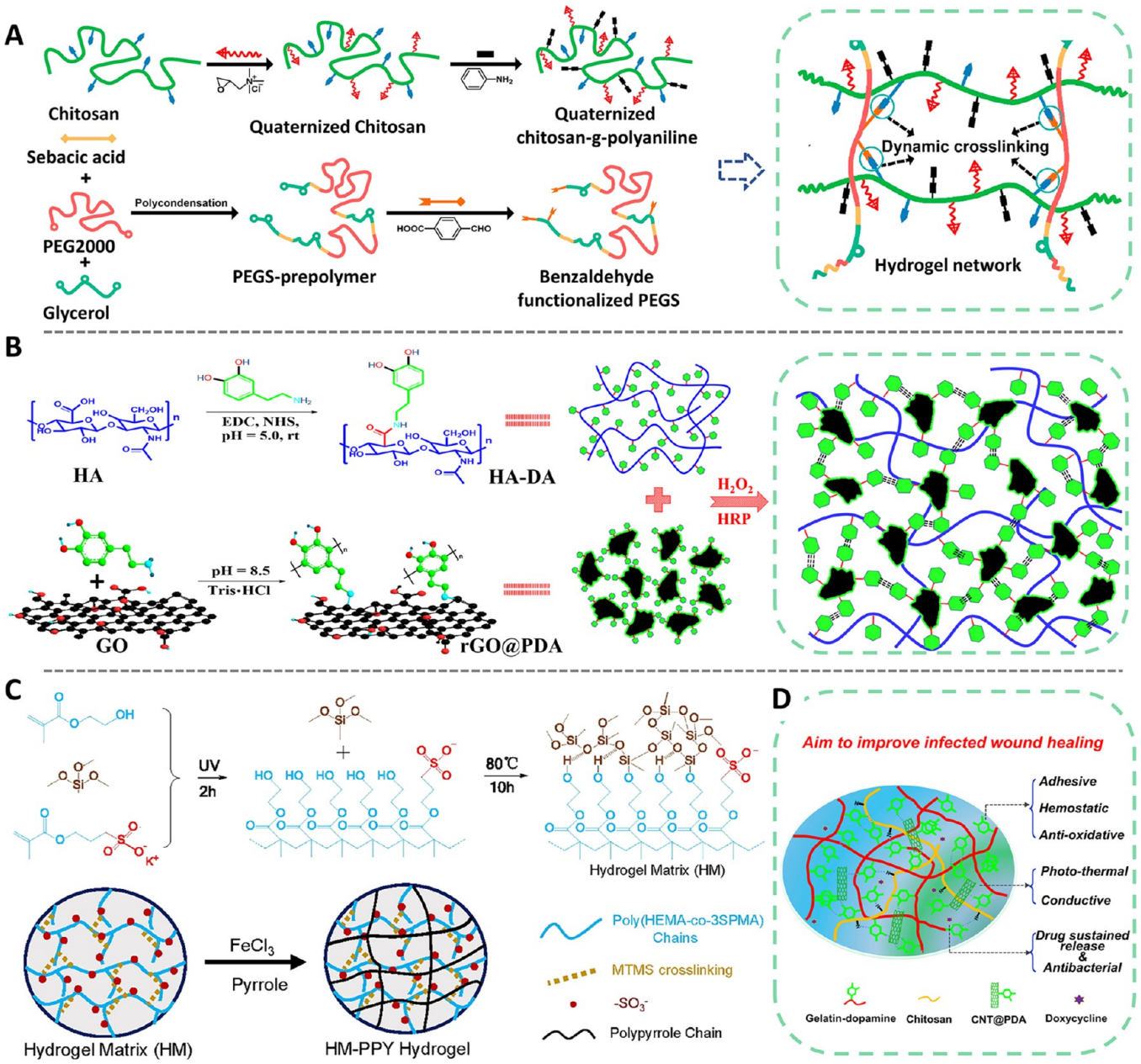

Figure 10. Conductive hydrogel wound dressing. (A) The preparation procedures of the conductive hydrogels based on dynamic Schiff base between quaternized chitosan-*g*-polyaniline and benzaldehyde group functionalized poly(ethylene glycol)-*co*-poly(glycerol sebacate). It also confirmed that the hydrogel with the conductive component PANI had a better effect on promoting the repair of damaged tissues than the hydrogel without PANI. Reprinted and modified with permission from ref 36. Copyright 2017 Elsevier. (B) A conductive hydrogel wound dressing based on HA-*graft*-dopamine and dopamine coated rGO was preparaed by dopamine cross-linking induced by H_2O_2/HPR system. The conductivity and photothermal antibacterial properties provided by rGO promoted the good effect of the hydrogel on skin tissue healing. Reprinted and modified with permission from ref 35. Copyright 2019 Wiley-VCH. (C) Schematic illustration of the preparation of the conductive poly(2-hydroxyethyl methacrylate) (polyHEMA)/polypyrrole (PPy) hydrogels. *In situ* doped PPy was realized by covalent incorporation of 3-sulfopropyl methacrylate into hydrogel network, and good conductivity of this hydrogel was ensured in weak alkaline physiological environment. Reprinted and modified with permission from ref 270. Copyright 2019 Elsevier. (D) A conductive hydrogels based on gelatin-*graft*-dopamine (GT-DA), CS, and dopamine coated CNTs (CNT@PDA). Reprinted and modified with permission from ref 57. Copyright 2019 Elsevier.

metal ions under acidic conditions.[251,252] Using the dissociation of Schiff base structure under acidic conditions, better insulin release promotes diabetic wound healing,[191] and better simultaneous release of Ag^+ and deferoxamine (DFO) was also confirmed to promote both antibacterial and angiogenesis.[253] In addition, a supramolecular hydrogel formed by the intermolecular forces, hydrogen bonds, and $\pi-\pi$ stacking of amphiphilic peptides with opposite charges at neutral pH was disassembled under acidic conditions, which leads to better release of cationic antimicrobial peptides and promotes better antibacterial and repair of diabetic wounds (Figure 9C).[106] However, the pH of chronic wounds is alkaline in the subsequent chronic repair phase (including the late stage of inflammation, and proliferation and remodeling phase), so some

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release-enhanced hydrogel dressings under alkaline conditions have also been developed. For example, the high ionization of coordination between the carboxyl group of alginate and metal ions under neutral or alkaline conditions resulted in charge exclusion, hydration, and swelling of hydrogel. So, hydrogel dressings with better release of bovine serum albumin[254] and hyaluronan oligosaccharides[133] under alkaline conditions have been used to promote the healing of chronic wounds. In general, many hydrogels with pH-responsive release properties have been used to promote wound repair. However, most of these hydrogels contributed to more release of substances under acidic conditions, and there are still few specific release systems for alkaline chronic wounds.

On the other hand, some pH-responsive swelling behavior changes in hydrogel dressings have been reported. For example, alginate hydrogels showed a higher swelling ratio at higher pH because the carboxyl groups in calcium alginate are more easily ionized to result in increased electrostatic repulsion.[133] Similarly, acrylic acid and CMC hydrogels also exhibit the same pH-responsive swelling properties, which is closely related to the carboxyl groups in its structure.[71,85] In addition, some pH-sensitive hydrogel dressings are used to monitor the status of wound in real time, which will be described in detail in the corresponding sections.

The biggest advantage of photoresponsive hydrogel dressings is that it is easy to control. The most common example for the photoresponsive hydrogels is the photothermal behavior, which has already been covered in the photothermal antibacterial section. In addition, Xu *et al.* reported a dual photoresponsive hydrogel dressing containing both photothermal nanomaterial GO and photobase reagent malachite green carbinol base (MGCB). In addition to adjusting temperature in response to NIR light, OH^- can also be released by the MGCB molecule in response to ultraviolet (UV) light, resulting in a gradient of pH value (Figure 9D).[255] Gao *et al.* reported a NIR light-controllable on-demand antibiotics release hydrogel dressing. The release of antibiotics from the hydrogels is small under physiological conditions but promoted in the case of NIR light. At the same time, the NIR photothermal effect of PDA can also lead to the destruction of bacterial integrity, leading to the coinactivation of bacteria.[60] At the same time, light-controlled multiple and timed release of small extracellular vesicles has been shown to be more effective than a single dose or multiple dose release in diabetic wounds.[256]

In addition to those hydrogel dressings that respond to a single condition, there have also been some hydrogel dressings that can respond to two or more conditions simultaneously. For example, hydrogels that have both light and pH responses. Due to the protonation of the amino group of CS at acidic pH, the subsequent electrostatic repulsion and enhanced hydrophilicity within the molecule caused the PF127-based thermoresponsive hydrogel to swell sharply and accelerate degradation, resulting in increased drug release.[50] Another example is to provide photoresponse by loading PDA, and pH response release of antibiotics by protonation of amino groups or hydrolysis of cellulose under acidic conditions, achieving a dual response to pH and light.[55] In addition, a pH and glucose dual-responsive hydrogels system has also been reported, in which the pH response is provided by changes in the stability of Schiff base under different pH, while the glucose response is provided by the competitive combination between glucose and phenylboronic acid.[191]

Conductive Hydrogel Wound Dressing. In the case of defects or wounds, the combination of positive charges in the wound and negative charges around the entire skin forms what is known as the skin battery, and the endogenous electric field at the wound site is also considered to be a directional signal leading cells to migrate into the wound during wound healing.[257] Studies have shown that applying external current to the electrode placed on the wound bed to simulate the endogenous current at the wound is conducive to the migration of macrophages, neutrophils, and keratinocytes and further accelerate the closure of wound.[258,259] Some important electrical signal molecules have also been found in this process, such as EGF receptor, integrin, V-ATPase H^+ pump, and PI3 kinase/Pten (phosphoinositide 3-kinases/phosphatase and tensin homologue).[257] However, the application of exogenous electrical stimulation may require the use of large-scale external electronic equipment, which brings inconvenience to patients. So, electroactive dressings containing conductivity similar to skin are developed and proved to be conducive to wound regeneration and repair.[260−268] Based on our previous research on conductive polymers, Zhao *et al.* used polyaniline-based conductive hydrogel in skin wound repair in 2017. It is further confirmed that the hydrogel with the conductive component polyaniline had a better effect on promoting the repair of damaged tissues than the hydrogel without conductive component (Figure 10A).[36] On the basis of this work, Qu and Zhao *et al.* prepared a conductive hydrogel based on oxidized HA-*graft*-aniline tetramer (OHA-AT) and CEC.[30] Next, inspired by the dopamine chemistry, two multifunctional self-healing antibacterial antioxidant conductive hydrogel dressings with the conductivity of CNT or GO based on gelatin and HA were prepared, respectively, by Liang and Zhao *et al.* (Figure 10B,D).[33,57] Among them, the dopamine-polymerized hydrogels between dopamine-grafted gelatin and dopamine-coated CNT induced by H_2O_2/HRP were further used to repair *S. aureus* infected skin defects.[57] On this basis, Liang *et al.* generated an *in situ* forming hydrogels based on glycidyl methacylate-functionalized QCS and methacrylate-functionalized gelatin. In addition, GO was compounded by electrostatic interaction to prepare a series of multi-antibacterial hydrogel dressing systems with multiple antibacterial activities including intrinsic antibacterial, photothermal antibacterial, and drug sustained release antibacterial abilities. The skin wound repair experiment of drug-resistant bacteria methicillin-resistant *Staphylococcus aureus* (MRSA) infection verified the prominent advantages of multiantibacterial in dealing with drug-resistant bacteria (Figure 13B).[108] In summary, we have initially confirmed that the conductive properties of the hydrogel have played a positive role in promoting wound healing based on the research of these conductive hydrogel dressing in our previous studies and further demonstrated the better promoting effects of conductive hydrogel dressing compared to nonconductive dressing in the common wound, infected wounds as well as the drug-resistant bacteria infection wound model through the wound closure ratio, collagen deposition, granulation tissue thickness, regeneration of some skin appendages such as hair follicles and blood vessels, and immunofluorescence detection of inflammation and angiogenesis.

Some other research groups have also reported related conductive hydrogel dressings. For example, Xu *et al.* fabricated conductive injectable hydrogels (QCS-*g*-PTA/PEG-PSS-BA) with poly(ethylene glycol)-*co*-poly(sorbitol sebacate) (PEG-PSS-BA) copolymer conjugated with QCS-*g*-polytetraaniline

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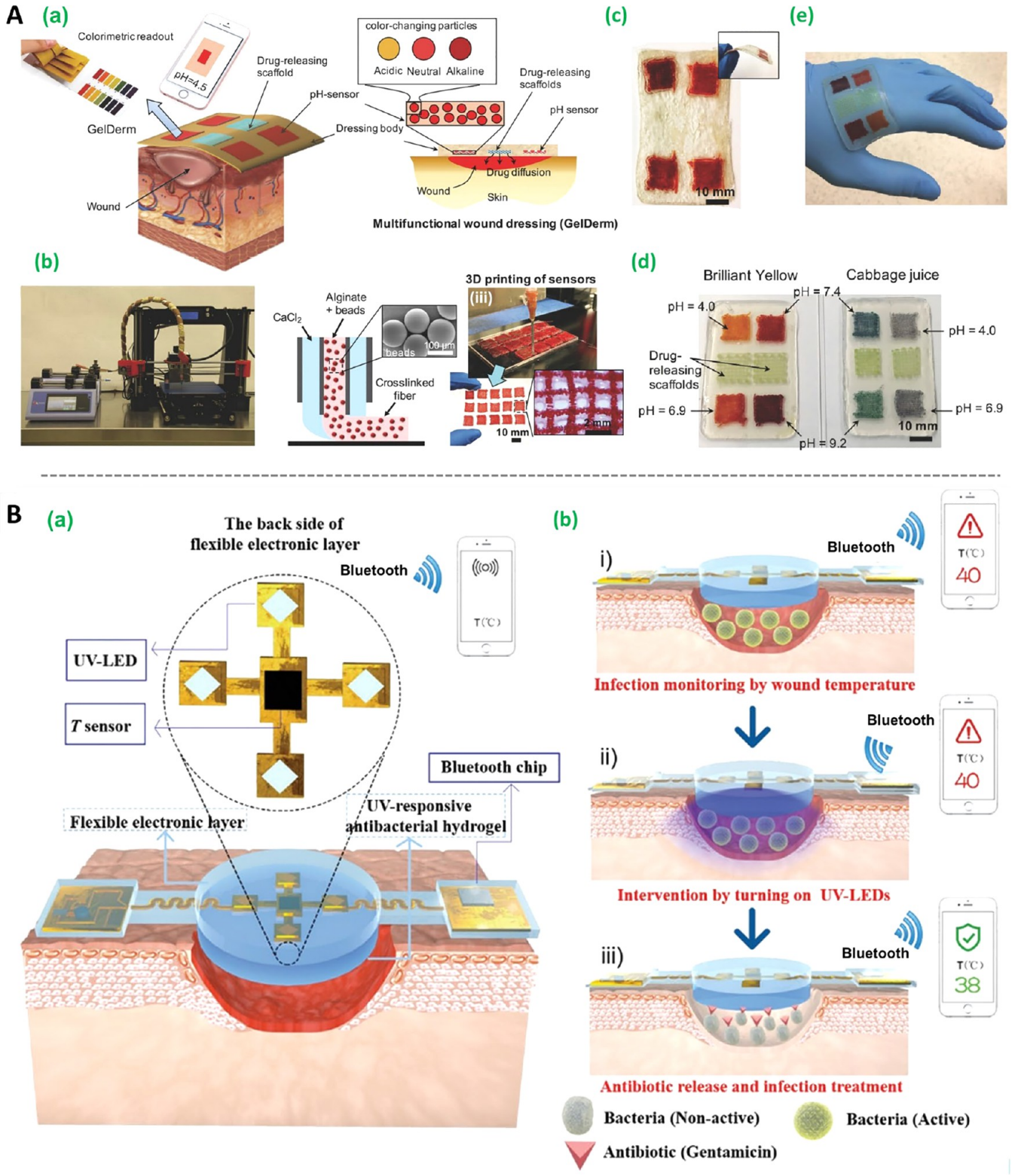

Figure 11. Wound monitoring hydrogel wound dressings. (A) An advanced multifunctional dressing (GelDerm) for monitoring and management of wounds; (a) schematic diagram of GelDerm hydrogel for the treatment of epidermal wounds; (b) schematic diagram of a 3D bioprint with a coaxial flow microfluidic nozzle; (c) representative photographs of the dressing; (d) synthetic brilliant yellow and naturally derived cabbage juice were used as model pH indicators for the fabrication of the sensors; and (e) GelDerm can maintain a conformal contact with irregular surfaces. Reprinted and modified with permission from ref 272. Copyright 2017 Wiley-VCH. (B) Schematics of the structures and working principles of the double-layer hydrogel sensor; (a) schematic diagram of sensor packaging and dressings construction; and (b) conceptual diagram of the process of temperature detection of infected wounds and on-demand release of antibiotics. Reprinted and modified with permission under a Creative Commons Attribution 4.0 International License from ref 273. Copyright 2020 Wiley-VCH.

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Table 2. Functional Requirements of Hydrogel Dressings in Different Types of Wounds

wound		functional requirements	implementation strategy of dressing function
acute wound	incisional wound	adhesion	catechol[145] and quadruple hydrogen bonding,[29] skin secretion of Andrias davidianus,[141] tyramine,[142] carboxyl[150]
		removability	photothermal-induced hydrogen bond elimination[29]
		hemostasis	chitosan[142]
	excisional wound	antibacterial property, adhesion and hemostasis, anti-inflammatory and anti-oxidation, substance delivery, self-healing, stimulus-response, conductivity, wound monitoring	
	infected wound	antibacteria	photothermal (CNTs)[57] and photodynamic antibacterial, cationic polymer (quaternary ammonium),[108] antibiotics, inorganic metals and metal oxides
		antibacteria	physical barrier,[299−301] honey,[118,165,303] Ag[75,95,98,101]
		moisture retention	most hydrogels
		removability	thiol−thioester exchange,[138] competitive dissociation of Schiff bases[236]
	burn wound	angiogenesis	dextran,[304] VEGF,[162] LLKKK18[46]
		anti-inflammatory	resveratrol,[162] LLKKK18[46]
chronic wound		cells delivery	keratinocytes,[192] fibroblasts,[194] and ADSCs[167]
		cytokines delivery	EGF, VEGF,[208] macrophage colony-stimulating factor (rhGM-CSF)[213]
		cells and cytokines delivery	SDF-1,[212] platelet-rich plasma,[305] exosomes[256]
		reducing blood glucose	GOx,[130,275] insulin-releasing,[191]
	diabetic wound	antibacteria	IKFQFHFD (self-assembly antibacterial octapeptide),[106] Ag[96]
		anti-inflammatory	curcumin,[177] An NPs[76]
		angiogenesis	DFO,[77] silicon,[306] hyaluronic acid oligosaccharides and VEGF[133]
		others	oxygen delivery[218]

(QCS-*g*-PTA), which provide conductivity by using AT.[269] Lin *et al.* prepared a hydrogel based on supramolecular assembly of PDA-modified Ag NPs (PDA@Ag-NPs), polyaniline, and PVA (PDA@Ag-NPs/CPHs), which provide conductivity by using Ag NPs and polyaniline, which showed good therapeutic effect in diabetic wounds.[74] Using the conductivity of GO, Tang *et al.* also developed a PDA-reduced GO-incorporated CS and SF (pGO-CS/SF) conductive hydrogel scaffold.[178]

As a common conductive polymer, polypyrrole (PPy) is also used to prepare conductive hydrogel dressings. Lu *et al.* prepared a conductive hydrogel dressing based on the covalent cross-linking between poly(2-hydroxyethyl methacrylate) (PHEMA) and 3-sulfopropyl methacrylate and doped the conductive component PPy into the hydrogel network under weak alkaline physiological environment. They also confirmed that this conductive hydrogel dressing has improved the wound healing effect than the traditional electrode-based electrical stimulation (Figure 10C).[270]

Polythiophene (PTh) is another widely studied conductive polymer, and PEDOT is a derivative of PTh. The properties of PEDOT are similar to PPy, but its electrical stability is better than PPy. Owing to its biocompatibility and high conductivity, PEDOT has been widely used to develop electroactive substrates for cell culture and biosensor. Self-healing and conductive hydrogels based on PEDOT:PSS/guar gum also showed great improvement in wound closure and tissue reorganization.[271]

In general, most of the current research on conductive hydrogels is focused on wearable and implantable biomedical devices, with little research on wound healing. In the future, we expect more multifunctional conductive hydrogel dressings for wound healing and even wound monitoring.

Wound Monitoring Hydrogel Wound Dressing. From the beginning of the single function of wound dressings to the development of multifunctional wound accessories in recent years, our focus has been on a simple one-time solution strategy, but wound healing is a complicated process and some parameters near the wound are also changing constantly, which means that more strategies are needed to implement wound management and monitoring. In 2017, Akbari *et al.* doped pH responsive color-changing mesoporous resin beads (Figure 11A) with alginate fibers and then constructed a hydrogel containing porous pH sensor array through 3D printing. This hydrogel can provide real-time data on wounds, such as bacterial infection and antibiotic release by measuring color changes. In addition, when connected to the image acquisition equipment, the multifunctional dressing can also achieve digital remote diagnosis and treatment.[272] Pang *et al.* developed a double-layer hydrogel sensor, with an upper layer of polydimethylsiloxane integrated with a temperature sensor and UV light-emitting diode, and a lower layer of UV-sensitive antimicrobial hydrogel (Figure 11B). This dressing provides early infection diagnosis through integrated sensors that enable real-time wound temperature monitoring and on-demand treatment of infections by releasing antibiotics from hydrogels *via in situ* UV radiation.[273] Furthermore, Mostafalu *et al.* developed a commercial wound dressing that includes both pH and temperature sensors. pH is one of the key parameters for monitoring chronic wounds, and temperature sensors are used to provide further information about wound inflammation. When temperature changes are detected, the dressings can also be used to deliver on-demand drug release for inflammatory changes by loading a thermally responsive drug carrier hydrogel and electronically controlled flexible heaters, and the drug release protocol can also be programmed for personalized treatment.[274] In 2019, Zhu *et al.* further developed a multifunctional zwitterionic hydrogel that can detect both pH and glucose levels to monitor wound conditions in diabetic patients. The wound dressing can successfully monitor pH values of 4−8 and glucose concentrations of $0.1-10 \times 10^{-3}$ M, while providing a moist healing environment that promotes healing of diabetic wounds. This multifunctional wound dressing can be used for the treatment of chronic wounds and guide the clinical application of diabetes.[275]

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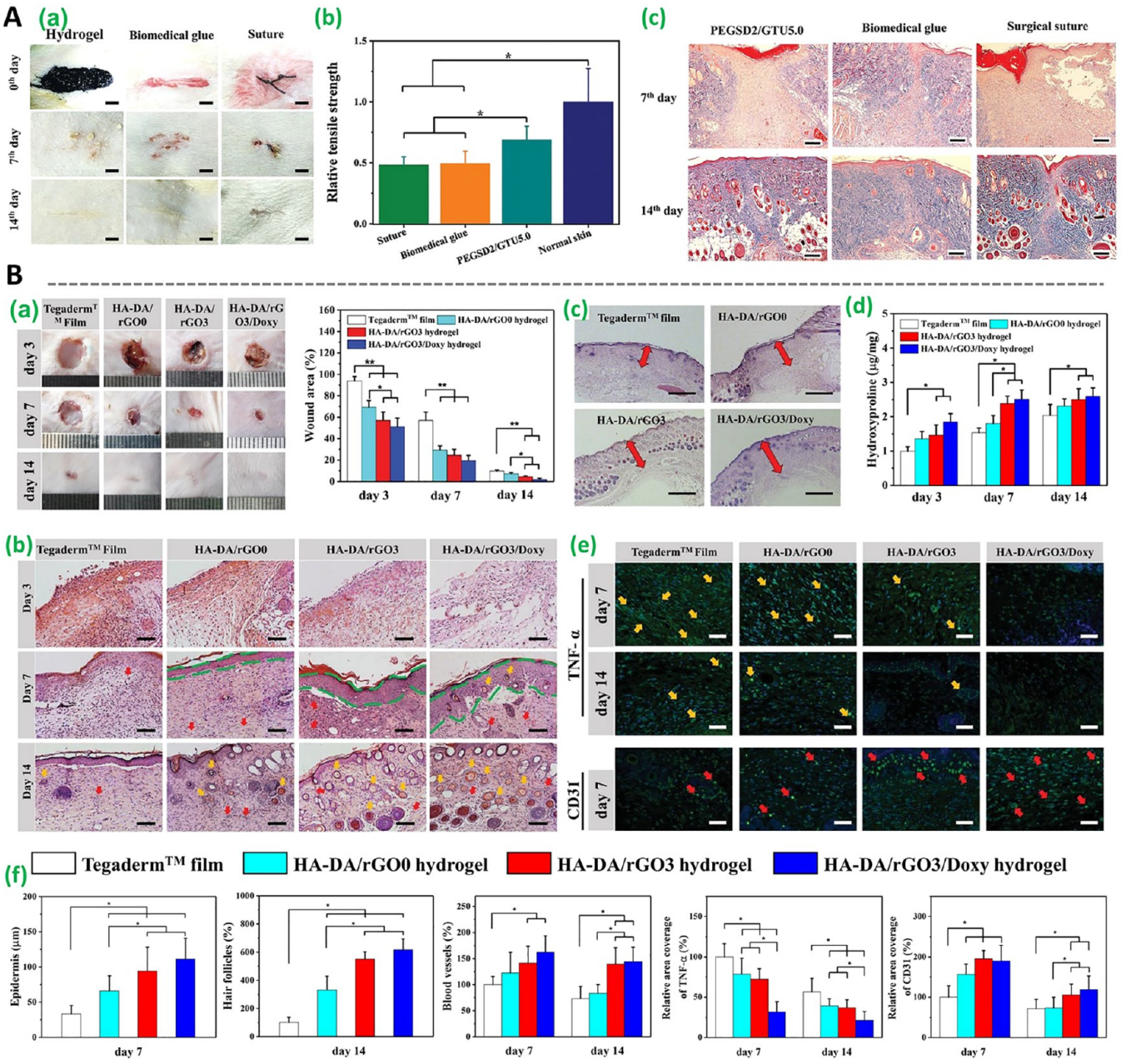

Figure 12. Conventional acute wound healing. (A) Incision wound healing. (a) Representative pictures of rat incision wounds at different day after surgery, scale bar: 5 mm; (b) relative tensile strength of healed skins after treated for 14 days; (c) Masson trichrome staining of harvested healing skins at days 7 and 14 postsurgery, scale bar: 100 μm. Reprinted and modified with permission from ref 29. Copyright 2020 Wiley-VCH. (B) Some evaluation indicators in excisional wound healing: (a) wound area; (b) HE staining for inflammation, re-epithelialization, and regeneration of blood vessels and hair follicles; (c) granulation tissue; (d) collagen; (e) immunofluorescence for inflammation and regeneration of blood vessels; and (f) Quantitative statistics of epidermal, vascular, and hair follicle regeneration through HE staining, and quantitative statistics of inflammation and angiogenesis through immunofluorescence. Reprinted and modified with permission from ref 35. Copyright 2019 Wiley-VCH.

TYPE OF WOUND APPLIED WITH HYDROGEL DRESSING

There are many types of skin wounds, and different types of wounds often require different dressings.[297] On the other hand, skin wound healing is an extremely complex process that relies on a complex interaction of highly regulated factors working together to restore the barrier function of damaged skin. However, it can go wrong in many steps along the way, especially in an underlying disease state such as diabetes. When wound healing does not work properly, it can lead to chronic wounds, which can be a huge burden on patients and the health care system.[298] So in this part, we will first discuss the problems that need to be paid attention to in the process of repairing different types of wounds, and then, we will start with some examples of chronic wounds caused by infection, burns, and diabetes and discuss the special needs in chronic wound healing (Table 2).

Conventional Acute Wound Healing. Acute trauma models are often similar to real surgery or trauma. The term "acute" refers to the rapid introduction of damage and the relatively rapid repair process. There are many types of acute

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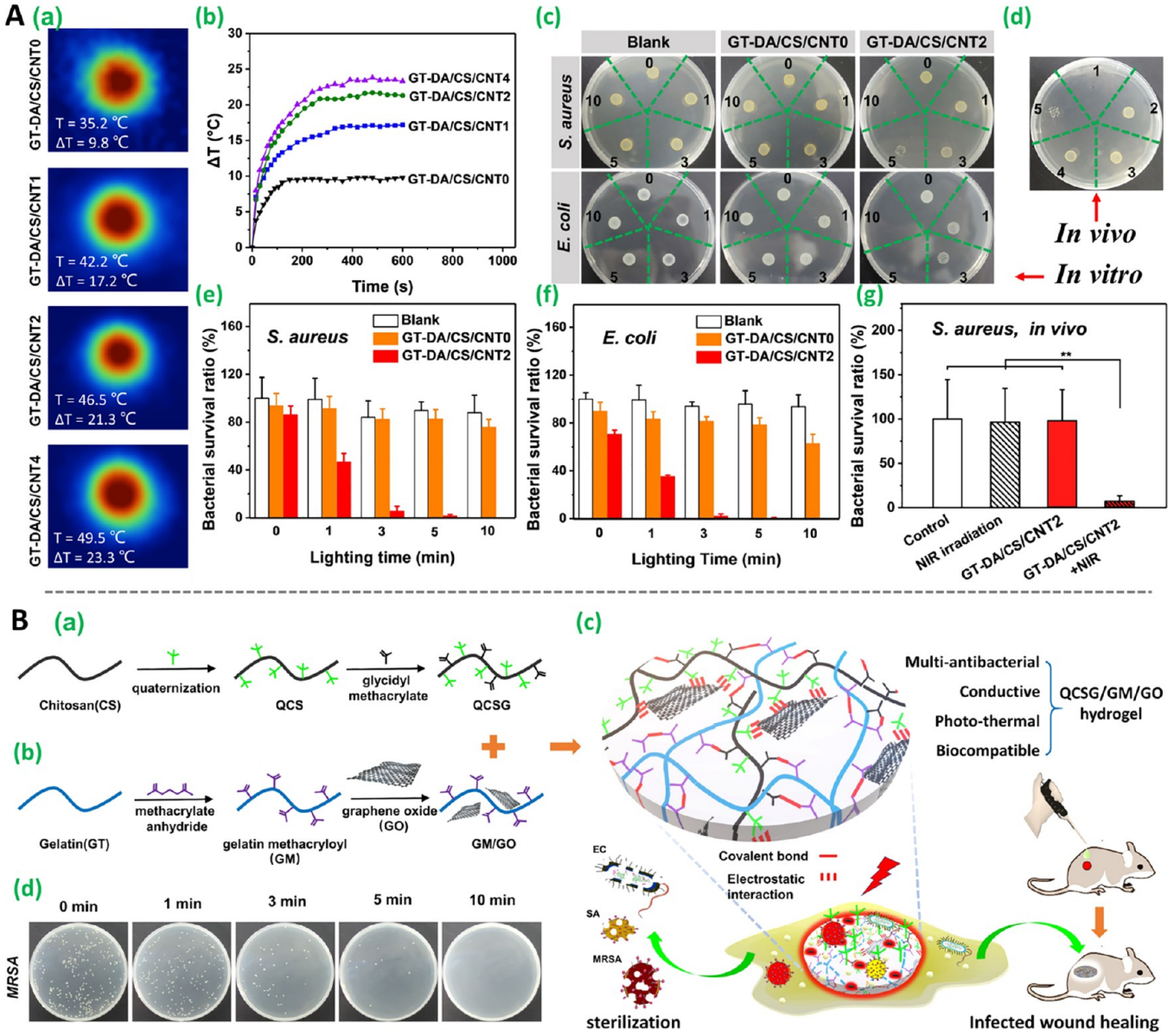

Figure 13. (A) A photothermal antimicrobial strategy. (a) Heat maps of GT-DA/CS/CNT hydrogels after 10 min NIR irradiation; (b) Δ*T*-NIR irradiation time curves; (c) NIR irradiation-induced *in vitro* antibacterial activity of hydrogels with 0, 1, 3, 5, and 10 min; (d) pictures of *in vivo* antimicrobial ability; bacterial survival ratios of (e) *S. aureus* and (f) *E. coli*; and (g) *in vivo* antibacterial activity test of *S. aureus*. Reprinted and modified with permission from ref 57. Copyright 2019 Elsevier. (B) A preparation strategy of multiple antibacterial hydrogel wound dressings combining cationic antibacterial, photothermal antibacterial, and antibiotic release bactericidal. (a) Schematic diagram of the synthesis of glycidyl methacrylate functionalized quaternized chitosan (QCSG) and (b) gelatin methacrylate; and (c) scheme of QCSG/GM/GO hydrogel's network and applications in sterilization and wound healing. (d) Representative images of antibacterial tests. Reprinted and modified with permission from ref 108. Copyright 2020 American Chemical Society.

injuries, and we will use only two kinds of what are common in the literature to illustrate the issues that need to be addressed in the healing process.

Incisional wounds usually refer to tissue splitting wounds with minimal collateral damage caused by sharp blade-like utensils. Strictly speaking, if the wound surfaces can be accurately butted in time, supplemented by good sutures or bandaging operations, it usually only produces a very small scar tissue, and its healing is also easier to achieve perfect repair. Besides, incisional wounds are also suitable for the test of tissue mechanical properties after healing. However, there are also some problems, such as the aesthetic appearance of the tissue near the wound caused by the traditional tissue suture and the complicated operation caused by the need to remove the suture, and the insufficient flexibility of the adhesive layer in the presence of commonly used cyanoacrylate tissue adhesives and potential toxicity after degradation. This also poses challenges to the healing of incisional wounds. Therefore, some hydrogel dressings based on incisional wounds have been proposed. For example, our research group recently developed a physical double-network hydrogel with shape adaptability, self-healing, tissue adhesion, antioxidant activity, and NIR/pH stimuli responsiveness based on poly(glycerol sebacate)-*co*-poly(ethylene glycol)-*g*-catechol prepolymer and UPy-hexamethylene diisocyanate synthon-modified gelatin (GTU). The Fe^{3+}-mediated cross-linking of catechol groups and the quadruple hydrogen bonding between

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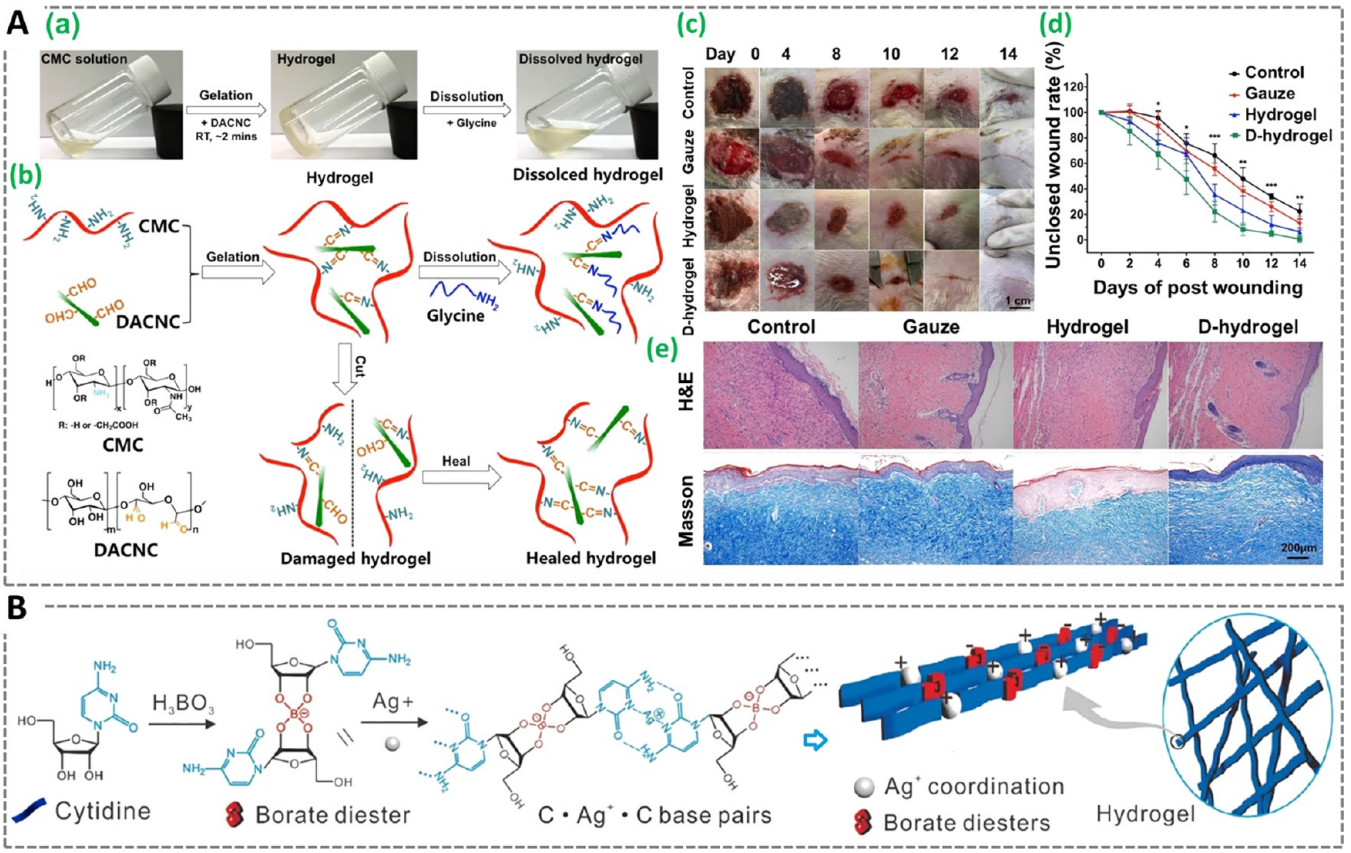

Figure 14. Hydrogel dressing for burn wound healing. (A) An on-demand dissolution burn wound hydrogel dressing based on Schiff base cross-linking between CMC and DACNC guided by competitive binding strategy. (a) Images of hydrogel formation and dissolution after adding competitive glycine; (b) schematic diagram of hydrogel structure, and dissolution caused by competitive binding of glycine; (c) representative pictures of wound area at different time in different experimental groups during burn wound repair, scale bar: 1 cm; (d) quantitative statistics of unhealed wound rate; and (e) H&E tissue staining and Masson staining images of wounds in different groups, scale bar: 200 μm. Reprinted and modified with permission from ref 236. Copyright 2018 American Chemical Society. (B) A functional antibacterial hydrogel formed by mixing $AgNO_3$ with cytidine and $B(OH)_3$ for the burn wounds. Reprinted and modified with permission from ref 75. Copyright 2019 American Chemical Society.

ureido-pyrimidinone system gives the hydrogel a double network. In addition to the strong response to multiple resistant bacteria and healing function for full-thickness wound benefitting from good antimicrobial antioxidant properties, good tissue adhesion and ease of removal properties also allow it to demonstrate its potential as a tissue adhesive to facilitate wound healing in incisional wounds. A corresponding animal test also proved its ability to promote better skin incision healing than sutures and tissue glue. In addition, the skin after healing with hydrogel adhesive also showed a significantly higher relative tensile strength than sutures and medical glue and close to normal skin (Figure 12A).[29] Coincidentally, due to its excellent tissue adhesion effect, a hydrogel adhesive prepared by Deng *et al.* based on the skin secretion of *Andrias davidianus* was also used to heal incisional wound, in addition to repairing tissue defects (Figure 4C).[141] Hydrogels prepared by Lih *et al.* based on tyramine were also used to promote the healing of incisional wound.[142] The hydrogel dressing for incisional wound healing must have good tissue adhesion properties in order to join the wound interface quickly and firmly. Therefore, some of the researches we have previously mentioned in the adhesive hydrogel dressing are also used to promote healing of incisional wounds.[145,150]

Unlike incisional wounds, excisional wounds usually have many tissue defects, which pose great challenges in repairing dressings. Among the excisional wounds, full-thickness wounds in which the epidermal layer, dermal layer, and subcutaneous fat are all lost are the most widely used. In this review, most of the research used this kind of wound. The larger material-tissue contact area makes it possible to obtain cells, tissues, RNA, exudate, and tissue specimens from larger cross-sectional area and volume, which is more conducive to the detection of some further biochemical and histological parameters. Specifically, various parameters such as wound closure rate, inflammation cell (not caused by bacteria), granulation tissue formation, re-epithelialization, collagen deposition, angiogenesis, hair follicle formation, and a series of healing-related cells[40,48,195,199] and cytokines were used to evaluate the healing process of excisional wounds. Figure 12B shows an example of the preparation of nanocomposite adhesive conductive self-healing antibacterial anti-oxidation multifunctional hydrogel based on the enzyme-catalyzed polymerization of dopamine between hyaluronic acid grafted dopamine and GO coated dopamine. The work has systematically evaluated wound closure rates, granulation tissue, collagen, and assessed the inflammation, re-epithelialization, and regeneration of blood vessels and hair follicles by HE staining. In addition, immunofluorescence was also used to evaluate inflammation, and regeneration of blood vessels.[35]

Chronic Infected Wound Healing. Bacterial infections are inevitable during wound repair and can even lead to serious

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complications, including sepsis. So, the control of infection has been considered one of the most critical challenges in bioengineering applications, especially in tissue regeneration, which poses a serious threat to public health. When a wound is infected, the bacteria cause persistent inflammation at the infected site, delaying the healing process in the inflammatory phase, and severe inflammation often leads to unsuccessful wound healing. At present, the most widely used clinically antibacterial strategy in wound healing is still antibiotics. However, the use of antibiotics promotes the development of drug resistance. In order to solve this problem, various antibacterial hydrogels have been prepared by different methods, including the physical loading of antibacterial substances and/or the inclusion of antibacterial components in the hydrogel network through chemical reactions. Among the many nanoparticles reported as antimicrobial agents for the hydrogel dressing, inorganic nanoparticles, including silver, copper, gold and zinc have been widely explored for potential antimicrobial applications. However, the use of these inorganic nanoparticles as antimicrobial agents is greatly limited by their nonspecific biological toxicity or possible *in vivo* long-term retention. Recently, metal-free antimicrobial agents such as antimicrobial peptides and polymers, GO, and quaternary ammonium salts have been reported for use in antimicrobial therapy. However, there are still some problems in different degrees, which limit their further application. On the other hand, the strategy of using local heat generated by some nano-photothermal agents such as gold, tungsten, and graphene under NIR light to sterilize has attracted attention. For example, gelatin grafted dopamine (GT-DA) and PDA-coated CNTs (CNT-PDA) were used to construct a antibacterial, adhesive, antioxidant, and conductive GT-DA/chitosan/CNT hydrogel by oxidative coupling of the catechol groups through a H_2O_2/HRP catalytic system. In addition, CNT-PDAs possess these hydrogels excellent photothermal effect and shows good antibacterial activity against Gram-positive and Gram-negative bacteria *in vitro* and *in vivo* (Figure 13A).[57] However, they generally increase the potential for thermal damage to surrounding healthy tissue because a relatively high temperature is required to kill bacteria. Therefore, we further developed a multi-antibacterial strategy combining intrinsic antibacterial, antibiotic releasing antibacterial, and photothermal antibacterial and hope it can play a role in the future when facing the possible complex infections (Figure 13B).[108] But, in general, there is still no perfect strategy for dealing with infections in wound healing.

Chronic Burn Wound Healing. Burns are the most common and destructive form of wound, often accompanied by life-threatening severe infections, excessive inflammation, reduced angiogenesis, insufficient extracellular matrix production, and insufficient stimulation of GFs, resulting in delayed healing. Rapid and dangerous fluid loss occurs when the skin is affected by high temperature, and the coagulation and loss of proteins, including immunoglobulin, can lead to irreversible tissue damage and susceptibility to infection. In addition, membrane dysfunction can lead to severe changes in the distribution of water and sodium, loss of extracellular fluid and consumption of sodium will further reduce blood volume, change electrolyte balance, and lead to the death of burn patients. Although superficial burns generally have less scarring after healing, the current treatment is still not satisfactory because second- and third-degree burns can damage many important functions of the epidermis and dermis. Hydrogel dressing, while ensuring good moisturizing effect, can also effectively prevent bacterial infection through physical barrier.[299−301] Moreover, the good universality of hydrogel makes it able to load a variety of functional factors, which have become a promising dressing source in burn wounds. Easy removal ability of hydrogels also avoids secondary injury and pain during dressing replacement (Figure 14A).[138,236] According to the main challenges of burn wound healing, the research progress of hydrogel dressings for burn wounds is mainly introduced below.

Infection is one of the most common complications associated with burn wounds and, in severe cases, can lead to septicaemia which can damage the immune and inflammatory responses throughout the body. Studies have shown that in burns covering more than 40% of the body surface area, sepsis or other complications caused by wound infection and the failure of some vital organs account for more than 75% of the deaths. Thus, in the treatment of burn wounds, control of infection is a particularly important link. Many researches focused on reducing infection in burn wound healing.[302] Honey, which reduces abscesses, ulcers, and has antibacterial properties, is often used as a wound dressing for burns.[118,165,303] Silver hydrogels are also widely used as wound dressings for burns (Figure 14B),[75,95,98,101] and there are already some clinically available products such as silver sulfadiazine, Acticoat, and PolyMem silver.

Angiogenesis is important in the healing of deep burn wounds, which lose more dermal blood flow than the superficial burns. The number of new blood vessels directly determines whether the nutrition and oxygen supply is adequate for the subsequent healing process, and whether the healing can be done quickly and primarily, instead of delaying the healing and even leading to necrosis and traumatic scarring. Sun *et al.* prepared a dextran-allyl isocyanate-ethylamine (Dex-AE)/polyethylene glycol diacrylate hydrogel and confirmed that the material−organization interaction can stimulate rapid angiogenesis and promote skin regeneration of burn wounds.[304] In addition, excessive inflammation is also a major obstacle in burn wound healing and skin regeneration. Some natural and synthetic substances with anti-inflammatory properties are also used to compound influent gel dressings.[167,180] But, reduced inflammation often does not provide the optimal healing environment for the normal wound healing process, because inadequate local angiogenesis may worsen the inflammatory response and lead to cell dysfunction, which makes wound healing more difficult. Therefore, some hydrogel systems that have both anti-inflammatory and vascular regeneration properties have been developed. For example, a system loaded with VEGF to promote angiogenesis while encapsulated with resveratrol to achieve anti-inflammatory effects[162] was designed. LLKKK18, an antimicrobial peptide that not only reduces oxidative stress and inflammation but also increases VEGF and microvascular development in the body, has also been used in burn wound dressings.[46]

The complex wound healing process also requires the synergy of various tissue and cell lineages as well as extracellular and intracellular signals. So, many cells such as keratinocytes,[192] fibroblasts,[194] and ADSCs[167] and cytokines such as EGF, VEGF,[208] and macrophage colony-stimulating factor (rhGM - CSF)[213] and so on are all studied to promote the healing of burn wounds.

Chronic Diabetic Wound Healing. Diabetes, the most common metabolic disease, is a major health and economic problem. Diabetes patients' wounds take longer to heal than normal wounds, and chronic wounds can even lead to

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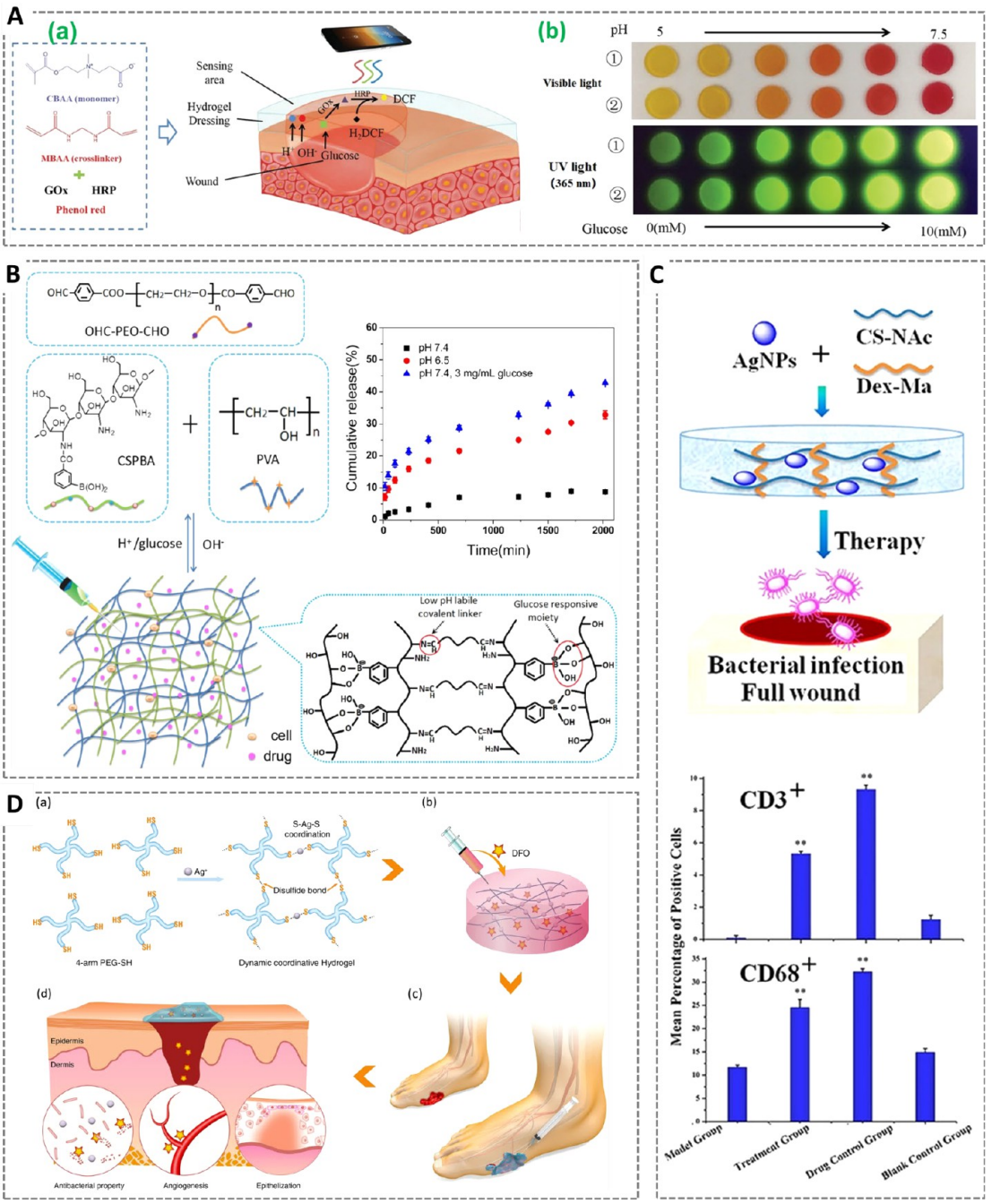

Figure 15. Hydrogel dressing for wound healing in diabetes mellitus. (A) Scheme of zwitterionic PCB hydrogel dressing encapsulated with a pH indicator dye (phenolic red) and two glucose-sensitive enzymes (GOx and HRP) for the detection of pH value and glucose concentration in wound exudate. (a) Schematic diagram of hydrogel; (b) functionalized wound dressing for simultaneous detection of pH values (under visible light) and glucose concentrations (under UV light). pH values: 5.0, 5.5, 6.0, 6.5, 7.0, and 7.5. Glucose concentrations: 0, 0.1, 0.5, 2, 5, and 10 × 10^{-3} m. PCB-PR-E hydrogel discs in ① PBS and ② AWE solutions. Reprinted and modified with permission from ref 275. Copyright 2020 Wiley-VCH. (B) A hydrogel wound dressing with pH and glucose dual-responsive insulin release function constructed by dynamic Schiff base and phenylboronic acid ester. After loading fibroblasts, a wound healing promotion strategy combining drug therapy, cell therapy, and extracellular matrix scaffolds was realized. Reprinted and modified with permission from ref 191. Copyright 2017 American Chemical Society. (C) A antipollution silver nanoparticle hydrogel dressing for the condition of low systemic cellular immunity. The upregulated expression levels of $CD68^+$ and $CD3^+$ indicated that hydrogel could trigger the immune response in the treatment of diabetic wound healing. Reprinted and modified with permission from ref 76. Copyright 2019 American Chemical Society. (D) Schematic illustration of the self-healing Ag(I)-thiol (Ag−S) coordinative hydrogel prepared by mixing 4-arm-PEG-SH, DFO, and $AgNO_3$ for diabetic wound healing; DFO can promote the secretion of hypoxia-inducible factor-1, so as to upregulate the expression of angiogenic GF. Reprinted with permission under a Creative Commons Attribution 4.0 International License from ref 77. Copyright 2019 Springer Nature.

amputations, making therapies to promote healing of diabetic wounds particularly important. Specifically, diabetic wounds are characterized by hyperglycemia, prolonged inflammation, hypoxia, poor vascularization, cellular infiltration, and granulation tissue formation. Successful wound healing requires the interaction of a highly organized sequential cascade of resident

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and recruited cell types, GFs, and cytokines. In the following, we will focus on the problems encountered in wound healing of diabetes mellitus and illustrate the current research progress one by one.

Cells delivered to diabetic skin trauma often do not have the high cell migration ratio that is found in many other tissues. Lee *et al.* prepared a thermosensitive hydrogel dressing from a biodegradable and biocompatible triblock copolymer PEG-PLGA-PEG. In diabetic mouse models, the engraftment of muscle-derived stem cells was increased by 20−30 times, thus significantly improving the healing of diabetic wounds.[246] In addition, exogenous cell and GFs can compensate for the absence or deficiency of endogenous cell and GFs to overcome the impaired wound healing in diabetic patients. So, many hydrogel dressings loaded with various cells and cytokines have been reported to promote healing of diabetic wounds. For example, SDF-1 is loaded in a hydrogel dressing due to its ability to promote endothelial progenitor cell homing and angiogenesis.[212] The use of platelet-rich plasma in diabetic wound healing has also been reported because it can provide a large number of autologous platelet-derived GFs such as TGF-β, insulin-like GF-I, VEGF, and bFGF.[305] Small extracellular vesicles, commonly referred to as exosomes, are cell-based vesicles with diameters of 50−200 nm that contain not only miRNAs but also other biomolecules such as proteins, lipids, and mRNA. It is also loaded into hydrogel to promote healing of diabetic wounds.[256]

Diabetic wound healing rates are significantly reduced by high blood sugar levels because they prevent nutrients and oxygen from providing energy to cells. In view of this, there are also studies to reduce the blood glucose around the wound by loading glucose oxidase (GOx).[130] For example, a pH indicator dye (phenolic red) and two glucose-sensitive enzymes, GOx and HRP, are encapsulated in zwitterionic poly carboxybetaine (PCB) hydrogel dressings to detect both pH and glucose levels and allow data to be transmitted to smartphones (Figure 15A).[275] Furthermore, Zhao *et al.* prepared a glucose-responsive insulin-releasing hydrogel. The hydrogel dressing system is also loaded with fibroblasts, combining drug therapy, cell therapy, and extracellular matrix scaffolds into one (Figure 15B).[191] Excessive sugar in wound blood also causes bacteria to grow faster than normal wounds, and high blood sugar levels also prevent immune cells from fighting off invading bacteria. So, the infections in diabetic wounds can make healing particularly tricky and severely lead to complications such as gangrene or sepsis. Therefore, many hydrogel dressings with antibacterial properties are also used in the treatment of diabetic wounds. For more difficult repaired biofilm-forming bacteria-infected wounds, related hydrogel dressings have also been developed.[106] A hydrogel based on innate immune molecule lactoferrin and the rare sugar-alcohol xylitol was used to treat bacterial biofilms.[96]

Furthermore, although chronic and acute wounds go through similar stages of healing, high blood sugar prevents the immune system from functioning effectively, increasing cellular inflammation. Chronic wounds seem to stall during the inflammatory phase of wound healing, which means that unnecessary excessive inflammation must be reduced. So, the application of anti-inflammatory hydrogel dressings in diabetic wounds is also a promising option. For example, in response to matrix metalloproteinases, which are often overexpressed in nonhealing wounds of diabetes, Liu *et al.* prepared gelatin microspheres containing hydrogels loaded with curcumin nanoparticles.[177] At the same time, Shi *et al.* also developed a antipollution silver nanoparticle hydrogel dressing for the condition of low systemic cellular immunity. The upregulated expression levels of $CD68^+$ and $CD3^+$ indicated that hydrogel could trigger the immune response in the treatment of diabetic wound healing (Figure 15C).[76]

Hypoxia is also thought to be a key factor in nonhealing diabetic wounds. So, Patil *et al.* prepared a oxygen-containing biomaterial hydrogel wound dressing to treat diabetic wounds and showed increased collagen synthesis and angiogenesis as well as increased skin tissue maturity.[218]

Another main reasons for the difficulty of wound healing in diabetes is wound vascularization. High glucose levels in the blood can block normal blood flow to the wounds, leading to a lack of nutrients, which can inhibit angiogenesis and delay the healing of diabetic wounds. DFO can promote the secretion of hypoxia-inducible factor-1, so as to upregulate the expression of angiogenic GF (Figure 15D).[77] Silicon ions can upregulate the expression of VEGF, so they are used in combination to promote vascular regeneration in diabetic wounds.[306] Besides, small fragments or hyaluronic acid oligosaccharides have been shown in various experimental systems to stimulate endothelial cell proliferation, migration and tubule formation, and induce angiogenesis, so it is used to promote blood vessels regeneration along with VEGF.[133]

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Hydrogels have become the most competitive candidates in the last decades and show a trend of increasing year by year in the application of wound dressing. With the continuous deepening and refinement of clinical needs, the function of hydrogels has also changed from the original single physical coverage or function to the current composite of multiple functions and shows a trend of further intelligentization. Therefore, this review summarizes the enhanced functions of hydrogel dressings mentioned in the existing reports including antibacterial, adhesion and hemostasis, anti-inflammatory and antioxidant, substance delivery, self-healing, stimulus response, conductivity, and recently exposed wound monitoring and the strategies used to achieve these functions. Bacterial infection is the most common and unavoidable challenges in wound healing. Therefore, antibacterial has become an eternal focus in the field of wound dressing, and it also faces the problem of bacterial resistance caused by the abuse of antibiotics. Various antibacterial strategies include improved antibiotics and their delivery systems, metal and metal oxide nanoparticle antimicrobial agents, cationic antimicrobial peptides and polymers, antimicrobial ingredients in natural products, photothermal antimicrobial agents, and combinations of multiple antimicrobial strategies have been proposed. However, there is still no perfect strategy to deal with wound infections and ensure that it remains effective against unknown future drug-resistant bacteria. Photothermal/photodynamic strategy and nanozyme antibacterial may be a breakthrough in the future, but it is still far from clinical application. In addition, hydrogels in use are often subjected to external forces in daily life, which often leads to hydrogel cracking and bacterial invasion. Therefore, many self-healing hydrogels based on dynamic chemical bond cross-linking have shown important application potential in wound repair. On the other hand, the adhesion hydrogels can not only prevent the shedding of dressings and the invasion of bacteria but also quickly block the early bleeding of wound. However, how to remove the adhesive hydrogel dressing on demand after

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use remains one of the biggest problems to be solved. Excessive inflammation often leads to the formation of chronic wounds, so anti-inflammatory and antioxidant functions have also been proposed. In addition, based on the skin battery theory of charge changes near the wound and the transmission of electrical signals between human cells, the promoting role of conductive hydrogel in skin repair has also been confirmed by many studies. Hydrogels as a delivery system have been widely studied. So in skin repair, some drugs, cells, cytokines, and other substances are also loaded into the hydrogel. In addition, in view of the complexity of the wound repair process and the need for coordination of various parts, hydrogels that can respond to environmental stimuli such as pH, light, and heat are also used for wound repair. The emergence of future-oriented smart hydrogels that can monitor wound parameters is also an important direction for future development. Of course, many composite multifunctional hydrogels have appeared in recent years. Our research group has also made some explorations in this regard. A series of hydrogels with injectable, antibacterial, conductive, adhesive, hemostatic, sustained-release, and antioxidant dressings have been prepared.[29,30,35,36,50,57,107,108,155]

However, due to the complexity of the wound repair process, many processes and the parameters involved are dynamically changing, which makes it difficult to have a dressing that can meet the needs of the entire process at the same time. For example, it is important to control inflammation during the inflammation phage of wound healing, but it is not necessary in other periods of wound repair. In addition, cells, cytokines, and functional components loaded in wound dressings are usually required only at a specific time, while at other times, they may even play the opposite effect. Therefore, first, providing functions on demand is a direction for further research. Although we have seen some research on wound monitoring, how to achieve responsive delivery of required dressing functions after obtaining dynamic data on wounds remains a challenge. Second, another important point is that the pH value of chronic wounds is alkaline, but most pH responsive systems seem to be more friendly to acidic pH at present. Therefore, further development of hydrogel dressings that can provide functions on demand under alkaline conditions is also an important direction. Third, mice or rats are generally selected as the model organism at present, but the skin of mice or rats will contract during the healing process, which is different from human skin, so it will also lead to deviations in experimental results. Although some researches have adopted various methods (like splint model) to reduce this error, they all have caused a greater workload and small improvements that do not match the workload. So, more suitable animal models are also need to be explored. Besides, the length of the repair process will be affected by various factors. So some parameters such as angiogenesis, collagen deposition, and granulation tissue thickness may vary at a certain point in time, resulting in poor contrast between different research results. Further exploration of standardized animal models is also necessary. Finally, the mechanism of various materials promoting wound repair still needs to be studied. Most of the studies have mentioned the promotion of granulation tissue generation, re-epithelialization, vascular regeneration, and collagen deposition, but they only stay in the superficial analysis and lack further in-depth mechanism exploration. In the end, for the perfect skin repair, we still have a long way to go.

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Notes

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VOCABULARY

Hydrogel, a gel with three-dimensional network structure and water as the dispersion medium; **granulation tissue**, the bright red granular, soft, and moist tissue formed during wound repair, which resembles fresh granulation, is composed of new thin-walled capillaries and proliferative fibroblasts and accompanied by inflammatory cell infiltration; **photothermal antibacterial**, a way for substances with photothermal ability to kill bacteria by converting absorbed light into heat; **hemostatic cryogel**, a sponge-like hemostatic material with uniform macroporous structure prepared by freezing gel technology; **rGO@PDA**, the reduction of graphene oxide caused by the self-polymerization of dopamine under alkaline conditions, forming a polydopamine coating layer on the surface of reduced graphene oxide.

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