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Animal tissue-derived biomaterials for promoting wound healing

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The skin serves as the primary barrier between the human body and external environment, and is therefore susceptible to damage from various factors. In response to this challenge, animal tissue-derived biomaterials have emerged as promising candidates for wound healing due to their abundant sources, low side-effect profiles, exceptional bioactivity, biocompatibility, and unique extracellular matrix (ECM) mimicry. The evolution of modern engineering technology and therapies has allowed these animal tissue-derived biomaterials to be transformed into various forms and modified to possess the necessary properties for wound repair. This review provides an overview of the wound healing process and the factors that influence it. We then describe the extraction methods, important properties, and recent practical applications of various animal tissue-derived biomaterials. Our focus then shifts to the critical properties of these biomaterials in skin wound healing and their latest research developments. Finally, we critically examine the limitations and future prospects of biomaterials generated from animal tissues in this field.

Wider impact

The skin serves as the primary barrier between the human body and the external environment, and is therefore susceptible to damage from various factors. In response to this challenge, animal tissue-derived biomaterials have emerged as promising candidates for wound healing due to their abundant sources, low side-effect profiles, exceptional bioactivity, biocompatibility, and unique extracellular matrix (ECM) mimicry. The evolution of modern engineering technology and therapies has allowed these animal tissue-derived biomaterials to be transformed into various forms and modified to possess the necessary properties for wound repair. This work highlights the animal tissue-derived biomaterials in the wound treatment field based on the evaluation of their critical properties, advanced design strategies and latest applications. Future research in this field should focus on developing new sources of animal tissue materials, and exploring new methods of biomaterial preparation and modification. Besides, future multifunctional dressings that can monitor and treat the wound environment are also better for managing wounds. It is envisaged that more advanced and intelligent wound dressings will offer distinctive and effective wound healing solutions.

1. Introduction

Skin, as the first barrier of immune defense, is easily subject to external damage since it is often subject to injury from the external environment.[1–5] When skin damage occurs, appropriate wound dressings are required to protect the wound region, restore its biological function, decrease infection risk and reduce scar formation.[6–10] Traditional wound dressings are mainly made of cotton fabric. They typically only have simple isolation functions and are unable to create a favorable microenvironment to promote wound healing, leading to low clinical cure rates and high rates of wound recurrence.[11,12] Recent innovations in molecular biology, material science, nanoscience and modern engineering technology have significantly improved the performance of wound dressings. Novel wound dressings, such as foam dressings, hydrogels, and tissue-engineered skin, provide resistance to external bacterial contamination and possess additional benefits like pain relief, hydration and tissue regeneration.[13–16] Synthetic polymers are composite nanobiomaterials with small pores and very high specific surface area. Their application for wound dressings is made possible using various techniques but mainly by electrospinning. Although some synthetic polymer-based materials such as PEG have made significant contributions to wound healing with multiple products

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translated to clinics, more synthetic polymers involved in those dressings require complex chemical synthesis procedures and crosslinking conditions using organic reagents, which might decrease their bioactivity and biocompatibility. Additionally, their inability to mimic the extracellular matrix (ECM)-based microenvironment remains a challenge for their clinical application. Thus, the development of dressings with safe sources and efficient functions for accelerating wound healing still remains an urgent need.

Natural biomaterials are mainly composed of polymers derived from animals, plants, or microorganisms.[17,18] They have been primarily employed in the areas of regenerative medicine, wound management, and drug therapy benefiting from their numerous inherent properties including bioactivity, biocompatibility, as well as biodegradability.[19–22] Animal tissue-derived biomaterials are attractive for their extensive biological sources, simple composition, and extracellular matrix-mimicking properties. Based on this, biomaterials formed with animal-derived collagen and polysaccharide have gained great research interest. Specifically, the purification and modification processes of these animal tissue-derived materials are generally milder, thus maintaining their inherent molecular structure and unique bioactivity. More importantly, the animal tissue derived biomaterials may contain a similar structure to the ECM, which possesses particular biochemical signals and protein binding sites to promote cellular adhesion, proliferation and migration throughout the biomaterial scaffold. This interaction between the biomaterial and cells enhances tissue integration and regeneration.[23,24] Given these characteristics, animal tissue-derived biomaterials are considered to be highly promising wound dressings.

In this review, we begin with the basic knowledge of wound repair, mainly introducing the four phases of the wound healing process and the factors that affect healing efficiency. We then illustrate the extraction and inherent properties of several animal tissue-derived biomaterials, from an acellular matrix to collagen, silk fibroin and chitosan. Their different forms in practical applications, such as gels, microspheres, microneedles and porous membranes are also discussed. Furthermore, we cast light on the necessary properties of these biomaterial-based dressings for skin wound repair, including the properties of antibacterial, angiogenesis, antioxidant, wound monitoring and others, as well as the relevant mechanisms and latest progress. Finally, we summarize the important elements and propose the future development goals of animal tissue-derived biomaterials in the wound management field.

2. Fundamental aspects of wound healing

The process of damaged tissue repair and regeneration is defined as wound healing. Hemostasis, inflammation, proliferation, and remodeling are the four phases included in the healing process. In order to achieve successful wound healing, these four phases should occur in the correct sequence. Factors affecting wound healing may affect one or more phases, impairing or causing incorrect wound healing. Local factors and systemic factors can be used to categorize the factors that affect healing efficiency. This section will discuss the molecular process in skin repair, some main factors that affect the healing status, as well as its mechanism and examples.

2.1. Wound healing process

After injury, the first step is hemostasis (Fig. 1a).[25] Due to a neurological reflex mechanism, wounded vessels constrict and thus stop bleeding for a short time. When blood leaks, platelets connect to the extracellular matrix, which causes the clotting factors to be released.[26–28] Then neutrophils and monocytes are responsible for mediating the inflammatory response, which begins in the late stages of hemostasis. Several injured cells, as well as additional pathogens and debris, are eliminated during this phase *via* the phagocytosis process. Specifically, neutrophils become sticky and adhere to post-capillary venules owing to the adhesion molecules' change. They roll along the endothelium as blood flows and finally reside between the endothelial cells accompanied with strong adhesion. Once the skin defect occurs, proteolytic enzymes and free oxygen radicals are released by neutrophils, which destroy and phagocytose microorganisms. The neutrophils also produce cytokines to amplify the inflammatory response. Monocytes subsequently differentiate into macrophages. Macrophages play an important role in promoting the inflammatory reaction and tissue debridement. Additionally, they express different growth factors and chemotactic factors. These factors are crucial in triggering cellular migration, proliferation and matrix production. Notably, the last activated cells during the inflammatory phase are lymphocytes which are attracted by interleukin-1, complement component, and immunoglobulin G.[29]

The hemostasis phase and inflammation phase are mainly for repairs, followed by the proliferation phase. To reconstruct the basement membrane, various proteins are released from migrating cells (*e.g.*, keratinocytes, endothelial cells, fibroblasts, and myofibroblasts). Commonly within three days, the epidermis's normal layers could be restored as the epithelial cells move upward in an expected way. Numerous signals

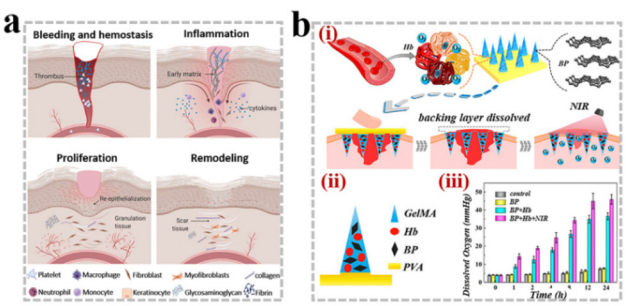

Fig. 1 (a) Schematic image of the wound healing process. Reprinted with permission from ref. 25. Copyright 2022, Solarte David, Güiza-Argüello, Arango-Rodríguez, Sossa and Becerra-Bayona. (b) Schematic illustration of (i) BP QDs and oxygen-carrying Hb loaded MNs for wound repair, (ii) the component of MNs. (iii) Oxygen releasing conditions in different groups. Reprinted with permission from ref. 42. Copyright 2018, Royal Society of Chemistry. Copyright 2020 American Chemical Society.

(*e.g.*, nitric oxide, cytokines, and growth factors) are produced in the wound region, which can promote re-epithelialization and angiogenesis. In this stage, it is crucial to provide extra nutrients and oxygen for promoting wound healing. As the ECM affects angiogenesis by acting as a scaffold and a signaling mechanism. Both the endothelial basement membrane and granulation tissues require normal replication and reorganization of the ECM's components. The transformation from granulation tissue to a closed wound is defined as remodeling. In this phase, fibroblasts and myofibroblasts lay down an organized collagen fiber-based network and use proteases to break down preexisting disordered tissue. As the mature type I collagen eventually replaces type III collagen, the comparatively frail and young granulation tissue fabricated during the proliferation phase becomes tight and mature. Additionally, the healing wound eventually decreases its vascularity.[30,31]

2.2. Factors affecting wound healing

Complete skin closure and restoration of normal physiological structure and function are the marks of wound healing. Numerous factors have been found to be able to accelerate or impair the wound healing process. In general, there are systemic and local influences.[32,33] Systemic factors (*e.g.*, age, gender, stress, illness, *etc.*) are the individual's general health or disease conditions that affect the ability to heal. While local factors, such as oxygen, may have a direct impact on the wound region. In this regard, it is viable to promote the wound repair process by affecting local factors. Especially, accompanying the significant innovations in the domains of medicine, materials science, biomedical engineering, and nanoscience, multiple novel strategies have been developed to enhance wound treatment.[34–37] It is notable that the most widely explored methods are the developments of wound dressings. Here, we mainly introduced oxygenation and infection, two of the key local factors that could be affected by wound dressing during the wound healing process.

A typical local factor is the amount of oxygen. The entire wound healing process depends on oxygen, which is essential for cell metabolism and energy production. It also stimulates angiogenesis, increases fibroblast proliferation and promotes collagen synthesis, protects wounds from infection, and encourages wound contraction. Besides, the formation of superoxide by polymorphonuclear leukocytes is highly reliant on oxygen concentration. Vascular disruption in wounded areas results in oxygen deprivation or hypoxia. Notably, transient hypoxia promotes wound healing while persistent hypoxia inhibits it.[38,39] Therefore, oxygen carriers are attracting a lot of interest in clinical wound treatment.[40,41] Zhao *et al.* created detachable responsive microneedles (MNs) with black phosphorus quantum dot (BP QDs) doping to realize oxygen delivery in wound areas, as shown in Fig. 1b.[42] The tips of MNs were composed of hemoglobin (Hb) and BP QD-loaded gelatin methacryloyl (GelMA). After a chronic wound is treated with these MNs, the local skin's temperature will rise owing to the BP QDs' photothermal conversion capacity, which will subsequently trigger responsive oxygen release due to Hb's reversible oxygen binding ability, finally delivering effective therapeutic benefits.

When the skin is injured, it provides an opportunity for microorganisms that are typically present on the surface of the skin to reach the underlying tissues. Inadequate removal of germs from wounds may result in an extended rise in pro-inflammatory cytokines and a prolonged inflammatory phase. If this keeps happening, the wound can become chronic and stop healing.[43–46] Therefore, it is vital to remove the contaminating microbes during the inflammation phase. In recent decades, numerous antibacterial agents have been developed and the existence of antibacterial materials could be classified into the following types: antibiotics, antibacterial nanoparticles and others. In addition to oxygenation and infection, some other factors can also affect the wound healing process. For example, the pressure or mechanical force caused by the attachment of wound dressings would affect the blood supply and wound contraction. Besides, the existence of reactive oxygen in the wound area may be harmful to some normal cells. As a result, the wide variety of influencing factors makes it challenging to develop ideal dressings for promoting wound healing.[47–49]

In summary, the primary objectives of a wound dressing are to preserve the ideal temperature and pH conditions required for healing, maintain a moist environment, control bleeding, prevent infection, alleviate excessive pain, enable gas exchange, and minimize psychological distress.[50] Designing and creating various types of polymeric dressings utilizing natural or synthetic polymers is one of the trendiest research fields right now. Natural polymer-based dressings are attractive candidates owing to their multiple inherent bioactivity properties. Commonly, natural polymers undergo milder purification and modification methods than most inorganic materials or synthetic polymers in order to preserve their underlying molecular structure.[51,52] Natural polymers are less hazardous than synthetic polymers in this aspect. In particular, because of the unique high water content, biodegradability, and biocompatibility, the animal tissue-derived biomaterials have extraordinary abilities to imitate the biological and physical aspects of natural ECM. Therefore, wound dressings based on several types of animal tissue-derived polymers are briefly introduced.

3. Animal tissue-derived biomaterials

Researchers are currently searching for bioactive substances with expected biosafety and biocompatibility to speed up the wound repair rate. Natural polymers extracted from animal tissues have been extensively studied in this field since they typically contain biological activity and low toxicity that facilitate wound regeneration. Notably, accompanying microfluidic, 3D printing and other modern engineering technologies, these animal tissue-derived biomaterials are processed into different morphologies (*e.g.*, microspheres, microneedles, films and fibers, *etc.*) to satisfy the practical requirements of moisture retention, oxygen permeability, mechanical properties, on-demand drug delivery and others. This section provides an overview of the extraction and important properties of various animal tissue-derived biomaterials, from decellularized ECM to

silk fibroin, collagen, and chitosan. In addition, their latest research progress in wound management is also discussed.

3.1. dECM-based biomaterials

A connective network made up of collagens, glycoproteins, proteoglycans, and tiny molecules is known as the ECM. Donor organs or portions of tissues have been processed to remove cells and cellular waste in order to create decellularized ECM (dECM). The dECM has various proteins, proteoglycans, and glycosaminoglycans that are necessary for cellular adhesion, growth factor sequestration, and remodeling activity, while not containing many immunogenic components (such as native cells, pigments and fat) of the native tissue. It is notable that two key aspects underlie the dECM's notable contributions to tissue regeneration. Firstly, it can provide support and attachment sites for cell surface receptors due to their unique 3D structure. Secondly, its bioactive substances may influence angiogenesis, cellular migration, and collagen orientation in wound repair.[53,54] As a result, dECM has been generated from a variety of tissue sources, including dermis, skin flaps, peritoneum, and intestinal tissues, for use as skin substitutes.[55–57] In particular, numerous methods for decellularization have been researched, such as acid treatment, alkali treatment, enzyme treatment, freeze/thaw cycles method and so on.[58–61] Practically, for a more global optimal decellularization protocol in actual experiments, their combinations are more frequently used.

Decellularized ECM (dECM) derived from diverse animal tissues has been applied in burn treatment and surgical reconstruction over the past few decades.[62,63] The most common strategy is to attach these dECM materials directly to the wound area. Among them, acellular dermal matrices (ADMs), a type of ideal dermal substitutes, are commonly used in wound repair. There is a wide range of ADM products derived from animals that are currently being employed in clinical settings. Because of their histological structure similar to human skin, pigs have become the main donor of xenotransplantation.[64] In addition to directly covered patches, porcine ADM has also been processed into powder and paste based materials. Hsieh *et al.* established an innovative porcine ADM to enhance deeper wound healing by using supercritical CO_2 ($scCO_2$) to fabricate ADM powder and ADM paste. In a rat model, these two materials with different forms are equally effective at promoting wound healing with nontoxicity and high biocompatibility.[65]

Despite significant advancements, it is inevitable that the use of porcine ADM carries risks that are similar to those associated with human ADM. These mammalian-derived ADMs might lead to the risks of infection, rejection, as well as failure or dehiscence of the wound, which greatly limited their clinical applications.[66,67] Interestingly, it has been found that the use of marine ADM was more successful in increasing healing rates than porcine ADM. The marine-derived ADMs have distinct advantages over land-derived ADMs in terms of cost, immunogenicity, and religious limitations. Notably, a fish ADM rich in omega-3 fatty acids has also been cleared for marketing in wound treatment and other applications.[68–70] Besides, Chen *et al.* prepared ADM from black carp's skin. They used combined

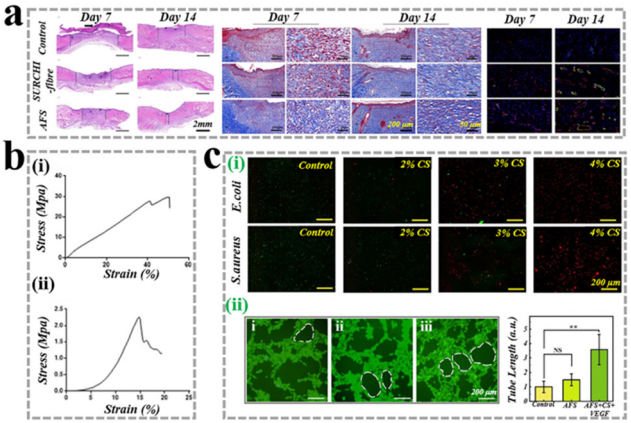

Fig. 2 (a) The promotion of wound closure, collagen deposition and vascular formation after wound treatment with AFS. Reprinted with permission from ref. 71. Copyright 2021, IOP Publishing. (b) (i) Mechanical test of dry AFS. (ii) Stitch tear resistance of AFS. Reprinted with permission from ref. 71. Copyright 2021, IOP Publishing Ltd. (c) The *in vitro* antibacterial and tube formation test of AFS loaded with CS and VEGF. Reprinted with permission from ref. 72. Copyright 2022, Elsevier.

methods of freeze/thaw cycles, Triton X-100 and trypsin washing to realize the decellularization. The resulting ADM has a high degree of hydrophilicity, high water absorption capacity, and excellent stitch tear resistance. It also has a highly porous structure, as well as a porous structure. In particular, in an *in vivo* wound healing test, this ADM showed capacities in promoting angiogenesis, collagen synthesis and wound healing, indicating its potential in helping promote full thickness wound healing (Fig. 2a and b).[71] Furthermore, to impart the ADM with more functions, our group prepared a novel acellular fish skin (AFS) with porous structures. The porous scaffold of the AFS was then injected with a chitosan pregel loaded with vascular endothelial growth factor (VEGF). As a result, this hybrid patch possesses angiogenesis and antibacterial properties owing to the incorporated effect of VEGF and chitosan. A full-thickness wound rat model has been employed to demonstrate its remarkable therapeutic efficacy in suppressing inflammation, promoting angiogenesis, collagen formation, and tissue growth (Fig. 2c).[72]

3.2. Silk fibroin-based biomaterials

Silk fibroin (SF) is the main component of silk worm protein, while SF makes up approximately 70% of the cocoon weight. SF is often extracted from the cocoon by degumming the silk sericin, while the residual SF is then recreated by dissolving and freeze-dying.[73,74] The brilliant biological properties of SF include its non-carcinogenic, biodegradable, less immunogenic, and biocompatible properties. Besides, due to the physicochemical characteristics of their intrinsic components, SF has exceptional toughness, mechanical strength, and customizable qualities (*e.g.*, permeability, composition, and sequencing). Moreover, it has been demonstrated that SF could promote cellular growth, proliferation and migration involved in the different phases of wound repair.[75,76] Ultimately, these properties make SF a great candidate for fabricating wound dressings. In recent decades, SF

has attracted great interest in wound healing. With the development of engineering technologies and advanced material science, SF has been discovered as a possible biomaterial with many different forms, such as solutions, films, electrospun, microfibre films, hydrogels, and sponges. All of them have obtained favorable findings *in vitro* and *in vivo*.[77–81]

Despite all the progress, the limitations of SF-based biomaterials, particularly those of hydrogel polymers, include lengthy synthesis times, complex condition assistance, and self-healing capabilities deficiency. To overcome these shortcomings, Guo *et al.* used SF, acryloyl-β-cyclodextrin (Ac-CD) and 2-hydroxyethyl acrylate to prepare a supramolecular hydrogel through simple photo-polymerization (Fig. 3a).[82] Its application as a wound dressing is more intriguing benefiting from its enhanced mechanical qualities, long-term stability, rapid self-healing capacity, injectability, and high biocompatibility. In another study shown in Fig. 3b,[83] Lv *et al.* prepared silk fibroin methacryloyl, which was formed from silk fibroin modified with glycidyl-methacrylate groups. Silk fibroin methacryloyl (SFMA) has stable mechanical properties and brilliant biocompatibility. In contrast, a microneedle (MN) patch is a typical minimally-invasive local delivery system, which could penetrate skin leaving no scar and delivering drugs almost painlessly. Accompanying the emerging MN patches, they successfully fabricated MN patches with multifunctions based on SFMA and other bioactive agents (Prussian blue nanozymes, VEGF and polymyxin). In this system, a SFMA hydrogel gave the patch the capacity of better biocompatibility, processability, and cheaper cost. As a result, this multifunctional MN exhibited excellent therapeutic effects and provided an advanced treatment method for chronic wounds.

Although these biomaterials all showed effective results in promoting wound healing, scar-free recovery is still quite difficult.[84–86] To further achieve scar-free therapy, Yan *et al.* proposed a novel scaffold by simulating the biochemical constituents and structures of ECM with hyaluronic acid (HA) and silk fibroin nanofibers (SNFs). HUVECs were then cultivated in this scaffold (Fig. 4a). In addition to the good physical properties, better cytocompatibility to enable cell spreading, proliferation and differentiation were also demonstrated by this SF-based scaffold in treating full-thickness skin defects, in addition to speeding up wound healing. These nanofiber-involved scaffolds also successfully regulated collagen organization by employing nanofibers as a template to avoid the creation of scars (Fig. 4b).[87]

3.3. Collagen-based biomaterials

Collagen, a highly abundant structural protein found in all mammals, is characterized by its triple helix structure. Its unique cell adhesion domains are known as the arginine–glycine–aspartic acid motif, that can support cellular growth, differentiation, and activity. Collagen is the most prevalent element of the ECM in humans, making up 20–30% of the total protein content.[88] The existing collagen was obtained from various animals including

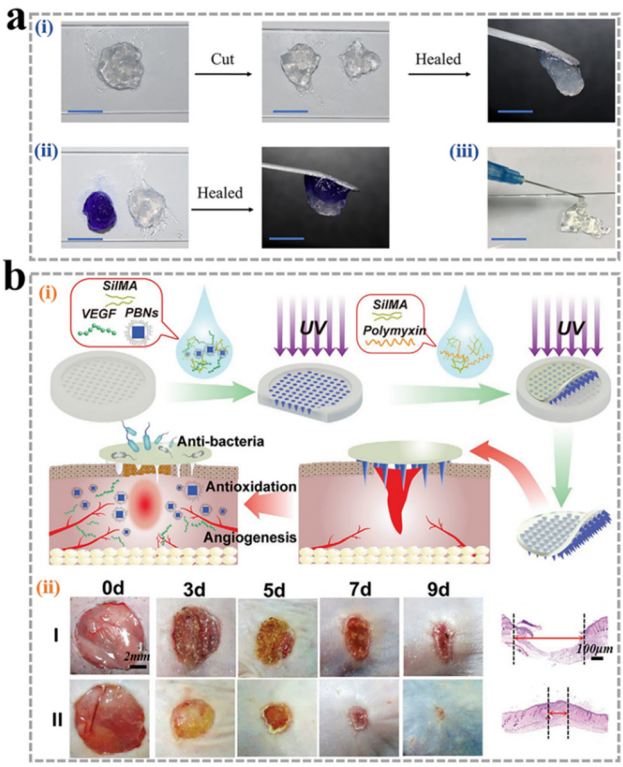

Fig. 3 (a) SF/Ac-CD hydrogel's (i) self-healing property and (ii) injectable property. Reprinted with permission from ref. 82. Copyright 2020, Elsevier. (b) (i) Working principle of preparing and using MN-PBNs-VEGF patches for treating diabetic wound healing; (ii) *in vivo* wound treatment (I is the DM group, II is the DM + MN-PBNs-VEGF group). Reprinted with permission from ref. 83. Copyright 2022, Wiley-VCH GmbH.

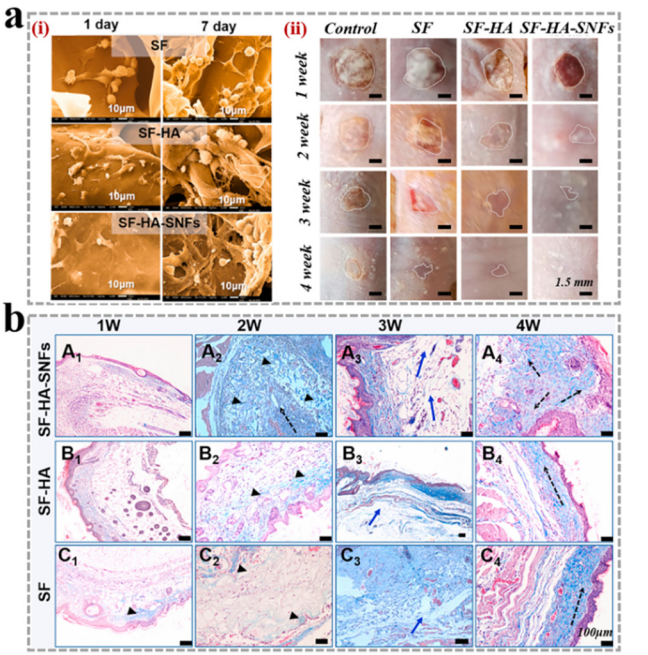

Fig. 4 (a) (i) SEM images of HUVECs; (ii) *in vivo* wound treatment. (b) Collagen in the SF and SF-HA groups was dense and oriented, while the collagen in the SF-HA-SNFs group continued to deposit, closely resembling biological tissue. Reprinted with permission from ref. 87. Copyright 2021, Elsevier.

mammals (*e.g.*, porcine and bovine) and marine life (*e.g.*, jellyfish and fish) after the process of impurity removement, degradation and disinfection. As for the biological properties of collagen-based biomaterials in wound management, first in the hemostasis phase, collagen could bind platelets and generate thrombin. Additionally, collagen activates macrophages and other crucial elements that promote angiogenesis during the healing progress. In a typical wound, a high level of MMPs may damage the native collagen, preventing the lesion from healing. The distribution of substitute collagen and the consequent decrease in elastase level in the wound environment make collagen dressings preferable to other dressings. The substitute collagen's MMP binding activity additionally slowed the progress of non-healing wounds. More importantly, collagen stimulates fibroblast activity to form granulation tissue by acting as a chemotactic agent to draw skin fibroblasts to the wound.[89,90]

Numerous studies have explored the use of collagen-based biomaterials for their potential to facilitate wound healing.[91–94] By using vacuum freeze-drying technology, a polyporous collagen sponge with the right pore size could be created, which was beneficial for wound healing due to its improved ability to absorb tissue exudates, improved cellular interaction, and increased gas exchange. The crosslinking on collagen sponges could further improve its properties. For example, after crosslinking with *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide/*N*-hydroxy succinimide, an ideal and secure cross-linker, the collagen sponge would show the greatest degree of hygroscopicity and superior mechanical properties. Based on this, a wound dressing involving coating (a spun-laced nonwoven with chitosan) and embedding (a collagen sponge matrix) has been prepared. This new dressing's effectiveness in wound repair was demonstrated using a full-thickness skin defect model.[95] In addition, Sun *et al.* employed the technology of electrospinning to prepare electrospun scaffolds composed of collagen-graphene oxide (Col-GO) and basic fibroblast growth factor (bFGF). By offering more binding sites for bioactive factors, GO could improve the mechanical properties and biological interactions when functionalizing collagen. The electrospun scaffolds' activities in promoting wound repair and improving skin tissue recovery have been demonstrated.[96] Additionally, collagen-based materials are also outstanding drug delivery carriers. For example, Franz *et al.* created an artificial 2-dimensional ECM based on a collagen network and high-sulfated hyaluronan (sHA). It is notable that sHA could leak from the matrix to influence monocyte to macrophage differentiation under inflammatory conditions and to activate regulatory macrophage functions. The resulting sHA-releasing hydrogels improved the healing rate of damaged tissues by reducing inflammation, enhancing pro-regenerative macrophage activation, increasing vascularization, as well as speeding up new tissue growth.[97]

In another way, collagen is hydrolyzed to produce gelatin. Gelatin demonstrates good biological interactions, biodegradability, biocompatibility, non-immunogenicity, and great processability, just like other top biomaterials.[98–100] A gelatin derivative known as gelatin methacryloyl (GelMA), which has high biocompatibility, biodegradability, and moldability, has been widely used in biomedical applications. GelMA hydrogels, which are comparable to the dermal ECM found in the skin and have tunable mechanical and degrading properties, can be used as the main component of wound dressings. By adjusting the level of substitution, GelMA might obtain improved mechanical and degrading properties as well as greater biocompatibility when compared to other collagen hydrogels. Through offering a similar microenvironment to the natural ECM, the GelMA-based microspheres are a novel class of functional materials that have the potential to operate as regulators in a range of biomedical disciplines. Their ability to precisely control stem cell behavior in culture and enhance therapeutic cloning techniques have made it possible to repair damaged tissues and organs without fault. The cutting-edge pairing of stem cells and microcarriers could also successfully transport and increase the viability of stem cells.[101–104] For instance, GelMA has been proven to be a good carrier for umbilical cord mesenchymal stem cells (UC-MSCs). As shown in the studies carried out by Hsieh *et al.*, UC-MSCs produced more angiogenesis-related genes and improved the production of microvasculature and cell migration more than MSCs from bone marrow.[105] The research carried out by Li *et al.* found that the application of MSC + GelMA microspheres (GMs) reduced type III collagen and transforming growth factor

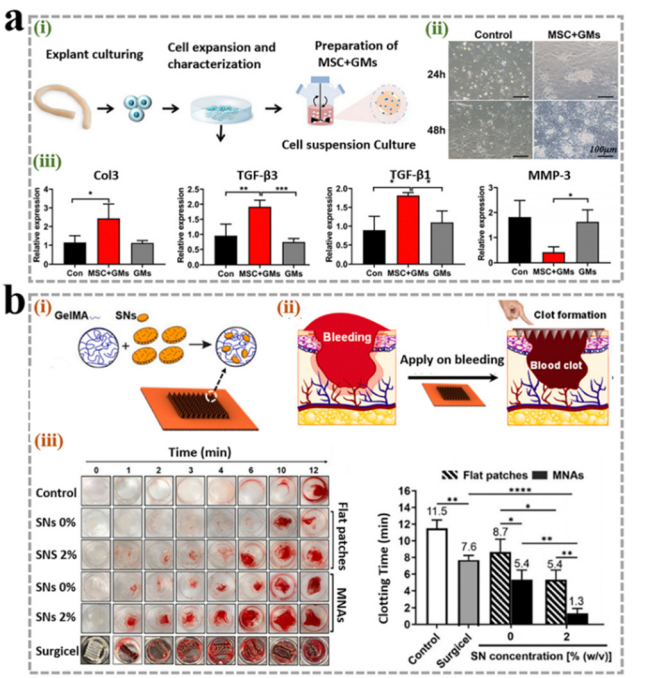

Fig. 5 (a) (i) The preparation of MSC + GM complexes. (ii) The proliferation of UC-MSCs co-cultured with GelMA microspheres. In MSCs co-cultured with GelMA microspheres, more UC-MSCs proliferated. (iii) Expression of genes associated with wound healing in mice at day 15. In the region of the wound, MSC + GMs suppress the expression of metalloproteinases while promoting the expression of Col3, TGF-1, and TGF-3. Reprinted with permission from ref. 106. Copyright 2022, IOP Publishing Ltd. (b) (i) The composition of the MNs. (ii) Working principle of facile MNA application onto a bleeding model to stop hemorrhage. (iii) Blood clotting over time for various MNAs compared to the commercially available positive control (Surgicel®) and needle-free flat patches. Reprinted with permission from ref. 112. Copyright 2022, Elsevier.

expression *in vivo*, resulting in new collagen deposition and angiogenesis, which sped up the recovery rate of skin tissues (Fig. 5a).[106]

Drugs can now be delivered more effectively and through deeper skin layers thanks to MNs.[107–110] In light of this, a polydimethylsiloxane (PDMS) mold imitating a variety of MN cavities was created. Chen *et al.* successfully used a methacrylate gelatin (GelMA) MN patch to deliver tazarotene and cell-derived exosomes transdermally. In this study, short chain PEGDA was added to the GelMA pregel solution to enhance its crosslinked network. The effective therapeutic effects of the GelMA-based MN patch were proved through a full-thickness cutaneous lesion created on a diabetic mouse model.[111] In another recent contribution, as shown in Fig. 5b,[112] for the management of hemorrhage on the wound area, silicate nanoplatelets (SNs) were hybridized with GelMA biomaterial to create microneedle arrays (MNAs). The needle-shaped patch enhances the blood contact area while the SNs render the MNAs hemostatic. These MNAs successfully sped up the blood clotting time from 11.5 minutes to 1.3 minutes. Combining micro- and nano-engineered features, these SN-integrated MNAs showed an ideal hemostatic effect *in vivo* and tissue adhesive properties for wound closure applications. And showed superior characteristics and wide applications in drug delivery, cell attachment, and promoting tissue regeneration. Most of the gelatin-based materials are derived from bovine or porcine sources, leading to the risks of immune rejection and limited clinical applications. Thus, biomaterials based on a safer gelatin source with lower immunogenicity and cost is still anticipated.

3.4. Chitosan-based biomaterials

The exoskeletons from arthropods such as shrimps, crabs, and insects are mostly employed to prepare chitin. Chitin would be further converted into chitosan (CS) through partial deacetylation. There are two main ways to obtain CS: chemical deacetylation and enzymatic deacetylation. Benefitting from the inherent reactive functional groups, lower cytotoxicity, and biocompatibility, CS is employed for various medical applications, including tissue regeneration, medication administration, and wound infection control.[113–115] Its wound healing capacity mainly benefits from the existence of *N*-glucosamine monomers. Strong hemagglutination results from the electrostatic interaction between CS's amine groups and the red blood cell membranes' negative charges. Additionally, it could absorb plasma proteins and fibrinogen, thus promoting platelet aggregation as well as intrinsic blood coagulation. CS is also in close electrical contact with a negatively charged mucosal surface as a result of its cationic composition, which provides unique qualities including encouraged mucoadhesion and targeted medication administration for improving therapeutic effects. Most significantly, CS is a strong natural antibacterial agent that eliminates or inhibits the growth of microorganisms, which is crucial for the healing of wounds.[116,117] These characteristics have led to chitosan's widespread application in the creation of numerous types of wound dressings, including membranes, hydrogels, fibers, powders, and nanoparticles.[118–122]

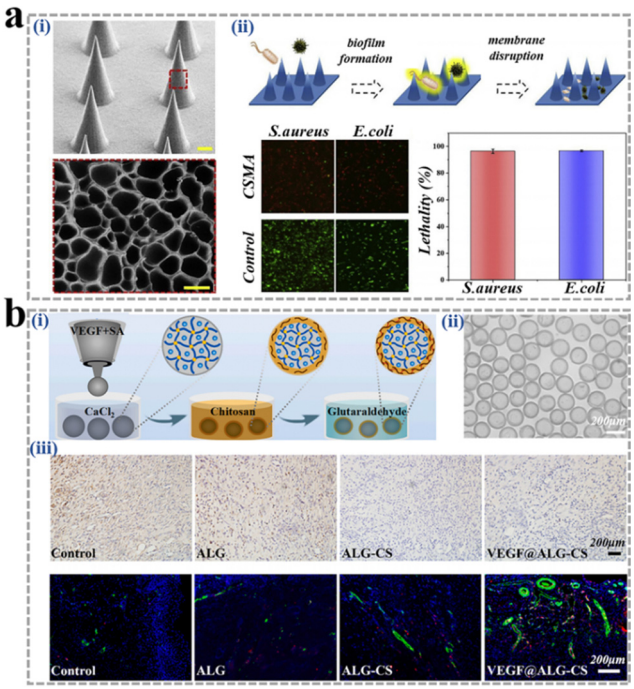

Fig. 6 (a) The (i) morphology and (ii) antibacterial properties of chitosan-based MNs. Reprinted with permission from ref. 123. Copyright 2020, Elsevier. (b) The (i) preparation method and (ii) image of ALG-CS microcapsules. (iii) The ALG-CS microcapsules' function in anti-inflammation and antibiosis. Reprinted with permission from ref. 124. Copyright 2023, Elsevier.

Considering the effective antibacterial property of CS, Zhao *et al.* successfully fabricated CS-based MNs through a simple polymerization (Fig. 6a).[123] In this study, the authors first dissolved CS powder in an acid solution to obtain CS pregel. Then the NaOH solution was used for the CS gelation. The CS MNs were discovered to have porous features, allowing other solutions to seep into the voids *via* capillary force. In this case, VEGF was loaded into this CS hydrogel to give MNs angiogenesis properties. In practical skin defect models, this MN patch demonstrated therapeutic effects by encouraging collagen formation, angiogenesis, inflammatory suppression, as well as tissue recovery during the healing process. Even so, the drug loading amount using this method is not satisfactory to further improve the capacities of drug loading, sustained drug release and therapeutic efficacy. By using microfluidic electrospray, this team further created composite microcapsules that have an alginate (ALG) core and a CS shell for accelerating wound healing. The high biocompatibility and antibacterial power of the microcapsules are guaranteed by this formulation. Additionally, VEGF can be added to the microcapsules and delivered in a sustainable manner. These benefits provide evidence for their roles in preventing bacterial development and encouraging angiogenesis during wound healing (Fig. 6b).[124]

It is notable that CS-based wound dressings have important applications in wound hemostasis. As the electrostatic interaction wound exist between CS's amine groups and the red blood cell membranes' negative charges, which would lead to

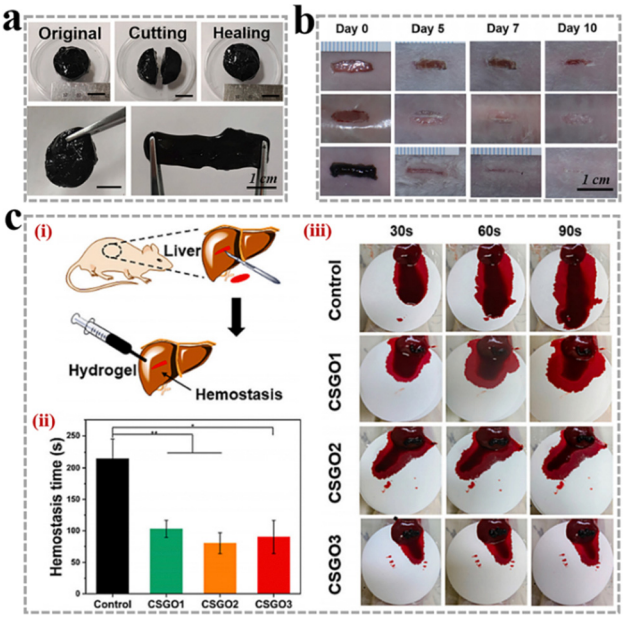

Fig. 7 (a) CSGO hydrogels' self-healing properties. (b) *In vivo* wound healing performance. (c) CSGO hydrogels' *in vivo* hemostatic ability. Reprinted with permission from ref. 125. Copyright 2023, Elsevier.

strong hemagglutination. Besides, CS could absorb plasma proteins and fibrinogen, thus promoting platelet aggregation as well as intrinsic blood coagulation. In the recent contributions of CS-based biomaterials applied in the wound hemostasis field, a typical example is chitosan–graphene oxide (CSGO) hydrogels. To create the CSGO hydrogels, Feng and Li recently suggested a new straightforward one-pot technique that did not require complex synthesis or further purification steps. This hydrogel has the necessary injectability and long life span owing to the reversible dynamic dissociation and recombination of noncovalent bonds between graphene and chitosan. It also showed tremendous promise in efficiently supporting hemostasis and wound healing (Fig. 7).[125] Notably, there is a significant relationship between the molecular weight of CS and its properties of hemostasis, antibacterial, repair and regeneration in wound management. It is still challenging to prepare CS-based wound dressings with different biological properties by regulating their molecular weight.

3.5. Hyaluronic acid-based biomaterials

Hyaluronic acid (HA) is a linear glycosaminoglycan naturally existing in some connective tissues (*e.g.*, skin, umbilical cord, synovial fluid and vitreous humor), and is made up of repeated monosaccharide units of linked glucose amine and uronic. In terms of HA production, researchers extracted HA primarily from umbilical cords, vitreous bodies, cockscomb, and streptococcus. HA has been proven to possess various advantages like strong biocompatibility, biodegradability, and adjustable characteristics.[126] Notably, HA's main chain contains some functional groups such as carboxylic acid and hydroxyl groups, implying that different functional groups might be linked to fabricate crosslinking hydrogels. Because of these benefits, HA and its derivatives are widely utilized in wound therapy, ophthalmology, and orthopedic surgery, in a variety of tunable forms such as hydrogels, films, microneedles, sponges, microspheres, and foams.[127–129] Specifically, HA collaborates with fibrin during the wound repair's early phases to recruit fibroblast and endothelial cells into the wound area, which is completed primarily through the interaction of HA with cellular surface receptors. Several studies have shown that low molecular weight HA can increase cell proliferation, neovascularization, and collagen deposition, as well as generate *in vitro* endothelial tube formation.[130]

Considering HA's high biological performance, HA is frequently added to other stent materials used for wound repair to boost the stent's therapeutic efficacy. Su *et al.* created HA and EGF-loaded decellularized pig peritoneum scaffolds. In this study, the regenerated skin layers were both thicker in wounds treated with HA and EGF-loaded scaffolds than in wounds covered with scaffolds alone.[131] In addition to being used as active drugs, HA-based hydrogel materials are also ideal wound dressings since they have strong absorbance and unique mechanical properties to maintain tissue hydration and favor cell infiltration. Meanwhile, these materials are excellent drug carriers for delivering bioactive agents such as bioactive proteins, peptides and growth factors. In a recent contribution, Yao *et al.* created an injectable HA-based wound dressing with antioxidative and antibacterial activity. This hydrogel was created by incorporating graphene oxide (GO) into a hydrogel system composed of tyramine-grafted HA (HT) and gallic acid-grafted gelatin (GGA). The obtained dressings exhibited great antioxidant, hemostatic, and photothermal antibacterial activities. *In vivo* investigations demonstrated that when combined with photothermal therapy, this HA-based hydrogel dressing can successfully prevent early infection and expedite wound repair, indicating its significant potential in wound treatment.[132]

As mentioned above, the main chain of HA contains abundant functional groups, which could be linked with different functional groups. The combination of HA's modifiable properties with advanced engineering technologies can provide HA-based biomaterials with more diverse properties and broader application areas. Since CS and HA are excellent candidates for fabricating hemostatic and wound dressings, Chen's group prepared *N*-succinyl chitosan (NSC) and oxidized hyaluronic acid (OHA). They then added Ca^{2+} and/or PEG1 into the hydrogel system to regulate its mechanical behavior (Fig. 8a). The resulting hydrogels demonstrated good self-healing and injectable properties, indicating they could be helpful in hemostasis and wound coverings for deep or irregularly shaped wounds.[133] Among those numerous modification options, it is noteworthy that light-initiated radical polymerization is capable of adjusting hydrogels' mechanical characteristics and biological activities to precisely control the crosslinking reaction spatiotemporally. Shavande *et al.* recently attached tyramine to the carboxyl groups of HA to generate phenol-functionalized HA (HA-Ty). Its carboxylic acid groups were then aminated with ethylenediamine to form HA-Ty-NH_2. HA-Ty-NH_2's principal amine groups might react with the peptide's carboxylic acids. Under visible light, the final HA-Ty-NH_2-C hydrogel has been 3D printed with various shapes, as shown in

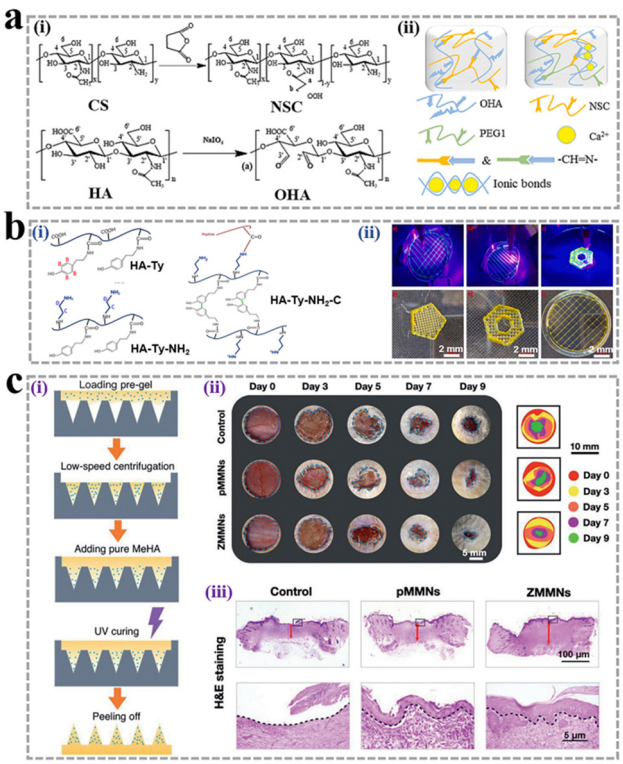

Fig. 8 (a) (i) Preparation scheme of NSC and OHA, and (ii) the formation mechanisms of NSC-OHA based hydrogels. Reprinted with permission from ref. 133. Copyright 2022, Elsevier. (b) (i) Preparation scheme of HA-Ty-NH_2-C, and (ii) different objects were 3D printed using HA-Ty-NH_2-C. Reprinted with permission from ref. 134. Copyright 2023, Elsevier. (c) (i) Schematic diagram of the MN fabrication process. (ii and iii) *In vivo* wound healing performance. Reprinted with permission from ref. 135. Copyright 2021 Wiley-VCH.

Fig. 8b.[134] Another typical HA-based photocrosslinked hydrogel is methacrylated hyaluronic acid (MeHA). For example, Zhao's team successfully used the molding method to fabricate Zn-MOF encapsulated MeHA microneedles. In this study, the zinc ion could be released constantly from the Zn-MOF to achieve antioxidative and antibacterial actions. Furthermore, the low molecular weight HA-based MNs are expected to degrade and are beneficial to tissue regeneration. *In vivo* skin regeneration tests have also revealed that the HA-based degradable MNs array is extremely beneficial for wound healing (Fig. 8c).[135]

4. Different requirements in wound healing

Repairing infected wounds is a difficult process. Even though these pure natural polymers are prospective tissue engineering materials, they have the severe drawback of insufficient functionality for wound healing. Natural biomaterials could be imparted with diverse requisite features by modifying themselves or adding active components to satisfy the various needs of wound repair. This section mainly reviews the recent advances of those animal tissue-derived biomaterials in meeting different requirements (*e.g.* antibacterial, angiogenesis and dynamic monitoring, *etc.*) in practical wound treatment.

4.1. Antibacterial property

One of the main issues related to failed wound healing is bacterial infection since invading bacteria can slow down wound healing progress through a variety of physiological processes. Bacteria produce endotoxins in addition to consuming the tissue's nutrients and oxygen. The bacterial invasion could also result in the local wound site expanding and becoming hypoxic, causing vascular blockage, and finally tissue death. The presence of Gram-positive bacteria is notable in the early stages of infection, whereas Gram-negative bacteria appear in the stably established wounds.[43,45,46] According to the findings of recent clinical trials, using contemporary wound dressings may be the most convenient, affordable, and successful way to treat unhealed wounds. As a result, wound dressing development has a lot of potential. In order to assure appropriate wound healing without bacterial infection, numerous materials have been created to date that are either composed of inherent antibacterial behavior or coupled with antibacterial agents in hydrogels, films, sponges, and nanofibers.[136–138] Some research teams in the field of natural biomaterials science concentrated on the creation of wound dressings employing polymers with inherent antibacterial activity, like chitin or CS. In addition, various antibacterial substances or nanoparticles have been added into polymeric materials for eliminating wound infections. These substances also involve gentamycin, vancomycin, and neomycin.[139,140] Here, we demonstrate the recent advances in the collaboration of antimicrobial agents and animal-derived biomaterials for wound antibacterial applications.

Since the 1940s, antibiotics have been used extensively to treat pathogenic strains. Traditional antibiotics mainly affect the bacterial structure or metabolic pathways by acting on intracellular targets.[141,142] One of the main tactics for curing wound infections when applying this antibiotic treatment is to deliver medications from dressings to the wound region. Currently, the creation of controllable local antibiotic delivery methods based on nontoxic biomaterials is receiving much attention. For example, amoxicillin is a widely used antibiotic with effective broad-spectrum antibacterial properties. The researchers used hyaluronic acid methacryloyl (HAMA) and graphene oxide quantum dot (GO QD)-doped GelMA to develop multifunctional hybrid hydrogel inverse opal particles (Fig. 9a(i) and (ii)).[143] In this system, the second hydrogel solution composed of amoxicillin-integrated gelatin and carrageenan (GT/CG) solution was finally added in the voids of the first inverse opal scaffold layer. Because of the GO QDs' photothermal conversion ability and second hydrogel's temperature induced phase-changing performance, GT/CG liquids could leak from these hybrid particles when exposed to near-infrared (NIR) radiation. Thus causing the encapsulated amoxicillin to be released into the wound region and exhibit its antibacterial function (Fig. 9b). Compared with the untreated wound, the wound treated with the prepared hybrid particles showed obviously higher closure rates (Fig. 9c). However, in recent years, with the abuse of antibiotics, bacteria are developing antibiotic

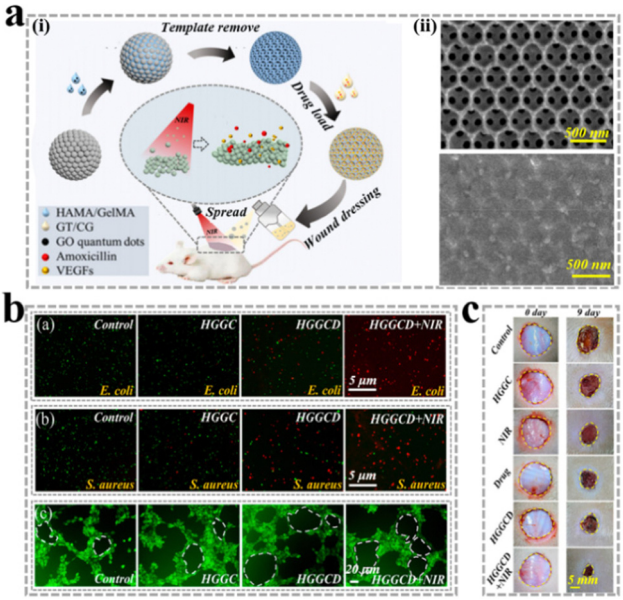

Fig. 9 (a) (i) Diagram illustrating the steps in the preparation as well as the physical self-bonding and manageable release of drug-loaded particles. (ii) An SEM image of the inverse opal scaffold and the scaffold filled with the second hydrogel. (b) An investigation on *in vitro* bacterial resistance and tube formation. (c) *In vivo* wound treatment. Reprinted with permission from ref. 143. Copyright 2022, American Chemical Society.

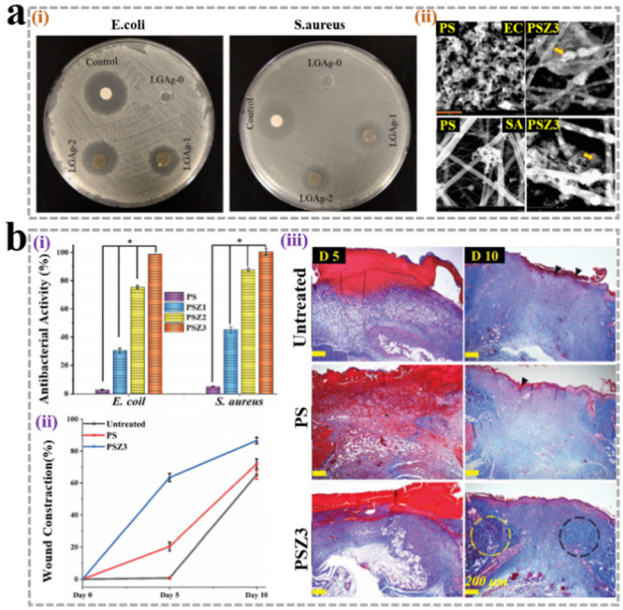

Fig. 10 (a) (i) LGAg-0, LGAg-1, and LGAg-2 inhibition zone for antibacterial activity against *S. aureus* and *E. coli*. Reprinted with permission from ref. 148. Copyright 2022, Elsevier. (ii) A SEM image demonstrating the development of bacteria on the NF membrane surface. (b) (i) *S. aureus* and *E. coli* antibacterial activity of different NF membranes. (ii) The wound healing rate in different groups. (iii) Collagen deposition statutes. Reprinted with permission from ref. 149. Copyright 2022, Royal Society of Chemistry.

resistance. Novel antibiotic-free antimicrobial agents (*e.g.*, nanoparticles and cationic polymers) have therefore attracted the interest of researchers.

In recent years, antibacterial nanoparticles have become an effective agent because of their unique physicochemical properties like increased specific surface area, small dimensions, higher surface energy and reactivity. Antibacterial nanoparticles could prevent the growth of bacteria and fungus by direct contact, disrupting their normal metabolism and adversely altering the membranes of the microorganisms.[134] Recently, experts have concentrated on the applications of antibacterial nanoparticles like zinc oxide (ZnO), copper, and silver (Ag) in biomedical fields.[144] Ag nanoparticles, because of their broad-spectrum antibacterial action, affordability, and low toxicity, are most frequently researched for wound treatments. Actually, a variety of Ag-based antimicrobial dressings, including those impregnated with silver nanoparticles, silver nitrate, and silver sulfadiazine, have already been marketed.[145–147] In recent research, Sudhakar *et al.* produced gelatin-stabilized AgNPs *in situ*. Gelatin hydrogels can be easily prepared using the Schiff base reaction and lactose as a cross-linking agent. Here, gelatin could reduce Ag ions *in situ*, avoiding the aggregation and dispersion problems associated with direct AgNP addition and could produce AgNPs quickly. The preparation was completed in a few minutes and the resulting hydrogel had antibacterial activity that facilitates wound healing (Fig. 10a(i)).[148] In another study carried out by Mo *et al.*, ZnO NPs were added to PLGA/SF (PS) nanofibrous (NF) membranes. The effective encapsulation of ZnO in the polymer matrix was validated by transmission electron microscopy (TEM). *In vitro* antibacterial experiments showed that the antibacterial activity of PLGA/SF/3% ZnO (PSZ3) increased accompanied with the ZnO concentration while remaining totally active against EC and SA. The outcomes of animal investigations showed that the NF membrane significantly improved the wound closure rate, together with the promotion of anti-inflammation, granulation tissue creation, collagen deposition, and angiogenesis (Fig. 9b and 10a(ii)).[149]

The development of practical wound dressing materials has greatly relied on cationic polymers including CS, PEI, lignin (LG), and antimicrobial peptides (AMPs).[150,151] The CS-based biomaterials have already been mentioned, while AMPs are currently being promoted as another promising therapeutic option due to their broad spectrum of activity against a variety of pathogenic microorganisms (Candida albicans, Pseudomonas aeruginosa, EC, SA) and fungi. Since AMPs mainly target bacterial membranes or other targets rather than proteins like the majority of antibiotics, they have offered intriguing possibilities for treatment-resistant strains. In order to treat chronic non-healing wounds, Lin *et al.* created an ALG/HA/collagen multifunctional wound dressing incorporating AMPs. In addition to the good antibacterial properties against SA and EC, these wound dressings containing AMPs also promoted collagen synthesis.[152]

4.2. Angiogenesis property

One of the primary challenges in modern regenerative medicine is promoting the development of new blood vessels in damaged tissues. The primary location for material transfer between blood and tissues is within blood vessels. Skin repair during the wound healing process depends on vascular regeneration, which supports nutrition transport and oxygen

exchange.[153,154] To date, many types of proangiogenic drugs have been developed. Deferoxamine (DFO) is a novel angiogenic drug, which was added into the injectable hydrogel based on chitosan and Ag^{+}. The hydrogel demonstrated the ability to encourage angiogenesis. The hydrogel treated with DFO displayed a longer blood vessel and a more complete vascular network topology.[155] More intriguingly, it has been suggested that the bioactive ion SiO_4^{4-} has the ability to stimulate endothelial cell growth and angiogenesis in promoting wound healing. In order to create bioactive CINP@SiO_2, an amorphous silica shell that could break down to release SiO_4^{4-} was consequently added to the surface of melanin nanoparticles extracted from cuttlefish ink (CINP). In particular, the prolonged release of SiO_4^{4-} from CINP@SiO_2 has tremendous promise for proangiogenesis, since it can promote endothelial cell proliferation and differentiation, as well as quicken collagen deposition and re-epithelialization (Fig. 11a).[156]

Biomaterials that incorporate growth factors (*e.g.*, VEGF, bFGF) have great potential to promote direct vascularization in addition to the delivery of angiogenic drugs. Liu *et al.* proposed CS/gelatin microspheres combined with bFGF by soaking microspheres in a basic bFGF solution. After that, these microspheres were blended with a CS scaffold to create the final wound dressings. Their study demonstrated that CS scaffolds incorporating microspheres would successfully improve laminin gene expression, accelerating fibroblast adhesion and proliferation, and boosting total DNA concentration. Here, a gene called laminin is associated with vascularization in skin wounds.[157] In another recent contribution, by employing high-voltage electrostatic drop technology, CS microspheres with a core–shell structure have been created. The center of these chitosan microspheres contained bFGF. Within 14 days, bFGF slowly released from the CS microspheres in a rat skin defect model. This *in vivo* research demonstrated that the best neovascularization and anti-inflammatory benefits were provided by CS microspheres carrying bFGF.[158] In addition, stem cells, including bone marrow-derived mesenchymal stem cells (BMSCs) and adipose-derived mesenchymal stem cells (ADSCs), could directly differentiate into epidermal cells, thus helping secrete multiple cytokines and growth factors that promote blood vessel formation and wound repair. For instance, Eke *et al.* placed ADSCs inside a hydrogel made of gelatin and hyaluronic acid. As a consequence, the hydrogels with ADSCs produced a 3-fold increase in the amount of angiogenesis when compared to hydrogels without cells. The binding of ADSCs to hydrogels proved to be a successful method to promote vascular regeneration and accelerate wound healing (Fig. 11b).[159]

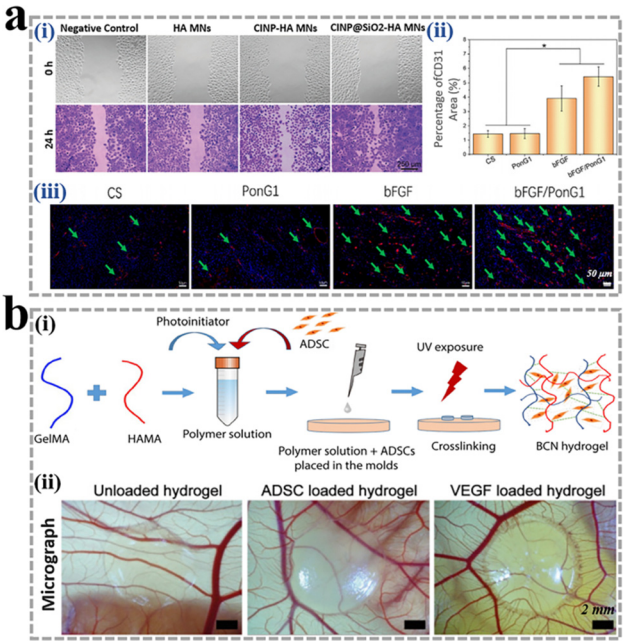

Fig. 11 (a) (i) Cell migration of HUVECs treated with HA MNs, CINP-HA MNs, and CINP@SiO_2-HA MNs media extracts. (ii and iii) The green arrows denote blood vessels and represent the angiogenesis feature of bFGF. Reprinted with permission from ref. 156. Copyright 2022, Wiley-VCH. (b) (i) By rehydrating lyophilized powders of both methacrylated gelatin and methacrylated hyaluronic acid in media by themselves (control hydrogel) or in media containing cells (cell-containing hydrogel), a solution of methacrylated gelatin and methacrylated hyaluronic acid was created. The solution was then crosslinked by the addition of a photoinitiator and UV irradiation for 40 s. (ii) Evaluation of the BCN hydrogel's angiogenic potential using the CAM (Chicken Chorioallantoic Membrane) experiment. Micrographs of the hydrogel, the hydrogel containing ADSCs, and the hydrogel containing VEGF (upper row) and pictures that have undergone semi-automatic processing (bottom row) (positive control). Reprinted with permission from ref. 159. Copyright 2022, Elsevier.

4.3. Antioxidant property

The expression amount of reactive oxygen species (ROS) can significantly rise in response to excessive inflammation, and the accumulation of ROS can further make the inflammation condition worse. Excessive ROS inhibits wound healing by affecting blood vessel regeneration in addition to harming cells and DNA.[160–162] Therefore, the development of antioxidant dressings to maintain low ROS concentrations is essential for wound healing. The majority of the currently used antioxidant wound dressings can be created by either grafting antioxidant molecules or directly doping antioxidants. Natural polyphenols (such as ferulic acid, tannic acid, anthocyanin, *etc.*) are frequently added to hydrogels as antioxidants because of their powerful anti-oxidant characteristics.[163–165] Zhang *et al.* fabricated dopamine-modified gelatin to improve the biomineralization and antioxidant qualities of gelatin (Gel-DA). Then this Gel-DA was compounded with guar gum (GG) to construct a multifunctional GelDA@Ag/GG hydrogel, which exhibited good antioxidant activity (Fig. 12a).[166] Notably, Cuttlefish ink-derived melanin nanoparticles (MNPs) are composed of a variety of monosaccharides and amino acids. MNPs have remarkable free radical scavenging abilities in addition to innate biocompatibility and degradability. Besides, nanoparticles similar to artificial melanin and rich in reduced functional groups have shown considerable promise in tissue repair. After surgically removing skin malignancies, Luo *et al.* presented a hyaluronic acid-based MN patch integrated with MNPs to promote tissue regeneration as a potent adjunctive therapy. In this investigation, MNPs were

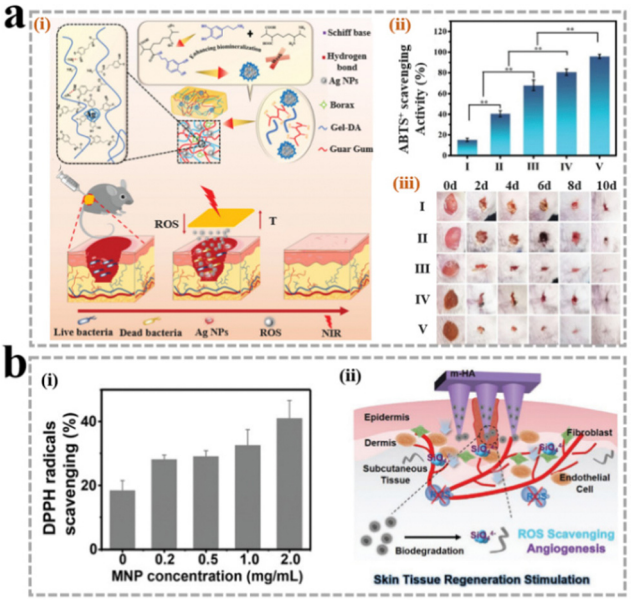

Fig. 12 (a) (i) Working principal for the fabrication and application of Gel-DA/GG@Ag hydrogels. (ii) Different hydrogel ABTS+ scavenging capacities (I is the control group, II is the GG group, III is the Gel-DA/GG group, IV is the Gel-DA/GG@Ag1 group, and V is the Gel-DA/GG@Ag1 + NIR group. Reprinted with permission from ref. 166. Copyright 2022, Wiley-VCH. (b) (i) Scavenging effect of MNPs/Alg hydrogel DPPH radicals. (ii) The biomineralized melanin nanoparticle-loaded microneedle patches' schematic therapeutic method. Reprinted with permission from ref. 156. Copyright 2022, Wiley-VCH.

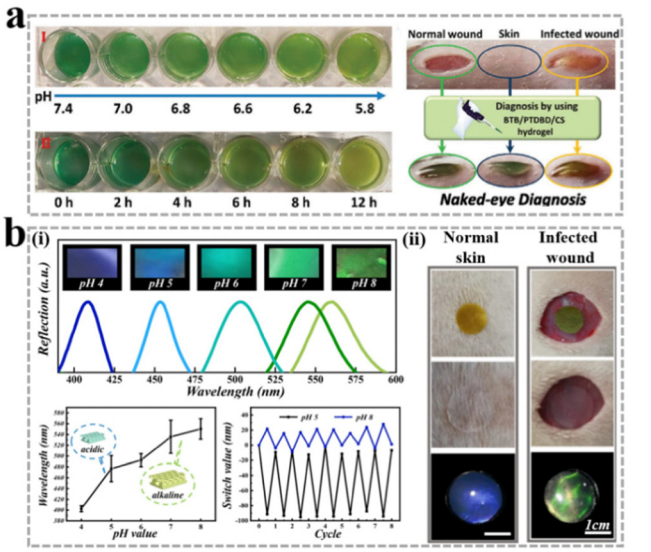

Fig. 13 (a) Use of smart hydrogels to detect and treat bacterial infections in mice. Reprinted with permission from ref. 169. Copyright 2022, American Chemical Society. (b) (i) The pH responsiveness property of the IOF. (ii) IOF's structure color change in normal skin and a bacteria-infected wound. Reprinted with permission from ref. 170. Copyright 2022, Springer.

successfully used to alleviate ROS-related negative effects that occurred during the wound repair process (Fig. 12b).[156]

4.4. Wound monitoring property

A wound monitoring property can be found in addition to the various therapeutic functions provided by the wound dressings. During the long period and complex process of wound healing, the elements in the wounded site's physiological environment are continually changing. The combination of wound dressings and effective biosensors that can monitor and treat wounds in real-time is crucial for the innovation of intelligent wound dressings.[167,168]

For the purpose of determining whether a wound was infected by bacteria, Wang's group devised a hydrogel based on the sensitivity of bromothymol blue to pH changes and an obvious color change. Additionally, near-infrared light technology was employed to meet the need for on-demand antibacterial treatment in response to the change in the color of the wound (Fig. 13a).[169] In order to further promote wound healing and dynamic monitoring, our team developed a unique inverse opal film (IOF) composed of fish gelatin methacryloyl, VEGF-loaded CS, and polyacrylic acid (PAA). The IOFs with obvious and detectable structural colors were fabricated by using hydrogel to replicate colloidal crystal templates. Since PAA acted as a pH response component, the change in the pH value of the environment would cause changes in the material's volume, structure color, and reflectance spectra. Given that, the IOFs' structural colors or reflectance spectra could be used to report the progress of wound healing (Fig. 13b).[170] In some other studies, zwitterionic thermosensitive hydrogels with a three-layer structure were created by Guo *et al.* The hydrogel could track different wound signals and offer information to support wound care (Fig. 14a).[171]

4.5. Drug delivery property

The therapeutic management of wounds can also benefit from drug intervention therapy. Recently, effective control of drug release through stimuli-responsive systems has received great attention. Compared with traditional delivery methods, the stimuli-responsive drug delivery systems would overcome disadvantages such as the low delivery efficiency, poor targeting ability, and lack of responsiveness, which also present great potential for timing, targeting, and quantitative drug release. This stimuli-responsive drug delivery system typically uses endogenous stimuli (*e.g.*, pH changes and enzymes) and exogenous stimuli (*e.g.*, temperature and light) to control the release of drugs. And thus realizing on-demand release, reduced side effects and enhanced efficacy of drugs.[172–175] For instance, SF/gelatin hybrid particles with an inverse opal structure have been proposed by our lab. Due to their adequate mechanical strength, BPQD-doped SF (BPQDs@SFGs) has been employed as stiff scaffolds, and the nanopores of the obtained SF inverse opal (SFIO) scaffolds were further filled with gelatin combined with growth hormones and antimicrobial peptides. In this approach, the short half-life issues caused by the direct drug delivery were resolved because the pharmaceuticals were well protected in the secondary hydrogels packed in the microstructures of the SFIO scaffold. The external gelatin hydrogel would melt when exposed to near-infrared light, which led to the encapsulated BPQDs to raise the local temperature, and

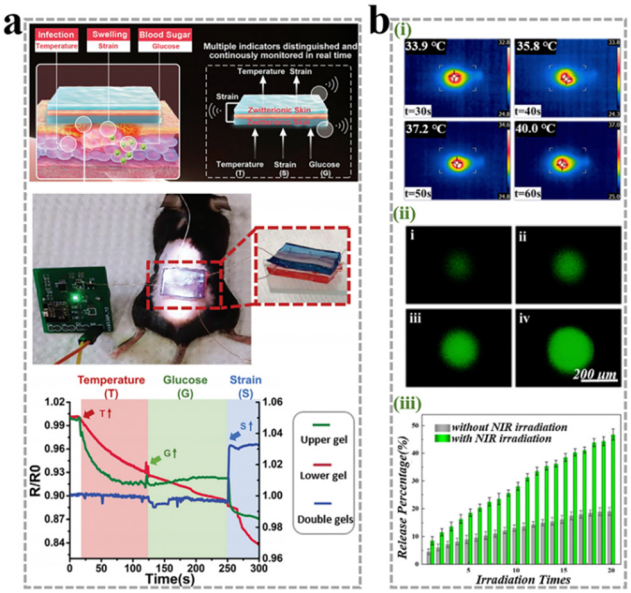

Fig. 14 (a) A sandwich-structured sensor for various sensations and aiding in the healing of diabetic wounds based on multi-response zwitterionic skin. Reprinted with permission from ref. 171. Copyright 2022, Wiley-VCH. (b) The BPQDs@SFGs' (i) photothermal conversion capability, (ii) confocal laser scanning photographs, and (iii) controllable drug release. Reprinted with permission from ref. 176. Copyright 2021, American Chemical Society.

finally causing the controlled release of VEGFs and antimicrobial peptides (Fig. 14b).[176]

5. Summary and outlook

The process of skin wound repair is a multifaceted phenomenon, and suboptimal treatment techniques can impede the progression of wound recovery. To aid in the promotion of wound healing, a plethora of wound dressings have been developed. In this review, we present an outline of the fundamental principles underlying the wound healing process, together with the factors that can influence it. Our focus then shifts to recent developments in animal tissue-derived wound dressings, where we outline the preparation methods and important properties of various biomaterials derived from animal tissues, such as acellular matrices, silk fibroin, collagen, and chitosan. Furthermore, we elaborate on the different forms of these biomaterials, including gels, microspheres, microneedles, and porous membranes, and conclude by summarizing the critical properties (such as antibacterial, angiogenic, antioxidant, wound monitoring, *etc.*) of animal tissue-derived biomaterials in the context of wound repair, along with the latest progress in the field.

Animal tissue-derived biomaterials provide a promising solution for the toxicity and complexity issues associated with synthetic polymer-based wound dressings, offering increased safety profiting from their biocompatibility, biodegradability, and ECM mimetic properties. Despite significant advancements in reducing inflammation and promoting tissue regeneration, there are still constraints in mechanical properties, long-term drug therapy and skin appendage regeneration. Specifically, wound dressings of animal origin are often prepared by simple surface modification and synthetic methods. Although the composition is safe enough, these dressings often do not have good mechanical properties and tear resistance. More scientific and logical design approaches to resolve the conflict are urgently required because present encapsulated medications with a single component and an extremely low loading amount in dressings have difficulty adapting to the complex and changing wound environment. Finally, the skin appendages (*e.g.*, hair follicles and sebaceous glands) still remain difficult to recover after injury due to their poor regenerative capacity. Since not sufficiently studied, the regeneration of skin appendages has been a technical problem for the complete restoration of skin structure and function.

In summary, animal tissue-derived biomaterials have been widely utilized in the field of wound management, with impressive achievements in wound anti-inflammatory, drug delivery, dynamic monitoring, and repair promotion. Future research should focus on developing new sources of animal tissue materials (such as marine source materials and animal-derived waste) and exploring new methods of biomaterial preparation and modification, focusing on improving the tissue microenvironment imitative ability and mechanical characteristics. Future multifunctional dressings that can monitor and treat the wound environment are also better for managing wounds. They are experts at monitoring bodily functions and relaying feedback data to actuators for regulated medicine delivery. To achieve this goal, the combination of electronic sensors with smart materials might be a potential solution. Additionally, it is anticipated that bioactive substances including sericin, skin-derived precursor cells, and hydrogen sulfide (H_2S) will be included in the wound dressing to aid in the regeneration of skin appendages. Finally, in order to promote the development of clinical dressing products, more *in vitro* studies and *in vivo* biological models should be applied to assess the potential clinical applications of biomaterials.

Author contributions

Conceptualization and supervision: Y. J. Zhao; writing – original draft: X. Y. Cao; writing – review & editing: X. Lin, N. Li, X. Z. Zhao, and M. Zhou.

Conflicts of interest

There are no conflicts to declare.

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