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Review

Novel Biomaterials for Wound Healing and Tissue Regeneration

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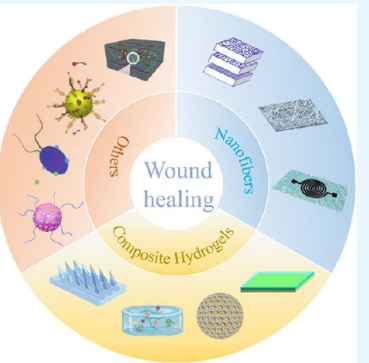
ABSTRACT: Skin is the first defense barrier of the human body, which can resist the invasion of external dust, microorganisms and other pollutants, and ensure that the human body maintains the homeostasis of the internal environment. Once the skin is damaged, the health threat to the human body will increase. Wound repair and the human internal environment are a dynamic process. How to effectively accelerate the healing of wounds without affecting the internal environment of the human body and guarantee that the repaired tissue retains its original function as much as possible has become a research hotspot. With the advancement of technology, researchers have combined new technologies to develop and prepare various types of materials for wound healing. This article will introduce the wound repair materials developed and prepared in recent years from three types: nanofibers, composite hydrogels, and other new materials. The paper aims to provide reference for researchers in related fields to develop and prepare multifunctional materials. This may be helpful to design more ideal materials for clinical application, and then achieve better wound healing and regeneration effects.



1. INTRODUCTION

The skin is the largest organ in the human body and the first defense barrier. It can protect the human body from the external environment.[1,2] Human skin is composed of keratinized stratified epidermis and collagen-rich dermal connective tissue, in which dermal connective tissue can provide support and nutrition.[3] Skin trauma can be divided into acute and chronic. Acute wounds can usually be repaired through the normal wound healing process, whereas chronic wounds do not heal properly and often lead to inflammation, pain, serious complications, etc.[4,5]

Wound repair is a dynamic process that generally consists of four overlapping but not identical phases: hemostasis, inflammation, proliferation, and remodeling.[6−9] During hemostasis, platelet plugs and then fibrin clots are formed.[10,11] Following tissue injury, neutrophils and monocytes are recruited to the wound, and inflammatory cells promote wound healing by engulfing bacteria to control wound infection.[7] Subsequently, the newly formed blood vessels in the tissue can promote the proliferation of fibrous cells by transporting oxygen and nutrients.[12,13] In most lesions, excessive cellular fibrosis leads to the production of partially dysfunctional tissue, which is often referred to as scar.[14−17] The formed scar tissue is nonesthetic and may even affect the mental health of the patient.

Traditional wound dressings such as cotton, bandages, and gauze.[18] They have been widely used in clinical practice and generally serve to stop bleeding and insulate wounds against infection.[19] However, they are less effective at stopping bleeding, are easily contaminated, and need to be replaced frequently.[20] If the dressings are in contact with the wound for a prolonged period of time, then they may cause tissue adhesion, leading to difficulty in removal, and may cause secondary injury when changed.[20] In addition, conventional dressings are not suitable for large wounds with diffuse and incompressible bleeding or organ tissue wounds, which require surgical closure.[21,22] Sutures are usually invasive and may also cause unsatisfactory tissue integration or result in leakage of tissue contents due to incomplete closure.[23,24] These drawbacks have stimulated interest in exploring novel wound dressings, and sutureless wound closure strategies are a hot research topic today, such as nanofibers, hydrogels, etc.

In recent years, nanofibers and composite hydrogels have attracted the interest of a wide range of researchers due to their unique properties, and a large amount of literature has been published on their application to wound repair.[25−28] Nanofibers have the advantage of having a high specific surface area and high porosity, which can mimic the natural extracellular matrix (ECM).[29] It can also be adjusted in structure or loaded with drugs to achieve increased permeability, resistance to infection, and induction of cellular phenotypic differentiation to further accelerate wound healing.[30−33] Composite hydrogels have obvious advantages in wound healing due to their three-dimensional network structure, high water content, good adhesion, and biocompatibility.[34−37] Wound repair is a

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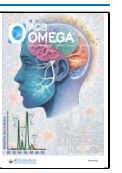

Table 1. Nanofibers for Wound Healing Applications

type	characteristics	material	ref
nanofibers	induction of cell phenotype or differentiation	poly(L-lactide) (PLLA)	30
nanofibers	induction of cell phenotype or differentiation	poly (ε-caprolactone) (PCL); pluronic F-127	31
nanofibers	antimicrobial	polyacrylonitrile; moringa leaf; ethanol; dimethyl formaldehyde	65
nanofibers	antimicrobial	ε-polylysine; dopamine hydrochloride; gelatin (Type A); polycaprolactone; 2,2,2-trifluoroethanol (TFE); acetic acid	64
nanofibers	antimicrobial	*Komagataeibacter xylinus* (strain ATCC 23770); 3-aminopropyltrimethoxysilane; glutaraldehyde (APTES); glacial acetic acid (AA); ethanol; pullulan; zinc oxide nanoparticles (ZnO-NPs, 30 nm)	75
nanofibers	intelligent response	glycerol; sebacic acid; polycaprolactone; silver ink; anhydrous chloroform; ethanol	27
nanofibers	intelligent response	*N*-isopropylacrylamide (NIPAAm); *N*-hydroxymethylacrylamide (HMAAm); 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP); *N*,*N*-dimethylformamide (DMF); 2,2′-azobis (2-methylpropionitrile) (AIBN); moxifloxacin hydrochloride (MOX); silver ink	33

complex, dynamic process affected by multiple factors.[3,14] As technology develops, more and more new technologies emerge. Researchers have applied new technologies in the preparation of biomaterials, developing and preparing new materials such as nanoadhesives, microrobots, mRNA sensors, and exosomes. Therefore, biomaterials applied to wound repair may be more conducive to wound healing if they can have multiple functions. This paper summarizes the outstanding work on wound repair in recent years and provides important reference cases for the design of relevant treatment strategies. We hope that this review can provide references for the design of advanced biological material preparation methods in terms of wound healing and tissue regeneration, including the selection of materials, the design of preparation methods, and the improvement of properties. It is beneficial for researchers to improve their research design so that biological materials can achieve more clinical practice. In the following section, nanofibers, composite hydrogels, and other new materials will be introduced.

2. NANOFIBERS

Nanofibers have attracted much attention in recent years, especially in wound repair, due to their large specific surface area and unique nanosize.[29] Nanofibers are divided into pure natural and synthetic preparations. Some natural products have nanostructures themselves, such as bacterial cellulose (BC).[38] BC can adjust the nanofibers produced by adjusting the medium composition of the bacteria or customizing the culture device.[38,39] Gmach et al. prepared oriented BC by designing a special inclined-plane bioreactor.[39] In addition, there are many methods to prepare nanofibers, such as self-assembly,[40−42] phase separation,[43,44] electrospinning,[30,45] and so on.

Self-assembly has the advantages of a simple method, easy operation, and low cost.[46] Self-assembly of micro- and nanofibers can use noncovalent interactions such as hydrogen bonds, hydrophobic interactions, van der Waals forces, and metal-hydrophilic interactions, and chemical cross-linking can also be used.[40,41] In a study,[42] cellulose nanofibers were self-assembled into hydrogels by hydrogen bonding, and two strategies of suspension casting and vacuum filtration were compared and evaluated. In the experiment, the performance of the samples prepared by vacuum-assisted filtration was compared with that of commercial BC. The results showed that the liquid absorption capacity of the samples was comparable to that of BC, but the mechanical strength and stiffness were lower than those of BC hydrogels. Although the self-assembly strategy is of great convenience, the long-term stability of nanofibers, especially the self-assembly of protein peptides,[47] should be paid attention to when using self-assembly to prepare nanofibers. At the same time, if the design strategy depends on pH and temperature,[48,49] then the influence of the wound microenvironment should be fully considered.

Phase separation is a common method of preparing nanofibers by forming two or more phases in solution and then selectively removing the phases, ultimately maintaining one phase.[50] For example, hollow fiber membranes can be prepared using thermally induced phase separation.[44,51,52] Sun et al. used nonsolvent-induced silk fibroin solution phase separation to prepare films with tunable nanopores.[43] This method optimizes the preparation method of silk fibroin film and saves time-consuming steps such as dialysis. It is worth noting, however, that the applicability of phase separation methods may not be relatively broad. It may only be applicable to specific polymer/solvent systems. In addition, careful study of parameters may be required to control fiber diameter.

Electrostatic spinning is a method of applying an electric field to make various polymers into nanofiber structures on a collector. It has the advantages of high porosity, a large aspect ratio, and a large specific surface area.[53] The design of an electrospinning device is of great significance to the structure and properties of nanofibers. The commonly used devices are emulsion electrospinning, roller electrospinning, coaxial electrospinning, and so on.[54−57] Coaxial electrostatic spinning can be used to fabricate nanofibers with core−shell or hollow structures. The core−shell structure may be effective in preventing the burst release of drugs, which will be beneficial for conducting the next step of drug-measured release studies.[57−59] Besides, covalent polymer grafting, plasma treatment, and ionized jet deposition techniques can be used for drug loading to achieve controlled drug release.[60,61] The structure of nanofibers prepared by electrostatic spinning is also inextricably linked to the collector. The commonly used collectors include flat collectors,[33] drum collectors,[54] angle collectors,[62] pattern collectors,[63] etc. The way of placing the collector is also classified as fixed placement,[62] rotating placement,[54] and so on. Yin et al. designed a self-made spherical cross-section free-surface electrospinning device to control the porous structure of nanofibers by adjusting the weight ratio of solvent and solute mixing.[45] Also, due to the change in solvent system and weight ratio in the mixture, the electrical conductivity and solution viscosity of the spinning solution changed, which further affected the nanofiber yield. The development of new technologies for preparing high-yield

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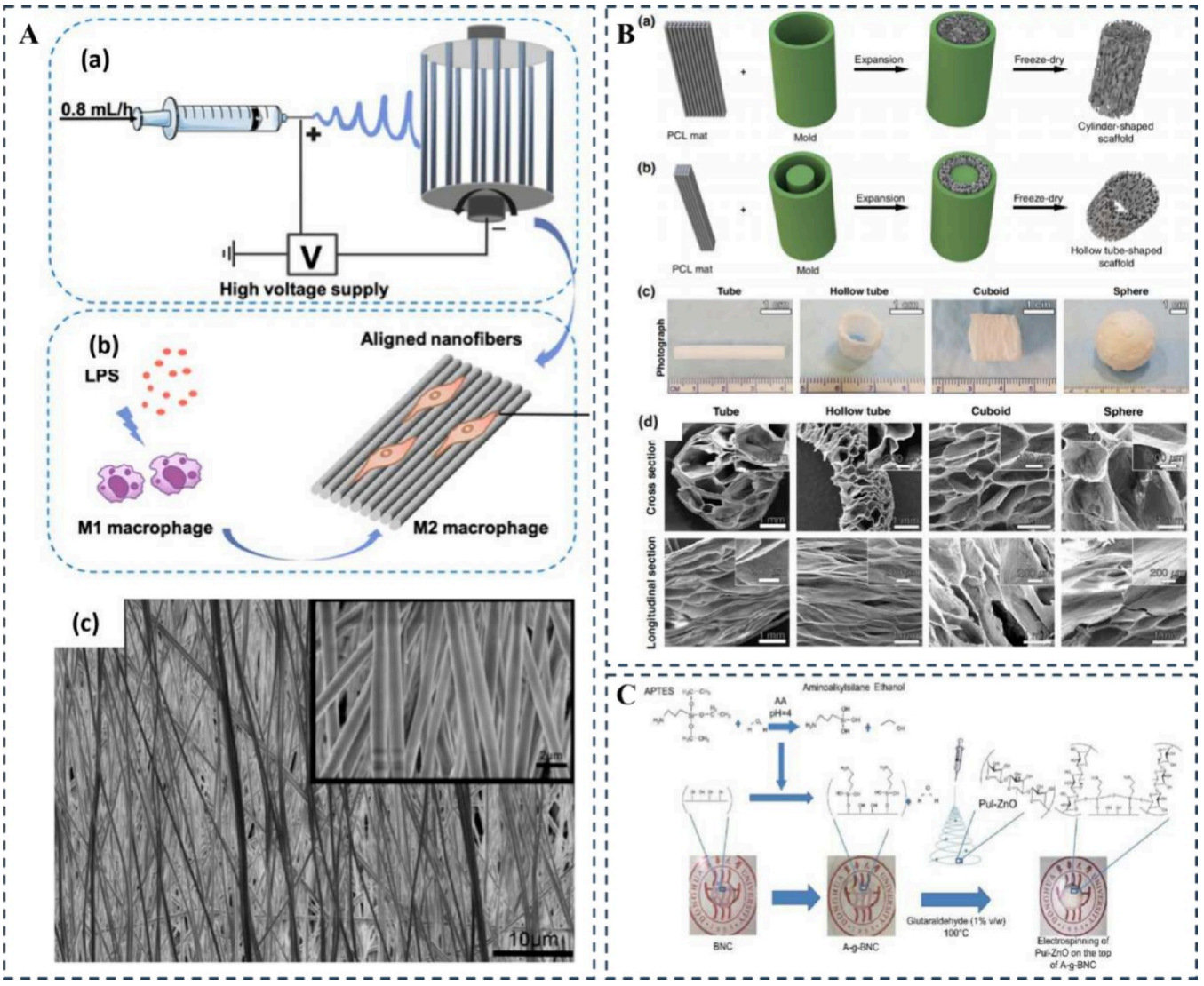

Figure 1. (A) The fabrication schematic diagram and SEM diagram of oriented electrospun PLLA nanofibers. (a) Schematic diagram showing the preparation of oriented electrospun nanofibers. (b) Oriented nanofibers promote macrophage M2-type polarization. (c) SEM image of oriented nanofibers. Reprinted with permission from ref 30. Copyright 2022, Springer Nature. (B) A schematic illustration of the rapid transformation of 2D nanofibrous membranes into preformed, molded 3D scaffolds with oriented porous structures and SEM images of the 3D scaffolds. The schematic illustrates the process of transforming 2D nanofibrous membranes into cylindrical nanofibrous scaffolds (a) and hollow tubular scaffolds (b) by expanding them in a custom-made mold. (c) Photographs of cylindrical, hollow tubular, rectangular, and spherical nanofiber scaffolds. (d) Cross-sectional and longitudinal SEM images of cylindrical, hollow tubular, rectangular, and spherical scaffolds. Reprinted with permission from ref 31. Copyright 2020, AIP Publishing. (C) Preparation schematic diagram and mechanism diagram of nanofiber membrane. APTES: hydrolysis of 3-aminopropyltrimethoxysilane; AA: acetic acid; BNC: bacterial nanocellulose; A-g-BNC: BNC membrane, Pul-ZnO: pullulan polysaccharides and zinc oxide nanoparticles. Reprinted with permission from ref 75. Copyright 2021, American Chemical Society.

nanofibers is conducive to mass production and can even be put into factory production to achieve result conversion.

Nanofibers can be endowed with different properties by adjusting the type of compound, the ratio of precursor solution, and the preparation device during the preparation process.[29] It can endow nanofibers with the functions of inducing cell phenotypic differentiation,[30,31] resisting infection,[64,65] etc., thus further accelerating wound healing. Nanofibers are classified and discussed below according to induced cell phenotype or differentiation, antimicrobial properties, and smart response properties. The materials of some nanofibers are listed in Table 1.

2.1. Induction of Cell Phenotype or Differentiation. The phenotype of macrophages plays an important role in wound healing. Polarization of the macrophage M1 to M2 phenotype typically involves a decrease in the expression of multiple pro-inflammatory cytokines and an increase in the expression of anti-inflammatory cytokines. It is the shift in macrophage phenotype that facilitates the transition of wound repair from the inflammatory to the proliferative phase.[7,30,66−69] Xie et al. used polylactic acid to obtain aligned electrospun by directional preparation on a cage drum collector (Figure 1A).[30] The results show that aligned nanofibers has better mechanical properties and lower water contact angle than random nanofibers, and it can also induce M2 polarization of macrophages.

As mentioned above, simply arranging nanofibers can attain the effect of improving performance. In order to further

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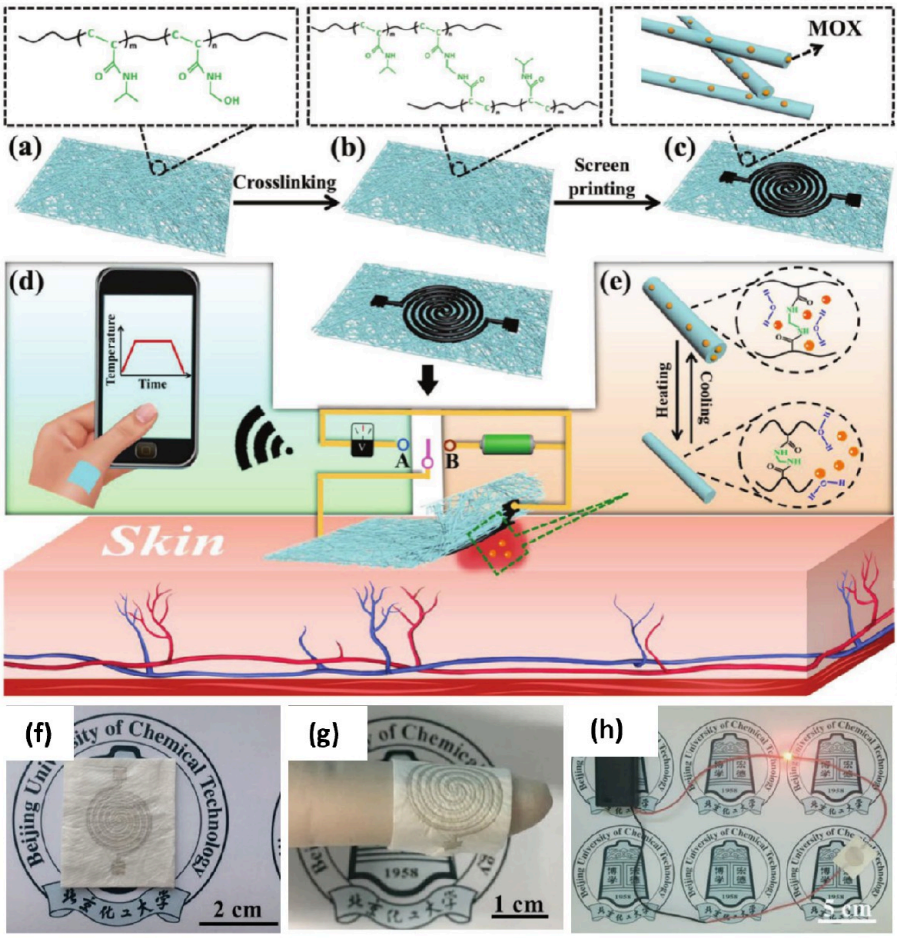

Figure 2. Schematic and photographs of the preparation of flexible, breathable skin electronics with temperature sensing capability and temperature-sensitive on-demand drug release. (a) Nanofiber film. (b) Nanofiber film after cross-linking. (c) Nanofiber film after printing conductive patterns. (d) Schematic diagram of the assembly of flexible, breathable skin electronics with an integrated temperature sensor. (e) Schematic of temperature-sensitive on-demand Moxifloxacin hydrochloride (MOX) release. (f) Photographs of patterned nanofibrous film and (g) flexible nanofibrous film attached to a finger. (h) Photograph of the nanofiber film (R = 24.3 Ω) in a circuit to light up a light-emitting diode bulb (applied voltage of 3.0 V). Reprinted with permission from ref 33. Copyright 2019, John Wiley and Sons.

enhance the performance, the researchers continue to expand the structure or composition into the 3D scaffold assembly by means of technical improvements.[31,70,71] Chen et al. mixed 2D polycaprolactone nanofibers with Pluronic F-127 of different proportions and prepared 3D nanofiber components with pore size gradients through gas foaming expansion technology (Figure 1B).[31] These components can load bone marrow mesenchymal stem cells and induce their expression and differentiation. After a series of studies, the research team successively deposited fibers of different order by increasing the rotation speed of the mandrel during the electrospinning process, and then prepared 3D nanofiber scaffolds by gas foaming expansion technology.[70] Furthermore, the team also prepared 3D nanofiber assemblies with composition gradients by diffusion, encapsulation, and cross-linking.[71] All of these designs provide a new strategy for the establishment of an induced cell expression differentiation model.

It is worth considering that wounds have a variety of constituent cells. Whether the oriented structure of nanofibers, while favoring the induction of macrophage phenotypes, may have an effect on other cells has not been reported conclusively. In addition, the oriented structure of the nanofibers needs to be stable in the wound environment so as to ensure that the structural guidance is maintained during the induction of cellular phenotype or differentiation.

2.2. Antimicrobial Properties. Infection is one of the major threats to wound healing. With the increasing use of antibiotics in clinical practice, the incidence of multidrug-resistant bacteria is also increasing.[72] The recommendation of the World Health Organization is to limit the abuse of antibiotics in order to avoid the evolution and spread of drug-resistant bacteria.[73] Nanofibers have an extremely fine pore size and high porosity, which can promote gas exchange at the wound site while isolating bacteria from the wound area.[20] Recently, plant extracts,[65,74] antimicrobial peptides,[32,64] and metal nanoparticles have been loaded into nanofibers as alternatives to antimicrobials for wound repair applications.[75,76] Fayemi et al. used Moringa leaf extract and polyacrylonitrile to prepare nanofibers for wound repair.[65] Ghomi et al. collected nanofibers doped with ε-polylysine on a drum-type collector at different rotational speeds before cross-linking the samples using dopamine hydrochloride.[64] The results of the study showed that the nanofibers containing ε-polylysine exhibited antimicrobial activity against methicillin-resistant *Staphylococcus aureus*, *Staphylococcus aureus*, *Escherichia coli*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*.

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In another study, Shahriari et al. prepared a spinning solution with a mixture of pullulan polysaccharides and zinc oxide nanoparticles and chemically grafted aminoalkylsilanes onto bacterial nanocellulose membranes. The membrane was used as a support to collect electrostatic spinning to prepare hybrid electrospun nanofibers (Figure 1C).[75]

Developing alternatives to antimicrobials for wound repair without causing the emergence of mutant strains. This is what all researchers are willing to accept and will be a great blessing for mankind. However, it should be noted that the extract may involve the use of toxic reagents, such as organic solvents, during the extraction process.[65,74] Residues from organic solvents may be cytotoxic. Whether metal nanoparticles are toxic to humans due to their particle size and surface loading has also been the subject of controversy.[77,78] Therefore, maintaining the effectiveness of the ingredients and ensuring the nontoxicity of the materials are the primary prerequisites for the development of antimicrobial alternatives.

2.3. Intelligent Response Performance. Current commercial dressings rely heavily on passive therapy.[19] Given the complexity of the wound healing process, active and effective proactive therapy may be a more effective treatment strategy.[8] Intelligent wound dressings with real-time monitoring and regulation of the wound microenvironment are promising as a way to provide reliable and optimal care.[33] With the emergence and development of wireless sensor technology, new materials combined with wireless sensor technology can be connected to smart phones to prepare wearable sensors.[79−81] The emergence of wearable sensors has brought new ideas for real-time monitoring of wound repair dynamics. Intelligently responsive wound conditions generally include: temperature,[33] pH,[48] deoxyribonuclease,[82] reactive oxygen species,[83] etc.

Electronic devices with different conductive patterns can be fabricated by screen printing with silver ink.[27] Gong et al. prepared an electrospinning solution by free radical polymerization. Moxifloxacin hydrochloride was added to the solution to prepare a spinning sheet, and a conductive pattern was printed in combination with silver ink (Figure 2).[33] The conductive polymer nanomeshes prepared by this method show excellent flexibility, reliable air permeability, and strong stability. It can also display the linear relationship between the resistance and temperature on the mobile phone device, so as to monitor the temperature of the wound tissue in real time.

Wound infection is a major clinical challenge, and timely detection of wound tissue environment is the key to effective interventions.[84,85] We all know that the wound environment is complex. Therefore, the specificity and sensitivity of the material's intelligent response need to be guaranteed, which is highly relevant to both the choice of the detectors and the nature of the material itself. Furthermore, focusing on the quorum sensing of bacterial populations or the combination of multiple monitoring methods may also be an effective strategy.[86−88]

3. COMPOSITE HYDROGEL

Hydrogel have obvious advantages in wound healing due to their 3D network structure, high water content, and strong swelling ability.[89] Good moisture content makes the hydrogel have good moisturizing ability and can promote wound autolysis debridement.[90,91] Moreover, the appearance of most hydrogels after application is transparent, which is convenient for monitoring wound healing.[92] Nowadays, due to the multistage nature of the wound healing process, researchers are favoring the preparation of multiperformance composite hydrogels.[62,93−98] It includes, but is not limited to high mechanical strength, high self-healing ability, intelligent responsiveness, high biocompatibility, and high biodegradability.

The cross-linking of composite hydrogels is generally classified into physical and chemical cross-linking.[99] Physical cross-linking refers to the bonding of polymer chains by noncovalent bonds, generally without the need for cross-linking agents, including hydrogen bonding, hydrophobic interaction forces, crystallization, and et al.[96,99−101] The interaction force between the physically cross-linked networks is generally relatively weak, and the hydrogel can form a reversible dynamic network. This property endows the hydrogel with self-adaptability and intelligent responsiveness.[102] Yu et al. prepared hydrogels with self-healing and adhesion properties using humic acid and polyvinylpyrrolidone by dynamic reversible hydrogen bond cross-linking.[96]

Chemical cross-linking is the formation of covalent bonds between the internal networks of hydrogels, including enzymatic reactions, free radical polymerization, etc.[103−105] The chemically cross-linked networks are bonded by covalent bonds and have strong and lasting interaction forces. The hydrogel network exhibits good stability and superior mechanical properties. For instance, lithium phenyl-2,4,6-trimethylbenzoylphosphonate is commonly used as a cross-linking agent to initiate free radical polymerization.[103] Covalent bonding is generally irreversible. Dynamic covalent bonds, which have recently been reported, have bond energies similar to those of covalent bonds and, at the same time, can dissociate and recombine in hydrogel networks.[106,107] Including the imine bond, boric acid bond, disulfide bond, Diels−Alder reaction, Michael addition reaction, and so on.[108−112] Liang et al. designed a dynamic hydrogel by cross-linking via Schiff base bonds and catechol-Fe coordination bonds.[106] However, the performance of hydrogels prepared by simple physical cross-linking, chemical cross-linking, or dynamic covalent cross-linking may still be unsatisfactory. Therefore, many studies have used a mixture of cross-linking methods to enhance hydrogel properties.[100] Hua et al. used poly(vinyl alcohol) as a stencil system to induce intense aggregation and crystallization of polymer chains using directional freezing and the Hofmeister effect. This method resulted in the preparation of hydrogels with high strength, toughness, and fatigue resistance.[113]

The cross-linking of composite hydrogels involves a variety of groups, with different groups giving the compounds different properties. Wang et al. used the reaction of hydroxyl groups with acryloyl chloride to graft carbon−carbon double bonds onto the surface of hydrogels, which were then copolymerized in situ to form hydrophobic lipogels.[114] Due to the positive charge of the carboxyl group and the negative charge of the amino group, the reduction of different sizes of hydrogels was achieved by using the condensation and drainage of the opposite charge.[115] Therefore, researchers can endow hydrogels with more functions by modifying the hydroxyl, carboxyl, sulfonic acid, amide, and other groups in the hydrogel matrix.[73,114,115] With various studies, researchers have given hydrogels a variety of functions.[108,116,117] For example, injectable hydrogels can increase fluidity and sealing, and can also fill irregular wounds.[118,119] The following section focuses on composite hydrogels by function into four levels of high

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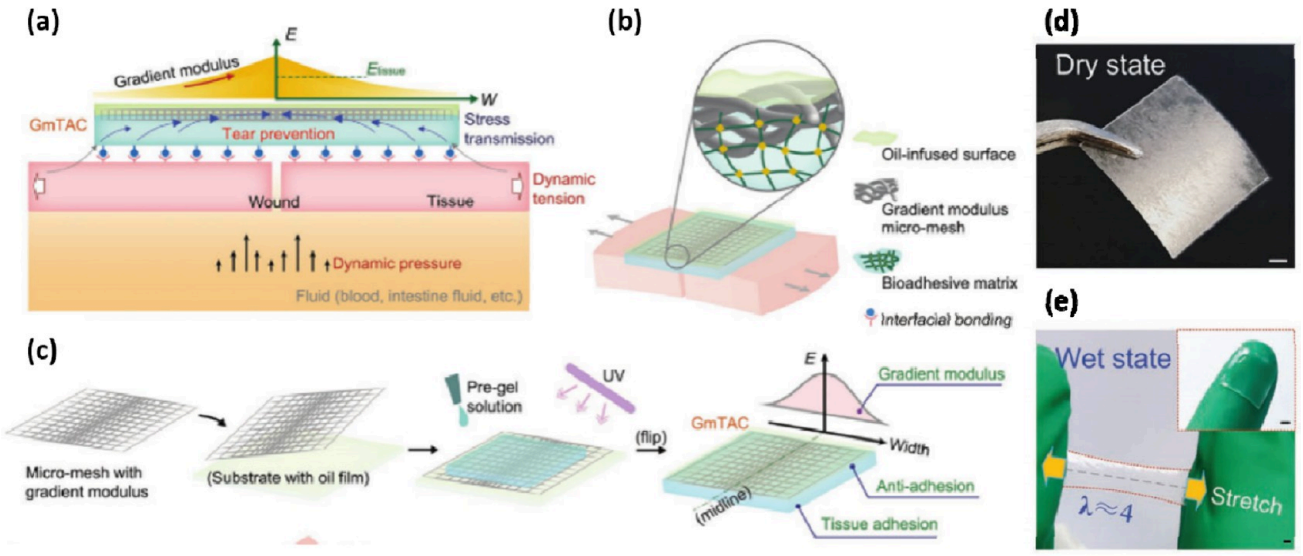

Figure 3. Composite hydrogels with gradient modulus. (a) Design and application for wound closure and antitear in dynamic and fluid-rich environments. (b) Three components: bioadhesive matrix, gradient modulus micromesh, and oil-injected antiadhesion surface. (c) Fabrication process. Photographs in dry (d) and wet (e) states. (Scale bar: 2 mm). Reprinted with permission from ref 62. Copyright 2022, John Wiley and Sons.

Table 2. Composite Hydrogel for Wound Healing Applications

type	characteristics	material	ref
composite hydrogel	high mechanical	gelatin; sodium alginate; methylacrylic anhydride; $CaCl_2$	103
composite hydrogel	high mechanical	genipin (GP); high-viscosity chitosan (HV-CS); NaOH; ethanol; acrylamide; *N*,*N*′-methylene bis(acrylamide) (MBAA); ammonium persulfate (APS); 1-ethyl-3-[3-(dimethylamino)propyl] carbodiimide hydrochloride (EDC); *N*-hydroxy succinimide (NHS); metronidazole; amoxicillin	23
composite hydrogel	high mechanical	carboxymethyl chitosan; oxidized glucan; γ-polyglutamic acid.	125
composite hydrogel	high mechanical	polycaprolactone; acrylic acid; gelatin; *N*-hydroxysuccinimide acrylate; gelatin methacrylate; α-ketoglutaric acid; silicone oil	62
composite hydrogel	self-adaptive	anhydrous ferric chloride; tris; protocatechualdehyde (PA); gelatin (GT); sodium alginate (SA)	106
composite hydrogel	self-adaptive	gelatin; deferoxamine; chitosan; 3-carboxyl-4-fluorophenylboronic acid; polyvinyl alcohol	107
composite hydrogel	self-adaptive	hyaluronic acid; methacrylic anhydride; graphene oxide; gelatin; carrageenan; 2-hydroxy-2-methylpropiophenone; silica nanoparticles; silicone oil; amoxicillin; vascular endothelial growth factor	13
composite hydrogel	photothermal	poly(γ-glutamic acid) (γ-PGA); EDC; $MgCl_2$; KOH; gallic acid; graphene oxide (GO); $AgNO_3$	141
composite hydrogel	photothermal	methylacrylic anhydride; gelatin; 2-methoxy-4-methylphenol; 1-propanol; sodium periodate; sodium alginate; vancomycin; quaternary ammonium salt chitosan; curcumin; zinc acetate	7
composite hydrogel	conductive	gelatin (Type A); methacrylate anhydride; chitosan; GO; glycidyltrimethylammonium chloride (GTMAC); glycidyl methacrylate; APS; TEMED	142
composite hydrogel	conductive	chitosan; glacial acetic acid; GTMAC; glycidyl methacrylate (GMA); PF127; triethylamine; anhydrous dichloromethane; acryloyl chloride; multiwalled CNTs; APS; TEMED	143

mechanical properties, adaptive, photothermal, and electrical conductivity to develop a specific introduction.

3.1. High Mechanical Properties. Natural compounds have received extensive attention due to their good biocompatibility and biodegradability.[120] However, the mechanical properties of hydrogels made from a single natural compound may not be satisfactory. The performance of natural compounds can be optimized by modification, mixing, or mixing after modification.[121] Gelatin-modified hydrogels have the advantages of similar microstructure to ECM, which can promote cell interaction and contain biological coupling groups.[122,123] If methacrylic anhydride is added to chemically modify alginate, then it will have stronger water absorption capacity.[124] Tavafoghi et al. used methacryloylate gelatin and methacrylate-modified alginate as materials for photo-cross-linking, and then used $CaCl_2$ for physical cross-linking to prepare a hybrid hydrogel with high toughness and stretchability.[103] This strategy provides a new idea for the development of sutureless sealing materials for highly stretchable tissue wounds.

In recent years, many researchers have focused on the use of interpenetrating networks, dual/multiple networks, topologies, etc. to enhance hydrogel properties. Inspired by ECM, Wu et al. prepared a double-network hydrogel.[23] When the hydrogel swells or is stretched, the double network structure plays a role of mutual restriction, so as to prevent the hydrogel from absorbing water and bursting, or being stretched and broken. In another study, Chen et al. made a three-network hydrogel with a double-tube syringe.[125] The three networks are composed of carboxymethyl chitosan, oxidized dextran, and

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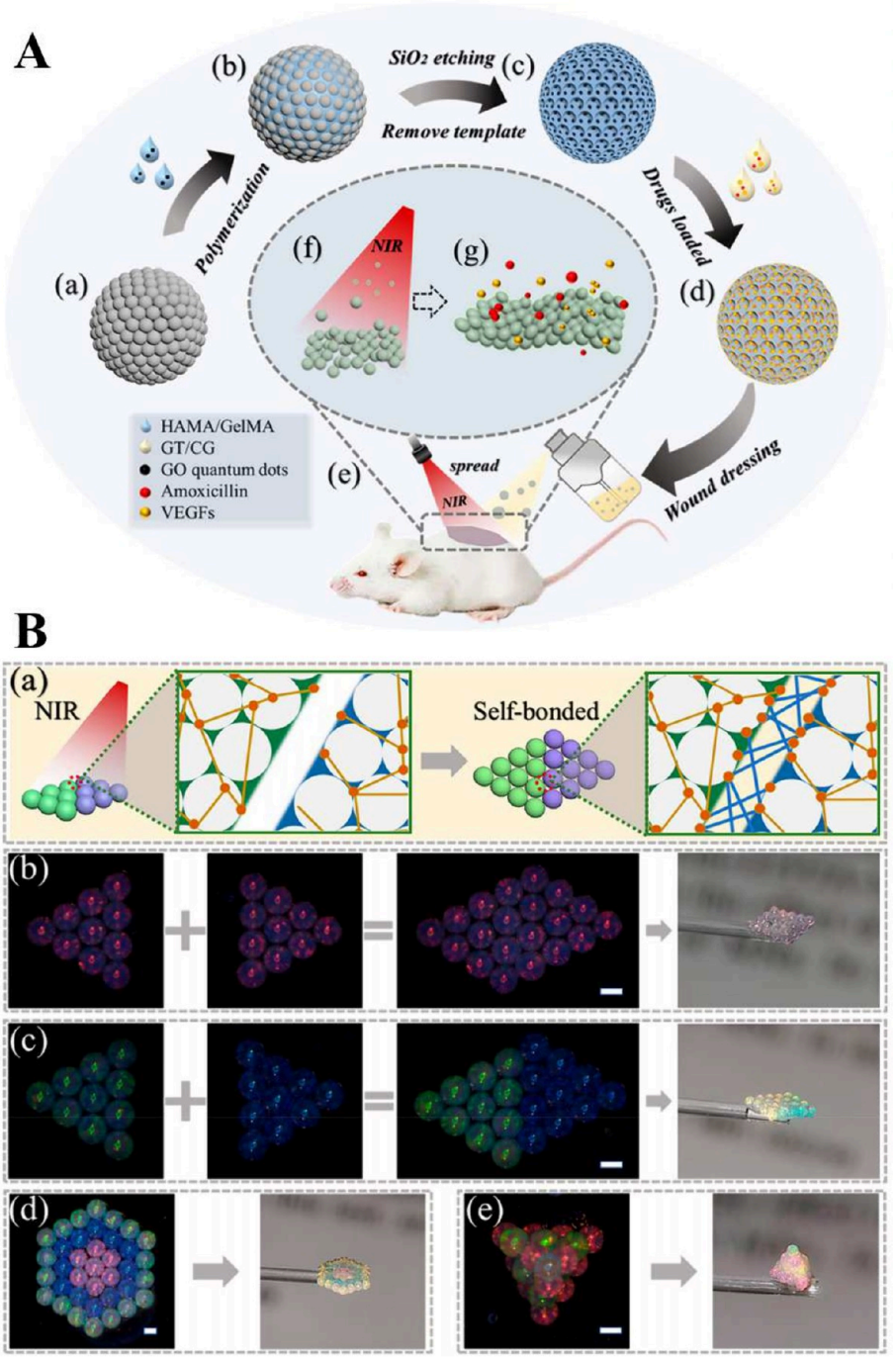

Figure 4. (A) schematic diagram of the preparation process and the physical self-binding and controlled release of drug-carrying particles and images of the self-healing process of the scaffolds. (a) Photonic crystal templates. (b) Light-cured polymer hybrid microspheres. (c) Hyaluronic acid methacryloyl/gelatin methacryloyl (HAMA/GelMA) inverse opal. (d) Drug-coated readhesive particles. (e) Drug-carrying particles at the wound site. (f) The self-binding process and the release of drug from the particles (g). (B) (a) Schematic representation of the self-healing process. Patterns are formed by mixed particles with single (b), dual (c), or multiple (d) structural colors. (e) A three-dimensional pattern formed by particles. The scale bar is 200 μm. Reprinted with permission from ref 13. Copyright 2022, American Chemical Society.

γ-polyglutamic acid by forming intramolecular amide bonds, intermolecular amide bonds, and dynamic Schiff base bonds. The 3D network of the hydrogel provides stronger mechanical properties for the hydrogel and avoids secondary damage when removing the hydrogel.

In addition to the multinetwork hydrogel, double-layer hydrogel dressing is a new wound healing strategy that can simulate the skin bilayer structure.[126−128] The upper layer acts as a protective layer to prevent water loss and bacterial infection, and the lower layer has high absorption and adhesion. Li et al. made polycaprolactone solution into gradient modulus microgrid by electrostatic spinning combined with angle collector, and added antiadhesion silicone oil layer on the surface of microgrid by penetration principle (Figure 3).[62] The hydrogel layer was prepared by mixing acrylic acid, gelatin, *N*-hydroxysuccinimide acrylate, gelatin methacrylate, and α-ketoglutarate. Finally, the composite patch was prepared by ultraviolet (UV) cross-linking. In the study,

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the patch can be firmly adhered to the surface of the nonplanar wet tissue and play a role in sealing the wound to prevent leakage. Concomitantly, the top layer of the oil-immersed surface can prevent the patch from adhering to the surrounding tissue. Surprisingly, the patch can also adjust the Young's modulus of the entire patch by changing the number of layers of the spinning microgrid, and adapt to the stress changes of different organ tissue wounds with the best gradient modulus. These effects are difficult to achieve with sutures or ordinary hydrogel adhesives.

It is worth noting that the complexity of preparation methods for high-strength hydrogels may be prevalent, which may be an obstacle limiting their development. Simplifying the preparation method of high-mechanical-property hydrogels and realizing mass production are promising future development directions. It is a difficult challenge for biomaterials to have both high mechanical properties and flexibility. In addition, hydrogels with high mechanical properties should also allow the coexistence of biological tissue growth. The materials of high-mechanical-property hydrogel are listed in Table 2.

3.2. Self-Adaptive. It is well-known that the traumatic microenvironment is constantly undergoing dynamic changes as the repair process proceeds.[8] Self-adaptive hydrogels, like human tissues, have the ability to dynamically respond to the wound microenvironment.[106] Reversible interactions (noncovalent or covalent bonds) are considered to be an effective method to induce the self-adaptability of hydrogels.[99] It mainly includes the hydrogen bond, host−guest interaction, metal coordination, imine bond, boric acid bond, disulfide bond, Diels−Alder reaction, Michael addition reaction, and so on.[106−112,129] They confer self-healing properties to the composite hydrogel through constant sacrifice and regeneration between bonds.[129] Polydopamine contains unique structures such as catechol and amine, which can undergo noncovalent binding (hydrogen bonding, $\pi-\pi$ interaction, etc.) and covalent binding (Schiff base reaction, Michael addition reaction, etc.).[130] Therefore, polydopamine is widely used in tissue engineering as an important component for self-adaptation.

Liang et al. inspired by mussels and brown algae, a dynamic hydrogel was designed by Schiff base bond and catechol-Fe coordination bond cross-linking.[106] Because the catechol structure is noncovalent cross-linked by chelating iron ions, the hydrogel is endowed with self-healing properties. In this paper, the temperature-dependent adhesion ability of the hydrogel makes it have shape adaptability, fault tolerance and repeatable thermal response adhesion properties. These properties increase operation convenience and patient compliance. In another study, Shao et al. designed an adaptive multifunctional hydrogel with self-healing and injectability based on borate ester bonds.[107] Experiments show that the hydrogel can scavenge reactive oxygen species (ROS) and release deferoxamine on demand to promote angiogenesis and cell proliferation. Wang et al. developed and prepared a self-adhesive hydrogel inverse opal particle used in the form of spray (Figure 4).[13] They used methacryloylate hyaluronic acid, methacryloylate gelatin and graphene oxide quantum dots to make inverse opal scaffolds. The hydrogel particles obtained by adding drug-loaded gelatin and carrageenan into the scaffold undergo liquid conversion under near-infrared irradiation to form a flexible patch. This patch has a three-dimensional interconnected porous structure. The most novel is that it can monitor the release of drugs by visualizing the structural color changes of the photonic band gap.

Self-healing hydrogels have significant advantages as injectable delivery platforms due to their excellent properties and can also be combined with intelligent systems to prepare smart delivery platforms, which are promising for clinical applications. However, clinical translation of adaptive hydrogels should also ensure that the materials are nontoxic, nonimmuno-rejection, and well biodegradable after implantation into the human body. Table 2 shows some examples of self-healing hydrogel.

3.3. Photothermal Performance. Studies have shown that human tissues can produce a "hot spring effect" at 30−42 °C, thereby stimulating local microcirculation blood flow, promoting cell proliferation, and promoting angiogenesis.[131−133] However, the human body cannot withstand this temperature condition for a long time. Therefore, how to use this temperature locally in wound healing for wound repair treatment has attracted the research interests. As an important platform for photothermal therapy, photothermal hydrogel shows attractive advantages in antibacterial therapy and wound healing due to its excellent biochemical properties.[134] Photothermal agents are usually added to the hydrogel system to prepare photothermal hydrogels.[135] Photothermal agents include metals and metal compounds,[136,137] carbon materials,[138] and organic materials (e.g., polydopamine[130,136]). Qi et al. prepared photothermal hydrogel by loading Ag on the surface of polydopamine nanoparticles and encapsulating it into a cationic guar gum hydrogel network.[136]

Metal−organic framework (MOF) has good photothermal properties.[139] Under the irradiation of 808 nm near-infrared light, MOF can form a low-high temperature environment in the wound.[140,141] Huang et al. synthesized a MOF multifunctional composite hydrogel (QCSMOF-Van) loaded with vancomycin (Van) and coated with quaternary ammonium salt chitosan (QCS) by free radical polymerization and Schiff base reaction (Figure 5).[7] Due to the addition of metal Zn^{2+} and vancomycin, the hydrogel has intelligent bacterial capture ability and can quickly kill the bacteria after capture. In addition, the addition of curcumin makes the hydrogel have anti-inflammatory properties. The experimental results show that it can also accurately regulate the balance of macrophage M1/M2 phenotype, thereby accelerating the wound healing process.

It is worth drawing our attention to the fact that in photothermal therapy for wound repair, the intensity and penetration of the light used should be different compared to oncological treatments because the therapeutic purpose is not exactly the same. When applying photothermal therapy to wound repair, special attention should be paid to whether it will cause thermal damage to tissues (whether injured tissues or surrounding healthy tissues). Combining photothermal therapy with other treatment modalities may be a promising strategy compared to photothermal therapy alone. The materials of photothermal hydrogel are listed in Table 2.

3.4. Conductive. With the emergence and development of new nanomaterials, it provides a new idea for the performance improvement of hydrogels.[94,95] The introduction of new nanomaterials can endow hydrogel patches with unique electrical and optical properties, so that they can be directly combined with physical therapy, photothermal therapy or biosensing.[127,142,143] When the appropriate frequency of electrical stimulation is introduced in the treatment of

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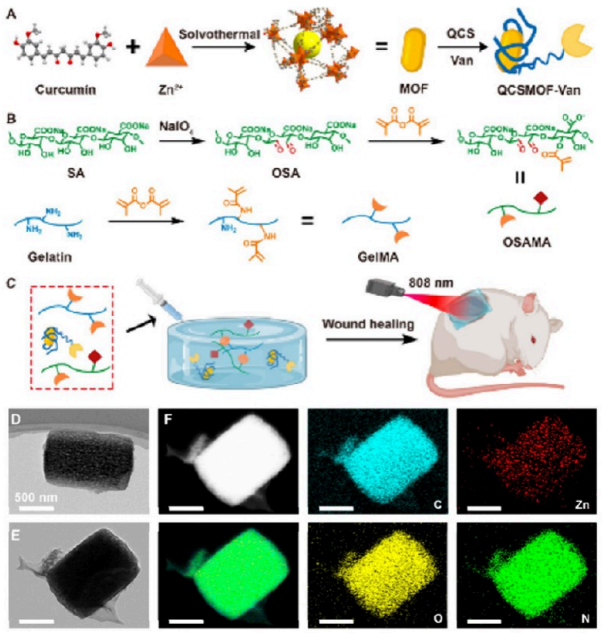

Figure 5. Schematic diagram of photohydrothermal gel preparation and the characterization images of MOF and QCSMOF. (a) Synthesis of QCSMOF-Van. (b) Synthesis of gelatin methacrylate (GelMA) and sodium methacrylic acid oxidized alginate (OSAMA). (c) QCSMOF-Van Hydrogel was applied to chronic wounds. TEM images of (D) MOF and (E) QCSMOF. (F) QCSMOF corresponding EDX element mapping analysis. Reprinted with permission from ref 7. Copyright 2022, American Chemical Society.

wound healing, it has the advantages of high efficiency, small side effects, and local small area application.[144] The preparation of conductive hydrogels usually involves introducing conductive substances into the hydrogel system, including metal and metal compounds,[145,146] carbon materials,[20,142] conductive polymers,[147] etc. Wang et al. fabricated conductive hydrogel patches from antibacterial silver nanowires (AgNW) and methacrylic acid alginate (Figure 6).[145] Experiments show that the patch not only has antibacterial properties, but also can promote orderly cell proliferation, improve re-epithelialization and tissue remodeling, induce directional regeneration and reduce scar formation. Different from traditional wound dressings and intravenous injection, as a new drug delivery system composed of microneedle arrays, microneedles have attracted extensive attention due to their noninvasive, simple operation, local controllable administration, and different drug loading.[97,98,148] Zhang et al. used polyethylene glycol diacrylate and 2-hydroxy-2-methylpropiophenone as materials to prepare eagle claw-like clamped microneedles.[146] The W-shaped liquid metal (LM) is embedded to connect the tip of the microneedle, and finally connected with the ventilated gauze. The double-layer conductive hydrogel microneedle patch is formed by UV irradiation. The eagle-claw-like clamping structure of the patch enables the patch to adhere firmly to the skin, and the stable space electric field provided by LM can guide cell migration and accelerate wound healing.

Conductive hydrogels have great potential for wound healing due to their softness and wide adjustability. However, there are still many challenges to be addressed. The dispersion and stability of conductive materials need to be guaranteed. Hydrogels have swelling properties. It should be ensured that there is a difference in conductivity before and after hydrogel swelling. The stability of the conductivity of conductive hydrogels under physiological conditions should also be explored to ensure the stable transmission of electrical signals. The stability of the electrode and power supply connecting the conductive hydrogel is also an important factor to be considered. The materials of conductive hydrogels for wound repair and regeneration are shown in Table 2.

4. OTHERS

In addition to the nanofibers and composite hydrogels discussed above, new biomaterials such as nanoadhesives, microrobots, mRNA nanosensors, and exosomes have been developed for wound repair. The introduction will be expanded below. Table 3 summarizes other types of materials used in wound repair.

4.1. Nanoadhesives. In recent years, nanoadhesives have received widespread attention due to nanobridging effects.

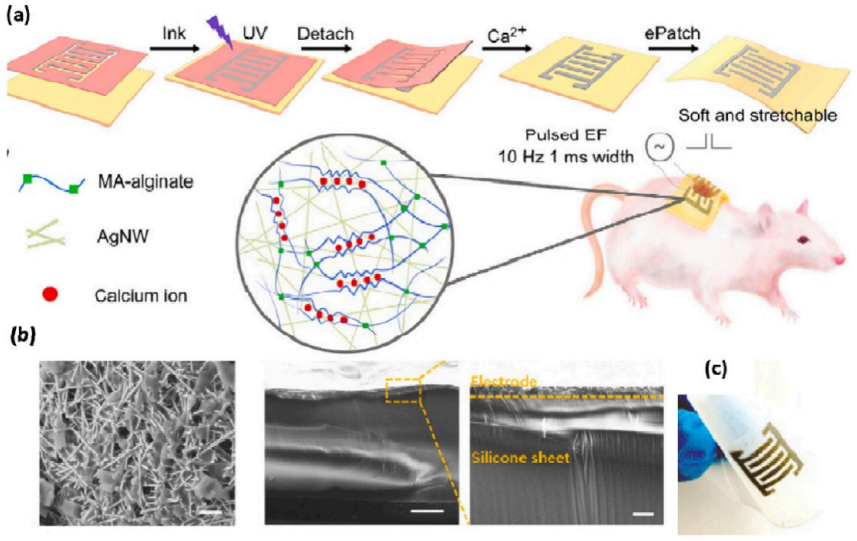

Figure 6. Conductive hydrogels. (a) Schematic diagram of the preparation. (b) SEM images of AgNW and electrode cross section. (c) Photograph of the sample. Reprinted with permission from ref 145. Copyright 2022, Elsevier.

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Table 3. Other Types of Materials for Wound Healing Applications

type	material	characteristics	ref
nanoadhesives	poly dopamine; silicon dioxide; PVA polymer	strong traction; ROS scavenging ability; anti-inflammatory properties; promoting angiogenesis	66
microrobots	chitosan; heparin sulfate; *Chlamydomonas reinhardtii*	liquidity; oxygen production performance; regulating immune response; improve tissue regeneration; promoting angiogenesis	154
mRNA nanosensors	optical nanoflares (NFs); mRNA biomarkers	specific identification of wound repair stage	157
exosomes-loaded conductive hydrogel	bone marrow stem cell-derived exosomes (BMSC-exosomes); gelatin; PBS; methylacrylicanhydride; Irgacure 2959; tannic acid (TA); pyrrole (Py); APS	continuously released BMSC-exosomes; biocompatibility; anti-inflammatory; promote neuronal and myelin-associated axonal regeneration; inhibit scar-forming gliosis; immunomodulatory properties	167
exosomes-loaded hydrogel	GelMA; polyethylene glycol diacrylate (PEGDA); HUVECs-derived exosomes; tazarotene; ethyl isocyanate acrylate (AOI); cyclodextrin	accelerate collagen deposition and epithelial regeneration; promote cell migration and angiogenesis	169

Nanobridging has significant advantages over other biomaterials in promoting deep and narrow wound closure.[149] Nanobridging allows nanoparticles to function not simply as individual dispersions in the wound environment but rather guarantees that the nanoparticles will fulfill their unique role while also possessing the ability to adhere to the wound interface.[66] At the physiological level, ROS act as a messenger of cell redox reaction.[150] When its concentration is too high, it acts as an oxidant to induce oxidative stress in vivo and resulting in cytotoxicity. Therefore, it is of great significance to control the level of ROS during wound healing. Huang et al. prepared silica hybrid mesoporous nanoparticles with highly integrated polydopamine by template synthesis method, and prepared polymer entangled porous nanobinder by mixing the particles with PVA solution through hydrogen bond entanglement (Figure 7).[66] Another study has shown that the prepared nanocomposites can enhance ROS scavenging ability, and also has anti-inflammatory and angiogenesis functions.[151]

4.2. Microrobots. Most of the biomaterials are based on passive transport for drug release, which is susceptibly limited by the concentration difference. The development of self-propelled power systems with navigation and high tissue penetration capabilities has now become a research boom.[152] Swimming biohybrid microrobots can have navigation, penetration, and drug release capabilities without additional fuel. This allows the opportunity for highly sensitive biosensing and active drug release.[153] Inspired by microalgae, Choi et al. used the electrostatic interaction between chitosan and heparin to prepare nanocomposites for the surface coating of *Chlamydomonas reinhardtii*, and designed a biological hybrid microrobot (Figure 8).[154] In the study, a microfluidic device[155] simulating blood clots was used to evaluate the fluidity of the robot, and the experimental data confirmed its ability to penetrate medium-density blood clots. The research shows that the microrobot can move autonomously at a speed of 33.3 μm/s and has the ability of photosynthesis. In addition, it can also regulate the immune response by binding to the inflammatory chemokine interleukin-8 and monocyte chemoattractant protein-1.

4.3. mRNA Nanosensors. Since wound healing is a dynamic process, it is meaningful to accurately determine which healing stage the wound is in. This will reduce the need to replace or remove the dressing for examination and enable targeted treatment. Such inventions are especially suitable for patients with chronic wounds. RNA-based therapeutics has great application prospects.[156] Hwang et al. designed a mRNA nanosensor that can be used to monitor the healing process of diabetic wounds (Figure 9).[157] The sensor monitors the state of wound healing in real time by locally applying nano-optical sensors. After a large number of screenings of biomarker genes, the final prepared PECAM1 sensor can reveal the inflammatory stage of ischemic wounds, and the FSP1 sensor can monitor the progress from inflammation to proliferation. However, since mRNA may also be expressed in other types of cells, the signal monitoring of these biomarkers may not have excellent specificity. Therefore, a lot of efforts are still needed to apply mRNA nanosensor to clinical practice. Nevertheless, this study still provides a new direction strategy for new wound healing materials.

4.4. Exosomes. The discovery of exosomes provides a new idea for the preparation of nanocarriers with good biocompatibility, more accurate and efficient targeting. Exosomes are

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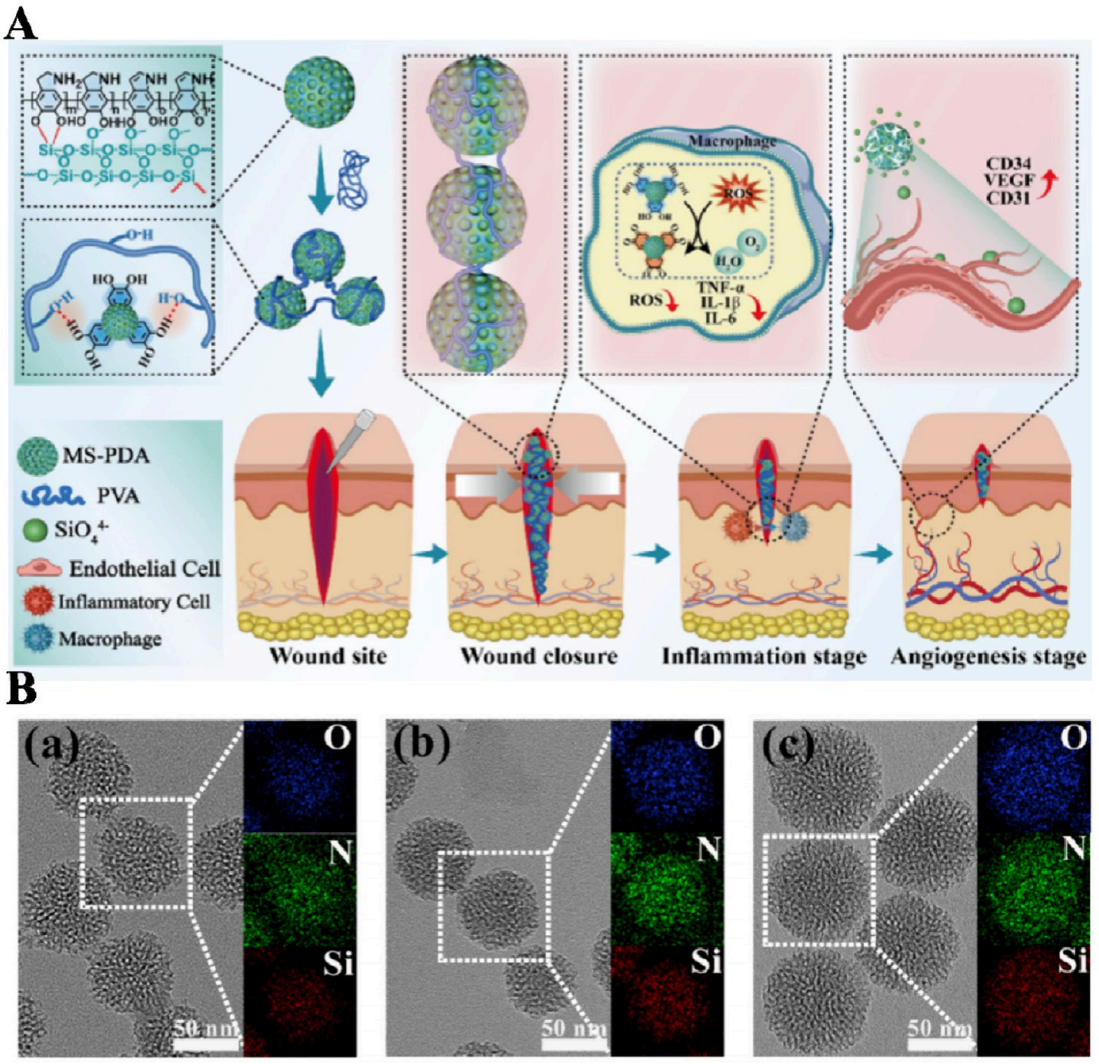

Figure 7. (A) Preparation and application of a nanoadhesive schematic. (B) The morphology and structure of MS-PDA particles. TEM and elemental mapping images of (a) MS-PDA-34, (b) MS-PDA-45, and (c) MSPDA-56. Reprinted with permission from ref 66. Copyright 2022, Elsevier. MS-PDA: hybrid mesoporous silica nanoparticles with highly integrated polydopamine.

recognized as an effective carrier for intercellular communication, with a size of 30−150 nm,[158] less cytotoxicity, and immunogenicity. As previously reported, almost all cells produce and secrete exosomes. Therefore, the selection of exosome donor cells is very important. It can prevent allergic reactions after administration, and can maintain the stability of the exosome system in the blood, and finally successfully deliver the drug to the targeted site.[159−162] Recent studies have shown that exosomes are also associated with the progression of various diseases, including cancer.[163] It can be seen that effective identification of cell markers related to wound healing can provide ideas for precise targeted therapy of exosomes.

The extraction methods of exosomes include: density gradient centrifugation (including ultracentrifugation),[164] ultrafiltration,[165] and size exclusion chromatography,[158] etc. At present, mesenchymal stem cells used for exosome research are bone marrow-derived mesenchymal stem cells, embryonic-derived mesenchymal stem cells, umbilical cord-derived mesenchymal stem cells, and adipose-derived mesenchymal stem cells, etc.[166]

With the further study of the purification, separation, and application of exosomes, it has been found that simple exosome delivery is prone to problems such as uncontrollable release and short survival time. The hydrogel has multifunctional adjustability and is used to encapsulate exosomes (Figure 10).[167,168] Yuan et al. made a methacrylate gelatin/polyethylene glycol diacrylate microneedle patch (MNs).[169] The MNs patch was loaded with Tazarotene and exosomes derived from HUVECs. The results show that the patch can accelerate collagen deposition, epithelial regeneration, and angiogenesis in wound tissue.

With the development of research, exosomes have also developed methods such as ultrasonic targeted release and multifunctional mesoporous bioactive glass release.[170] The intrinsic properties of exosomes in regulating complex intracellular pathways make them have potential application value in the treatment and control of many diseases.

5. CONCLUSIONS AND FUTURE PROSPECTS

In this review, we discuss the current status of the development and preparation of wound materials in wound healing and tissue regeneration. Through analysis and summary, we introduce the great potential of such materials in managing and promoting the wound healing process.

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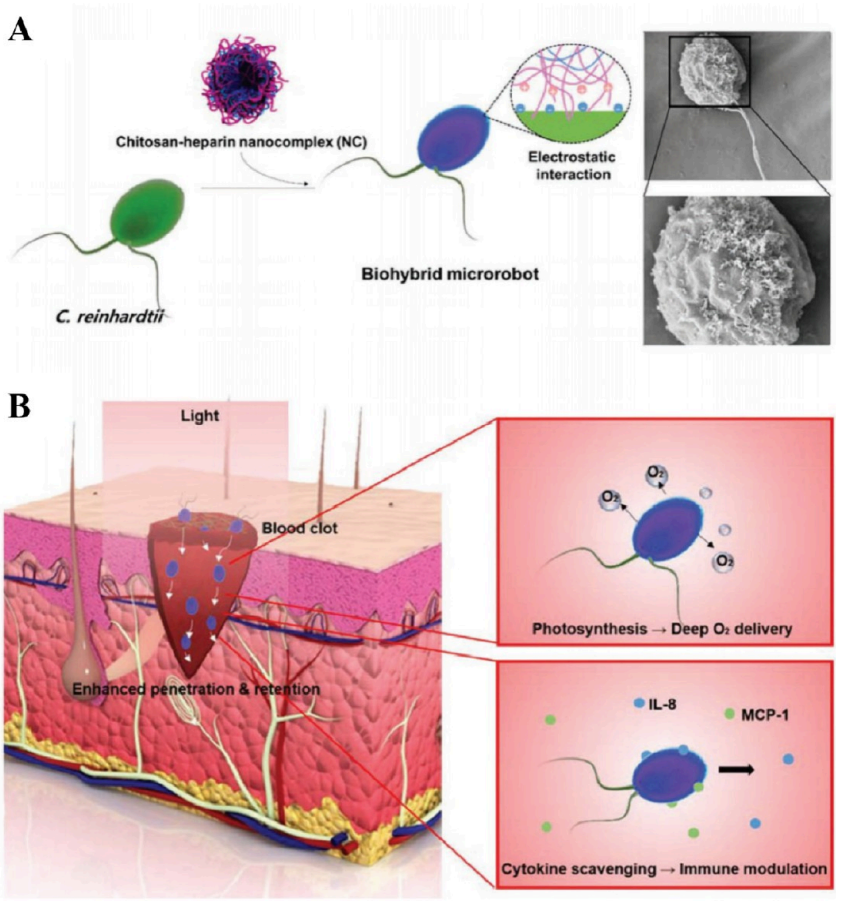

Figure 8. (A) Schematic diagram for making biohybrid microrobots. (B) Biorobots act as oxygen deliverers and enhance inflammatory cytokine clearance during wound healing. Reprinted with permission from ref 154. Copyright 2022, John Wiley and Sons.

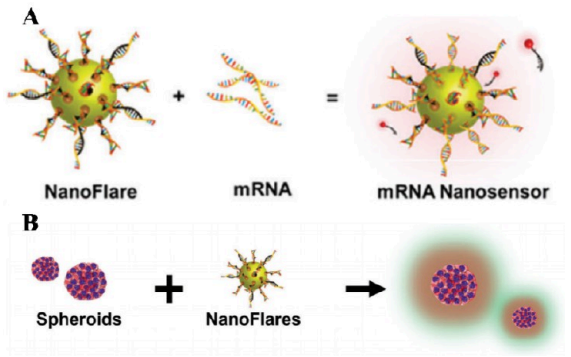

Figure 9. (A) Schematic diagram of the mRNA nanosensor. (B) Schematic of coculturing the nanoflares with 3D spherical cells. Reprinted with permission from ref 157. Copyright 2022, John Wiley and Sons.

Once the tissue is damaged, it is difficult to fully recover for various reasons, and it is impossible to have complete functions as the original tissue. Therefore, it is of clinical significance to make new materials with ideal properties for wounds. The ideal wound dressing needs to meet the following requirements: (1) good biocompatibility and biodegradability; (2) the ability to maintain a moist microenvironment to promote the migration of host cells to the wound; (3) the ability to protect the internal environment of the tissue as a defensive barrier; (4) good tissue adhesion; (5) rapid hemostasis; (6) antibacterial and anti-inflammatory effects; (7) enhanced cell activity by delivering therapeutic drugs; (8) allowing wound tissue to deform and function like intact tissue before injury; and (9) real-time monitoring of wound healing process and regulation. With the development of science and technology, more and more advanced technologies (such as microfluidic generation; electrostatic spinning; 3D printing and wireless sensing) have been introduced into the strategy. The research and development trend of wound dressings also tends to be more multifunctional and specific. Wound fluid pH, temperature, oxygen and moisture can also be used as diagnostic parameters to evaluate wound condition. However, for different skin tissues and structures, functional materials with unique and special intelligent response are needed. This also further promoted the development of medicine, physical chemistry, computer science, and other disciplines.

Although the prospect is promising, there is currently no uniform measurement standard for the performance of novel materials applied to wound repair. Most of the studies used conventional dressings as a control group, and whether this is comparable may need to be further explored. It can be seen that the clinical transformation of materials is a key issue, which needs to be solved urgently and is of great significance. This challenge would require concerted efforts from scientists, designers, researchers, and clinicians. It is also important to optimize the preparation process before the clinical transformation of the material. The process steps for the preparation of biomaterials should be as stable and simple as possible, and the biomaterials should be prepared in a way that

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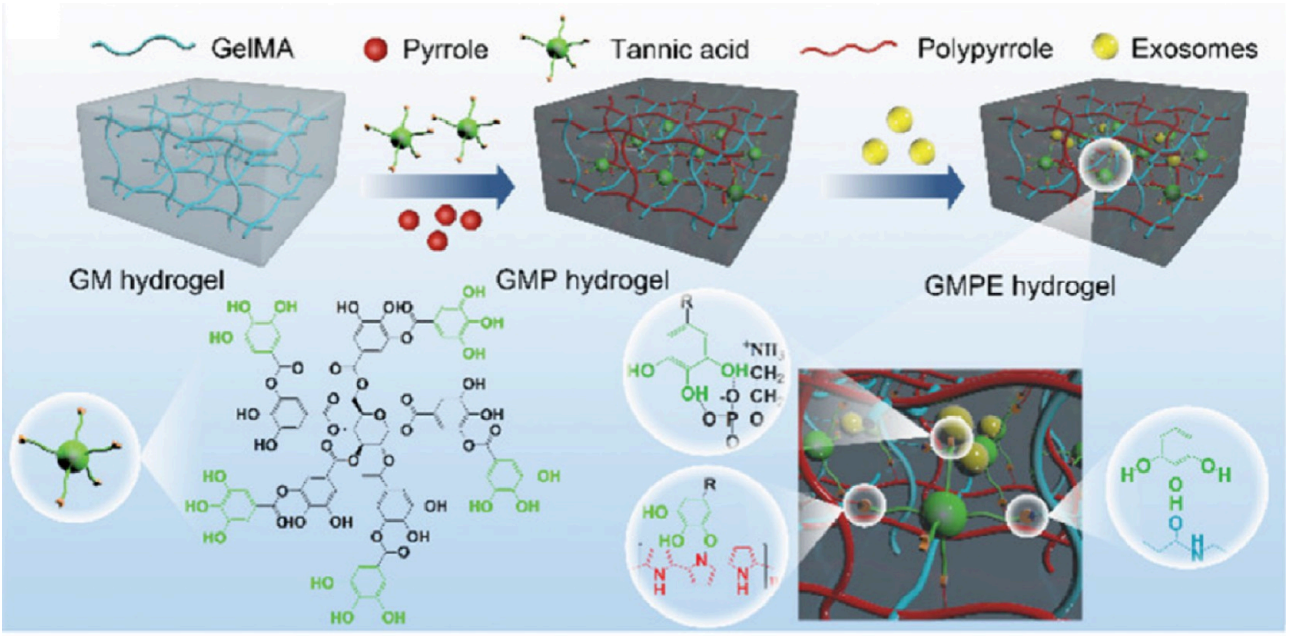

Figure 10. Preparation diagram for exosome composite hydrogel. Reprinted with permission from ref 167. Copyright 2022, John Wiley and Sons.

guarantees the stability of their properties. Existing research needs a lot of effort if it is to be put into mass production. Increasing numbers of biological material can be put into clinical reality and can alleviate the pain of patients are what we look forward to.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c02775.

Links to the copyrighted studies (ZIP)

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Conceptualization, Y.Z.; Investigation, Y.Z., H.C., E.W., L.W., Q.L.; writing—original draft preparation, Y.Z.; writing—review and editing, N.T., H.C., N.W., and Y.W. All authors have read and agreed to the published version of the manuscript.

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Notes

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