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REVIEW

Antibacterial Electrospun Nanofibrous Materials for Wound Healing

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Abstract

One of the leading causes of wound healing delays is bacterial infection, which limits the process of restoring the histological and functional integrity of the skin. Electrospun nanofibrous materials (ENMs) are biocompatible and biodegradable, and they can provide specific physical, chemical, and biological cues to accelerate wound healing. Based on this fact, a series of multifunctional ENMs for complex clinical applications, particularly infected skin injuries, have been developed. Antibiotics, antimicrobial peptides (AMPs), metals and metal oxides (MMOs), and antibacterial polymers have previously been incorporated into ENMs through advanced material processing techniques, endowing ENMs with enhanced and excellent antibacterial activity. This review summarizes wound healing issues and provides recent advances in antibacterial ENMs created by cutting-edge technology. The future of clinical and translational research on ENMs is also discussed.

Keywords Electrospinning · Nanofiber · Wound dressing · Antibacterial activity · Skin tissue engineering

Introduction

Skin is the human body's largest organ, which plays a vital role in regulating the internal physiological environment, such as maintaining body temperature, resisting bacterial infection, reducing the loss of water and electrolytes, and facilitating the growth of hair as well as the sweat gland [1]. The histological components and structures of the skin include the epidermis, dermis, and subcutaneous tissue. Figure 1a shows that the hair follicles, sweat glands, sebaceous glands, and thermoreceptors exist in the dermis [2]. There are abundant arterial–venous interactions between the dermis and adjacent subcutaneous tissue, which are essential for maintaining homeostasis and body temperature [3]. For diabetic patients, persistent hyperglycemia can lead to the destruction of the histological structure and dysfunction of blood vessels, which eventually results in diabetic foot and chronic wounds [4]. The regenerative time as well as the quality of wound healing are highly correlated with wound size. As presented in Fig. 1b, the skin can be irregularly divided into nine areas for primitively measuring the wound size [2]. This model has been widely applied for clinical diagnosis and treatment.

A cutaneous wound is defined as any break in the skin's structural and functional integrity, and skin injuries occur by a series of factors, such as external force tearing, skin tumors, burning, and endocrine disorders [5, 6]. For instance, force-induced skin injury is characterized by acute bleeding and destruction of tissue integrity (Fig. 1c). Melanomas can be surgically resected. However, it inevitably leads to a large area of full-thickness skin defects. Burning is the most serious type of skin injury, and it is classified into four distinct degrees (Fig. 1d, e) [7]. Septicemia and hypovolemic shock prevention are critical factors in improving the survival rate of severe burn patients [8]. Diabetic foot is characterized by diabetes microangiopathy, persistent bacterial infection, and skin tissue necrosis [9]. As presented in Fig. 1f, the mechanism of the

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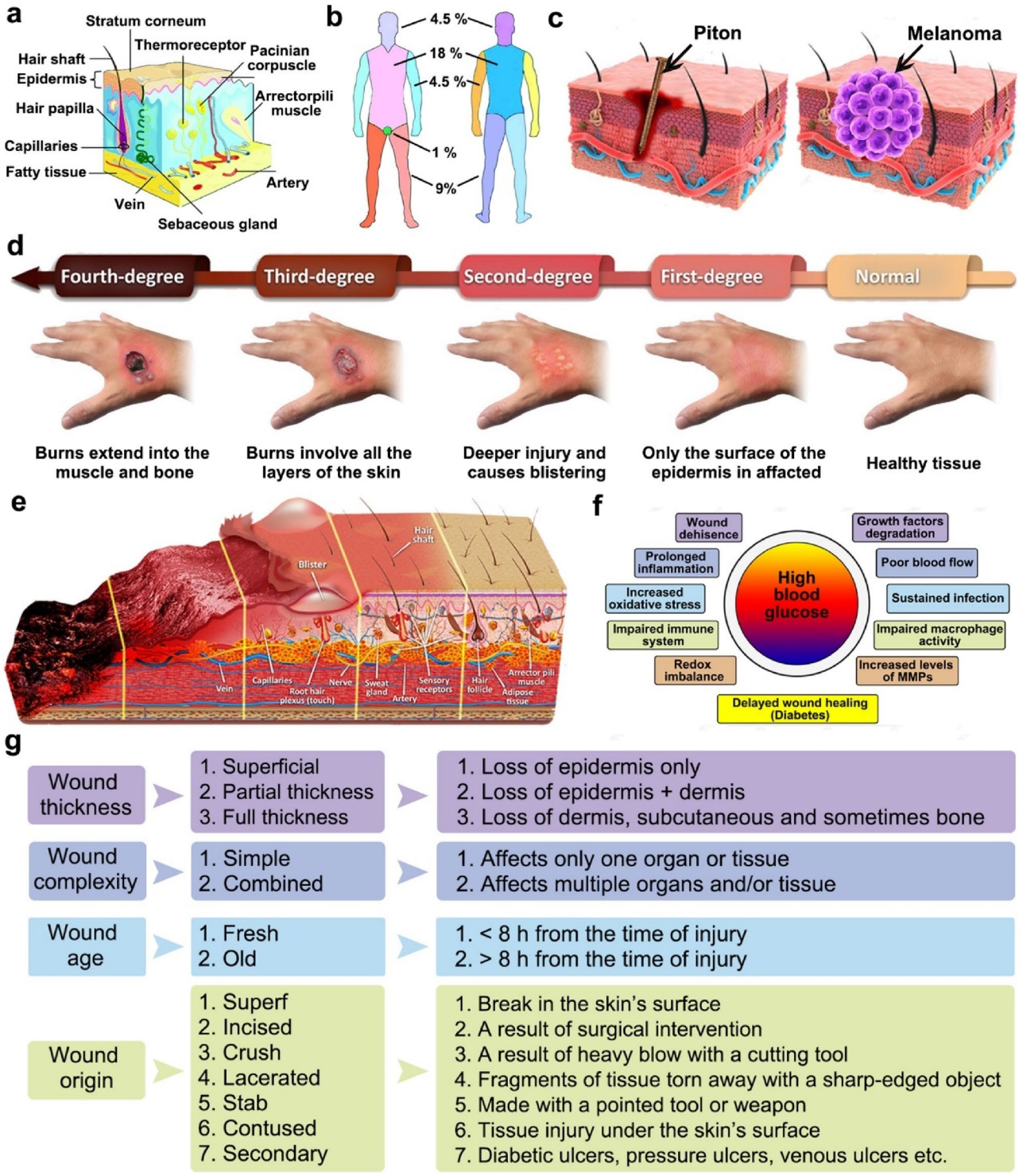

Fig. 1 **a** Histological structure of the skin, reproduced with permission from ref [2]; Copyright 2020, RSC Pub. **b** Estimation model of wound area. **c** Trauma and skin tumor, **d**, **e** classification of burn injury, reproduced with permission from ref [7]; Copyright 2018, Elsevier. **f** Pathogenic factors of diabetes foot. **g** Clinical evaluation criteria for skin injury, reproduced with permission from ref [12]; Copyright 2015, Elsevier

diabetic foot has not been thoroughly discovered [10], and the treatment of diabetic foot is still a great clinical challenge. It is still difficult to realize satisfactory results with standardized, comprehensive, and whole-course interventions. Based on

actual technology conditions, tissue engineering wound dressings have emerged as a potential pathway for the treatment of diabetic foot, and a series of multifunctional and stimulus-responsive wound dressings have been developed [11].

To facilitate diagnosis and treatment, a clinical criterion (Fig. 1g) has been proposed to assess the severity of skin injury [12]. The treatments for skin injury include removing the primary causes (sharp tools, hyperglycemia, heat source, and chemical reagents), stopping bleeding, cleaning the wound site, preventing bacterial infection, and eliminating other hazardous factors [8]. Wound dressings (WDs) are commonly used for accelerating wound healing. The traditional view that a dry environment is conducive to wound healing has been overturned by advanced tissue engineering theory and clinical practice [13]. An advanced WD can maintain a moist microenvironment (MME) at the wounded site and thus promote vascularization and re-epithelialization as well as the synthesis of collagen fibers. On the other hand, the WDs can also serve as carriers of other bioactive components, such as seeding cells, exosomes, recombinant proteins, and small molecule inhibitors [14, 15]. Currently, the development of advanced WDs can be divided into electrospinning nanofibrous materials (ENMs), biomolecular hydrogels, porous sponges, 3D printing scaffolds, etc. [16].

ENMs are light and flexible and fit well with wrinkled skin and even sports joints [17]. ENMs with a penetrating network structure can simulate the extracellular matrix (ECM) of natural skin and support the adhesion and growth of host cells. To accelerate wound healing, the biocompatibility, biodegradation, and bioactivity of ENMs can be precisely designed by modulating the chemical compositions and physical structure (diameter, surface roughness, hydrophobicity, orientation degree, etc.) [18–20]. Meanwhile, ENMs have a relatively large specific surface area, which is convenient for chemical and functional modifications. As a result, ENMs exhibit great advantages over other types of WDs. Advanced ENMs with desirable antibacterial, antioxidant, angiogenic, and hemostatic properties have recently received considerable attention [21–23]. In this review, we focus on antibacterial ENMs and provide a comprehensive summary of the clinical requirements, preparations, modifications, and antibacterial strategies of ENMs. The clinical efficacy, safety, and fundamental mechanisms of various antibacterial strategies are also highlighted to provide a bench-to-bedside perspective on medical device approval. Finally, we discuss the current challenges and future prospects for antibacterial ENMs.

Clinical Requirements of Wound Dressings

An ideal WD should have specific bioactivity that matches the dynamic process of wound healing. As shown in Fig. 2a, the wound healing process can be divided into four complex and overlapping phases, including hemostasis, inflammation, proliferation, and remodeling [24]. In particular, a series of host cells, inflammatory factors, physiochemical cues, and cellular signal transduction pathways may be involved in this complex process, resulting in the orderly and effective progress of wound healing [25]. Some WDs have the ability to stop bleeding and induce the sustained release of various bioactive factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and platelet-derived growth factor (FDGF), thereby accelerating the physiological wound-healing process. [26]. Notably, the types and doses of bioactive factors required for wound healing markedly vary among phases. Thus, researchers have developed an intelligent strategy for the time-dependent release of two or more bioactive factors [27]. WD can also remodel the pathological process caused by hazardous internal/external factors, especially bacterial infection.

External bacteria migrate to the wound site as soon as the injury occurs and rapidly multiply in a moist and warm microenvironment made up of cell debris, blood clots, and tissue exudations [28]. Local bacterial infection is one of the most common causes of suppuration, ulceration, and delayed wound healing. Local bacteria can also spread into the blood and induce systemic sepsis [29]. The skin has an effective self-defense system in which immune cells with chemotaxis play a key role, as shown in Fig. 2b. Immune cells eliminate pathogens by phagocytizing pathogens, presenting antigens to start adaptive immunity, and remodeling the wound microenvironment (WME) by secreting a series of bioactive factors [30]. The biological function of immune cells is phased during the wound healing process [31, 32]. For example, M1 macrophages can promote inflammatory responses, clear necrotic tissue, and remodel the WME in the early stage of wound healing. M2 macrophages replace M1 macrophages in the middle and late stages, promoting host cell proliferation and extracellular matrix (ECM) remodeling. Currently, it is of increasing interest to accurately regulate the type, quantity, and biological function of immune cells in the wound healing process.

Antibacterial properties are the fundamental clinical requirements for WDs. The history of antibacterial WDs can be traced back to the first linseed oil and phenol-loaded bandage developed by Joseph Lister et al. [33]. The applications of sulfonamides in 1935 were a great success in preventing bacterial infection. However, the extensive application of antibiotics can lead to drug resistance [34]. The appearance of novel drug-resistant bacterial strains has forced researchers to develop new antibiotics, such as vancomycin, thiomycin, tetracycline, and quinolones. Meanwhile, nonantibiotic reagents have also been developed, and metal and metal oxides (MMO), such as Ag, Cu, ZnO, TiO_2, and Fe_3O_4, exhibit excellent antibacterial activity [35]. Synthetic and natural antibacterial polymers have excellent

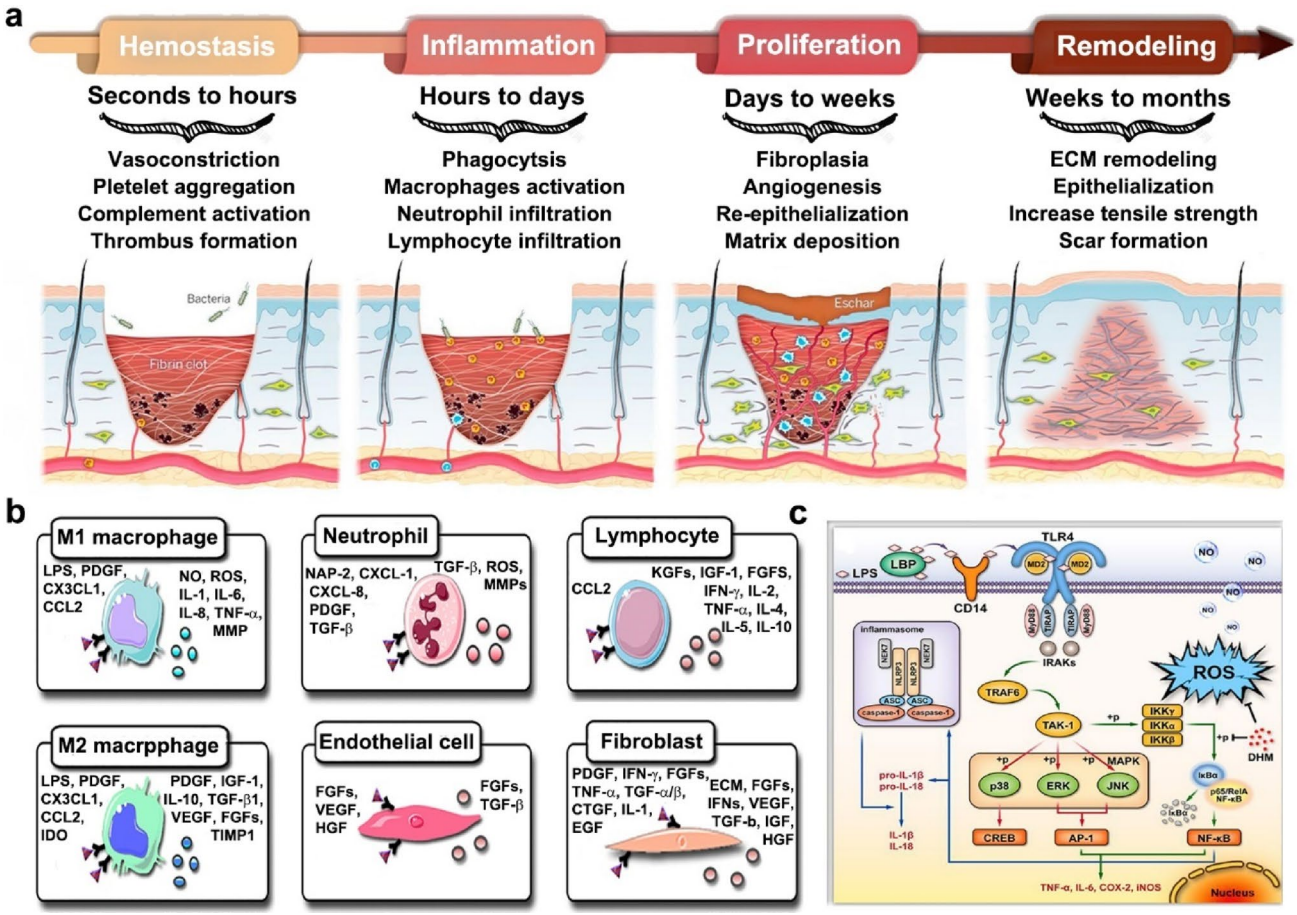

Fig. 2 **a** Dynamic process and biological characteristics of skin regeneration, Reproduced with permission from ref [24, 25]; Copyright 2018, Elsevier. **b** Inflammatory cells, inducers, and effectors regulating wound healing, Reproduced with permission from ref [30]; Copyright 2020, Elsevier. **c** Molecular mechanism of lipopolysaccharide (LPS) induced inflammatory response in wound healing, Reproduced with permission from ref [45]; Copyright 2022, Springer Nature

biocompatibility and processability and have potential applicability in fabricating complex WDs. In recent decades, several antimicrobial peptides (AMPs) have been approved by the U.S. Food and Drug Administration (FDA) [36]. With the help of cutting-edge technology, researchers can easily screen out bacteria-specific or bacteria-targeted AMPs to address major public health events, such as the prevalence of superbacteria [37, 38].

Currently, the development of antibacterial WDs requires a higher standard, especially for chronic wound management, because the four usual phases of wound healing (hemostasis, inflammation, proliferation, and remodeling) fail to follow this regular procedure to complete coverage (frequently in the inflammatory phase), and the wounds fail to progress toward healing within 4 weeks. All chronic wounds should be treated as if they are contaminated with bacteria, and the degree of wound bioburden is an important element in deciding whether a wound can heal. Reducing the bioburden in all wounds is an important part of wound bed preparation and individualizing treatment for each wound [39, 40]. Not all surface bacteria cause illness or even contribute to the chronicity of a lesion. Planktonic bacteria are not bound together and must adhere to the wound's surface similar to microorganisms connected as a biofilm. Standard microbiological swabbing for culture and sensitivity of wound bacteria may result in the identification of a species that is not harmful, and hence, treatment may not promote healing. Biofilms contribute to the wound's bioburden, and the degree of wound bioburden is an important element in deciding whether the wound can heal. Reducing the bioburden in each wound is an important part of wound bed preparation and individualizing therapy for each lesion [41, 42]. The combination of debridement and wound dressing appears to be an effective strategy for treating biofilms. For example, once a specific bacterial species or combination has been identified, debridement is needed, followed by repeated surgical debridement during follow-up visits until contamination in the wound has been reduced to an

acceptable level. Debridement dissolves biofilm structures, exposing constituent microorganisms and increasing the effectiveness of treatment drugs when the biofilm regrows [42]. Antibacterial ENMs are applied to the wound sites after debridement and can significantly improve wound healing efficiency.

Prevention and control of bacterial drug resistance remain arduous tasks. Topical antimicrobials can minimize contamination in a wound, but are ineffective against invasive infections; in general, they should not be used for more than 2 weeks. As an anti-infective, several dressings contain antimicrobials, and most demonstrate efficacy in laboratory tests; however, clinical efficacy is proven to be less evident. Because of their low cytotoxicity at high concentrations, topical antibiotics are appealing. Topical administration can deliver extremely high concentrations with minimal systemic absorption and potential toxicity. However, due to concerns about antibiotic resistance, treatments should be limited to two weeks [43]. In recent years, the inflammatory response induced by dead bacteria has attracted considerable attention. As shown in Fig. 2c, the lipopolysaccharide (LPS) released by dead gram-negative bacteria can act on the TLR4/MD receptor complex to upregulate the inflammatory response and reactive oxygen species (ROS) [44, 45]. As a result, there is an urgent need for WD with antibacterial and anti-inflammatory activity. To meet the requirements of a clinically complex application, antibacterial WDs should also incorporate additional biological functions, such as immunity regulation, ROS scavenging, angiogenesis promotion, and induction of hair follicle and sweat gland regeneration [46]. A hypertrophic scar inevitably easily forms after wound healing, which seriously affects wound regeneration. The absence of hair follicles and sweat glands in large scar tissue also leads to the dysfunction of thermoregulation. Mascharak et al. revealed the molecular mechanism of the Engrailed-1 gene in scar formation and screened out a selective anti-scar antagonist (Verteporfin) [47]. Kim et al. inversely differentiated precursor cells into hair follicle stem cells and successfully realized hair follicle regeneration [48]. Fu et al., the academician from the Chinese Academy of Engineering (CAE), proposed the concept of inducing sweat gland regeneration worldwide [49]. In the future, more fundamental research achievements are expected to improve the prognosis of wound healing.

Processing of Antibacterial ENMs

As presented in Fig. 3a, electrospun nanofibrous materials (ENMs) have a long history of research and development (R&D) [50]. Since 2020, the production capacity of ENMs, one of the important raw materials for medical masks, has rapidly grown [51]. Figure 3b shows an optical picture of a desktop high-voltage electrospinning device (HVED). Research grade HVED has been fully localized in China, greatly reducing the purchase and maintenance costs. As presented in Fig. 3c, the basic HVED is composed of a high-voltage power supply, peristaltic pump, sample chamber and needle, negatively charged receiver, and conductive wire [52, 53]. Advanced HVED will also be equipped with a light source, motion module, temperature and humidity controller, etc. The HVED can be conveniently modified by the demand. For example, the core/shell structure of ENMs can be fabricated using a multichannel needle instead of a traditional single-channel needle [54]. The flat plate receiver is replaced by the roller receiver device to prepare nanofibers with different orientations [55].

The principle of electrospinning technology is explained as follows. The high-voltage power supply forms a strong electric field environment between the anode and cathode, driving the electrospinning solution to spray from the needle to the receiver. In this process, the electrospinning solvent rapidly volatilizes, and the solute solidifies to form nanofibers. The diameter and orientation of ENMs are deeply affected by the types of raw materials and parameters of solvents, voltage, electrode distance, temperature and humidity, the rotation rate of the receiver, and other factors [56]. As shown in Table 1, the raw materials of ENMs are mainly synthetic polymers, including polycaprolactone (PCL), poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), polyvinyl alcohol (PVA), etc. PCL and PLGA have relatively good biosafety and biodegradability in vivo and are the favorite electrospun synthetic polymers. Natural polymers are generally not spinnable and can be blended with synthetic polymers to be effectively electrospun. Representative natural polymers include chitosan (CS), silk fibroin (SF), and soybean protein isolate (SPI); however, most natural polymers do not have antibacterial activity except for CS. Fortunately, natural polymers are rich in chemically modifiable groups, and their antibacterial activity can be effectively tuned by chemical modifications [53, 57].

The solvents of ENMs can be distilled water, hexafluoroisopropanol (HFIP), dichloromethane, *N*,*N*-dimethylformamide, chloroform, dimethyl sulfoxide, and their mixtures [71]. HFIP is a strong polar organic solvent with strong solubility and easy volatilization; thus, it has relatively low requirements for ambient temperature and humidity [72]. Because HFIP has a strong corrosivity to the eyes, skin, and respiratory mucosa, it should be handled with caution. Appropriate high voltage and electrode distance parameters are critical for the successful preparation of ENMs. In general, with a higher voltage and a smaller electrode distance, a greater electric field and a smaller average ENM diameter can be achieved. Increasing the electric field strength will shorten the flight time of liquid flow, and the solvent may not be fully volatilized and sprayed over the receiver.

Table 1 Raw materials of the electrospun nanofibrous materials

Raw materials	Abbreviations	Chemical formula	Solvent	Biodegradable	Refs.
Polycaprolactone	PCL	$(C_6H_{10}O_2)n$	Dichloromethane, HFIP	Yes	[19, 58]
Polylactic acid	PLA	$(C_3H_4O_2)n$	HFIP	Yes	[59]
Poly(lactic-co-glycolic acid)	PLGA	$HO(C_3H_4O_2)n(C_2H_2O_2)mCH_3$	HFIP	Yes	[60]
Polyvinyl alcohol	PVA	$(C_2H_4O)n$	Distilled water	Yes	[61, 62]
Polyethylene oxide	PEO	$HO(CH_2CH_2O)nH$	Formic acid	Yes	[63]
Polyvinylpyrrolidone	PVP	$(C_6H_9NO)n$	90% ethanol and 10% acetic acid	Yes	[64]
Chitosan	CS	$(C_6H_{11}NO_4)n$	10% CF and 90% DMF	Yes	[65]
Collagen	N/A	N/A	HFIP	Yes	[66]
Gelatin	N/A	N/A	2,2,2, Trifluoroethanol	Yes	[67]
Hyaluronic acid	HA	$(C_{14}H_{21}NO_{11})n$	Distilled water	Yes	[68]
Silk fibroin	SF	N/A	Trifluoroacetic acid, HFIP	Yes	[69]
Soy protein isolate	SPI	N/A	HFIP	Yes	[70]

The structures and properties of neat ENMs are relatively simple, making it difficult to fully meet the clinical needs of wound healing. As shown in Fig. 3d, researchers have designed and developed a series of physical and chemical methods to endow ENMs with specific biological functions [73]. Coaxial electrospinning is used to fabricate ENMs with shell–core structures, realizing inner and outer materials with different components. The shell and core layers can be also loaded with different bioactive factors as well as the faster release dynamics of the shell layer. Therefore, coaxial electrospinning is widely used to prepare intelligent drug-release materials. Chemical immobilization is used to immobilize active components, such as antibacterial peptides (AMPs), enzymes, and bioactive factors, onto the surface of nanofibers through a chemical cross-linking strategy [74]. The chemical cross-linking reaction is always performed under physiological conditions to avoid damaging the structure and function of the bioactive component. For the layer-by-layer (LBL) assembly technique driven by electrostatic attractions, the ENM is immersed alternately in polymer solutions with opposite charges [75]. Polyelectrolyte complexes form via electrostatic interactions and are then deposited on the surface of the ENMs.

Advanced ENMs feature complex microstructures and components. In general, a scanning electron microscope (SEM) equipped with an energy dispersive spectrometer (EDS) is used to observe the morphology and elementary compositions of the surface of ENMs. However, SEM is not suitable for in-deep analysis. Zhou et al. applied a transmission electron microscope (TEM) to identify coaxial ENMs [76]. The shell or core layers of coaxial ENMs can be loaded with uranium acetate and phosphotungstic acid to improve the contrast ratio of TEM. The infrared spectrum (IR) and X-ray diffraction spectrum (XRD) can be used to characterize the chemical composition. Tensile strength and hydrophobicity are also vital physical properties of ENMs and can be tested by a universal material testing machine and a dynamic video capture system, respectively. The biocompatibility of ENMs is strictly supervised. In the scope of wound healing, several model cells, including mouse lung fibroblasts (L929), mouse embryonic fibroblasts (NIH/3T3), human dermal fibroblasts (HDF), and human umbilical vein endothelial cells (HUVECs), are widely used for biocompatibility and bioactivity evaluations in vitro. Meanwhile, Wang et al. also constructed an abdominal transplantation model for comprehensive evaluations in vivo [77].

As shown in Fig. 3e, the applications of functional ENMs include heart patches, artificial tendons, bone repair membranes, and wound dressings [73]. Of note, the antibacterial ENMs have achieved good efficacy in various complex applications such as full-thickness skin defects, infectious skin defects, and even diabetic foot. The number of published papers in the field of antibacterial ENMs has significantly increased since 2014, as shown in Fig. 3f, and the global volume of wound dressings will reach US $20.4 billion by 2021 [78]. Based on the clinical need, we assume that high-performance antibacterial ENMs will have great commercial value.

Antibacterial Strategies of the ENMs

Antibiotics

Antibiotics, produced by microorganisms, are divided into seven groups, including β-lactam, macrolide, aminoglycoside, tetracycline, lincomycin, chloramphenicol, and antimicrobial peptide [79]. Antibiotics eliminate bacteria by inhibiting the biosynthesis of biomass, such as cell walls, protein, DNA, and RNA, increasing the permeability of cell membranes, and intervening in bacterial folate metabolism [80]. Due to the abuse of antibiotics, some specific bacteria

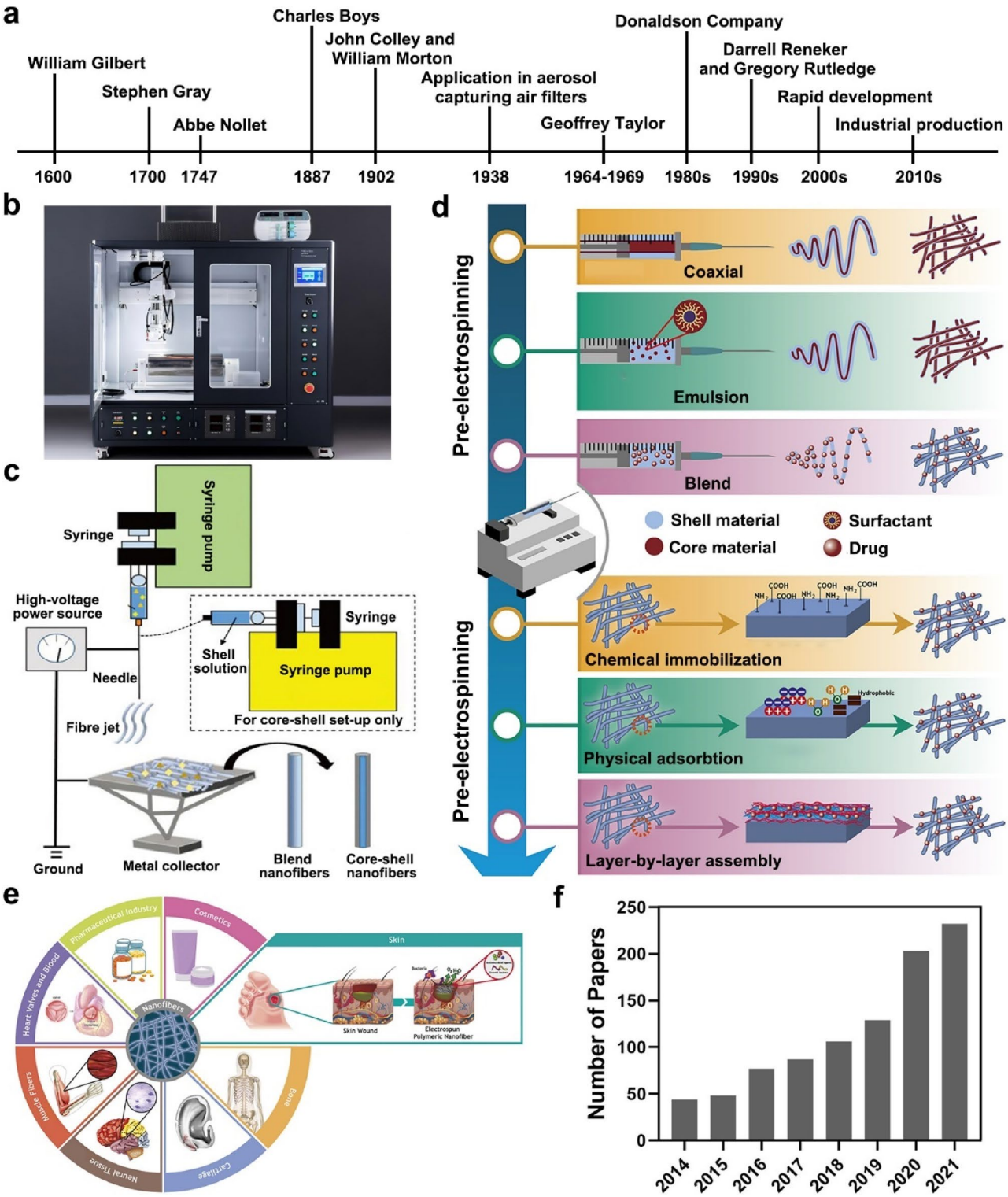

Fig. 3 **a** Development history of electrospun nanofibrous materials (ENMs), reproduced with permission from ref [50]; Copyright 2019, ACS. **b** Photo of a desktop electrospinning machine. **c** Schematic diagram of electrospinning device. **d** Functional modification techniques of ENMs, reproduced with permission from ref [73]; Copyright 2018, Elsevier. **e** Biomedical applications of ENMs, reproduced with permission from ref [73]; Copyright 2018, Elsevier. **f** Number of papers published in the field of antibacterial ENMs-based wound dressings

have evolved inactivating enzymes for antibiotics. Under strong selection pressure, mutant bacteria proliferate in large numbers, leading to the failure of anti-infection treatment [81]. In this context, the medical community has suggested a call for the rational use of antibiotics and strictly supervising the prescription authority. The formation of biofilms is also one of the critical factors for drug resistance. A series of tissue engineering wound dressings (TEWDs) can eliminate bacterial biofilms and thus significantly improve their antibacterial effect [82, 83]. In the clinic, appropriate antibiotics are selected based on the results of drug susceptibility tests.

As shown in Table 2, extensive antibiotic-loaded ENMs have been developed to address the challenges brought by bacterial drug resistance. These antibacterial ENMs are sufficient to kill most drug-resistant bacteria. They have the advantages of local administration, reduced dosage, and avoiding systemic toxicity. Nevertheless, new antibiotics and composited ENMs are still being developed to kill emerging drug-resistant bacteria. Skin tissue engineering (STE) focuses on loading antibiotics onto nanofibers through advanced material processing technology and the application effect of the products. Currently, dozens of types of antibiotic-loaded ENMs, such as ampicillin, ciprofloxacin, tetracycline, erythromycin, doxycycline, and vancomycin, have been reported. Vancomycin is a powerful glycopeptide antibiotic that is used alone or in combination with other antibiotics to treat severe infections caused by methicillin-resistant Staphylococcus aureus [84]. Vancomycin is considered the last line of defense against bacterial infection. Vancomycin is also listed as a special antibacterial drug in the "Notice of the General Office of the Ministry of Health on Further Strengthening the Management of Clinical Application of Antibiotics", and its clinical application is strictly supervised.

The key to the fabrication of antibiotic-loaded ENMs is to accurately regulate the sustained-release performance of antibiotics. To solve this problem, researchers have extensively attempted to optimize the substrates of ENMs and the encapsulation of antibiotics. Hydrophilic substrates, such as gelatin, chitosan, and silk fibroin, are conducive to the rapid release of antibiotics, while hydrophobic substrates, such as PCL, PLGA, and PLA, are conducive to the long-term sustained release of antibiotics. The drug-release performance of the antibiotic-loaded ENMs can be facilely manipulated by adjusting the type, weight ratio, and physical state of hydrophilic and hydrophobic substrates. Antibiotics are mainly loaded onto ENMs by the blending electrospinning technique and then released via a simple diffusion process. Thus, the inhibition zone test is widely used to evaluate the antibacterial activity of antibiotic-loaded ENMs [85]. Antibiotic-loaded ENMs have different degrees of burst release in the early stage, which may lead to excessive local drug concentrations and potential side effects. To reduce burst release, a feasible method is to increase the proportion of hydrophobic substrate, which will greatly prolong the overall release time. Another method is to prepare ENMs with a shell–core structure by coaxial electrospinning technology. The antibiotics in the core layer are shielded by the outer shell structure to delay the release dynamics [67].

Antimicrobial Peptides

In 1980, Boman et al. discovered the first antimicrobial peptide (AMP) and named it cecropin [36]. In the following decades, more than 3000 AMPs have been reported. AMPs are a special type of antibiotic that are usually composed of 6–50 amino acid residues. [105]. The structures of several types of AMP are shown in Fig. 4a. The secondary structure of AMP includes α-helical and β-sheet, which forms the functional basis of antibacterial activity. As shown in Fig. 4b, AMPs are diverse. Classical α-helical AMPs are common in nature, and their hydrophilic and hydrophobic amino acids are distributed at both ends of the molecular chain. A few α-helical AMPs, whose hydrophilic and hydrophobic amino acids are located on both sides of the a-spiral wall, have also been found [106]. Of note, a small number of AMPs, such as nisin, do not have secondary structure [107]. AMPs can be isolated from bacteria, fungi, insects, mammalian cells, and even human-derived cells. AMPs can be easily prepared and purified by solid-phase organic synthesis if the primary sequence of the AMP is discovered. In recent decades, library-based screening technology for high-throughput screening of potential AMPs has been developed. For example, Peter't Hart et al. used the phage display library to screen a series of phages targeting lipid II and then used gene sequencing to obtain a series of AMPs on Gram-positive bacteria. [108]. The diversity of the library is sufficient to identify all potential pathogens. Therefore, library-based screening technology is expected to be one of the most powerful weapons to deal with superbacterial infection.

The mechanism of AMPs includes membrane translocation and membrane perturbation [36]. As shown in Fig. 4c, some AMPs can be transported into the cell membrane and interfere with the biosynthesis of bacterial DNA, RNA, and protein, as well as protein folding. Another AMP can destroy the integrity of the cell membrane, including three typical approaches: barrel stave, carpet, and toroidal pore. As shown in Fig. 4d, the AMPs may also have complex physiological functions in the wound healing process, such as promotion of NETs, recruitment and polarization of T cells, neutralization of LPS, differentiation of dendritic cells, induction of chemokines, and so on. Currently, loading AMPs onto ENMs without damaging their secondary structure and bioactivities remains a difficult task. Blending electrospinning, coaxial electrospinning, and LBL self-assembly technology

Table 2 Antibiotics-loaded electro-spun nanofibrous materials developed since 2016

Antibiotics	Carriers	Loading methods	Drug loading	Sustained releasing time	Fiber diameters	Sensitive bacteria	In vivo applications	Refs.
Ampicillin	PLA	Blend	8%	96 h	400.2 ± 10.8 nm	N/A	N/A	[79]
Cefadroxil	CS/PVA	Blend	2%	800 min	290 ± 86 nm	*S. aureus*	N/A	[80]
Cefazolin	CS/PEO	Blend	0.5%	15 d	70 ± 15 nm	*S. aureus, E. coli*	Incised wound of Wistar rats	[81]
Ceftazidime	SF/GE	Blend	50%	6 h	825.02 ± 70.3 nm	*P. aeruginosa*	N/A	[82]
Cephradine	GE/PVA	Blend	6%	N/A	390 ± 61 nm	*E. coli*	N/A	[83]
Chloramphenicol	PCL	Blend	4%	N/A	1.97 ± 0.30 μm	*E. coli*	NA	[84]
Ciprofloxacin	CS/PEO/SiO_2	Blend	1.5%	13 d	422 ± 70 nm	*S. aureus, E. coli*	Incised wound of BALB/c mice	[85]
Ciprofloxacin & AgNPs	PVP/EC	Janus	9% of ciprofloxacin, 26% of AgNPs	30 min	0.84 ± 0.24 μm	*S. aureus, E. coli*	N/A	[86]
Doxycycline	PLA	Blend	15%	3 d	424 ± 62 nm	*E. coli*	Type 1 diabetic wound of SD rats	[87]
Doxycycline	PCL of shell, PVA of core	Coaxial	100 μg/mL for both core and shell solutions	N/A	N/A	*S. aureus*	N/A	[88]
Gentamicin	Cellulose ether/PVA	Blend	10%	19 d	325 ± 30 nm	*S. aureus, E. coli*	Incised wound of Wistar rats	[89]
Levofloxacin	PCL	Blend	0.5%	15 min	2.865 ± 3.0 μm	*S. aureus, E. coli*	N/A	[90]
Moxifloxacin	PVA/SA	Blend	2%	26 h	175 ± 75 nm	*S. aureus, P. aeruginosa*	Incised wound of SD rats	[91]
Moxifloxacin	PNH copolymers	Blend	0.1%	N/A	0.62 ± 0.16 μm	*S. aureus*	N/A	[92]
Moxifloxacin	PVA/CS	Blend	38.09 mg/g	N/A	170 ± 20 nm	*S. aureus, P. aeruginosa*	N/A	[93]
Silver sulfadiazine	EC/PLA/Collagen	Blend	0.75%	12 h	101.65 ± 17.90 nm	*Bacillus, E. coli*	N/A	[94]
Silver sulfadiazine	PAN	Chemical immobilization	N/A	N/A	146.94 nm	*Bacillus, E. coli*	N/A	[95]
Teicoplanin	CS/PEO	Blend	4%	12 d	601.80 ± 135.99 nm	*S. aureus*	Incised wound of Wistar rats	[96]
Tetracycline	PVA/CS	Blend	5%	4 h	309 ± 68 nm	*S. epidermidis, S. aureus, E. coli*	N/A	[97]
Tetracycline	CS/GE/HAP	Blend	0.33%	14 d	265 ± 37 nm	*S. aureus, E. coli*	N/A	[98]
Tetracycline	PVA/CS/SS	Diffusion	N/A	60 h	371 ± 27 nm	*S. aureus, E. coli*	Second-degree burn injury of BALB/c mice	[99]
Vancomycin	CS/PEO	Blend	2.5%	72 h	428 ± 37 nm	*S. aureus, MRSA*	Incised wound of Wistar rats	[100]

Table 2 (continued)

Antibiotics	Carriers	Loading methods	Drug loading	Sustained releasing time	Fiber diameters	Sensitive bacteria	In vivo applications	Refs.
Vancomycin	pDA-crosslinked gelatin	Ammonium carbonate diffusion	0.5%	20 d	N/A	*S. aureus 29,213, S. aureus 4001R, MRSA 21,455, MRSA DM9809R, E. faecalis 29,212, E. hirae 9790*	Partial thickness burn injury of Yorkshire pigs	[101]
Vancomycin & Gentamicin	PLGA	Coaxial	10% of gentamicin, 10% of vancomycin	21 d	371 ± 162 nm	*S. aureus, E. coli*	The infected diabetic wound of SD rats	[102]
Vancomycin & ImipeENM/Cilastatin	PEO/CS of shell, PVP/GE of core	Coaxial	5%	24 h	474 ± 57 nm	*S. aureus, E. coli, P. aeruginosa, MRSA*	N/A	[103]
Vancomycin, $AgNO_3$ & $Ga(NO_3)_3$	PCL of shell, F127 of core	Coaxial	2.5%	28 d	N/A	*P. aeruginosa, MRSA*	N/A	[104]

can be used to solve this problem. Notably, strong polar solvents such as HFIP should not be used during the processing to prevent the denaturation and inactivation of the AMPs. There is an inevitable burst of AMPs loaded by physical methods. Song et al. successfully grafted Cys-KR12 AMP onto silk fibroin nanofibers using the EDC/NHS reaction [109]. The EDC–NHS reaction is widely used in crosslinking among natural and synthetic proteins. The reaction conditions are relatively mild to avoid the destruction of the structure and function of AMPs [110]. Immobilization of AMPs on ENMs can not only inhibit burst release but also reduce the dosage of AMPs as well as the nonspecific side effects caused by the diffusion of AMPs.

Compared with traditional antibiotics, the molecular weight of AMP is relatively large. Thus, the ability of AMP to penetrate the barrier structure of the skin is significantly blocked. To solve this problem, Yajuan Su combined the microneedle patch and ENM to create a transdermal drug delivery system [111]. Janus-type dressings are depicted in Fig. 5a, b, which consist of an AMP-loaded nanofiber and a microneedle patch, with the AMP released after the microneedle pierces the skin tissue. The authors also investigated and calculated the sustained-release dynamics of AMP using computer simulation, as shown in Fig. 4c. Compared with percutaneous absorption, the efficiency of transdermal drug delivery was significantly enhanced. Polymeric pseudopeptides (PPPs) are a new class of antibacterial molecules constructed from polymer skeletons and antibacterial peptide functional groups [112]. Compared with AMPs, PPPs have lower immunogenicity and are not easily cleared by the host immune system. Minseong Kim designed a modular PPP based on polyethylene glycol (PEG), which successfully simulated the lysine/serine/leucine residues of AMP, and the obtained products showed good antibacterial properties against various bacteria [113]. Because AMPs and PPPs are not only antibacterial but also potentially toxic to hosts, improving their biocompatibility remains a significant challenge. Jianhao Wang described a pH-converted AMP-loaded wound dressing [114]. The researchers created an octapeptide (IKFQFHFD) that is biocompatible under neutral conditions, but only has antibacterial activity in the acidic environment of infected wounds.

Metal and Metal Oxides

Metal-based antibacterial reagents have a long history, dating back to the use of silverware to store food in ancient China. Over a century ago, researchers first used $AgNO_3$ solution to treat infectious wounds. $AgNO_3$ is a highly toxic reagent that rapidly oxidizes. When exposed to light or organics, it quickly decomposes. Ag nanoparticles (Ag-NPs) have lower toxicity, are easier to store, and have a wide range of applications [115]. Ag-NPs dissociate a small amount of

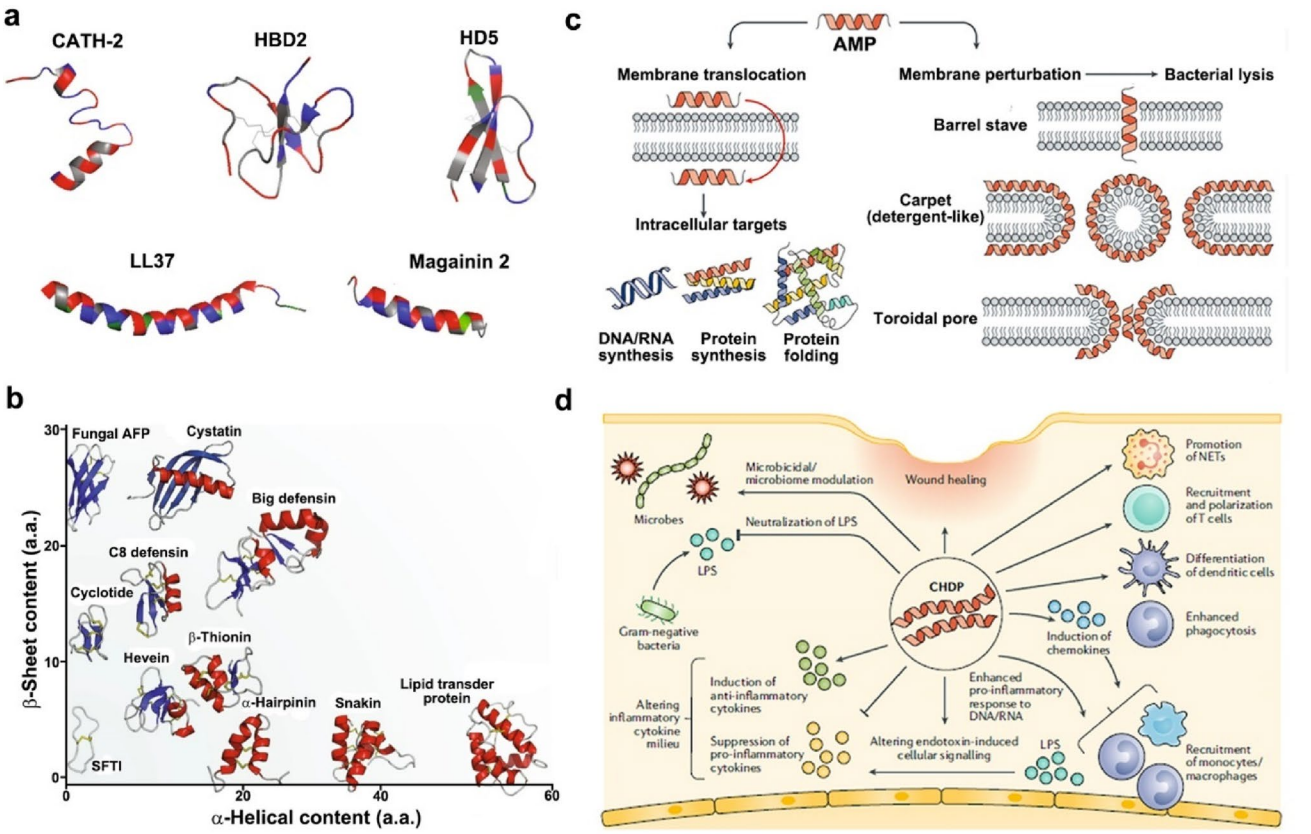

Fig. 4 **a** Structures of several kinds of AMP. Side chains of amino acids are marked. Red: hydrophobic, blue: basic, green: acidic. **b** Diversity of AMP differentiated by the secondary structure content, including a-Helical and b-Sheet. Blue: β-Strands, red: α-helices, yellow: disulfide bonds. **c** Antibacterial mechanism of AMP. **d** Immunomodulatory role and mechanism of the AMP on wound healing. Fig. **a**–**d** reproduced with permission from ref [36]; Copyright 2019, Springer Nature

Ag ions on wound sites, effectively sterilizing and avoiding the toxic effect of Ag ion expulsion. The antibacterial effect of Ag NPs is significantly affected by the topological morphology. This phenomenon can be attributed to the specific surface area and stability of Ag NPs [116]. Michał Moritz summarized the synthetic methods of Ag NPs, including chemical, physical, and biological reduction methods [35]. In recent decades, the chemical reduction of Ag NPs using dopamine or plant extracts as raw materials has been widely reported [117–120]. These renewable and nontoxic reducing agents will strongly promote the development of green chemistry.

Metal oxides derived from early transition metals demonstrated unique physicochemical properties, including selective oxidation, dehydration, photocatalysis, and electrocatalysis. Surface area and quantum effects are two important aspects that contribute to the unique features of metal oxides. Metal oxide nanoparticles have a higher surface area per unit mass than their bulk-sized counterparts. The characteristics of metal oxides change as the surface area grows. Quantum effects are caused by the continuous movement of atoms within metal oxides. An increase in surface area will result in an increase in the number of surface atoms in continual motion, which will eventually alter the optical, electrical, and magnetic properties of metal oxide NPs [121, 122].

Metal oxides can be generated in various forms and sizes ranging from 1 to 100 nm in size. Thus, metal oxide NPs have various properties as well as broad biomedical uses, including the ability to permeate the cell membrane and interior cellular organelles and even traverse the blood−brain barrier. Magnetic metal oxide nanoparticles (NPs) are of particular interest in biomedical research due to their ability to be manipulated by an external magnetic field [123], and the physicochemical properties of these metal oxide NPs are highly related to their size and shape [124]. Some of them exhibit biocompatibility and chemical stability and can eliminate cancer cells at low doses while remaining nontoxic toward normal cells; thus, an increasing number of advances have been made in retinopathy, biological sensors, and cancer treatment [125–127].

Except for Ag-NPs, Au, Cu, ZnO, TiO_2, Fe_3O_4 and other metal and metal oxides (MMOs) also have good antibacterial effects [128–131], because small NPs can enter bacterial cells and dissolve, releasing harmful metal ions. As shown in

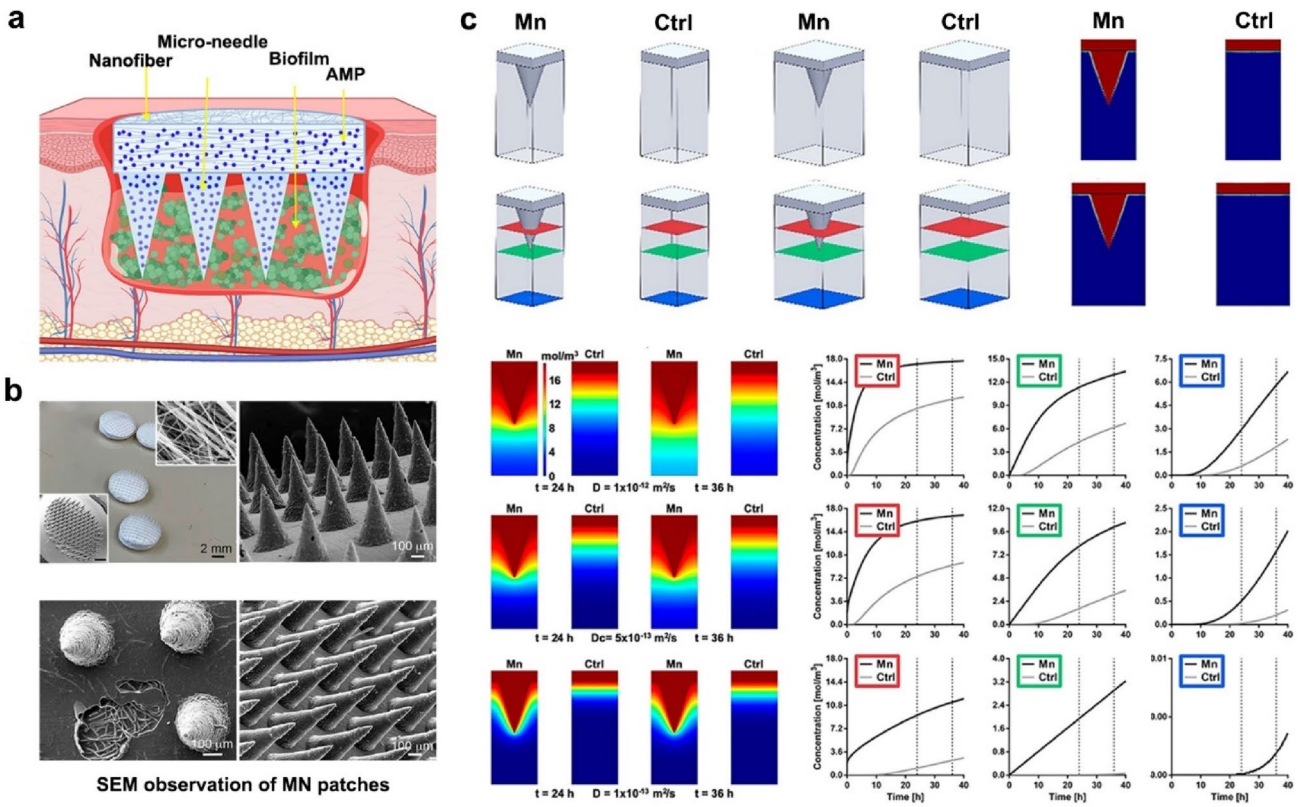

Fig. 5 **a–b** Janus-type dressings consisting of AMP-loaded nanofiber and microneedle patch. **c** Computational simulations of the releasing kinetics of AMP from the Janus-type dressings, reproduced with permission [111]; Copyright 2020, ACS

Fig. 6, the antibacterial mechanisms of MMOs include the destruction of the bacterial cell wall and plasma membrane, the inactivity of biochemical processes, and DNA damage [78, 132]. Reactive oxygen species (ROS) plays key roles in the process of bacterial death. MMOs also have some additional eye-catching functions. For example, TiO_2 NPs can shield from ultraviolet rays and reduce DNA damage [133]. Zn^{2+} is an essential cofactor of more than 300 enzymes, such as alkaline phosphatase (ALP), dopachrome tautomerase, metallothionein and metalloproteinase [134, 135]. Jiang Chang reported promoting hair follicle regeneration in burns by the synergistic release of Zn^{2+} and SiO_3^{2-} [135]. Yuanjin Zhao fabricated a ZIF-8 metal organic framework (MOF)-loaded microneedle patch, which can release Zn^{2+} to promote wound healing [136]. Exploring the characteristics of MMOs is a feasible way to construct composite bioactive wound dressings.

The blending electrospinning technique is commonly used to prepare MMO-loaded antibacterial ENMs. However, the size distribution of MMO-NPs is uneven, and their dispersion is very poor. It is easy to block the pipeline in the process of electrospinning. Thus, researchers should choose MMOs with smaller particle sizes, increase the viscosity of the spinning solution, fully disperse the particles, and shorten the time of electrospinning. In situ synthesis technology can also be used to prepare MMO-loaded antibacterial ENMs. For example, Alippilakkotte Shebi reduced $AgNO_3$ into Ag NPs on a polylactic acid (PLA) nanofiber membrane using extracts of Momordica charantia [137]. In situ synthesized MMO-NPs are distributed on the outside of the ENM and directly contact the bacteria, so the antibacterial effect is better. Lee believes that MMO-NPs can not only release antibacterial ions but also be directly swallowed by bacteria to cooperate with antibacterials [138]. On the other hand, Marius and others believe that the formation of aggregates and anchoring of MMO-NPs on the surface of bacterial cells is the main reason for the enhancement of their antibacterial properties [139]. Host cells can also devour refractory nanoparticles, leaving long-term pigmentation. Thus, the in vivo application of MMO-NPs should be given special attention.

Toxicity is a significant consideration for the safe and successful use of metal oxides in biomedical applications. In several studies, metal nanoparticles have been confirmed to be hazardous to humans, while the toxicity of metal nanoparticles is determined by their size and surface load. Thus, it is necessary to identify any potential health risks associated with these metal oxide NPs. For biomedical applications, metal oxide NPs and their complex ENMs should

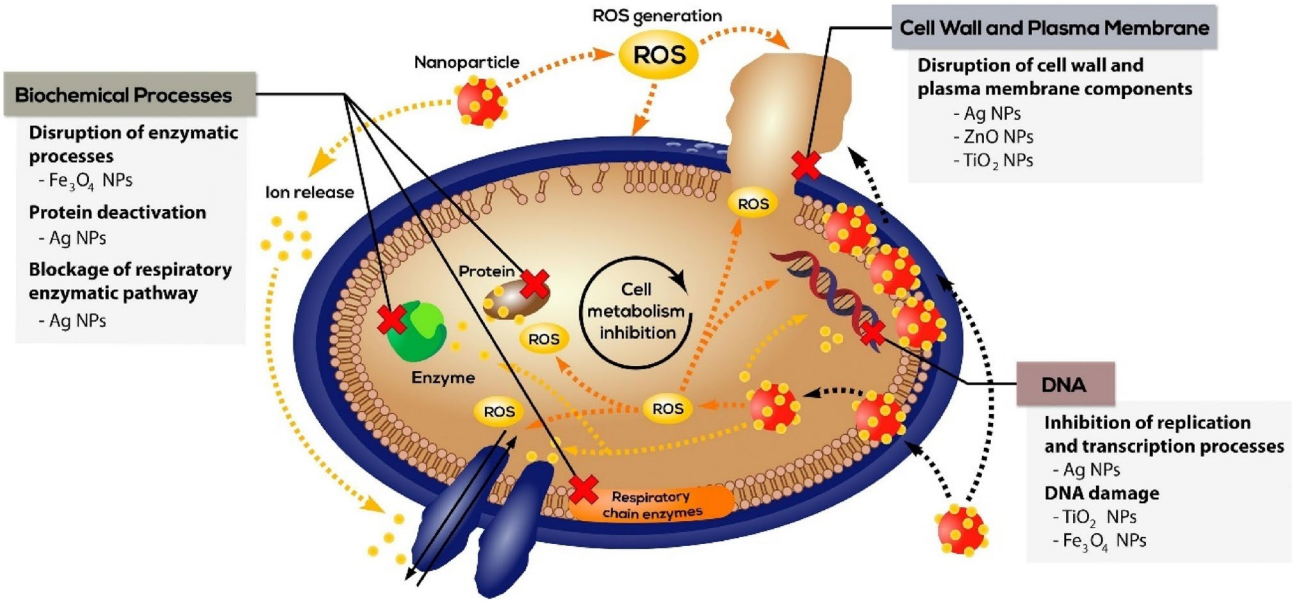

Fig. 6 Antibacterial mechanism of representative metal and metal oxides (MMOs), including Ag NPs, ZnO NPs, TiO_2 NPs, Fe_3O_4 NPs, Reproduced with permission from ref [132]; Copyright 2018, Elsevier

ideally have the following characteristics: (1) chemically stable, (2) resistance to wear and scratching, (3) biocompatible, and (4) nontoxic [140]. Today, the usage of metal oxides has attained an internationally recognized standard; these international standards outline the requirements and accompanying test techniques for biocompatible metal oxide materials for medical applications.

Antibacterial Polymers

Antibacterial polymers are of increasing interest. A series of natural polymers, such as chitosan, cellulose, silk fibroin (SF), collagen, and hyaluronic acid (HA), and synthetic polymers, such as polyvinyl alcohol (PVA), polycaprolactone (PCL), and polyethylene glycol (PEG), have been widely reported in the field of skin tissue engineering (STE) [141, 142]. Except for chitosan, the antibacterial properties of most natural and synthetic polymers cannot meet the clinical requirements. Thus, those polymers are commonly used as the substrate of ENM to load antibacterial agents such as antibiotics, Ag NPs and AMPs. Polymers with functional chemical groups can be endowed with unprecedented antibacterial activity through chemical modifications. Currently, cationic quaternary ammonium salt (CQAS) is the main antibacterial polymer under research.

In recent years, great progress has been made in the preparation and medical application of CQAS. As shown in Fig. 7a, b, Zhang's group applied KOH/urea solution to dissolve chitin at low temperature and then reacted it with epoxy propyl trimethyl ammonium chloride (EPTAC) under alkaline conditions to prepare a series of quaternized chitin (QC) with different degrees of substitution [143]. QC exhibited good biocompatibility and antibacterial effects toward four different pathogens. Other CQASs, such as quaternized chitosan, quaternized agarose, and quaternized cellulose, have also been synthesized [144–146] and could serve as the ideal molecular frameworks of wound dressing materials via various crosslinking strategies [147]. As shown in Fig. 7c, our group has previously fabricated a series of QC-based composite ENMs via layer-by-layer (LBL) self-assembly [17]. As one of the important upstream raw materials, the emergence of CQAS has strongly promoted the development of a series of polymer-based antibacterial wound dressings. Baolin Guo's group designed a series of hydrogel wound dressings with quaternized chitosan as the antibacterial component, realizing an organic combination of multiple physical, chemical and biological activities, such as antibacterial activity, tissue adhesion, conductivity, antioxidation, hemostasis, self-healing, and shape memory [148–151].

The mechanism of CQAS and the composited antibacterial ENM is shown in Fig. 8a. The negatively charged bacteria are drawn to the positively charged groups on the molecular chain of CQAS. The hydrophobic molecular chain inserts into the bacterial cell membrane, while the hydrophilic part remains outside, destroying the cell membrane's integrity and eventually resulting in bacterial lysis and death [26]. Compared with antibiotics, the use of CAQS will not lead to drug resistance. Our group has also synthetized an antibacterial polymer with completely independent intellectual property rights (IPR) [152]. As

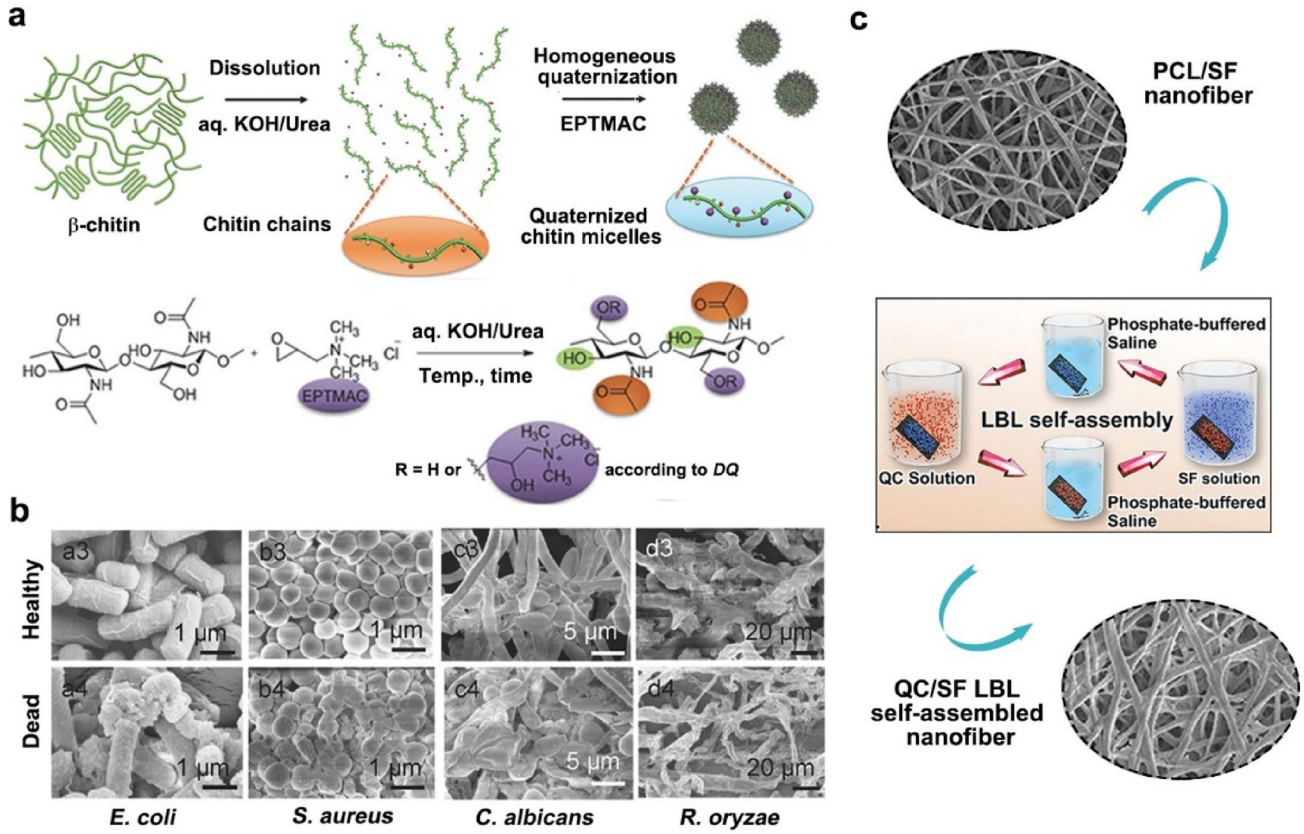

Fig. 7 **a, b** Chemical synthesis of quaternized chitosan (QC) and the antibacterial effect towards four different pathogens, including *E. coli*, *S. aureus*, *C. albicans*, and *R. oryzae*. The dead bacteria were treated with 100 μg/mL QC for 12 h. EPTMAC: epoxy propyl trimethyl ammonium chloride, Reproduced with permission from ref [143]; Copyright 2018, Wiley. **c** Fabrication of QC-based composited ENM via a layer-by-layer (LBL) assembly technique. PCL: polycaprolactone. SF: silk fibroin, Reproduced with permission from ref [17]; Copyright 2020, Wiley

shown in Fig. 8b, melamine-modified silk fibroin (SF-Mel) with antibacterial activity was obtained by a chemical crosslinking method. Furthermore, SF-Mel was dissolved in HFIP and blended with polycaprolactone (PCL) to obtain a series of PCL/SF-Mel composite ENMs. These products exhibit broad-spectrum antibacterial activity, promoting epithelial cell proliferation and revascularization, and have been successfully used in the wound healing of full-thickness skin defects in rats.

Compared with traditional polymers, the cytotoxicity of modified antibacterial polymers (MAPs) is relatively high. To reduce the cytotoxicity, the water solubility of MAPs should be inhibited to reduce the local diffusion among the wound sites. Jiahui He used the molecular cage effect of PCL to immobilize quaternized chitosan [153]. The antibacterial CQAS can also form a polyelectrolyte complex with another polymer with opposite charge and then be loaded on the ENMs. This physical immobilization method is expected to achieve the coordination and unity of antibacterial and biocompatibility of ENMs.

Translational Research from Bench to Bedsides

Wound dressings are classified as Class 2 or Class 3 medical equipment. Since June 1, 2021, the revised regulations on the Supervision and Administration of Medical Devices have been officially implemented by the State Council, which put forward more comprehensive requirements for the clinical evaluation of medical devices. Preclinical research and clinical trials according to national standards are necessary for wound dressing transformation [154]. Despite the publication of several studies, only a handful have been effectively translated and clinically applied. One of the main concerns is that research finding derived from cells and animal models is insufficient to fulfill the criteria of medical devices. Currently, research achievements on wound dressings are mainly created by scientists and technical workers from the fields of materials science, chemistry, and biomedical engineering. In the context of

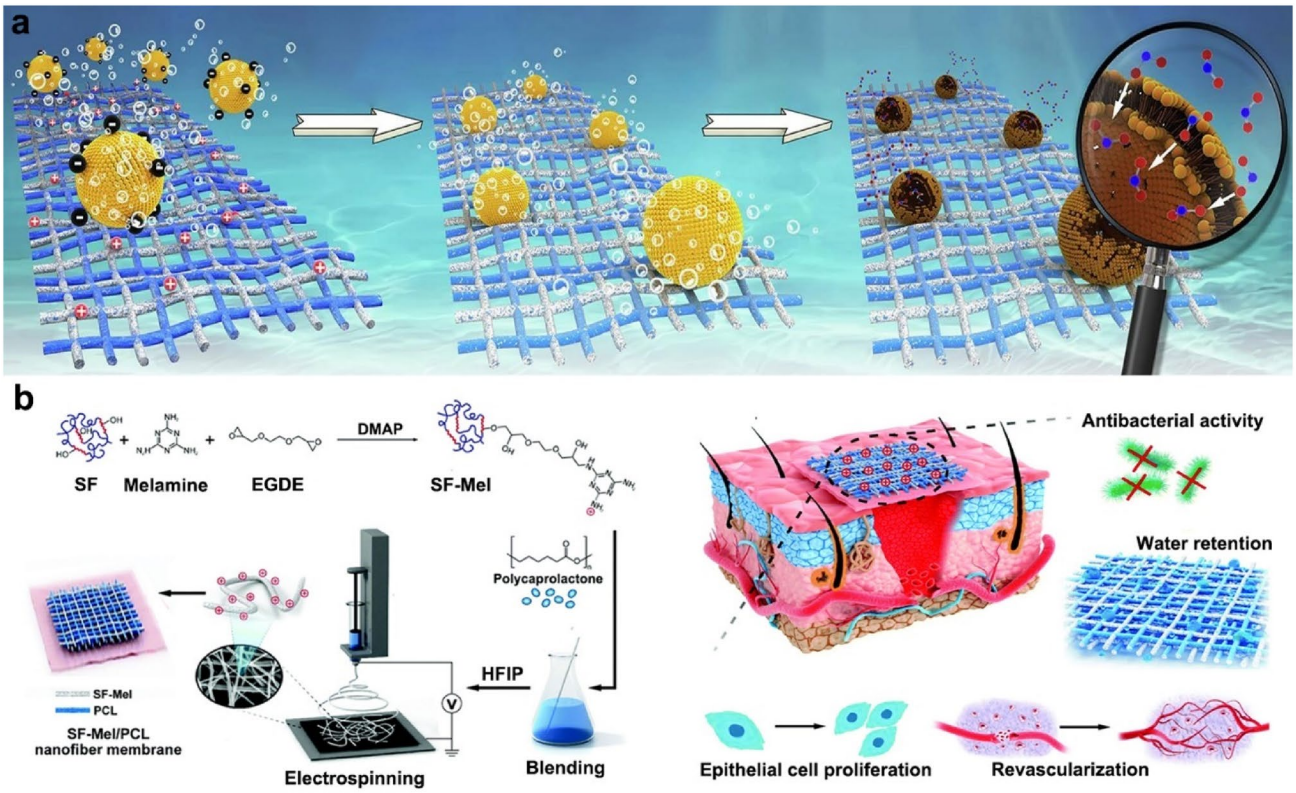

Fig. 8 **a** Diagram of the antibacterial mechanism of cationic quaternary ammonium salt (CAQS)-based ENMs, reproduced with permission from ref [26]; Copyright 2021, Elsevier. **b** Antibacterial melamine-modified silk fibroin (SF–Mel) was synthesized and used for preparing multifunctional wound dressings. The products exhibited good antibacterial activity, water retention ability, promotion of epithelial cell proliferation and revascularization, Reproduced with permission from ref [152]; Copyright 2019, RSC.

translational medicine, clinicians, with their superior etiology, clinical thinking and surgical skills, have joined the research and development of medical devices in an unprecedented role. Of note, most high-quality clinical trials are performed by foreign institutions, while the number of domestic high level clinical trials is significantly lower. The State Council has announced and issued the "Opinions on Deepening the Reform of the Review and Approval System and Encouraging the Innovation of Drugs and Medical Devices", which aims to promote the supervision and sustainable development of the medical device industry in China. The Chinese Society for Biomaterials (CSBM) is committed to promoting medical device evaluation and clinical translation and is looking forward to achieving good results.

The authors searched and gathered information on wound dressings registered with the National Medical Products Administration (NMPA), including 1040 domestic products and 223 imported products. These commercial wound dressings can be divided into hydrocolloid dressings, foam dressings, silver ion dressings, alginate dressings, chitosan dressings, cellulose dressings, silicone dressings, etc. ENM-based wound dressings are rarely found, because ENM-based wound dressings exhibit varied size-dependent physical and chemical properties, and evaluation criteria from regulatory authorities for ENM-based wound dressings are deficient. In addition, the authors also surveyed the current status of clinical application of wound dressings, and some clinicians reported that the curative effect of wound dressings was not fully satisfactory, and there are some flaws, such as tissue adhesion and difficulties changing wound dressings. Thus, the establishment of a systematic evaluation system for medical devices is urgent. As shown in Fig. 9a, Do et al. established a skin defect model in pigs to evaluate the clinical efficiency of wound dressings [155]. Compared with other small animal models, the skin of pigs is closer to the human body. Affected by body size, pigs also have significant advantages in constructing a large-area full thickness skin injury model. In addition, skin defect models based on nonhuman primates have rarely been reported. As shown in Fig. 9b, Seungkuk Ahn et al. constructed a humanized research model that simulates the whole process of wound healing by culturing donor skin tissue in vitro [156]. The humanized model retains the pathophysiological characteristics of wound healing to the greatest extent, and its research is much more significant than that of the traditional models. In the future,

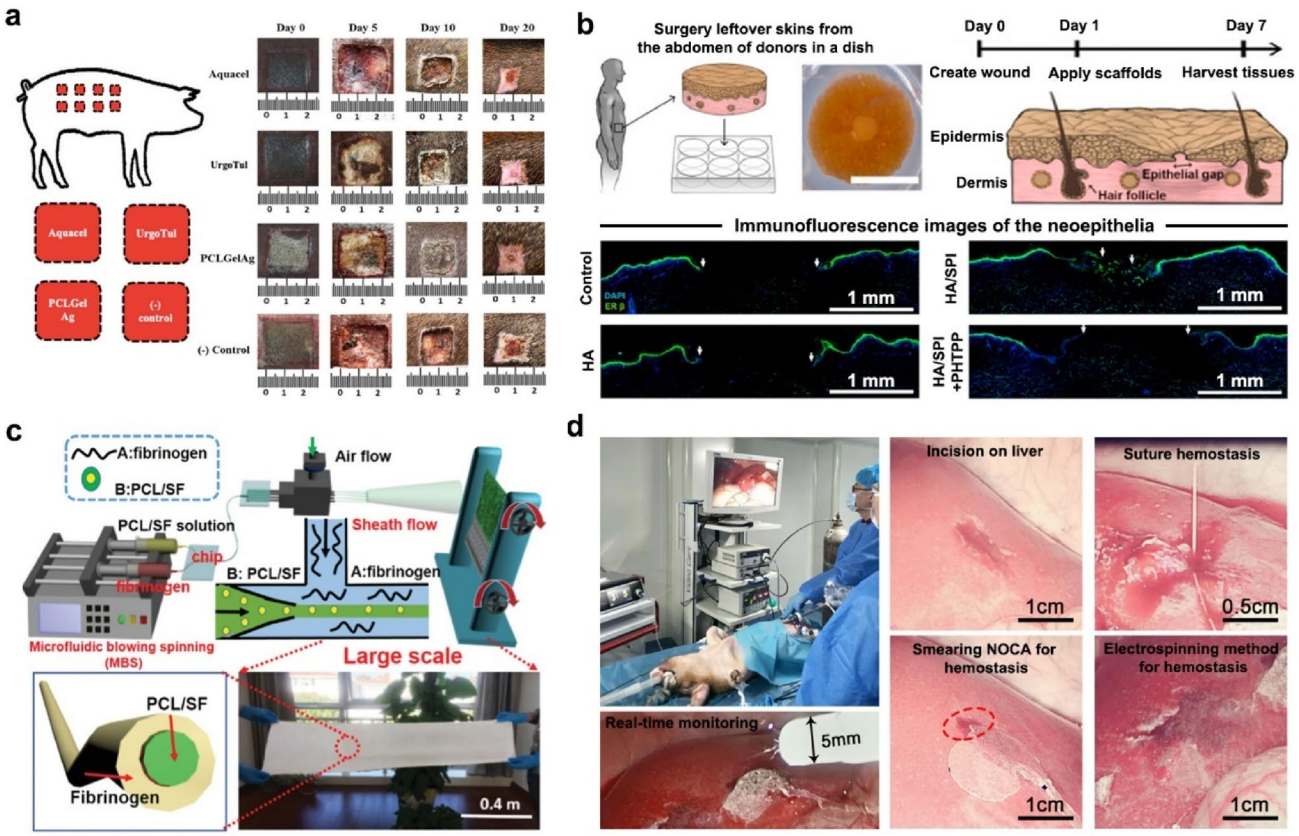

Fig. 9 **a** Porcine skin injury model was constructed for wound healing evaluation in vivo. Reproduced with permission from ref [155]. Copyright 2021, MDPI. **b** Preparation and application of ex-vivo human skin models for the re-epithelialization analysis, reproduced with permission from ref [156]; Copyright 2020, Elsevier. **c** Schematic illustration for large-scale fabrication of biodegradable fibrinogen-coated PCL/SF nanofiber scaffold by microfluidic blow-spinning, reproduced with permission from ref [157]; Copyright 2020, Wiley. **d** In vivo laparoscopic hemostasis using the long-needle electrospinning device, NOCA: medical glue N-octyl-2-cyanoacrylates, Reproduced with permission from ref [159]; Copyright 2020, Elsevier

more humanized models (organoids, patient-derived xenografts) and large animal models (pig, cynomolgus monkey) will be developed. In terms of biosafety evaluation, the U.S. Food and Drug Administration (FDA) issued "select updates for biocompatibility of certain devices in contact with intact skin" in 2020. This draft guidance will further improve the review efficiency and reduce the waste of resources on the premise of ensuring the biosafety of medical devices.

An important issue in the translation of medical devices is the unannounced inspection of products, and its core demand is to increase output and reduce energy consumption. Researchers have made extensive attempts and have successively developed array electrospinning, needle-free electrospinning, and other advanced technologies. As shown in Fig. 9c, Cui et al. designed a microfluidic wind-spinning device that successfully realized the large-scale production (40×140 cm^2) of PCL/SF-fibrinogen nanofiber films with a shell–core structure [157]. Microfluidic wind-spinning technology greatly improves the output of nanofibers and can be used to load various antibacterial reagents, which will have further potential applications. Portable electrospinning devices are another landmark achievement in engineering. Different from traditional electrospinning technology, portable electrospinning technology can conduct in situ electrospinning by coating conductive materials on the surface of living tissues and using them as negative electrodes [158]. Jun Zhang et al. designed a long needle electrospun device and prepared electrospun nanofibers in situ under the assistance of laparoscopy for the first time, which was used to stop bleeding of the liver (Fig. 9d) [159]. The combination of portable electrospinning technology and endoscopic technology has formed a new breakthrough in minimally invasive surgery.

Conclusions and Future Perspectives

In this paper, we summarize the clinical characteristics and requirements of STE, as well as the preparation and modification methods of ENMs. We updated the research advances

of antibacterial ENMs, focusing on their antibacterial components, antibacterial mechanisms, biocompatibility and bioactivity evaluations, and material processing techniques. We also collected information from preclinical and clinical research and revealed the promising translational prospects of wound dressings. In the future, the field of antibacterial ENMs will usher in a stage of rapid development to fully fill the higher clinical needs. Several frontier directions should be emphasized.

Antibacterial ENMs can be upgraded by other advanced antibacterial methods and materials. In recent years, photothermal therapy (PTT), photodynamic therapy (PDT), antibacterial traditional Chinese medicine (TCM), and antibacterial metal-organic frameworks (MOFs) have made significant progress [160]. PTT can efficiently kill bacteria and inhibit the formation of biofilms. Extensive photothermal raw materials, such as polydopamine (PDA), black phosphorus (BP), methylene blue (MB), and composite products, have been developed for potential clinical applications [161]. However, local high temperature induced by PTT may cause damage to normal tissues and cells. Yuanjin Zhao's group reported that ZIF-8, a zinc-doped MOF, exhibited excellent broad-spectrum antibacterial activity by the sustained release of Zn^{2+} [162]. Another inorganic nanomaterial, named BP nanosheets, exhibits antibacterial properties by a nanoknife effect [163]. These antibacterial methods and materials can be introduced into ENMs by potential material processing techniques. For example, PDA was self-polymerized on the surface of curcumin nanocrystals to endow them with enhanced photothermal activity [164]. BP nanosheets and ZIF-8 can be loaded onto ENMs by blend or coaxial electrospinning and LBL self-assembly techniques [165, 166]. It is strongly recommended that two or more antibacterial methods and materials should be combined to improve the clinical effectiveness and safety.

Antibacterial ENMs can integrate with other specific bioactivities and functions. Based on clinical experiences, it was concluded that multifunctional and stimulus-responsive WDs are more competitive. Several regeneration-related bioactivities, including hemostasis, antioxidant, follicle regeneration, ECM remodeling, stem cell and macrophage regulation, and improvement of the harsh wound microenvironment, are of increasing interest [167, 168]. Notably, a brand-new strategy of photobiomodulation has been recently developed to provide a noninvasive and real-time intervention for wound healing [169]. ENMs offer a high potential for incorporating antibacterial activity and other bioactivities due to their unique structural characteristics. In recent years, flexible electronics with diagnostic functions have been gradually introduced into the field of STE. Dachao Li's group developed a thermally activated epidermal biomicrofluidic device for accurate monitoring of blood glucose, which is the most important prognostic index of diabetic feet [170]. Novel flexible electronics have also been reported for monitoring somatic movement, pH value and sweat [171, 172]. The currently available flexible electronics typically have poor biodegradability and biocompatibility in vivo. There are great challenges and opportunities to integrate the advantages and disadvantages of antibacterial ENMs and flexible electronics for the collaborative diagnosis and treatment of skin injury.

Uncovering the molecular mechanism of antibacterial ENMs by means of biology is of high interest. For biomaterials science, one of the problems is the lack of an in-depth understanding of the intrinsic links between chemical compositions, physical structures, and biological applications. Researchers have performed many experiments, such as fluorescence quantitative polymeric chain reaction, Western blot, and flow cytometry [173]. However, these experimental methodologies have certain limitations. High-throughput technologies, such as transcriptome sequencing, proteome sequencing, and single-cell sequencing, have been steadily expanded to the field of biomaterials science [174]. Ouyang Hongwei and his collaborators uncovered the mechanism of bone regeneration by transcriptome sequencing combined with Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) analysis [175]. Compared to traditional methodologies, high-throughput technologies are more competitive in reflecting the real world. In recent years, biology has made great progress in disease development, such as copper death, ubiquitination, and autophagy. Below are some crucial problems to be solved. (1) Will biomaterials work through these specific biological mechanisms? (2) Can biomaterials be designed to regulate specific biological mechanisms? Yihang Pan's group has just published the first article on the use of copper-based biomaterials to induce copper death and antitumor therapy [176]. More interdisciplinary works in biomaterials science and biology are emerging and accelerating the clinical translation process.

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Declarations

Conflict of interest The authors declare no competing financial interests in this work.

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