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Intelligent electrospinning nanofibrous membranes for monitoring and promotion of the wound healing

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ABSTRACT

The incidence of chronic wound healing is promoted by the growing trend of elderly population, obesity, and type II diabetes. Although numerous wound dressings have been studied over the years, it is still challenging for many wound dressings to perfectly adapt to the healing process due to the dynamic and complicated wound microenvironment. Aiming at an optimal reproduction of the physiological environment, multifunctional electrospinning nanofibrous membranes (ENMs) have emerged as a promising platform for the wound treatment owing to their resemblance to extracellular matrix (ECM), adjustable preparation processes, porousness, and good conformability to the wound site. Moreover, profiting from the booming development of human-machine interaction and artificial intelligence, a next generation of intelligent electrospinning nanofibrous membranes (iENMs) based wound dressing substrates that could realize the real-time monitoring of wound proceeding and individual-based wound therapy has evoked a surge of interest. In this regard, general wound-related biomarkers and process are overviewed firstly and representative iENMs stimuli-responsive materials are briefly summarized. Subsequently, the emergent applications of iENMs for the wound healing are highlighted. Finally, the opportunities and challenges for the development of next-generation iENMs as well as translating iENMs into clinical practice are evaluated.

1. Introduction

Skin, the largest organ in the human body, are vulnerable to unpredictable events or some stubborn diseases such as diabetes, vasculopathy, and cancers. Recent observations show that millions of people have been afflicted with various kinds of wound per year [1,2]. Once the integrity and protective function of human skin are destroyed, the wound is susceptible to various harmful materials and bacterial invasion, resulting infections and inflammatory cascades [3,4]. Thus, in the absence of specific wound cares, common skin wounds will likely become an intractable trouble associated with torturous physical pain and even financial burden [5,6]. Despite the skin could self-repair to restore its structure and function, the wound healing is a slow and complicated process [7]. The treatment and management to avoid infections, alleviate pain and accelerate the healing process remains a high priority, especially for chronic non-healing wounds in some cases [8,9].

The wound healing is known to a consecutive phase requiring the coordination of multiple growth factors and cell types, which generally

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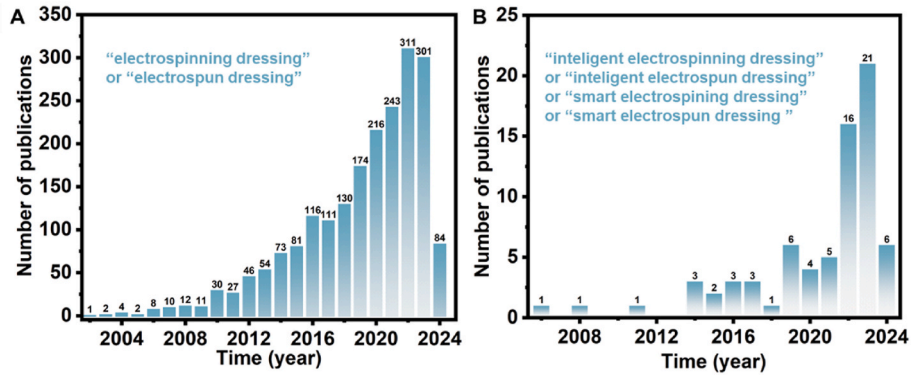

Fig. 1. Number of annual publications. (A) The literary search is based on the terms 'electrospinning dressing' or 'electrospun dressing' in the 'Web of Science' database from 2000 to 2024; (B) The literary search is based on the terms 'intelligent/smart electrospinning dressing' or 'intelligent/smart electrospun dressing' in the 'Web of Science' database from 2000 to 2024.

occurs in four overlapping stages, i.e., hemostasis, inflammation, proliferation, and remodeling [10,11]. As a result, the standard of wound care consists of debridement to promote cell proliferation, treating infections and dressing for protecting the wound from infections [12]. Wound dressings are common clinical articles for dealing with various wounds and they have developed versatile adaptive functions for accelerating the wound healing over the hundreds of years. Out of them, electrospinning nanofibrous membranes (ENMs), one of the currently most popular wound dressings, present remarkable advantages as dermal substitutes compared to conventional dressings such as gauzes and non-fibrous materials since penetrating network structures can simulate the native extracellular matrix (ECM) of the skin to support the

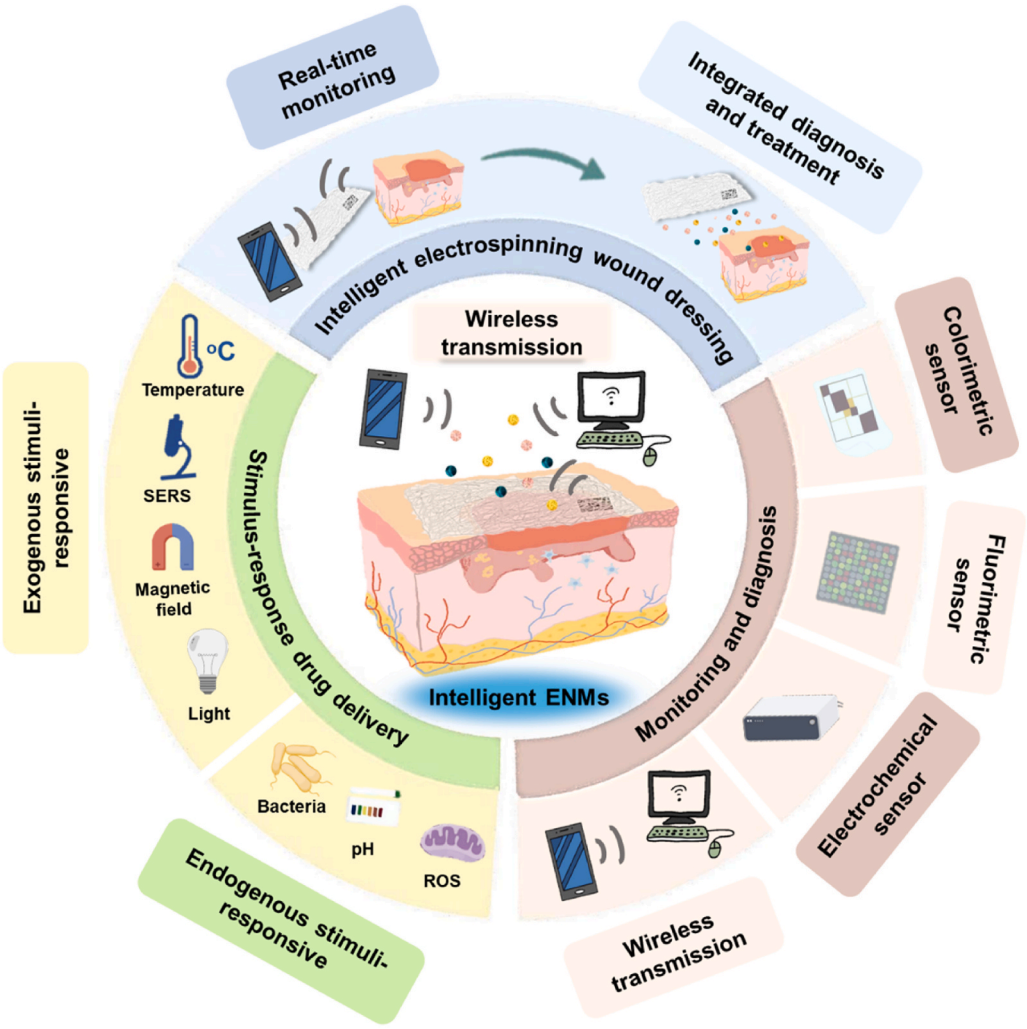

Fig. 2. Schematic illustration of the intelligent electrospinning wound dressings integrated with various biomarkers detected sensors and advanced drug delivery systems for the real-time monitoring and early diagnosis, on-demand treatment, and the all-in-one management of wound healing.

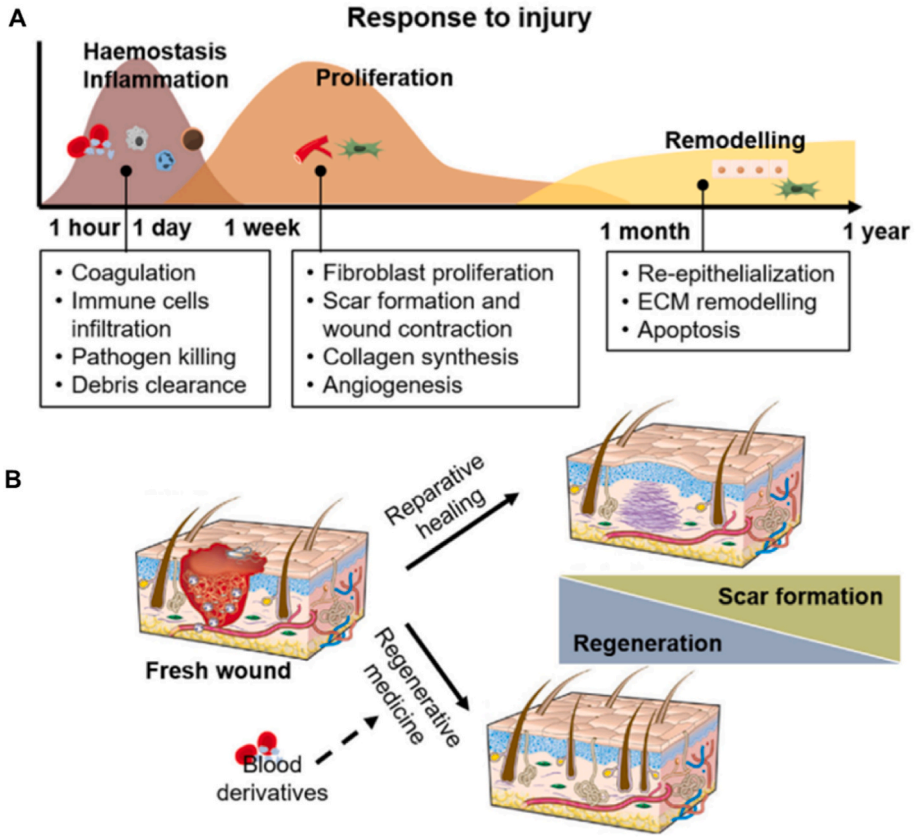

Fig. 3. Overview of the classical wound healing phases *vs* regenerative medicine therapy approach. (A) Major wound healing events in a controlled spatial and precisely temporal response to injury. (B) Tissue repair (scarring) and tissue regeneration after injury. Adapted with permission from Ref. [52]. Copyright 2008, Nature Publishing Group.

adhesion and growth of host cells [13–15].

Benefiting by adjustable preparation processes, ENMs can also be designed with controllable structures, devisable functions, and biocompatibility to adapt to various practical scenarios. Relying on the better understanding of cellular and molecular stages of the wound healing process and progresses achieved in biomaterials, current ENMs can serve as a multifunctional platform for diagnosis and treatments of wounds [16]. Besides, rapid developments of the human-machine interaction and artificial intelligence has driven the boom of biomedical sensors and wearable electronic devices, thus a new generation of ENMs has been constructed to realize the real-time monitoring for precision diagnosis and wound therapy [17,18]. Over the past decades, ENMs are evolving to provide the more programmable and innovative design to realize the "intelligent" performance and personalized functions rather than a single or passive property for wound care [19,20].

The term 'electrospinning dressing' has been referenced in 2047 papers within the globally recognized database 'Web of Science.' Alternatively, the term 'electrospun dressing' has also been used. The annual publication trend from 2000 to 2022 can be observed in Fig. 1A. During the early 2000s, various research groups started adapting traditional electrospinning devices to generate electrospun materials. Since 2010, there has been a consistent annual growth in publications related to electrospinning. Recently, a significant amount of electrospun fibers have found applications across different biomedical areas, with wound dressing emerging as a prominent focus. Post-2020, there has been a surge in research papers discussing intelligent electrospinning dressings, marking a new avenue in electrospinning research (Fig. 1B).

Electrospun fibers are extensively utilized in biomedical applications due to their unique benefits. Wu et al. [21] conducted a thorough review of electrospun fiber applications in the biomedical field, such as surgical sutures, tissue engineering stents, and wearable implant devices. They underscored the clinical application demands and future prospects of electrospun fibers. Li et al. [22] focused on gelatin-based electrospun wound dressings to elaborate on the role of fiber membranes, with or without therapeutic agent, in enhancing wound healing and tissue regeneration, offering innovative approaches for clinical wound management. Furthermore, Li et al. [23] provided detailed insights into surface coating and drug loading technologies for fiber surgical sutures, highlighting the development of sutures capable of real-time monitoring of wound status to tailor treatment accordingly. While there are numerous high-quality and systematic reviews available, our specific emphasis is on intelligent electrospun nanofiber wound dressings that incorporate wound marker monitoring and integrated diagnosis and treatment. The goal is to offer valuable references for clinicians in the field of wound care.

Recent research has been dedicated to the development of iENMs to improve wound healing. iENMs, characterized by their large surface area, high porosity, and ease of functionalization, have emerged as promising platforms for drug delivery systems. Responsive micro/nanofibers exhibit significant potential for controlled drug release in response to external stimuli (such as light, temperature, and magnetic fields) and internal stimuli (such as temperature, pH, and reactive oxygen species) [24]. Additionally, intelligent micro/nanofibers can trigger programmable shrinkage behavior in response to stimuli like temperature and moisture, providing effective biomechanical stimulation to accelerate wound closure [25]. The development of conductive iENMs has introduced a novel approach for enhancing tissue regeneration through electrical stimulation [26,27]. To enable real-time monitoring of wound status, indicator molecules responsive to wound biomarkers have been integrated into fibers, allowing for optical signal assessment based on color change and fluorescent signals [28,29]. Moreover, the integration of fibrous materials with wearable sensors has

led to the advancement of sophisticated electrical detection methods, offering high specificity and sensitivity [30]. The current trend in wound management is towards the development of smart wound dressings, with a range of iENMs, including stimuli-responsive iENMs, shape memory iENMs, and conductive iENMs, being utilized in various biomedical applications.

Herein, we aim to provide a brief review of electrospinning wound dressings, focusing on recent advances in iENMs and their unique activities for monitoring and promotion of the wound healing (Fig. 2). The iENMs integrated with various biomarkers detected sensors are highlighted. We specifically discussed drug delivery systems for the real-time monitoring and early diagnosis, on-demand treatment, and the all-in-one management of wound healing. In conclusion, a perspective toward advanced ENMs with rational design of their functionality as high sensitivity and safety for the wound care is presented.

2. Wound

"Wound" is used to describe skin that has encountered an injury or break in its surface [31], and based on the different healing time, which can be classified to acute wounds or chronic wounds [32]. Generally, acute wounds can be caused by a mechanical, thermal, electrical or chemical stimulation, while chronic wounds are most often the result of a complication of several diseases (such as infections, inflammation, diabetes and tumors) [33,34]. As for the healing, acute wounds routinely need an ordinary support in protection against infection whereas additional substances initiating an appropriate healing process would be necessary for chronic wounds where the biological signals may be scarce [35]. Therefore, this part mainly reviews the general process of wound healing and related markers which can affect the wound healing.

2.1. Wound healing process

Wound healing is a complex and dynamic process requiring the coordination of multiple growth factors and cell types [36]. The entire wound recovery process is commonly combined into four stages: hemostasis, inflammation, proliferation and remodeling [37] (Fig. 3). Hemostasis is initiated by the formation of blood clots consisting of red blood cells, activated platelets and fibrin, which could act as a temporary barrier to prevent secondary blood flow and protect the injury site from pathogen contamination [38,39]. Meanwhile, the blood clot can also arouse the inflammatory response through the interaction of blood coagulase and pro-inflammatory factors. Subsequently, the defined inflammatory phase begins 24–48 h after the wound formation [37,40]. During this period, inflammatory mediators and chemokines related to the assembly and differentiation of leukocyte, lymphocyte and monocyte would increase sharply [41,42]. With the enrichment of these cells and chemokines, the proliferation of fibroblasts and endothelial cells begins in earnest. In addition, the whole proliferation stage also includes granulation tissue formation, vascular remodeling and collagen deposition [43,44]. The final stage is the remodeling stage. With the transformation of reticular collagen (type III) to fibrous collagen (type I), the tensile strength of the new skin tissue gradually increases followed by the formation of complete skin. However, bacterial infection [45], inflammation [46], diabetes [45,47] or reactive oxygen species (ROS) may delay the healing process, leading to the formation of chronic wounds [48]. Thus, a timely diagnosis and treatment of wound complications is necessary to improve therapeutic outcomes and even patient survival. Clinical studies have recognized that many physiological parameters, enzymes, metabolites, signaling molecules, and various bacteria are closely related to the dynamic wound healing process [5,26,49]. Continuous monitoring of these biomarkers can effectively prevent wound deterioration (such as infection and inflammation) and provide a basis for early treatment [9,50,51]. Therefore, the next section will focus on the dynamic relationship between easily monitored wound markers (such as temperature, pH, glucose, reactive oxygen species, bacteria-specific markers, enzymes, and inflammatory factors) and abnormal wound healing events.

2.2. Wound-related biomarkers

2.2.1. Temperature

Temperature is recognized as one of the most significant parameters for the assessment of wounds status since a series of factors relevant to healing including local blood flow, oxygenation, wound infection and inflammation will lead to the change of temperature around the damaged skin site [9,51,53]. It has been confirmed that local vasodilatation and angiogenesis can increase the wound temperature and the infiltration of inflammatory cell will also induce the increase of wound temperature [54]. Lou et al. traced the temperature change of skin wound of Bama pig during the healing process. It was showed that the wound temperature went through three stages within two weeks: the rising stage (below 39 °C) from day 1 to day 5; the plateau stage (39–39.5 °C) from days 5 to day 9; and the falling stage (below 39 °C) from day 9 to day 14. These three stages of wound temperature were demonstrated to be associated with the wound biological events of inflammatory, angiogenesis and wound healing, respectively [55]. In addition, temperature is also an established marker of wound infection [56]. A sudden temperature increase (>2.2 °C) in a wounded area could be an early predictor of infection before any other obvious clinical symptoms (such as redness, swelling and smell) occurring at the wound site [57]. Conversely, the decreased temperature will weaken the activities of fibroblasts, neutrophils, and epithelial cells as well as further hinder the wound healing [58,59]. Thus, the decrease in wound temperature could indicate the presence of partial ischemia and delayed wound healing [60].

2.2.2. pH value

pH is another important indicator of wound status, which can significantly influence the physiological processes including collagen formation, inflammatory response, and angiogenesis during the wound healing process [61]. Generally, the pH of normal skin and healed wound is slightly acidic (pH = 4–6) to support the proliferation of fibroblasts, promote the angiogenesis and epithelialization, as well as maintain a resident commensal bacteria level [51,62]. When a wound forms, the exposure of tissue under the skin results in a neutral environment (pH = 7.4) of the local wound. It has been reported that the pH values of acute wounds easily return to an acidic level during inflammation, however, due to the presence of an ischemia-reperfusion injury cycle, the pH of chronic wounds usually remains alkaline for several months (pH = 7–9) [63–65]. In addition, the alkaline wounds are vulnerable to bacterial colonization and infection, which further induce bacterial growth and an ultra-high pH value (pH = 10) might be achieved in some case [66]. Hence, monitoring wound pH represents a meaningful indicator to predict bacterial infection and estimate wound healing stages. Nevertheless, current evidence indicates that not all bacterial bioburden may cause an increase in wound pH [67,68]. The pH value of an infected wound could be influenced by the type of bacteria and wound environment (i.e., anaerobic or aerobic conditions) [69,70]. Therefore, cautions should be taken when using pH alone for analyzing wound status. More accurate diagnosis for evaluating wound healing processes should be made by combing the pH with other key biomarkers.

2.2.3. Other related markers

Monitoring blood glucose levels is meaningful in assessing wound healing, especially for diabetic chronic wounds. The glucose concentration in chronic wound fluid ranges between 0 and 1.2 mmol/L (M) [71]. It has been proved that the higher blood glucose level would interfere the synthesis of the transcription factor hypoxia-inducible factor-1 (HIF-1), which should be highly expressed in the early stage of normal wound healing process and subsequently regulate the activity of cytokines and cell oxygen homeostasis. As a result, the improper

Table 1
Application and comparison of electrospinning technology.

Technology type	Scope of application	Advantage	Disadvantage
Conventional electrospinning	Monocomponent	Simple structure and simple preparation	Single function, limited effect
Blend electrospinning	Different solvent systems	Variety of therapeutic effects	For insoluble drugs, the distribution in the fibers is uneven
Emulsion electrospinning	Polymer emulsion	Loaded with various types of drugs (hydrophilic or hydrophobic)	The drug-loaded fibers exhibit a higher level of uniformity
Parallel electrospinning	Janus nanofibers	It can achieve different functions on both sides of the fiber	Relatively complex process
Coaxial electrospinning	Core-shell nanofibers	Reduce drug sudden release and increase release time	Relatively complex process
Triaxial electrospinning	Core-shell nanofibers	The slow-release effect was further enhanced	Relatively complex process

expression of HIF-1 leads to the failure of capillary blood vessel networks formation and tissue necrosis [72,73]. In addition, a higher blood glucose concentration is also a conducive environment for bacterial growth [74]. Thus, continuous monitoring of glucose concentration at an injured site could reflect wound conditions and guide effective treatments for accelerating the healing of diabetic wounds.

Enzyme substances, including neutrophil enzymes such as myeloperoxidase (MPO), human neutrophil elastase (HNE), cathepsin G (CAT G), lysozyme (LYS), and matrix metalloproteinases (MMPs), are crucial in the early stages of infection analysis [75]. These enzymes play a significant role in assessing wound condition and monitoring. Proteases are considered a valuable biomarker for assessing wound condition and the likelihood of specific treatments improving clinical outcomes [28]. These enzymes play a crucial role in wound healing by breaking down proteins like the extracellular matrix and connective tissues, facilitating the removal of damaged tissue and foreign materials to promote new tissue formation [75,76]. However, prolonged high activity of proteases in non-healing wounds can impede proper healing and increase the risk of infection [77]. Infected wounds have been found to exhibit significantly elevated levels of various proteases and an imbalance in the protease/protease inhibitor ratio compared to uninfected wounds, highlighting their potential as biomarkers for infection detection in wounds [77,78].

The reactive oxygen species (ROS) level and some bacterial-specific secretions can also be used to reflect the healing status of wounds. ROS is considered a double-edged sword. Specifically, the slightly elevated level of ROS helps in wound healing by promoting the release of cytokines and growth factors as well as inhibiting minority microbial colonization [48,79]. while excessive ROS levels will show deleterious effects on wound healing by extending the inflammation phase [80]. Consequently, ROS level is an important indicator of infected or chronically inflamed wounds, and the timely detection of ROS levels at wound can effectively prevent wound inflammation from worsening.

The biochemical products secreted by bacteria at the wound site can be used as specific reference to directly detect bacterial infections. For example, both *Staphylococcus aureus* and *Pseudomonas aeruginosa* can secrete specific toxins such as phospholipase A_2 and hemolysin, while pyocyanin is exclusively secreted by the *Pseudomonas aeruginosa* strains [81,82]. Lastly, the rise in inflammatory factors like IL-1β, IL-6, and TNF-αat the wound site serves as evidence of the ongoing inflammatory response [83,84]. TNF-α, in particular, is the primary and earliest inflammatory mediator in this process, with the ability to stimulate neutrophils and lymphocytes [85,86].

The status of wound healing can be evaluated by the numerical changes of the abovementioned physiological signals as early alerts on wound lesions. Therefore, it is necessary to first select dressings as carriers to monitor target wound markers for promoting wound healing.

3. Electrospinning wound dressing

Traditional wound dressings, such as bandages and gauze, have been widely used in clinical practice to wound healing. However, poor hemostatic effects, easy to be polluted by tissue fluids and forming tissue adhesions are inherent drawbacks accompanying with the application of traditional wound dressings, which might greatly compromise their therapeutic effects [87,88]. In comparison to traditional dressings, ENMs have made significant advancements in wound management, showing promising potential for developing intelligent, functional, adaptive, and personalized wound dressings [89,90]. With a programmed and adjustable preparation process, the morphology of the ENMs can be precisely regulated. Additionally, the high porosity of ENMs not only allows water and gas to pass through readily, but provide the high surface area-to-volume ratio for improving the loading efficiency of various biomolecules, which can well meet the most requirements for would healings [91,92]. More importantly, the structure of nanofibers could mimic the natural structure of the ECMs, making them ideal candidates for the wound healing [93]. Hence, this section will start with a simple introduction of the specific preparation technology for ENMs and how ENMs have been exploited as ordinary wound dressing to achieve one certain function such as hemostasis, angiogenesis, epithelialization or infection inhibition.

3.1. Electrospinning technology

Electrospinning technology equipping with quick, easy, and efficient characteristics to create nanofiber materials is firstly developed in 1934. Currently, it has grown to be one of major techniques for building nanofibrous membranes based wound dressings [94]. The morphology and structure of electrospinning fibers can be intricately tailored by adjusting the properties of the electrospinning solution and process parameters [95,96]. Various electrospinning techniques, such as conventional electrospinning, blend electrospinning, emulsion electrospinning, parallel electrospinning, coaxial electrospinning, and triaxial electrospinning, are commonly employed to manipulate fiber composition and structure [22]. A detailed comparison of the advantages and disadvantages of these techniques in wound dressing preparation can be found in Table 1. Despite structural differences, the biomimetic nature of electrospun fibers provides both topographical and biochemical cues that are essential in regulating cell behavior, ultimately facilitating tissue regeneration and wound healing.

3.2. ENMs for promoting wound healing

Whether it is an acute or chronic wound, the primary goal of the dressing in the initial stage of wound formation is to stop bleeding [97,98]. In recent years, due to its unique structural form, ENMs has shown easily adjustable physical and chemical properties, making it a promising alternative method for hemostasis treatment [99]. Wang et al. [100] used gelatin and PCL with high the adhesion and absorption to make nanofiber membranes, which can interact with red blood cells, platelets, plasma proteins and other components in blood to form a thrombotic structure attached to the wound, effectively sealing the wound and preventing the continuous bleeding (Fig. 4A). Pandey et al. [101] designed and fabricated a bioabsorbable nanofiber dressing using thrombin (TMB) as the hemostatic agent and PVA/gelatin/polylactic glycolic acid as the material. The dressing showed a short bleeding time,

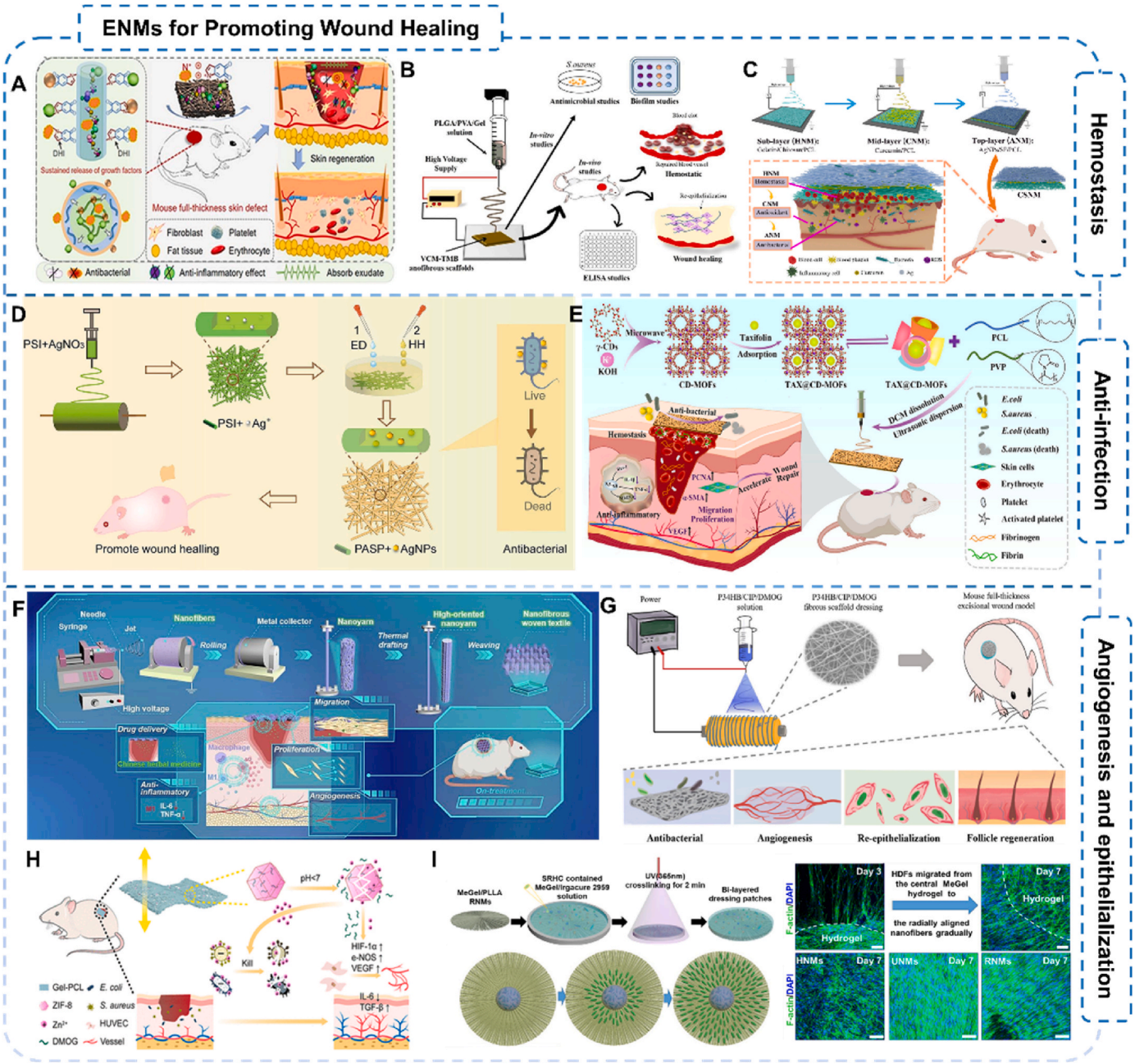

Fig. 4. ENMs for promoting wound healing. (A) Schematic illustration of the preparation and application of chitosan-based bioactive coaxial nanofibers. Reproduced with permission of [100]. Copyright 2023, Elsevier; (B) Schematic illustration of multilayered nanofibrous scaffold of Polyvinyl alcohol/gelatin/poly (lactic-co-glycolic acid). Reproduced with permission of [101]. Copyright 2023, Elsevier; (C) Schematic illustration of curcumin-loaded sandwich-like nanofibrous membrane. Reproduced with permission of [102]. Copyright 2021, Elsevier; (D) Schematic illustration of the preparation of Preparation of PAHy/AgNPs nanofiber hydrogel mats. Reproduced with permission of [103]. Copyright 2024, Elsevier; (E) Antibacterial, anti-inflammatory, rapid hemostasis, and accelerated repair by multi-functional metal–organic frameworks fibrous scaffolds for diabetic wounds. Reproduced with permission of [104]. Copyright 2023, Elsevier; (F) Schematic diagram of bioactive electrospun nanoyarn-constructed textile dressing patches. Reproduced with permission of [105]. Copyright 2024, Elsevier; (G) Schematic diagram of the production and application of antibacterial and angiogenic wound dressings based on PHA fibrous scaffolds. Reproduced with permission of [106]. Copyright 2023, ACS; (H) Schematic illustration of DMOG@ZIF-8/Gelatin-PCL Electrospinning Dressing. Reproduced with permission of [107]. Copyright 2023, ACS; (I) Schematic illustration of novel bi-layered dressing patches constructed with radially-oriented nanofibrous pattern. Reproduced with permission of [108]. Copyright 2022, Elsevier.

rapid blood clotting and good wound healing in rat models (Fig. 4B). In addition to the use of coagulation materials or factors, the hemostatic effect can also be improved through the development of electrospinning technology. Chen et al. [102] employed continuous electrospinning to fabricate a three-layer nanofiber film, resulting in enhanced hemostatic properties compared to single-layer fibers (Fig. 4C). Briefly, ENMs can achieve hemostasis effectively through three main mechanisms. Firstly, the high viscosity and absorption rate of the fiber polymer can promote rapid platelet aggregation for hemostasis. Secondly, fibers can be loaded with hemostatic factors or drugs to directly facilitate hemostasis. Lastly, enhancing the structure of the fiber membrane, such as creating multi-layered membranes, can improve the overall hemostatic efficacy.

Chronic wounds or wounds that are challenging to heal often create a high-nutrient environment that attracts a significant amount of bacteria

Table 2
Summary of common ENMs materials and drugs.

Polymer 1	Polymer 2	Polymer 3	Drug	Effects	Ref
Polyvinylpyrrolidone (PVP)	Polyvinyl butyral (PVB)	poly(ε-caprolactone) (PCL)	Medical glues of N-octyl-2-cyanoacrylates (NOCA)	Hemostasis	[115]
Chitosan (CS)	Gelatin (Gel)	–	Epidermal growth factor (EGF), basic fibroblast growth factor (bFGF) and dopamine hydrochloride (DA)	Hemostasis, antibacterial, anti-inflammatory, absorption of fluid and re-epithelialization	[100]
PCL	Polyvinyl alcohol (PVA)	Quaternized chitosan	Collagen	Hemostasis and antibiosis	[116]
PVA	Gel	Poly (lactic-co-glycolic acid (PLGA)	Thrombin (TMB) and vancomycin (VCM)	Hemostasis and antibiosis	[101]
Gel	PCL	CS	Silver nitrate ($AgNO_3$)	Hemostasis and antibiosis	[102]
Poly(3-hydroxybutyrate-co-4-hydroxybutyrate) (P34HB)	–	–	Ciprofloxacin (CIP) and pro-angiogenic dimethyloxalylglycine (DMOG)	Antibiosis, angiogenesis and re-epithelialization	[106]
Gel	PCL	–	DMOG and ZIF-8	Antibiosis and Angiogenesis	[107]
Polyvinylidene fluoride (PVDF)	PCL	Gel	Ag NPs	Angiogenesis, antibiosis and re-epithelialization	[26]
Gelatin methacryloyl	–	–	Matrix metalloproteinase-9, stromal-cell-derived factor 1α (SDF1α) and diclofenac sodium (DS)	Anti-inflammatory and re-epithelialization	[117]
Poly (L-Lactic-co-caprolactone) (PLCL)	Gel	–	Epigallocatechin-3-O-gallate (EGCG)	Hemostasis, antibiosis and antioxidant	[109]
Methacrylated gelatin (MeGel)	poly (L-lactic acid) (PLLA)	–	Salvia miltiorrhiza Bunge-Radix Puerariae herbal compound (SRHC)	Hemostasis, angiogenesis, antibiosis and anti-inflammatory	[108]
PVA	CS	–	Mupirocin (MP) and cerium oxide nanoparticles (CeNPs)	Antibiosis and antioxidant	[118]
PVP	PCL	–	Taxifolin (TAX) and cyclodextrin metal–organic frameworks (CD-MOFs)	Angiogenesis, antibiosis, anti-inflammatory and re-epithelialization	[104]
PLLA	PCL	–	Ciprofloxacin (CIF)	Antibiosis	[119]
PCL	Gel	–	Zeolitic imidazolate framework-8 (ZIF-8)-derived nanocarbon	Antibiosis, anti-inflammatory and re-epithelialization	[120]
Bagasse pulp cellulose fibre (CF)	Polyethyleneimine (PEI)	–	Indocyanine green (ICG), pluronic®F-127 (F-127), Gallic acid (GA), Fe_3O_4 magnetic nanoparticles and mitomycin C (MMC)	Antibiosis	[113]
Polysuccinimide (PSI)	Polyasparthydrazide (PAHy)	–	Ag NPs	Antibiosis, re-epithelialization and collagen deposition	[103]
Gel	PLLA	–	SRHC	Anti-inflammatory and re-epithelialization	[108]

colonization [109,110]. Additionally, these wounds commonly experience persistent inflammation and blood circulation issues, hindering the transition from the inflammatory stage to the proliferation and remodeling stages of wound healing [28,111]. Recently, numerous ENMs have been designed to tackle these challenges and enhance the process of wound healing.

According to different antibacterial principles, antibacterial dressings can be primarily categorized into three groups. The first category involves dressings without additional antibacterial agents, often made using materials like chitosan for minimal side effects [112]. The second category utilizes nanofibers to load antibacterial drugs or metal particles for sterilization. Zhang et al. [103] developed a wound dressing composed of polyasparthydrazide nanofiber hydrogel with in situ incorporation of nano-silver, resulting in improved mechanical strength and potent antibacterial activity (Fig. 4D). Similarly, Wang et al. [104] incorporated cyclodextrin metal-organic frameworks (MOFs) into nanofibers, resulting in a gradual release of metal particles that targeted the bacterial surface, leading to bacterial rupture and a bactericidal effect. The third category involves grafting or loading antibacterial substances onto fiber membranes, releasing drugs as needed based on external stimuli like near-infrared or microwave stimulation (Fig. 4E). Dong et al. [113] designed a magnetic three-dimensional nanonetwork wound dressing equipped with a temperature switch, a near-infrared switch, and a magnetic switch for controlled drug release, effectively combating infections.

Angiogenesis is a critical determinant of all wound-healing processes and outcomes [114]. Li et al. [105] developed a novel woven fabric dressing patch by modifying fiber microstructure and incorporating natural herbs. This dressing promotes wound healing by enhancing collagen deposition, improving re-epithelialization and angiogenesis, and stimulating hair follicle growth (Fig. 4F). Li et al. [106] achieved successful preparation of poly(3-hydroxybutyric acid--co-4-hydroxybutyric acid) (P34HB) fiber wound dressings through electrospinning, incorporating the angiogenic drug dimethylglycine (DMOG). The application of this dressing was found to enhance wound healing and stimulate vascular regeneration (Fig. 4G). Yin et al. [107] encapsulated DMOG in ZIF-8 and incorporated it into fibers. Upon degradation of the fibers, the ZIF-8 nanoparticles disintegrate, releasing angiogenic DMOG molecules. This sequential process is designed to match the specific stage of wound healing, ensuring precise bioavailability and sustained release of the active compounds to promote the development of new blood vessels at the wound site (Fig. 4H). Wu et al. [108] developed a series of double-layer dressing patches, with a lower radially arranged nanofiber layer to guide dermal fibroblast arrangement and enhance proliferation. The upper hydrogel layer provides good water absorption and hemostatic properties. Additionally, two different concentrations of Salvia miltiorrhiza Bunge-Radix Puerariae herbal (SRHC) were incorporated into the raw hydrogel layer to further boost the biological functionality of the double-layer dressing (Fig. 4I). In short, to promote angiogenesis and epithelialization at the wound site, two main methods are utilized. The first method involves promoting angiogenesis or epithelialization through the use of drugs. The second method involves guiding the proliferation of epithelial cells or fibroblasts by adjusting the fiber structure, such as the radial structure.

It can be concluded that ENMs can enhance wound healing through four key mechanisms: leveraging specific polymers to facilitate healing, utilizing fiber-loaded drugs for healing promotion, altering fiber layer number or structure, and incorporating responsive substances into fibers for targeted drug delivery to aid wound healing. Table 2 presents some examples of materials utilized in promoting the preparation of ENMs.

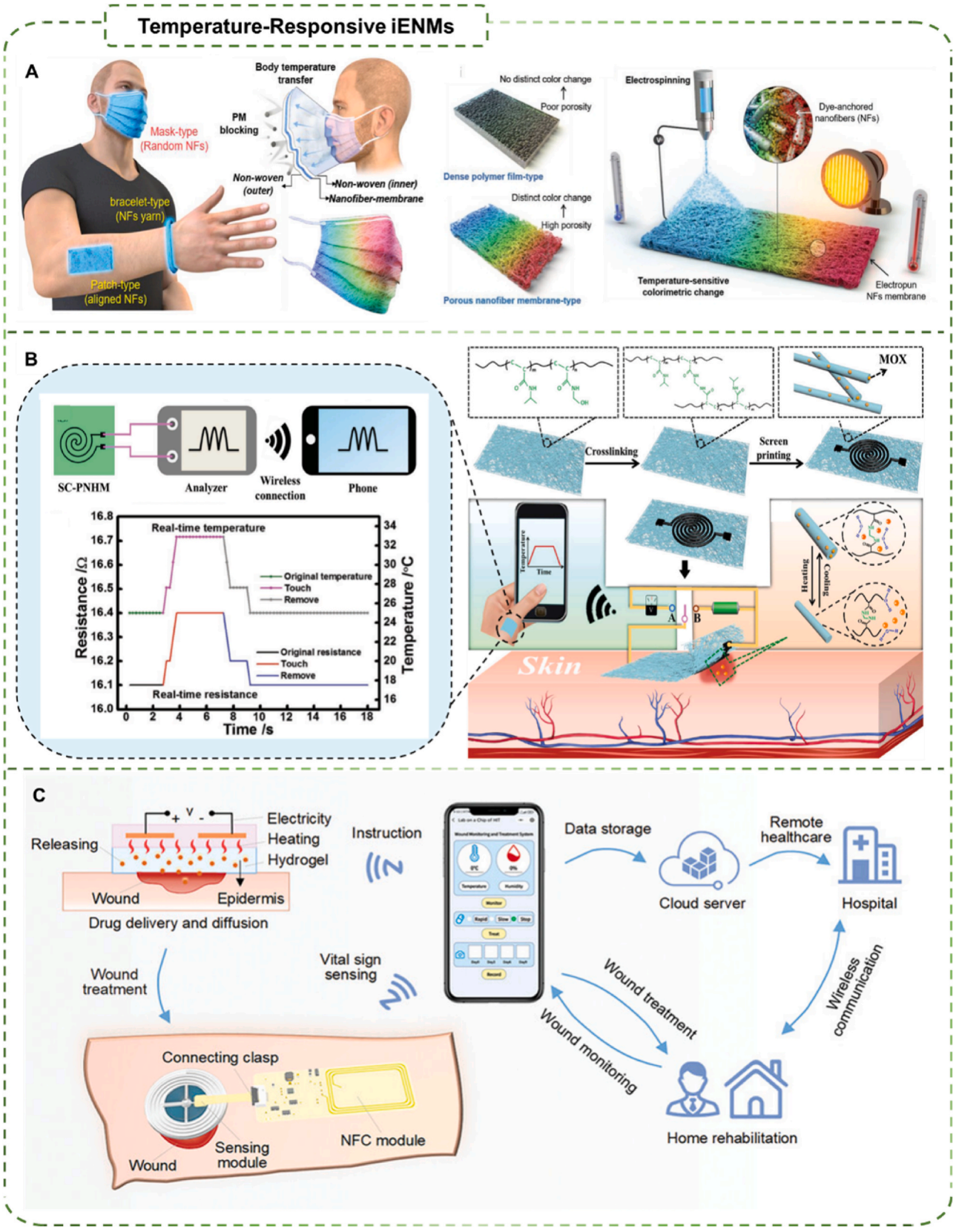

Fig. 5. Temperature-Responsive iENMs. (A) Flexible Breathable Nanomesh Electronic Devices for On-Demand Therapy. Reproduced with permission of [121]. Copyright 2022, Wiley; (B) The fabrication of flexible and breathable on-skin electronic devices featuring temperature-sensing capability and temperature-sensitive on-demand drug release. Reproduced with permission of [109]. Copyright 2019, Wiley; (C) A schematic of the design, structure, and operational overview of a multifunctional IWD for managing wound exudate and treating chronic wounds. Reproduced with permission of [51]. Copyright 2023, Wiley.

Table 3
Summary of representative iENMs stimuli-responsive materials.

Type of stimulus	Responsive material	Other polymers	Drug	Therapeutic outcomes	Ref
Temperature	GelMA	–	ASP, PDA	Promote cell proliferation	[122]
	NIPAAm	PNLA, PLLA	RFP	Anti-bacterial infection	[123]
	HMAAm, NIPAAm	–	MOX	Anti-bacterial infection	[109]
	Pluronic®F-127	CF, PEI	MMC	Anti-bacterial infection	[113]
	poly(N-isopropylacrylamide)	CF	DOX, ICG	Antibacterial, anti-tumor	[124]
	Nanodiamond	SF	–	Anti-bacterial infection	[125]
pH	Curcumin	PVA, PCL	TH	Antimicrobial, antioxidant	[126]
	Bromothymol blue	PVA, PAA	CIP	Anti-bacterial infection	[127]
	TA and Fe^{3+}	PCL	–	Anti-bacterial infection	[128]
	HPMCAS	–	Theophylline	Reduce the suffering of patients and the required frequency of drug administration	[129]
	3-diethylaminopropyl isothiocyanate material grafted glycol chitosan (GC-DEAP)	PCL, CS	CIP	Anti-bacterial infection	[130]
	Eudragit L100–55	PCL	DOX	Anti-bacterial infection	[131]
	Eudragit S-100	EC	GEN, DIC	Antimicrobial, antioxidant	[132]
ROS	Eu CPs	PAN	–	Antioxidant, vascularization	[133]
	Thiol hyaluronic acid (SH-HA) and disulfide-bonded hyperbranched Polyethylene glycol (HB-PBHE)	HA	Ag NPs, CUR	Anti-bacterial infection, vascularization	[134]
	MSPA	CMCS	APS, NBT, GSH, MV	Reduce wound infection, relieve oxidative stress, promote collagen deposition and angiogenesis in infected wounds	[135]
	ROS-degradable polyurethane (PFKU)	GelMA	DOXH	Collagen deposition, revascularization, re-epithelialization, downregulating ROS	[136]
NIR	Fe-doped phosphomolybdic acid (Fe-PMA)	PVA, CMC	–	Anti-bacterial infection, tissue repair and regeneration	[137]
	Indocyanine green	CF, poly(N-isopropylacrylamide)	DOX	Antibacterial, anti-tumor	[124]
	Lauric acid (LA)	PCL, PDA	Ibuprofen (IBU)	Antibacterial, anti-inflammatory, drainage wound fluid	[138]
	zeolitic imidazolate framework-8 (ZIF-8)-derived nanocarbon	PCL, Gel	CIP, PAA	Anti-bacterial infection	[120]
	A eutectic mixture of fatty acids	Alginate	RFP	Anti-bacterial, anti-inflammatory, angiogenesis, collagen deposition	[139]
Magnetic	Fe_3O_4	Cellulose	–	Anti-bacterial	[113]
	Superparamagnetic iron oxide nanoparticles (SPIONs), Fe_3O_4 and γ-Fe_2O_3 MNPs	N-hydroxymethylacrylamide	DOX	Anti-bacterial	[140]

Although ENMs have been widely used for wound dressings in recent decades, most of the ENMs currently on the market are only used to deliver drugs to promote wound healing. These dressings are based on (semi-)blind assessment methods that often do not allow real-time observation of the healing process and therefore impair treatment effect. Modern wound dressings should also include real-time monitoring and diagnostic functions to assess the wound progress during the healing process. Therefore, the development of intelligent dressings that integrate diagnosis and treatment will be the trend of the time.

4. Intelligent electrospinning wound dressing

The current trend in wound management involves the advancement of iENMs, which utilize a variety of smart micro/nanofibers including stimuli-responsive, shape memory, and conductive fibers [24]. These cutting-edge fibers are being more frequently employed in a range of biomedical applications. Currently, the methods for producing iENMs for wound treatment primarily consist of 2D manufacturing technology and 3D manufacturing technology [15]. The following chapter focuses on the common classification of iENMs, current research progress, and provides an introduction and comparison between 2D and 3D manufacturing techniques.

4.1. Stimuli-responsive iENMs

4.1.1. Temperature-responsive iENMs

Temperature-responsive systems are extensively utilized in smart materials due to the ease of temperature control and the abundance of heat resources. Temperature-sensitive polymers, characterized by their ability to shift with temperature, typically undergo a phase transition of polymer chains above the lower critical solution temperature (LCST) or below the upper critical solution temperature (UCST). For example, Kim's team integrated a thermochromic dye $(C_3H_6N_6{\cdot}CH_2O)_x$ into fibers, enabling the membrane to accurately monitor real-time local skin temperature [121] (Fig. 5A). Gong et al. [109] used thermoresponsive poly(N-isopropyl acrylamide-co-N-Methylol acrylamide) (C-PNHM) as a sensor to create temperature-responsive intelligent electronic nanomaterials (iENMs) for monitoring temperature at wound sites and delivering medication as needed for healing (Fig. 5B). Ge et al. [51] employed commercial sensors (SHT21, Sensirion, Switzerland) along with external integrated circuits to transmit data to smartphones, allowing precise monitoring of temperature and humidity levels on the skin (Fig. 5C). In addition, the most common temperature-responsive materials in recent years are listed in Table 3.

4.1.2. pH-responsive iENMs

pH-responsive polymers are polyelectrolytes with acidic or basic groups that can either accept or donate protons when the pH changes. Yang et al. [141] utilized the stability and high ionic strength of precious metal silver ions in acidic media to load them into fiber films, creating a relatively sensitive pH sensor through surface-enhanced Raman technology. Zhang et al. [142] incorporated pH chromogenic agents such as purple cabbage and phenol red into nanofibers to estimate the pH of wound sites (Fig. 6A). In a similar study, Li et al. [143] utilized various colors of curcumin in different pH solutions to load curcumin into fibers for local pH monitoring (Fig. 6B). Additionally, Zhang et al. [144] introduced glucose oxidase/carbon dot@Copper metal-organic framework into fibers to induce local fluorescence via a catalytic reaction, and

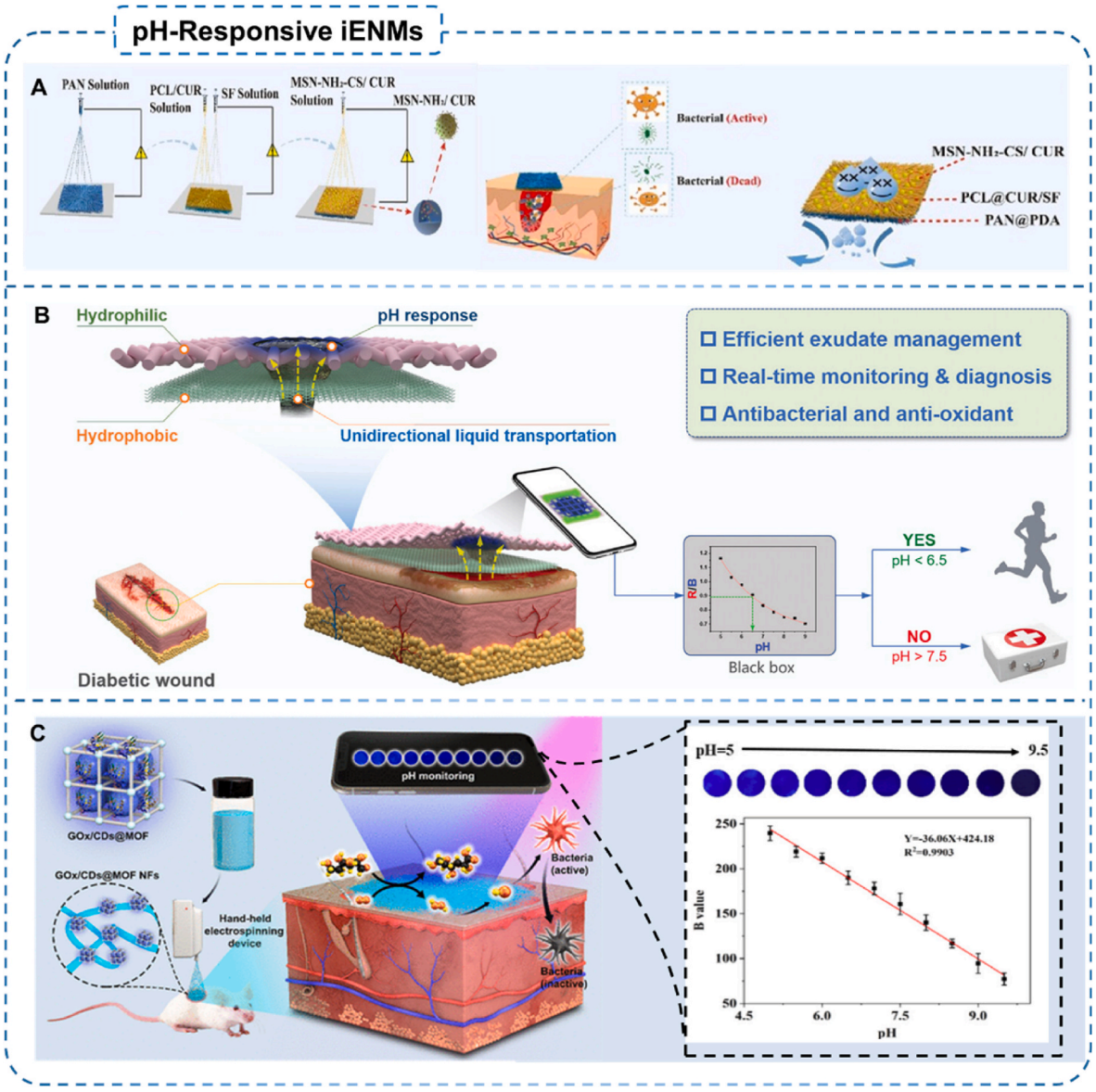

Fig. 6. pH-Responsive iENMs. (A) Preparation technology of composite film; Antibacterial schematic diagram; Structure and unidirectional liquid delivery. Reproduced with permission of [143]. Copyright 2023, Elsevier; (B) Schematic illustration of the Janus wound dressing based on cellulose nonwovens for diabetic wound healing and monitoring. Reproduced with permission of [145]. Copyright 2023, Wiley. (C) Schematic diagram of GOx/CDs@MOF NF dressing for visual monitoring and antibacterial treatment of diabetic-infected wounds. Reproduced with permission of [144]. Copyright 2023, ACS.

established a connection with smartphones for digital intelligent wound management (Fig. 6C). In addition, the most common pH-responsive materials in recent years are listed in Table 3.

4.1.3. ROS-responsive iENMs

Reactive oxygen species (ROS) like hydrogen peroxide (H_2O_2), hydroxyl radical (•OH), superoxide anion radical ($•O^{2-}$), and singlet oxygen ($_1O^2$) are instrumental in bacterial destruction and immune response, crucial for tissue regeneration [146]. However, an overabundance of ROS can lead to oxidative stress, hindering the healing process [147]. To address this issue, various ROS-sensitive materials with responsive components such as sulfide, selenium, tellurium, Europium, thioketal, and aryl borate bonds have been developed to detect and neutralize excess ROS. For example, Wu et al. [133] incorporated Eu CPs into the fibers to eliminate ROS at the wound site, causing the fibers to change color for local monitoring purposes. Likewise, Li et al. [148] embedded Prussian blue nanocrystals into the fibers to eliminate ROS and simultaneously monitor variations in local ROS levels. In addition, the most common ROS-responsive materials in recent years are listed in Table 3.

4.1.4. NIR- responsive iENMs

Near-infrared (NIR) light has been widely used in the biomedical field due to its unique advantages, such as remote control capability, deep tissue penetration, and minimal invasiveness [149]. Various NIR-responsive photothermal polymers like polydopamine [150], polypyrrole (PPy) [151], have been utilized to create intelligent light-responsive fibers. Additionally, a variety of photosensitizers including Au nanorods/nanocages [152], indocyanine green (ICG) [153], rGO [95], and Fe_3O_4 particles [154] have been integrated into fibers through blend spinning or postprocessing methods. Leveraging the photothermal effects of these NIR-sensitive agents, the resulting fibers have achieved diverse functionalities, such as antibacterial properties, photodynamic therapy (PDT), and responsive drug delivery. In addition, the most common NIR- Responsive materials in recent years are listed in Table 3.

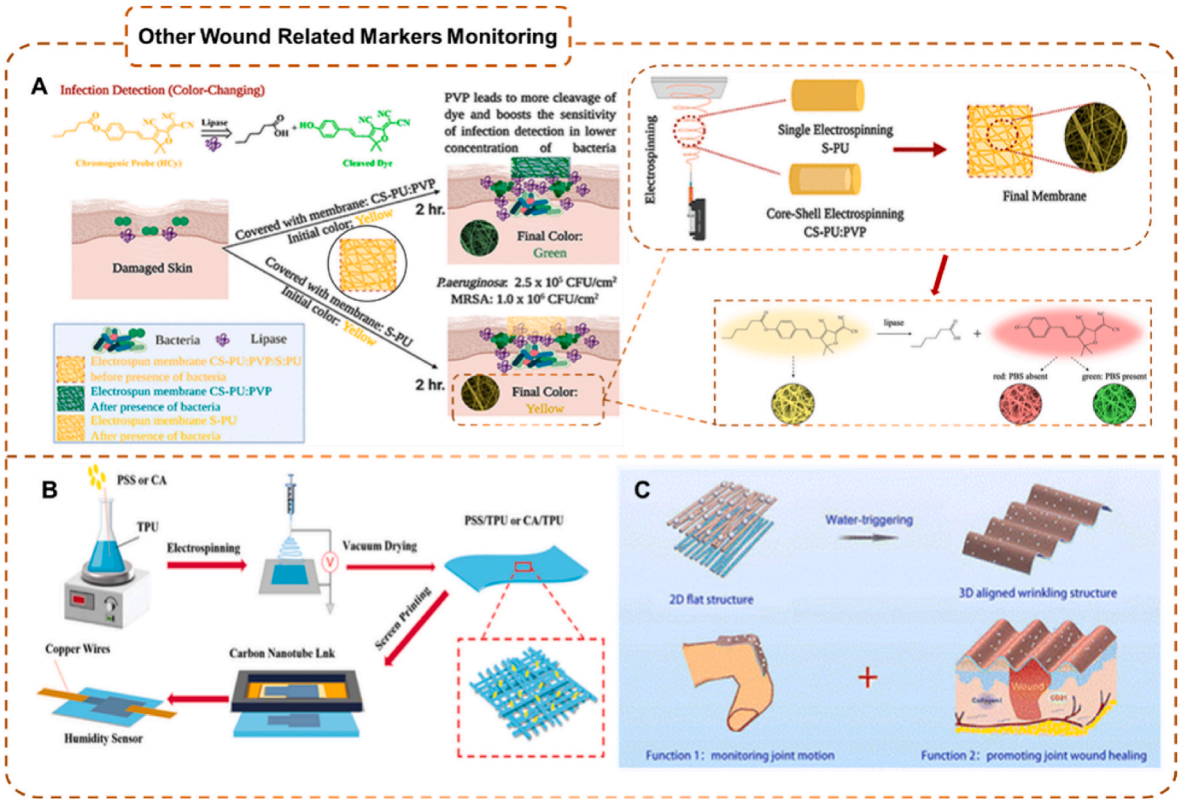

Fig. 7. iENMs for Monitoring of other Wound Related Markers in Wound Healing. (A) Synthetic Scheme for the Nanofibrous and chromogenic response of membranes to *P. aeruginosa* (ATCC 27853) and MRSA (ATCC 33592) after 2 h incubation with bacterial lawns at various concentrations. Reproduced with permission of [158]. Copyright 2020, ACS; (B) Preparation process of bifunctional humidity-pressure sensor. Reproduced with permission of [30]. Copyright 2022, Wiley; (C) Schematic illustration of the fabrication of Janus conductive nanofibrous membrane, formation of bioinspired aligned wrinkles, and dual functions of the bioinspired dressing. Reproduced with permission of [159]. Copyright 2022, Wiley.

4.1.5. *Magnetic-responsive iENMs*

Magnetic-responsive fibers incorporating magnetic nanoparticles (MNPs) have become a focus in modern medicine. Commonly used MNPs include iron, cobalt, nickel, and their oxides. These fibers show promise in hyperthermia therapy and smart drug delivery systems due to their favorable magnetothermal effect under alternating magnetic fields [155]. Kim et al. [140] developed smart hyperthermia nanofibers using a temperature-sensitive copolymer of NIPAm and N-hydroxymethylacrylamide, Fe_3O_4 and γ-Fe_2O_3 MNPs, and doxorubicin (DOX) for controlled drug delivery under alternating magnetic fields. These fibers, containing 31 wt% MNPs, exhibited efficient heat generation leading to a temperature rise of 44 °C in 600 s, facilitating drug release triggered by temperature-induced swelling. Moreover, magnetic-responsive fibers are commonly employed to fabricate structured scaffolds that offer topographical cues for guiding cell behavior. Superparamagnetic iron oxide nanoparticles (SPIONs) have become popular in biomedical applications due to their exceptional magnetic properties and biocompatibility. In addition, the most common magnetic-Responsive materials in recent years are listed in Table 3.

4.1.6. *iENMs for monitoring of other wound related markers*

Apart from measurable physical parameters like temperature and pH value, the healing process is also influenced by changes in the microenvironment at the wound site and certain chemical reactions [156,157]. These factors can serve as markers to monitor and control the healing process in real time. For instance, local bacterial infection at the wound site can be considered as one such marker. Dramatically, while all wounds have some level of bacterial contamination, it may not necessarily impede healing. However, when the bacterial load exceeds a critical level, it triggers an inflammatory response and can potentially damage tissues of host, hindering the wound healing process. Bacterial reactive discoloration wound dressings offer a valuable platform for continuously monitoring the wound bed and aiding in the early detection of bacterial infections. Currie et al. [158] introduced a highly sensitive electrospun core-shell nanofiber dressing by incorporating dye probes onto the surface of PVP fibers. The hydrolyzability of PVP allows for the precise monitoring of bacteria by the fibers, making it an optimal system for prompt on-site detection of wound infections (see Fig. 7A).

Moreover, it has been shown that wet wound environments promote wound healing more than dry wound environments, but high humidity can hinder wound healing [17,160,161]. Therefore, it is of great importance to detect and control the humidity of the wound site. Ding et al. [30] utilized citric acid (CA) and sodium polystyrene sulfonate (PSS) as humidity sensitive materials to develop thermoplastic polyurethane (TPU) nanofiber films that are sensitive to water. The CA/TPU wet pressure sensor exhibits excellent permeability, high sensitivity, low hysteresis, and fast humidity response (Fig. 7B), providing a novel breathable sensing platform for monitoring and intelligent wound dressings.

Given that wounds can occur in different areas of the human body, it is important for wound dressings to be adaptable and customizable to suit the specific treatment requirements. Joint skin wounds present unique challenges in treatment due to their frequent and vigorous movement. As a result, there is a critical need for dressings that can both monitor real-time joint movement and promote the healing process of these wounds. In their study, Zhou et al. [159] combined electrospinning technology with a water-induced self-assembly method to develop bionic conductive fillers with aligned folds, achieving the desired dual functions. The bionic dressing, with its high electrical conductivity and unique arrangement of folds, enables accurate tracking

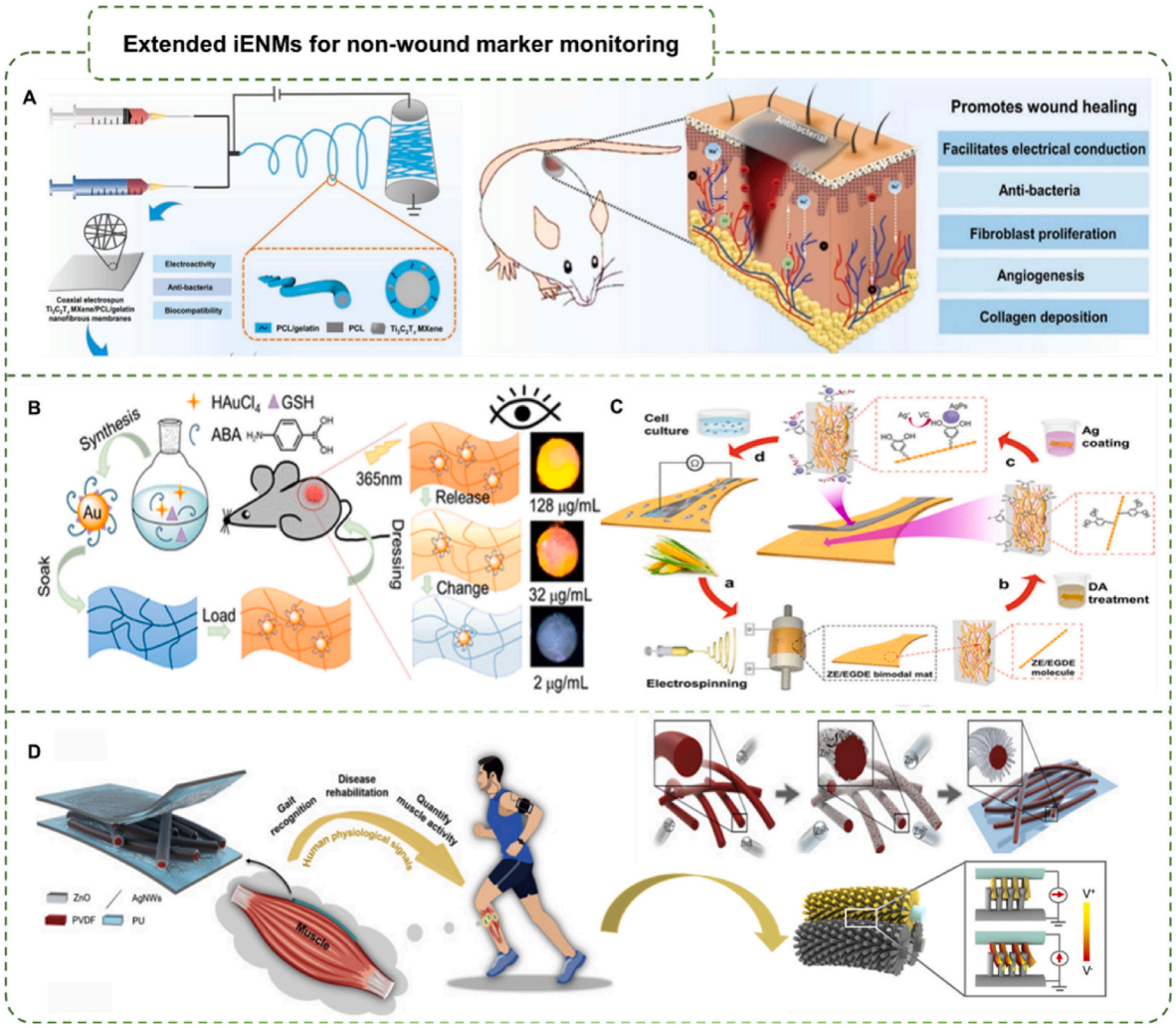

Fig. 8. Extended iENMs for non-wound marker monitoring. (A) Preparation diagram of $Ti_3C_2T_x$ MXene/poly (ε-caprolactone)/gelatin coaxial electrospinning nanofibers membranes. Reproduced with permission of [27]. Copyright 2023, Springer; (B) Schematic illustration of the BC scaffold loaded with A-GNCs as antibacterial wound dressing to address the issue of MDR-infected skin wounds. Reproduced with permission of [162]. Copyright 2021, ACS; (C) Schematic illustration of the preparation process of intelligent scaffolds. Reproduced with permission of [163]. Copyright 2023, ACS; (D) The schematic diagram of the three-dimensional hierarchically interlocked PVDF/ZnO fibers-based PME for muscle behavior monitoring. Reproduced with permission of [164]. Copyright 2020, Elsevier.

of various joint movements (Fig. 7C). Notably, the dressing was able to precisely track a range of mouse neck motion patterns, including left/-right and up/down movements. In vivo wound healing results demonstrated that the bionic dressings, by promoting collagen deposition, hair follicle regeneration, and epithelialization, can expedite the healing process of active wounds in the neck of mice. This integration of real-time motion monitoring and wound repair functions in the bionic dressing opens up new possibilities for improved management of joint wounds. This stimuli-responsive iENMs can monitor changes in the wound site's microenvironment and chemical reactions, offering a novel approach for early diagnosis and care of clinical wounds.

Currently, there has been an emergence of new intelligent electrospinning dressings in addition to the monitoring of wound related markers. Xu et al. [27] utilized dressings to monitor and adjust the internal electric field for promoting skin wound healing (Fig. 8A). Wang et al. [162] proposed a novel method to directly monitor the residual amount of dressing change by colorimetry, aiming to accurately determine the appropriate time for dressing change thereby minimizing secondary damage (Fig. 8B). Liu et al. [163] prepared a dressing that can directly monitor the deformation of the skin wound, allowing for better assessment of the wound condition (Fig. 8C). In clinical treatment, external physical stimulation has been found to improve the wound microenvironment and promote wound healing. One promising approach is the use of wearable friction nanogenerators (TENGs), which generate an electric field locally in the wound area to facilitate wound healing. In the research conducted by Yang and colleagues [164], ZnO nanorods were grown epitaxially on the surface of electrospun PVDF nanofibers to create a three-dimensional interlocked PVDF/ZnO nanofiber piezoelectric sensor layer. This innovative approach allows for precise detection of intricate physiological signals like breathing, wrist pulse, and muscle behavior. Furthermore, this material shows promise for monitoring wound pressure at targeted locations, as illustrated in Fig. 8D.

4.2. Shape memory iENMs

Shape memory fibers, a subset of responsive fibers capable of transitioning from temporary shape to original shape under various stimuli, have emerged as promising candidates in biomedical applications [24]. The most commonly used shape memory fibers are thermally induced [165,166]. The shape memory effects typically involve two phases: the switch phase responsible for fixing the temporary shape, and the fixed phase determining the original shape. Samples are initially treated above the transition temperature (Ttrans) to achieve the desired

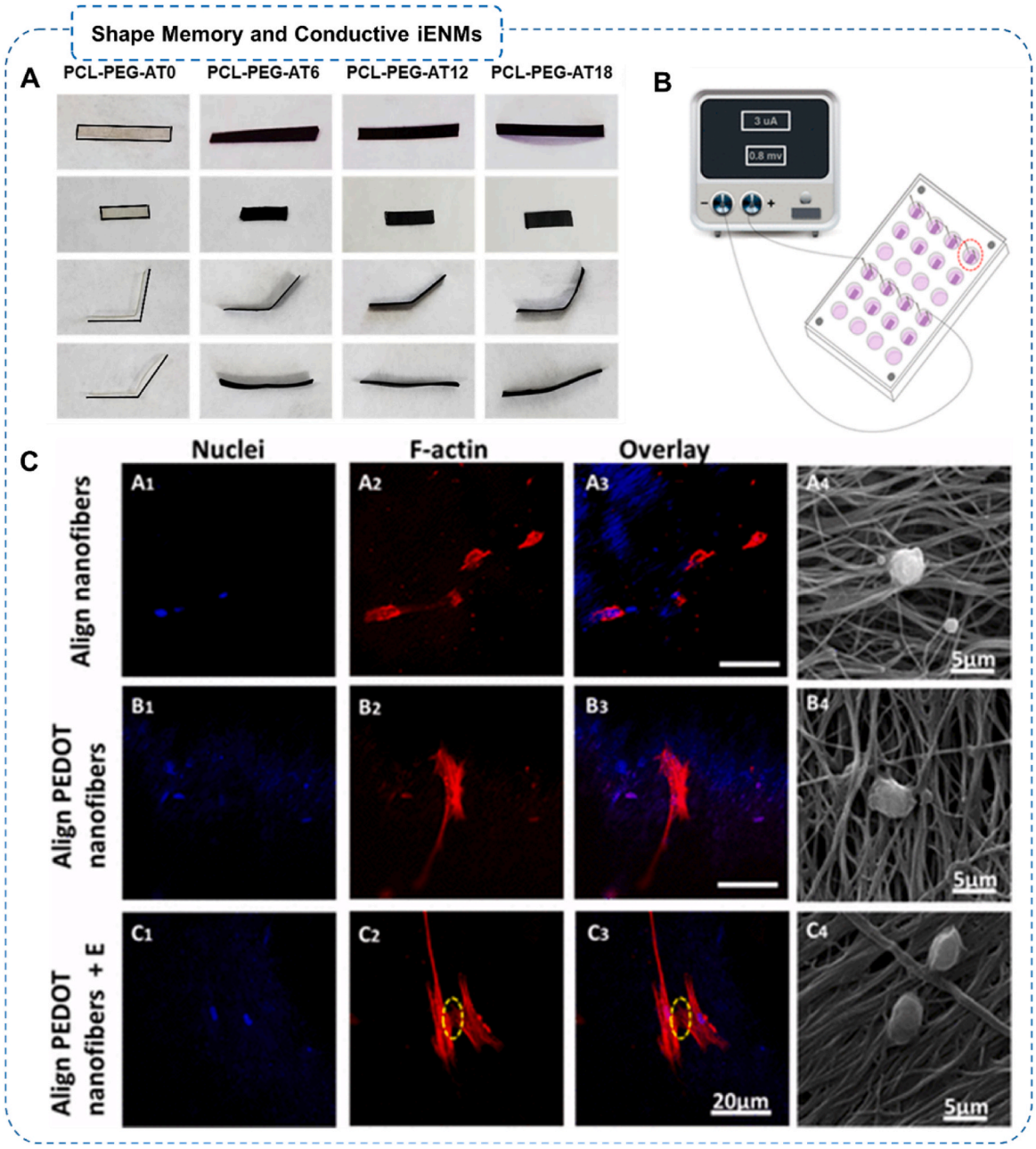

Fig. 9. Shape memory and conductive iENMs. (A) The folding shape memory behavior of PCL-PEG-AT films. Reproduced with permission of [168]. Copyright 2019, Elsevier; (B) Schematic illustration of cell cultures on the 2D-ACNFs with electrical stimulation environment. Reproduced with permission of [169]. Copyright 2021, ACS; (C) (A1–3–C1–3) Fluorescence and (A4–C4) SEM images of hMSCs cultured on 2D aligned nanofibers before and after coating conductive polymer after 7 days cultured with/without electrical stimulation. Reproduced with permission of [169]. Copyright 2021, ACS.

temporary shape under external force, then cooled below the Ttrans in a programming cycle. Upon reheating above the Ttrans, the polymer chains release entropic energy and return to their initial state [167]. Notably, the shape memory effects of fibers have been designed to mimic the dynamic microenvironment that regulates cell behavior. Li et al. [168]combined the mechanical properties of polycaprolactone (PCL) segment, the wettability of polyethylene glycol (PEG) segment, and the electrical activity of aniline trimer (AT) segment to design and synthesize a series of electroactive shape memory polyurethane-urea elastomers (Fig. 9A). These elastomers have antibacterial, antioxidant, and electroactive properties, making them suitable for skin wound healing applications. The films exhibit appropriate hydrophilicity and swelling rate, outstanding mechanical and shape memory characteristics, electrical activity, free radical scavenging ability, non-adhesion properties, and biocompatibility. In the future, shape memory nanofibers could potentially be used to mechanically contract wounds for faster closure, a concept that has garnered considerable attention.

4.3. Conductive iENMs

Conductive fibers incorporating conductive polymers and inorganic materials have been widely used in tissue repair for nerve, skin, and bone regeneration [170]. These fibers are designed to provide electrical stimulation to cells and tissues either through external electrical stimulation or by coupling with endogenous electric fields. Various types of conductive polymers, such as PPy [171], polyaniline (PANI) [172], and poly(3,4-ethylenedioxythiophene) (PEDOT) [173], have been commonly used in the fabrication of conductive fibers through blend

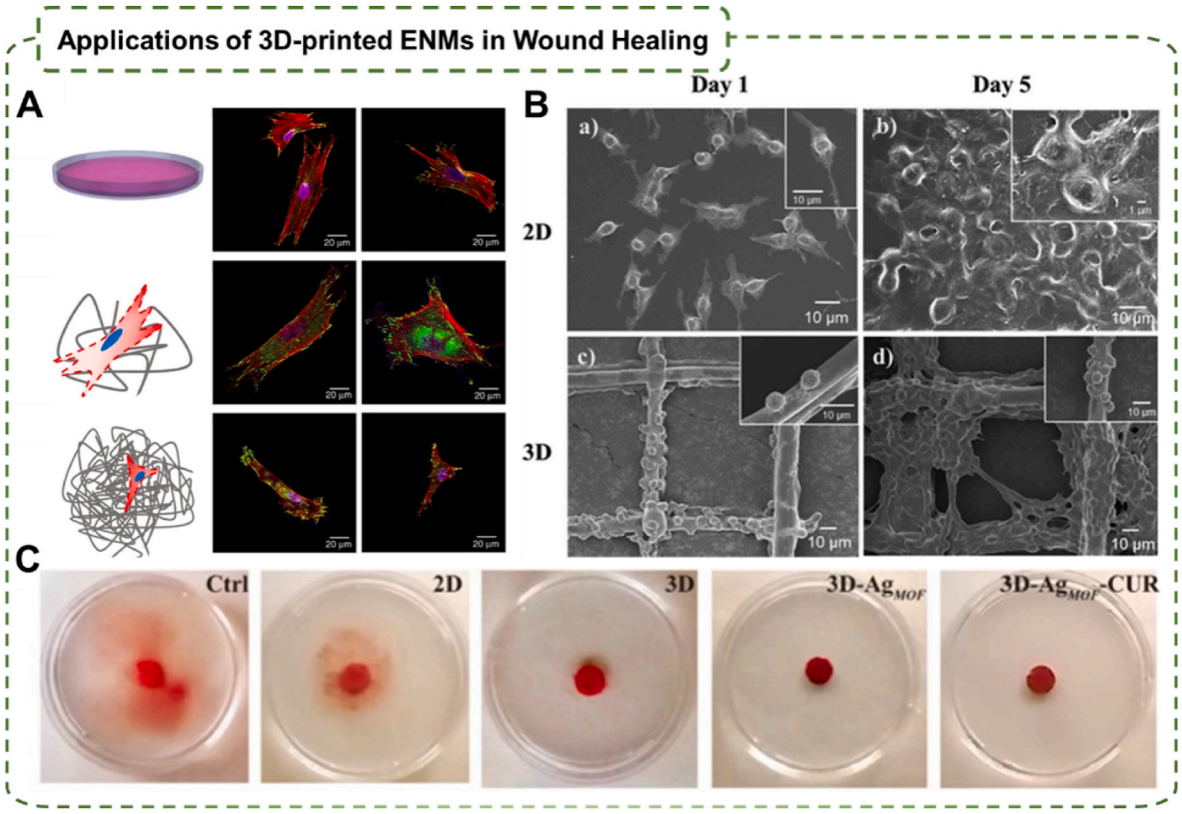

Fig. 10. Applications of 3D-printed ENMs in Wound Healing. (A) Cell morphology of representative neonatal human dermal fibroblasts (NHDFs) for each mesh. Reproduced with permission of [183]. Copyright 2019, Springer; (B) SEM images of RAW 264.7 cells on 2D plate after day 1 (a) and day 5 culture (b); and on 3D PCL scaffolds after day 1 (c) and day 5 culture (d). Reproduced with permission of [184]. Copyright 2021, ACS; (C) The images of the blood-clotting. Reproduced with permission of [185]. Copyright 2022, Elsevier.

spinning with non-conductive polymers or post-processing surface modification. For example, Jin et al. [169] developed a poly-L-lactic acid (PLLA) aligned nanofibrous membrane functionalized with conductive PEDOT through self-polymerization. The impact of electrical stimulation on human mesenchymal cell behavior was assessed by applying external pulsed electrical potential, revealing the effectiveness of electrical stimulation and aligned fiber topography in enhancing cell proliferation (Fig. 9B and C). Additionally, inorganic conductive materials like carbon nanotubes (CNTs) [174], graphene [175], and metal-based materials such as Au [176], copper [177], and zinc oxide (ZnO) [156] have been utilized in the creation of electroactive fibers. Electrochemical fibrous sensors offer a promising avenue for real-time healthcare monitoring.

4.4. Applications of 3D-printed ENMs in wound healing

Traditional ENMs are typically 2D and prioritize enhancing cell adhesion over supporting tissue formation. To enhance wound healing, it is crucial to integrate 3D printing and electrospinning technologies. This section provides an in-depth analysis of the current status of 3D ENMs and highlights their individual advantages.

Wound healing is a complex process that can be influenced by various external and internal factors, such as bacterial infection and inflammation. These factors can impede the normal healing process, leading to delays or complications [178]. To address this, wound dressings, scaffolds, and skin substitutes need to be designed with specific functions to support the healing process. Recent research has identified four key therapeutic strategies that have shown effectiveness in promoting wound healing: antibacterial treatments, regulation of inflammation, promotion of cell migration and proliferation, and cell therapy [48,179,180]. These strategies have become integral features of many skin repair materials. Studies on wound dressings have primarily focused on how they interact with vascular endothelial cells, fibroblasts, and macrophages [181]. Cells grown on three-dimensional scaffolds exhibit different adhesion morphology, synthesis, and secretion compared to those grown in a traditional two-dimensional environment [15,182]. This highlights the importance of using three-dimensional scaffolds for cell culture, as they better mimic the natural growth conditions of cells in vivo. The unique three-dimensional structure of these scaffolds has been shown to play a crucial role in skin wound repair and regeneration.

Researches have shown that fibroblasts and macrophages display distinct cellular behaviors in 3D environments of 3DP-ESF scaffold cultures compared to 2D environments. In a study utilizing PCL scaffolds prepared using EHDP technology, different orientations of the scaffolds had varying effects on the behavior of neonatal human dermal fibroblasts (NHDFs) [183]. The adhesion behaviors of fibroblasts on these scaffolds differed, with some adhering orthogonally, elongating along a single fiber, or spreading at fiber intersections (Fig. 10A). The extent of cell spreading depended on the number of fibers at these intersections. In contrast to the orthogonal model, the 45° diagonal model created smaller triangular pores within square pores, enabling cell movement between fibers. Immunofluorescence staining images further supported these findings, showing fibroblasts expressing minimal adhesive spot protein at fiber sites and moving between fibers in a 'bridging' manner.

Another study demonstrated an intriguing phenomenon regarding the impact of PCL scaffolds on cell behavior. Mouse mononuclear macrophages (RAW264.7) were cultured in PCL scaffolds with a pore size of 100 μm and a fiber diameter of 10 μm, and their responses in 2D and 3D culture settings were compared [184]. The results revealed that RAW264.7 cells exhibited distinct adhesion behaviors when on the scaffold compared to when on a Petri dish (Fig. 10B). Specifically, cells

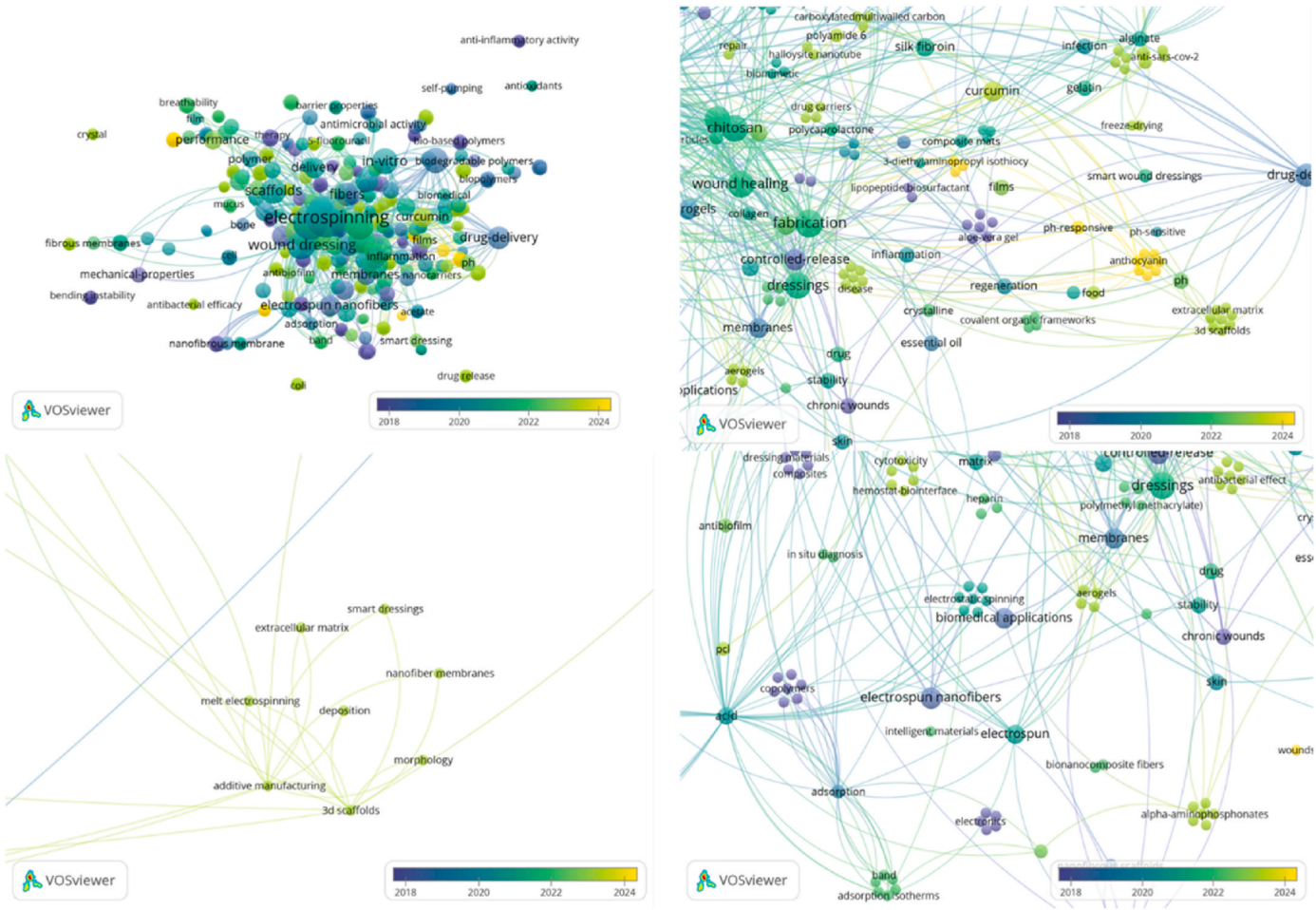

Fig. 11. Cocluster analysis of keywords in literatures on iENMs from 2010 to 2024.

in the scaffold displayed a more spherical shape rather than spreading across the surface. Moreover, they initially adhered to the fibers and then gradually infiltrated the pores with increasing cell numbers, leading to a denser cell accumulation. Notably, gene expression and secretion of pro-inflammatory factors were significantly higher in the 3D culture group compared to the 2D group. This difference may be attributed to the spherical shape of cells in the 3D group, which potentially exposes them to more receptors, rendering them more sensitive to lipopolysaccharide (LPS) stimulation.

Lastly, Xia and Yang collaborated to create a PCL/GEL 2D nanofiber film using electrospinning [185]. They then transformed this 2D nanofiber film into a 3D nanofiber sponge using gas foaming technology, and subsequently grew Ag-MOFs on the 3D nanofiber sponge in-situ. This process resulted in the formation of 3D-AgMOF. Finally, curcumin (CUR) was loaded into the 3D-AgMOF to produce 3D-AgMOF-CUR. The 3D nanofiber structure significantly improved the hemostatic capabilities of the wound dressing (Fig. 10C).

In short, 3D iENMs offer advantages beyond those of 2D iENMs, including improved histocompatibility and non-toxicity. They also demonstrate faster wound healing, enhanced biodegradability, and effective antibacterial properties to prevent infection. Additionally, they possess good moisturizing properties that promote cell and tissue regeneration, as well as sufficient mechanical strength to withstand repeated forces. The potential applications of 3D iENMs in wound healing and tissue regeneration are vast and promising.

5. Summary and perspectives

Wound dressings have evolved significantly over centuries, with researchers developing a variety of dressings tailored to different stages of wound healing. A new concept called ‘Intelligent wound dressings’ has emerged, featuring built-in sensors and smart materials for real-time monitoring and care. Various types of intelligent wound dressings have been documented in scientific literature. Data statistics and label co-clustering analysis were conducted on the documents using VOSviewer software, with results shown in Fig. 11.

The result shows that the current research in this field has identified two primary areas of focus: the versatility of iENMs and the controlled drug delivery at wound sites. To address these objectives, researchers are exploring modifications to fiber structures to leverage the programmable advantages of electrospinning. This has led to the development of various types of fiber dressings, such as braided, radial, and Janus fiber dressings, enhancing the biological properties of fiber membranes. Additionally, researchers are investigating the use of different polymers and therapeutic drugs with diverse properties to enable multiple therapeutic effects within a single drug delivery system. Techniques like blend, coaxial, and triaxial electrospinning methods are being employed to load different drugs onto various polymers, allowing for the multifunctionality of fiber membranes. In recent years, stimuli-responsive, biosecurity, and 3D printing have gained popularity in related fields. Stimulus-responsive dressings often undergo changes in cross-linking density or chemical properties, necessitating careful attention to safety. Many current iENMs are infused with nanoscale components like nanoparticles, which can enhance wound dressings

with healing properties, improved monitoring sensitivity, and controlled drug release. However, the release of nanoparticles from dressings into the circulatory system through the wound site poses a potential risk of blood clot formation. While significant advancements have been made in creating 3D electrospun structures, challenges persist in replicating the intricate anatomy and physiology of skin. Existing 3D wound-like skin dressings are still not as sophisticated as the complex and layered structure of natural skin. Looking ahead, the focus of iENMs development should prioritize enhancing biosafety, while also delving deeper into mechanism research to design 3D printed electrospun structures that closely mimic the skin's structure for more effective wound healing.

Despite the lack of change in clinical practice, recent advances in wound treatment and management have paved the way for the clinical translation of ENMs and intelligent engineered nanomaterials iENMs. In recent times, the use of in-situ electrospinning devices in clinical wound treatment has emerged due to commercialization. However, the safety of these devices requires ongoing evaluation. The clinical application of ENMs is expected to grow significantly in the coming decades, thanks to extensive research efforts over the years and increased interest from pharmaceutical companies in advanced ENMs and the commercialization of iENMs. Electrospun nanofibers have demonstrated their innovative potential, with ENMs and iENMs showing promise for advanced therapeutic applications in wound care. Further progress in this interdisciplinary field will unlock the therapeutic capabilities of ENMs and iENMs, leading to enhanced treatment outcomes.

CRediT authorship contribution statement

Zhi Qu: Writing – review & editing, Writing – original draft, Software. **Yang Wang:** Writing – review & editing, Writing – original draft. **Yanhong Dong:** Writing – review & editing. **Xinmeng Li:** Writing – review & editing. **Lingwan Hao:** Writing – review & editing. **Liwei Sun:** Writing – review & editing. **Lu Zhou:** Writing – review & editing. **Rujian Jiang:** Writing – review & editing, Writing – original draft. **Weihua Liu:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

Data availability

No data was used for the research described in the article.

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