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REVIEW

Polysaccharide Electrospun Nanofibers for Wound Healing Applications

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Abstract: As a type of biological macromolecule, natural polysaccharides have been widely used in wound healing due to their low toxicity, good biocompatibility, degradability and reproducibility. Electrospinning is a versatile and simple technique for producing continuous nanoscale fibers from a variety of natural and synthetic polymers. The application of electrospun nanofibers as wound dressings has made great progress and they are considered one of the most effective wound dressings. This paper reviews the preparation of polysaccharide nanofibers by electrospinning and their application prospects in the field of wound healing. A variety of polysaccharide nanofibers, including chitosan, starch, alginate, and hyaluronic acid are introduced. The preparation strategy of polysaccharide electrospun nanofibers and their functions in promoting wound healing are summarized. In addition, the future prospects and challenges for the preparation of polysaccharide nanofibers by electrospinning are also discussed.

Keywords: polysaccharide, electrospun nanofibers, wound healing, preparation strategy, function

Introduction

An important application of electrospun nanofibrous membranes in the biomedical field is wound dressing.[1,2] Electrospun nanofiber dressings exhibit high porosity, which allows proper oxygen, moisture, and nutrient exchange without causing wound dehydration and enables effective control of the moist microenvironment of the wound.[3,4] The small pore size of the nanofibers can effectively inhibit the penetration of microorganisms from the external environment, and the high specific surface area can efficiently release loaded drugs. Nanofibers can form similar natural external matrix structures, provide sites for cell adhesion and proliferation, and modulate cellular responses.[5] In addition, various active ingredients and drugs affecting wound healing, including antibiotics, growth factors, vitamins, herbal extracts and even cells have been loaded into nanofibers for controlled release to enhance the desired wound healing properties.[6–8]

At present, a wide range of materials can be used for electrospinning technology.[9] The most common and earliest applications of electrospinning technology use various polymers, including various synthetic polymers and natural polymers.[10,11] Synthetic polymers such as polylactic acid (PLA), polycaprolactone (PCL), polyvinyl alcohol (PVA), polyurethane (PU) and other materials have controllable mechanical strength and physical properties, and are easy to process.[12] Natural polymers have become a better choice for wound dressing materials prepared by electrospinning as synthetic polymers lack biological properties.[13,14] Polysaccharides from natural polymers are widely used as materials for electrospun wound dressings due to their low toxicity, good biocompatibility, degradability and reproducibility. Natural polysaccharides are biopolymers that widely exist in various organisms and are connected by monosaccharides through glycosidic bonds. Functional groups such as primary hydroxyl, secondary hydroxyl, amino and carboxyl groups on the macromolecules of natural polysaccharides show various chemical properties and strong chemical reactivity. Some of the molecular structures of polysaccharides such as chitosan, starch, alginate and hyaluronic acid are similar to glycosaminoglycans in the extracellular environment and thus have received extensive attention in the field of wound

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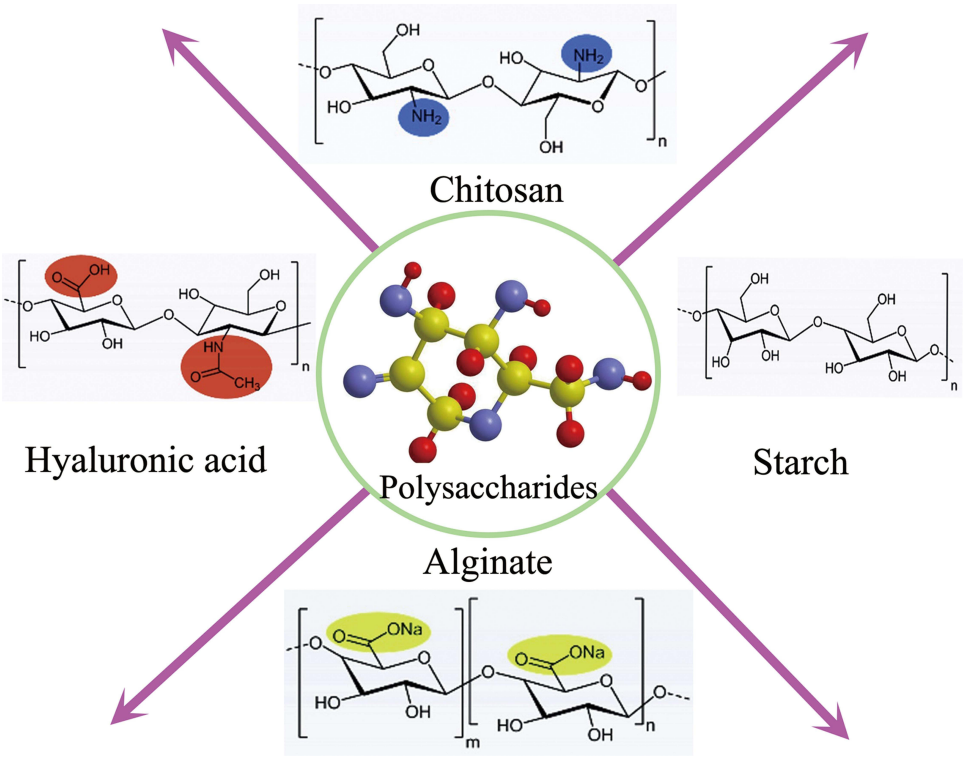

Figure 1 The chemical structure, bioactive groups, monosaccharide units and sites that can be used for biological modification of conventional polysaccharides (chitosan, starch, alginate and hyaluronic acid).
Notes: Reprinted from: Rahimi M, Noruzi EB, Sheykhsaran E, et al. Carbohydrate polymer-based silver nanocomposites: Recent progress in the antimicrobial wound dressings. *Carbohydr Polym*. 2020;231:115696. doi:10.1016/j.carbpol.2019.115696.[20] © 2019 Elsevier Ltd. All rights reserved. With permission from Elsevier.

therapy.[15,16] Figure 1 shows the chemical structure, bioactive groups, monosaccharide units and sites that can be used for biological modification of conventional polysaccharides (chitosan, starch, alginate and hyaluronic acid). A variety of polysaccharides can promote cell growth and proliferation, accelerate skin tissue regeneration and repair, and have good compatibility and biodegradability with body tissues.[17] Therefore, polysaccharides have natural advantages as electrospun wound dressing materials.[18,19]

This paper introduces a variety of polysaccharide electrospun nanofibers, including chitosan, starch, alginate and hyaluronic acid, and discusses their application prospects in the field of wound healing. The preparation strategy of polysaccharide electrospun nanofibers and their functions in promoting wound healing are summarized in Figure 2. In addition, the future prospects and challenges for the preparation of polysaccharide nanofibers by electrospinning are also discussed.

Electrospinning Technique

Electrospinning technology is a common method used to prepare continuous nanofibers and has the advantages of simple operation, low cost, wide raw material sources and controllable process parameters.[21] Electrospinning equipment mainly includes a solution propulsion device, a high voltage power supply and a collector.[22] The process and principle of preparing nanofibers by electrospinning are as follows: First, a high-voltage electric field is formed between the spinning nozzle and the collector using a high-voltage power supply. The surface of the spinning liquid droplet at the top of the spinning nozzle is subject to the electrostatic force of the external high-voltage electric field as well as its own surface tension.[23,24] The electrostatic force promotes the stretching and formation of fibers by the droplet, while the surface tension provides the resistance to the deformation of the droplet. When the applied electrostatic force is large enough to overcome the surface tension of the spinning solution, the droplets will be continuously stretched under the action of a high-voltage electric field to form nanofibers with extremely large specific surface areas.[25] The solvent in the spinning fluid between the spinning nozzle

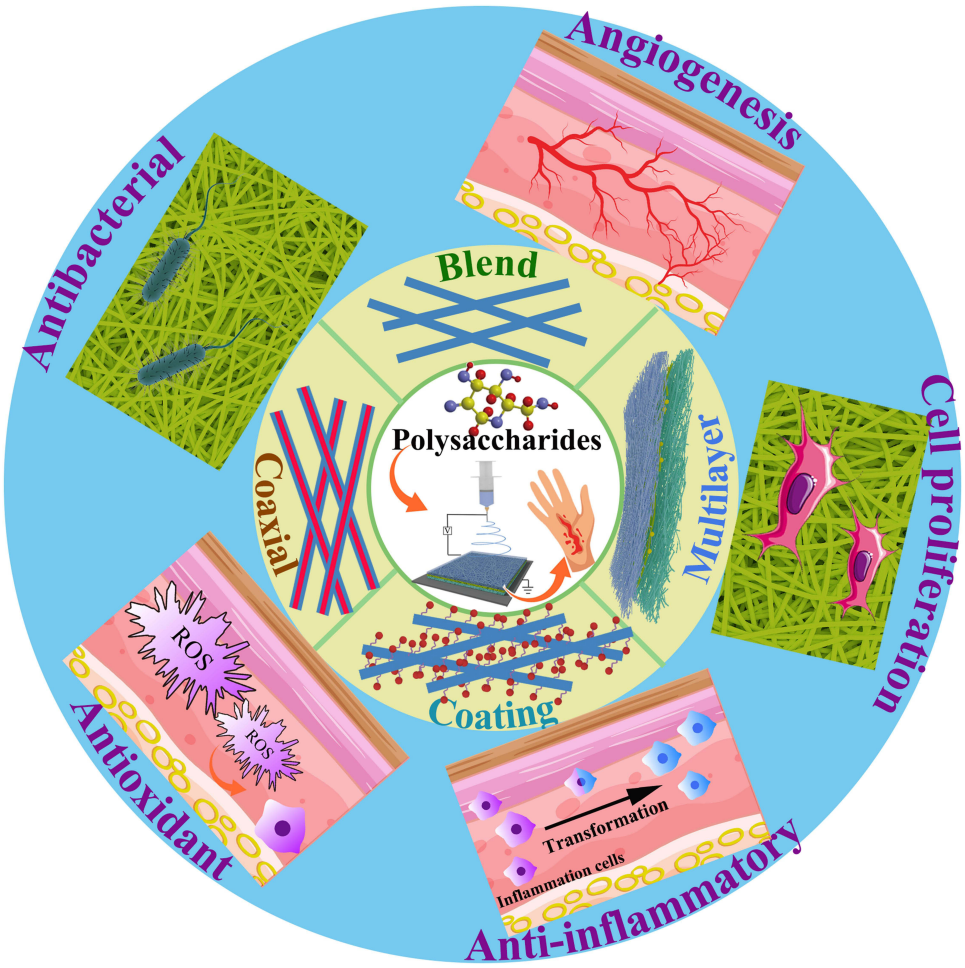

Figure 2 Schematic illustration of the structure characteristics and the function of promoting wound healing of polysaccharide electrospun nanofibers as wound dressings.

and the collector is continuously volatilized, resulting in the formation of solidified polymer nanofibers.[26] After a period of continuous spinning, a certain thickness of nanofiber membrane is obtained. The process is shown in Figure 3.

The electrospinning process is controlled by many parameters, including solution parameters, process parameters and environmental parameters.[28] Solution parameters include the viscosity, conductivity, molecular weight, and surface tension of the solution.[29] Process parameters include the voltage, spinning distance, and the flow rate of solution.[30] Each of these variables affects the diameter and shape of the fiber. By adjusting these parameters, fibers of the desired diameter and shape can be obtained. In addition to these variables, environmental parameters (humidity and temperature) also play an important role in the morphology and diameter of electrospun nanofibers.[31]

Potential Polysaccharide Electrospun Nanofibers for Wound Healing

Natural polysaccharides are very important natural macromolecules that exist widely in animals, plants, algae and other organisms. Polysaccharide electrospun nanofibers have great potential in wound treatment because of their excellent biological properties.[32,33] In this paper, several common natural polysaccharides such as chitosan, starch, alginate, hyaluronic acid and their properties in wound healing by electrospinning are summarized (Table 1).

Chitosan

Chitosan is a mucopolysaccharide macromolecule formed by the partial deacetylation of chitin, which is an alkaline natural polysaccharide substance that mainly exists in the exoskeletons of arthropods, including crustaceans.[57] Due to

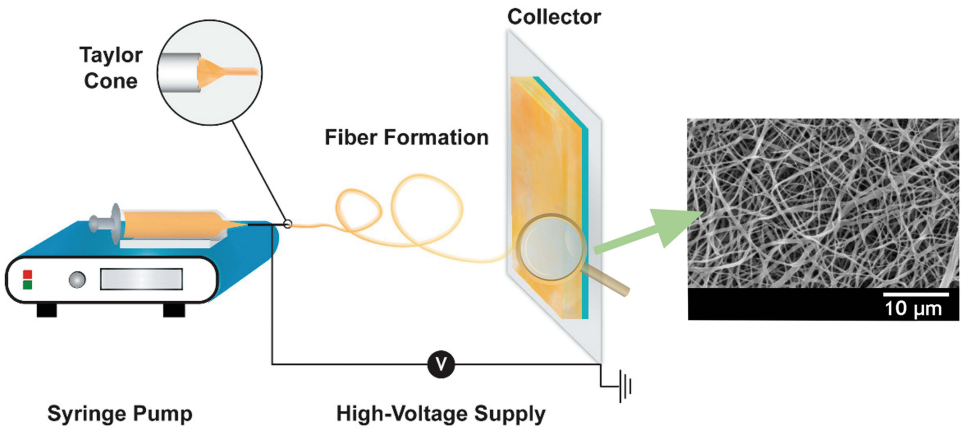

Figure 3 Illustration of a conventional electrospinning apparatus used in the production of nanofibers.
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deacetylation, the amino group on the molecular chain of chitosan is easily protonated and has a positive charge, which endows chitosan with broad antibacterial properties and hemostatic effects.[58] Furthermore, chitosan possesses essential the properties of ideal wound dressings such as biocompatibility, biodegradability, and low toxicity.[59] Therefore, chitosan has become an excellent choice for the preparation of wound dressing materials.[38] Chitosan solution alone is not easy to electrospin due to the high viscosity of the solution. Hence, synthetic polymers such as polyvinyl oxide (PEO) or

Table 1 Natural Polysaccharide for Wound Dressing Prepared by Electrospinning

Polysaccharide	Other Polymers	Co-Solvent	Electrospinning	Functions	Ref
Chitosan	Collagen/PEO	Acetic acid	Blend	Cell proliferation	[34]
	PEO	Acetic acid	Blend	Antibacterial	[35]
	PCL	Formic acid: Acetic acid	Blend	Antibacterial	[36]
	PVA	Water: HCl	Blend	Antibacterial, and antioxidant	[37]
	PVP	Water: Acetic acid	Blend	Cell proliferation	[38]
	PCL	DCM: Ethanol/Acetic acid	Coaxial	Anti-inflammatory and pro-angiogenic	[39]
	PLA	Acetone/Acetic acid	Blend/Coating	Antibacterial, and cell proliferation	[40]
	PCL	Acetone/Acetic acid	Blend/Coating	Antibacterial	[41]
Starch	TPU	DMF	Blend	/	[42]
	PVA	Ethanol (10% v/v)	Blend	Cell proliferation	[43]
	Pullulan	Water	Blend	/	[44]
	HA/PU	Water/DMF	Coaxial	Cell proliferation	[45]
Alginate	PEO	Water	Blend	/	[46]
	PVA	Water	Blend	Cell proliferation	[47]
	Gelatin/PVA	2-Propanol: Water	Blend	Cell proliferation	[48]
	PVA	Water	Coaxial	Antibacterial, and cell proliferation	[49]
	Collagen/PVA	Acetic acid	Coaxial	Anti-inflammatory	[50]
	PCL/ Pluronic	Chloroform: Methanol/Water	Blend/Coating	Antibacterial, and anti-inflammatory	[51]
Hyaluronic acid	Collagen	Water/Acetic acid	Blend	Cell proliferation	[52]
	PEO	DMEM	Blend	Cell migration	[53]
	PLGA	HFIP/Water	Coaxial	Cell proliferation and angiogenesis	[54]
	PLGA	DCM/Water	Blend/Coating	Inhibits scar hyperplasia	[55]
	Chitosan/PEO	Acetic acid/Water	Blend/Coating	/	[56]

Abbreviations: DCM, Dichloromethane; DMF, Dimethylformamide; DMEM, Dulbecco's modified eagle's medium; HCl, Hydrochloric acid; HFIP, Hexafluoroisopropanol; PCL, Polycaprolactone; PEO, Polyethylene oxide; PLA, Polylactic acid; PLGA, Poly(lactide-co-glycolide); PU, Polyurethane; PVA, Polyvinyl alcohol; PVP, Polyvinyl pyrrolidone; TPU, Thermoplastic polyurethane.

polyvinyl alcohol (PVA) are usually added to reduce the viscosity of the chitosan solution to achieve the desired spinning effect.[60]

Bayat et al prepared bromelain-loaded chitosan nanofibers by electrospinning.[61] PEO was added to the spinning solution to improve the spinnability of chitosan. Chitosan nanofibers loaded with bromelain showed better physicochemical properties, release properties and lower cytotoxicity. In addition, the chitosan nanofibers with bromelain exhibited excellent wound healing activity.

The natural advantage of chitosan for wound healing is its antimicrobial activity. This activity is due to the interaction of the protonated amino groups (NH_3^+) of chitosan with the negatively charged bacterial cell membrane. A layer of polymer film is formed on the cell surface, which changes the permeability of the cell membrane and interferes with the normal metabolism of the bacterium, thereby inhibiting bacterial growth. Adeli et al prepared PVA/chitosan/starch nanofibers by electrospinning.[62] Antibacterial tests showed that the nanofibers had good antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*. Furthermore, the increased proportion of chitosan in the nanofibers increased antibacterial activity.

Chitosan is a potential hemostatic material. The hemostatic mechanism of chitosan is related to its positive charge, which can promote the aggregation of negatively charged red blood cells and increase the adhesion of platelets, thereby promoting blood coagulation. Deineka et al prepared porous chitosan electrospun nanofiber membranes.[63] In vivo liver bleeding experiments showed that chitosan nanofibers had high hemostatic performance and a high degree of biodegradation at the later stage of surgery. The results show that chitosan nanofibers have great application potential in the treatment of bleeding wounds.

Starch

Starch is a natural biodegradable polysaccharide consisting mainly of dehydrated glucose units forming two distinct polymers, amylose and amylopectin.[64] The intrinsic physicochemical properties of starch can affect the endogenous coagulation pathway. Starch can act as a natural adhesive to reversibly shrink epithelial cells and promote the repair of damaged cells. Starch is an attractive polymer for wound healing because of its wide availability, low cost, biocompatibility, biodegradability and promotion of wound healing.[65,66]

Waghmare et al successfully prepared electrospun starch nanofibers using 30:70% w/w starch and polyvinyl alcohol.[43] This ratio of polymers yielded fibers with dimensions suitable for wound healing applications. Starch nanofibers can promote the growth and proliferation of skin cells, suggesting their potential to promote wound healing.

However, the high hydrophilicity and poor mechanical properties of starch hinder its application in wound healing. Mistry et al prepared electrospun nanofibers by combining starch with the hydrophobic synthetic polymer TPU and further cross-linked them using glutaraldehyde.[42] The cross-linked starch nanofibers exhibited higher water stability and greater mechanical strength. The cytotoxicity results confirmed the biocompatibility of starch nanofibers. In vivo and histological evaluations indicated that starch nanofibers could enhance the speed of wound healing.

Alginate

Alginate is a natural anionic polysaccharide isolated from brown algae.[67] It is widely used to promote wound healing due to its advantages of biocompatibility, biodegradability, low cytotoxicity and mucosal adhesion.[68] In addition, calcium ions in alginate dressings exchange with sodium ions in wound secretions, causing alginate to gel at the wound site and provide the appropriate moist environment for wound healing. Therefore, the preparation of alginate into electrospun nanofibers has great potential for wound healing. However, the molecular weight of alginate is low, and it is easily forms a gel when the concentration is slightly higher, so it is difficult to electrospin pure sodium alginate.[69] Researchers often blend it with synthetic polymers to prepare electrospun nanofibers.[70] Lu et al blended alginate with PEO solution to improve the spinnability of alginate for producing alginate nanofibers with exceptional antimicrobial properties of oregano essential oil (OEO) as a natural antimicrobial agent.[71] The cross-linking of the alginate nanofibers with calcium chloride improves its mechanical properties, particularly the tensile strength. Antibacterial tests showed that OEO-loaded alginate nanofibers successfully inhibited the growth of gram-positive and gram-negative bacteria. These alginate

nanofibers with good mechanical properties and bacteriostatic effects have great application prospects as wound dressings.

Hyaluronic Acid

Hyaluronic acid (HA) is an anionic aminoglycan produced naturally by the human body and widely distributed throughout the body in connective tissue, the eyes and the skin.[72] Hyaluronic acid is a major component of the extracellular matrix, which plays a critical role in tissue regeneration, the inflammatory response, angiogenesis, skin wound repair, etc. Hyaluronic acid plays an important physiological role at multiple stages of wound healing, including promoting the proliferation and migration of fibroblasts and keratinocytes, regulating inflammatory responses, enhancing angiogenesis and collagen deposition at the wound site, and reducing scar formation.[73] Hyaluronic acid nanofibers are novel bioactive wound dressings with unique properties such as similarity to the extracellular matrix and accelerated wound healing, which play an important role in wound management.[74] However, the poor mechanical properties of hyaluronic acid nanofibers may limit their biological application.[75] Hussein et al improved the mechanical properties of nanofibers by incorporating cellulose nanocrystals in hyaluronic acid nanofibers, and loaded L-arginine as a wound-healing promoter to enhance the wound-healing ability of nanofibers. The nanofibers exhibited good biological activities such as cell proliferation, cell adhesion, antibacterial activity and wound healing.[76]

Preparation Strategy of Polysaccharide Electrospun Nanofibers

With the continuous development of electrospinning technology, an increasing number of different preparation strategies for polysaccharide electrospun nanofibers as wound dressings are being developed to meet the different needs of wound treatment or to speed up wound healing. Several preparation strategies for electrospun polysaccharide nanofibers and their advantages in wound healing will be presented in detail.

Blend Electrospinning

Single-layer nanofiber membranes prepared by single nozzle electrospinning are the earliest and most studied wound dressings made by electrospinning.[77] These membranes are typically prepared by blending polymer materials with antibacterial agents or substances that promote wound healing.[78] The core requirement of blend electrospinning is that multiple components can be dissolved in the same solvent. The spinning process is simple, the spinning difficulty is low, and the solvent selection is flexible. Kharat et al prepared *Calendula officinalis* extract (CO)-loaded chitosan nanofibers by blending electrospinning to dissolve CO and chitosan in 50% aqueous acetic acid.[79] The prepared nanofiber scaffolds had suitable properties including high biocompatibility, appropriate mechanical properties, proper biodegradability and excellent wettability. In addition, the antibacterial activity of chitosan nanofibers against *Escherichia coli* and *Staphylococcus aureus* was improved by adding CO into the nanofibers. The nanofibers exhibited excellent wound healing ability by improving collagen synthesis, tissue re-epithelialization and tissue remodeling.

Coaxial Electrospinning

The preparation of nanofibers by blending drugs with materials is simple and reproducible. However, the drugs are dispersed on nanofibers with a high specific surface area, which can easily lead to the explosive release of drugs on the surface of the nanofibers and thus cannot be sustained for an extended period of time. In addition, some fragile drugs (such as proteins) are not stable in organic solvents, which also limits their application in the field of wound treatment. Therefore, researchers developed coaxial electrospinning technology to prepare core-shell structure nanofibers to address the above problems.[80] Coaxial electrospinning uses a concentric circular needle structure to spray two different components of the spinning solution at the same time to prevent the interference of blending between components.[81] The drug or active substance is encapsulated in shell-core nanofibers by coaxial electrospinning. The drug in the core gradually dissolves through the shell, or the drug is released through hydrophilic holes in the shell, and the release rate is slower than that of the shell.[82] Guo et al successfully prepared chitosan-PEO/PCL nanofibers using coaxial electrospinning technology with chitosan-PEO as the shell and PCL as the core, realizing the co-loading and sequential delivery of the two drugs (Figure 4).[83] Lidocaine hydrochloride for pain relief was added to the shell, and the anti-inflammatory

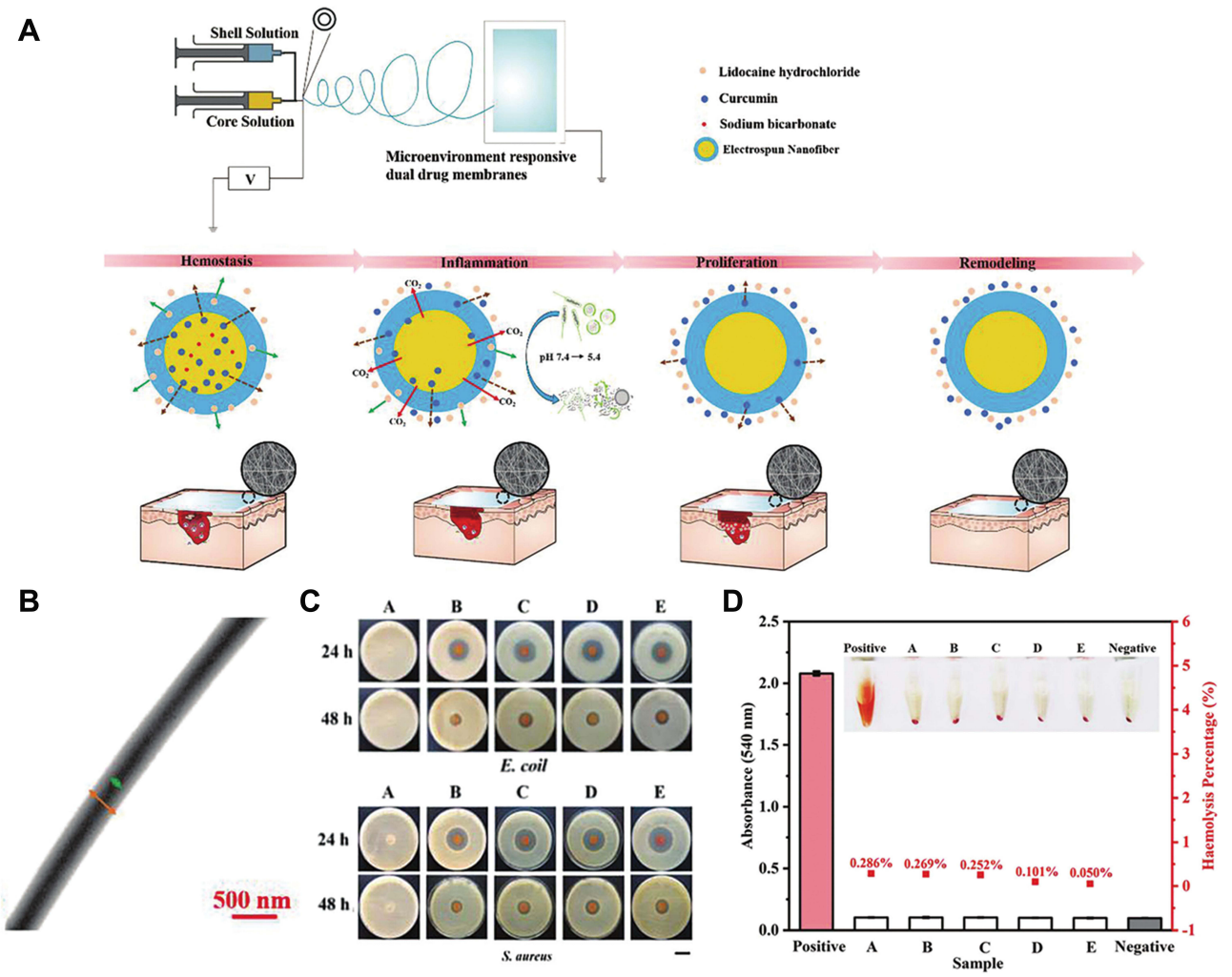

Figure 4 Sequential release of drugs forms a dual-delivery system based on pH-responsive nanofibrous mats towards wound care. (**A**) Illustration indicating wound healing with the help of microenvironment-responsive dual-drug-loaded wound dressings. (**B**) TEM images of core–shell nanofibers. (**C**) The inhibition zone of different samples against *E. coli* and *S. aureus* at 24 h and 48 h. (**D**) The results of hemolytic tests.

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agent curcumin was added to the core. Sodium bicarbonate was also added to the core to provide microenvironment sensitivity at the wound site. The rapid release of lidocaine hydrochloride in the shell and the sustained release of curcumin in the core can provide immediate analgesic effects and long-term antibacterial activity during wound healing. In vitro experiments showed that the prepared nanofibers have sustained antibacterial properties against *Escherichia coli* and *Staphylococcus aureus* and have good coagulation, blood compatibility and cytocompatibility to L929 cells, making them ideal dressings for wound care in the future.

Multilayer Electrospun Nanofiber Membranes

The ideal wound dressings must have multiple functions such as acting as a protective barrier to prevent the invasion of microorganisms.[84,85] In addition, these dressings should also have hemostatic and antibacterial properties, the ability to absorb wound exudate, suitable gas–liquid exchange capacity, and the ability to promote cell proliferation and migration, angiogenesis, tissue remodeling, etc. However, the single-layer nanofiber membranes prepared by blending electrospinning or coaxial electrospinning have relatively simple functions. Most single-layer nanofibers release antibacterial agents or substances that promote wound healing to the wound site, and cannot achieve more complex functions to meet the

needs of wound healing. Therefore, electrospun polysaccharide nanofiber membranes with multilayer spatial structures have been further studied for wound dressings to meet the complex environment of wound healing.[86–88] Miguel et al prepared two interconnected electrospun asymmetric hyaluronic acid films to mimic the epidermis and dermis of the skin.[89] Hyaluronic acid provides high hydration and water absorption and retention and also allows cell attachment, migration and proliferation. Thus, the porous bottom layer composed of hyaluronic acid and silk fibroin forms a dermis-like structure, which can absorb wound exudate and promote cell adhesion and proliferation. Simultaneously, the addition of herbal thymol to the bottom layer of the membrane enhances its antibacterial and antioxidant properties. The top layer is prepared from silk fibroin and PCL to reproduce the compactness and water repellency of the epidermis. This bilayer membrane has multiple functions such barrier formation, waterproofing, absorbing wound exudate, and promoting cell proliferation, bacteriostasis and antioxidation, which enhance the application of this membrane as a wound dressing.

In addition, many researchers have developed three-layer nanofiber membranes to achieve more complex functions to accelerate wound healing. Chen et al prepared a three-layer chitosan wound dressing with a spatial structure by sequential electrospinning.[90] This three-layer nanofiber membrane composed of chitosan, PVA and nanobioglass (nBG) provided the functions of hemostatic and antibacterial in the sub-layer (chitosan), moisture retention and exudate absorption in the mid-layer (chitosan-PVA), and promoting tissue generation in the top-layer (PVA-nBG). This layered multilayer structure is expected to organize the function of membrane components corresponding to the healing stage and to speed up the healing process. The results of in vitro and in vivo studies confirmed that the three-layer chitosan nanofiber membrane has great potential in acute and chronic wound healing (Figure 5).

Electrospun Nanofiber Coating Polysaccharide

A high viscosity caused by inherently high molecular weights and electrical charges also produces poor electrospinnability of some polysaccharides. In addition, polysaccharide electrospun nanofibers have poorer mechanical properties and water resistance. Synthetic polymers have good spinnability and superior mechanical properties. The synthetic polymer nanofibers can be prepared by electrospinning, and then the polysaccharide is coated on the surface of the nanofibers to obtain the polysaccharide-coated nanofibers.[51] These nanofibers not only ensure the excellent mechanical properties of synthetic polymers but also have the functions of polysaccharides such as moisture absorption, good biocompatibility and promotion of wound healing. Croisier et al prepared charged nanofibers by electrospinning poly(ε-caprolactone) (PCL) with a block-copolymer bearing carboxylic acid functional groups. After deprotonation of the acid groups, the layer-by-layer deposition of polyelectrolyte polysaccharides, notably chitosan and hyaluronic acid, was used to coat the electrospun fibers. A multilayered structure was achieved by alternating the deposition of positively charged chitosan with the deposition of a negatively charged polyelectrolyte. The polysaccharide-coated nanofibers retained the excellent biological properties of polysaccharides while avoiding the limitation of direct electrospinning of polysaccharides.[91]

Polysaccharide Electrospun Nanofibers with Different Functions for Use as Wound Dressings

Wounds can be classified into acute wounds and chronic wounds according to the length of the healing time.[92] Acute wounds such as mechanical wounds, surgical wounds, burns and chemical injuries heal in a short period of time following an orderly wound healing process. Chronic wounds cannot be repaired through an orderly healing process and take longer to heal. The most common chronic wounds are diabetic foot ulcers, bedsores, venous leg ulcers, and burns.[93] The main causes of delayed wound healing are chronic inflammation, growth factor secretion disorder, microbial infection and destruction of angiogenesis.[94,95] In addition, reduced proliferation, migration, and relocation of fibroblasts severely impede the wound healing process. Therefore, the development of wound dressings with specific functions such as antibacterial, anti-inflammatory, promotion of cell proliferation and migration, and promotion of angiogenesis can correct the disrupted stages of wound healing and guide the wound to follow an orderly healing procedure.[96,97]

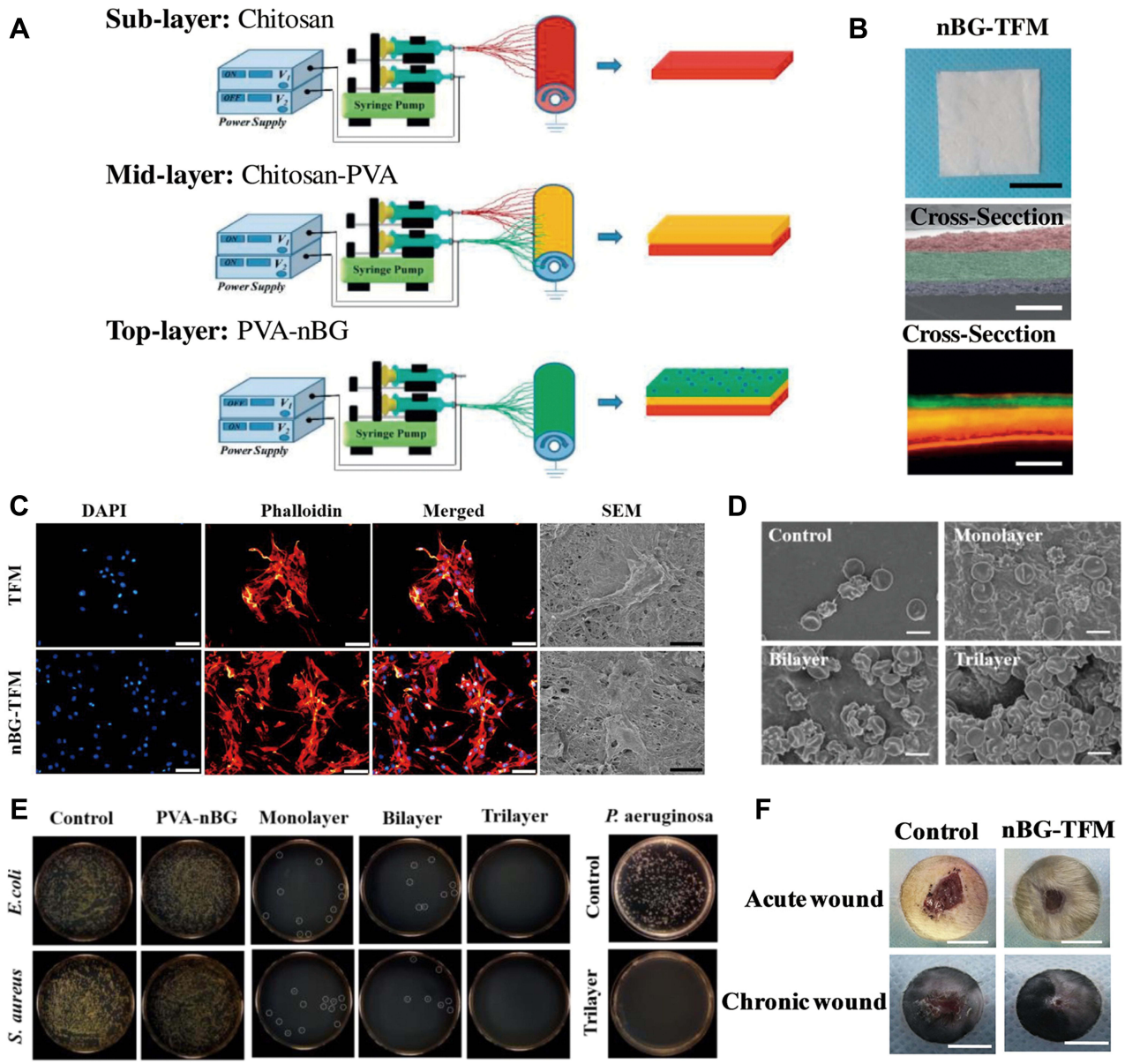

Figure 5 Electrospun chitosan/PVA/bioglass Nanofibrous membrane with spatially designed structure for accelerating chronic wound healing. (**A**) Schematic of nBG-TFM fabricated by sequential electrospinning. (**B**) Photographs, SEM images and fluorescent images of electrospining membranes. (**C**) Cell morphology of HDFs cells cultured on trilayer membranes with nBG (40%) (nBG-TFM) and without nBG (TFM) was observed by fluorescent staining and SEM. (**D**) The effect of membranes on the aggregation of red blood cells was observed by SEM. (**E**) Surface antibacterial activity of membranes for *E. coli, S. aureus* and *P. aeruginosa*. (**F**) Evaluation of nBG-TFM on acute and chronic wound healing in rats.

Notes: Reprinted from: Chen Q, Wu J, Liu Y, et al. Electrospun chitosan/PVA/bioglass Nanofibrous membrane with spatially designed structure for accelerating chronic wound healing. *Mater Sci Eng C Mater Biol Appl*. 2019;105:110083. doi:10.1016/j.msec.2019.110083.[90]

Antibacterial Activity

Natural polysaccharides have been widely used in wound dressings. However, most natural polysaccharides have no antibacterial properties except for a few polysaccharides, such as chitosan, that have limited antibacterial properties. Therefore, the application of natural polysaccharides in bacteria-infected wounds will be limited. Harmful bacteria will adhere to polysaccharide dressings, proliferate and secrete more harmful substances on the dressings, which will not only fail to promote wound healing, it will actually hinder wound healing.[98] Therefore, the preparation of polysaccharide wound dressings with antibacterial properties can greatly improve the application of natural polysaccharides in wound dressings by loading suitable antibacterial agents. Researchers are currently preparing electrospun polysaccharide

nanofibers functionalized with antimicrobial agents such as antibiotics, metal nanoparticles, plant extracts, and antimicrobial peptides (Table 2).[99,100]

Antibiotics have the advantages of quick efficacy and strong bactericidal properties, and are widely used in the clinical treatment of wound infections.[123] Therefore, adding antibiotics into electrospun polysaccharide nanofibers can achieve a good antibacterial effect.[124,125] Chronic wounds are caused by multiple factors, such as nosocomial infections, dermal bacteria, and surgical site infections. Therefore, Kalalinia et al prepared vancomycin-loaded chitosan/PEO nanofibers by blending electrospinning to control infection.[104] Nanofibers exhibit good mechanical properties, biocompatibility, and antibacterial properties. Furthermore, in vivo experiments showed that chitosan/PEO nanofibers loaded with 2.5% vancomycin had a faster healing time compared with other treatment groups.

Antibiotics have a good antibacterial effect, but the widespread use of antibiotics leads to bacterial resistance.[126,127] Unlike traditional antibiotics, metal nanoparticles do not bind to specific receptors on bacterial cells, which makes it difficult for bacteria to develop drug resistance and also expands the broad spectrum of antibacterial activity.[128] Therefore, polysaccharide electrospun fibers loaded with metal nanoparticles were used to prevent bacterial infection at the wound site.[129,130] Dodero et al prepared alginate nanofibers loaded with ZnO nanoparticles by electrospinning and crosslinked them with Sr^{2+} ions. These nanofibers can effectively inhibit the growth of *Escherichia coli*.[111]

Plants are a natural treasure trove of bioactive compounds, and there are many types of active components with antibacterial activity, such as volatile oils, alkaloids, flavonoids, phenolic alcohols, quinones, saponins, and glycosides.[131,132] These

Table 2 Details of Recent Works on Antibacterial Polysaccharide Nanofibers Fabricated by Electrospinning

Classification	Antimicrobial Agents	Polymers	Bacterial Species	Ref
Antibiotics	Cefadroxil	Chitosan/PVA	*S. aureus*	[101]
	Cefazolin	Chitosan/PEO	*S. aureus* and *E. coli*	[102]
	Chloramphenicol	Chitosan/β-Glucan /PEO/HPMC	*S. aureus* and *E. coli*	[103]
	Vancomycin	Chitosan/PEO	*S. aureus* and methicillin-resistance *S. aureus*	[104]
	Ciprofloxacin	Chitosan/PEO	*S. aureus* and *E. coli*	[105]
	Ciprofloxacin	Alginate/PLGA	*S. aureus*	[106]
	Moxifloxacin	Alginate/PVA	*Aeruginosa* and *S. aureus*	[107]
	Doxycycline	HA/Pullulan	*P. aeruginosa* and *S. aureus*	[108]
Metal nanoparticles	AgNPs	Chitosan/PVA	*S. aureus, E. coli, P. aeruginosa* and *Candid albicans*	[109]
	AgNPs	HA/PGA/PVA	*Bacillus Subtilis, S. aureus* and *E. coli*	[110]
	ZnO NPs	Alginate/PEO	*E. coli*	[111]
	ZnO NPs	Chitosan/Collagen	*S. aureus* and *E. coli*	[112]
	ZnO NPs	Chitosan/PVA	*E. coli, P. aeruginosa, B. subtilis* and *S. aureus*	[113]
	ZnO NPs	HA/Silk fibroin	*E. coli* and *S. aureus*	[114]
	Cu NPs	Chitosan/PVA	*E. coli, P. aeruginosa, S. aureus* and *Bacillus cereus*	[115]
	Cu-MOFs	Chitosan/PVA	*S. aureus* and *E. coli*	[116]
Plant extracts	CO extract	Chitosan/PEO	*S. aureus* and *E. coli*	[79]
	Henna extract	Chitosan/PEO	*S. aureus* and *E. coli*	[117]
	AG extract	Chitosan/PVA	*P. aeruginosa* and *S. aureus*	[118]
	Aloe vera	Chitosan/PCL	*S. aureus* and *E. coli*	[119]
	OEO	Alginate/PEO	Methicillin-resistant *S. aureus, Listeria monocytogenes, Klebsiella Pneumoniae* and *Salmonella enterica*	[71]
Antimicrobial peptides	CM11	Chitosan/Silk fibroin	*S. aureus, E. coli* and *P. aeruginosa*	[120]
	OH-CATH30	Chitosan/PVA	*S. aureus* and *E. coli*	[121]
	ε-Polylysine	HA/PEO	*S. aureus* and *E. coli*	[122]

Abbreviations: AG, *Agrimonia eupatoria* L.; AgNPs, Silver nanoparticles; *B. subtilis, Bacillus subtilis*; CO, *Calendula officinalis*; Cu NPs, Copper nanoparticles; *E. coli, Escherichia coli*; HA, Hyaluronic acid; HPMC, Hydroxypropyl methyl cellulose; MOFs, Metal-organic frameworks; OEO, oregano essential oil; *P. aeruginosa, Pseudomonas aeruginosa*; PCL, Polycaprolactone; PEO, Polyethylene oxide; PLGA, Poly(lactide-co-glycolide); PVA, Polyvinyl alcohol; PGA, Polygalacturonic acid; *S. aureus, Staphylococcus aureus*; ZnO NPs, Zinc oxide nanoparticles.

ingredients come from a wide range of sources and have less biotoxicity and superior wound healing properties. Therefore, many researchers have loaded plant extracts with antibacterial activity into electrospun polysaccharide nanofibers to promote wound healing.[133,134] Yousefi et al added henna leaf extract with antibacterial activity to chitosan/PEO nanofibers, which showed significant inhibitory effect on both gram-negative and gram-positive bacteria, enhancing the antibacterial performance of chitosan/PEO nanofibers alone. In vivo results confirmed that chitosan/PEO nanofibers loaded with henna extract significantly accelerated the wound healing process.[117] Henna extract has a variety of pharmacological components for burn healing, so the wound dressing loaded with henna extract is promising for the treatment of severe burns.

Antioxidant or Anti-Inflammatory Activity

Chronic wounds exhibit chronic inflammation as they heal.[93,135] Chronic inflammation is mainly caused by high levels of reactive oxygen species (ROS), proinflammatory chemokines and bacterial infections.[136] The use of dressing materials to modulate the wound inflammatory microenvironment, including ROS removal, adsorption of inflammatory factors, and regulation of the phenotype and number of immune cells, can reduce the inflammatory response of the wound and accelerate the healing of chronic wounds.[137,138] Therefore, polysaccharide electrospun nanofibers with the ability to regulate the wound inflammatory microenvironment have great potential in the treatment of chronic wounds.[139,140]

Honey is an ancient natural wound-healing agent with antibacterial, antioxidant and anti-inflammatory properties that has been reintroduced into modern clinical wound care. Tang et al added honey to alginate/PVA electrospun nanofibers to develop a wound dressing with antioxidant properties.[141] With the increase in honey content, the nanofibers showed enhanced antioxidant activity, indicating that it could control the excessive production of reactive oxygen species. The addition of honey to nanofibers can also effectively inhibit the growth of gram-positive bacteria and gram-negative bacteria. The MTT test demonstrated that the nanofibers have good biocompatibility. Therefore, honey-loaded alginate/PVA nanofibers are expected to be an effective wound dressing.

High molecular weight hyaluronic acid (HHA) can promote the transformation of macrophages from the proinflammatory M1 phenotype to the M2 phenotype. M2 phenotype macrophages can greatly reduce inflammation and promote cell proliferation by releasing anti-inflammatory cytokines and growth factors.[142] Liu et al developed a nanofiber-absorbable hyaluronic acid hydrogel for the synergistic regulation of the inflammatory microenvironment of diabetic wounds (Figure 6).[149] The electrospun thioether grafted hyaluronic acid nanofibers (FHHA-S/Fe) can form hydrogels in situ on the wound bed. The hydrogels gradually degraded and were absorbed within three days. The grafted thioether on the surface of HHA can rapidly remove reactive oxygen species and reduce the inflammatory response in the early stage of inflammation. In addition, HHA can promote the transformation of aggregated M1 macrophages into the M2 phenotype, thus co-accelerating the transition from inflammation to proliferation and remodeling in the wound healing phase. In vitro and in vivo results demonstrated that the nanofiber hyaluronic acid hydrogel can significantly accelerate wound healing in chronic diabetes, particularly in the early stage of wound healing. Therefore, this simple dressing strategy with intrinsic dual regulatory mechanisms of the wound inflammatory microenvironment can be used as an effective and safe therapeutic strategy for diabetic wound management.

Promoting the Proliferation and Migration of Fibroblasts

In the process of wound healing, normal fibroblasts at the edge of the wound continue to proliferate and migrate to the wound surface. Fibroblasts produce fibrous tissue and matrix, thereby promoting skin tissue remodeling to complete wound healing. Therefore, the proliferation and migration of wound tissue cells are of great significance for wound healing.[143] Ghalei et al prepared an alginate coated electrospun fibroin capable of delivering amniotic fluid (AF) to the wound site.[144] An alginate coating on the surface of nanofibers can enhance the cell-matrix interaction and promote the proliferation and migration of fibroblasts. In addition, AF contains a variety of growth factors, such as FGF, EGF and TGF-β, which can promote cellular response and wound healing. Cultured fibroblasts on manufactured dressings showed that the nanofibers could promote the proliferation and migration of fibroblasts and increase collagen secretion (Figure 7).

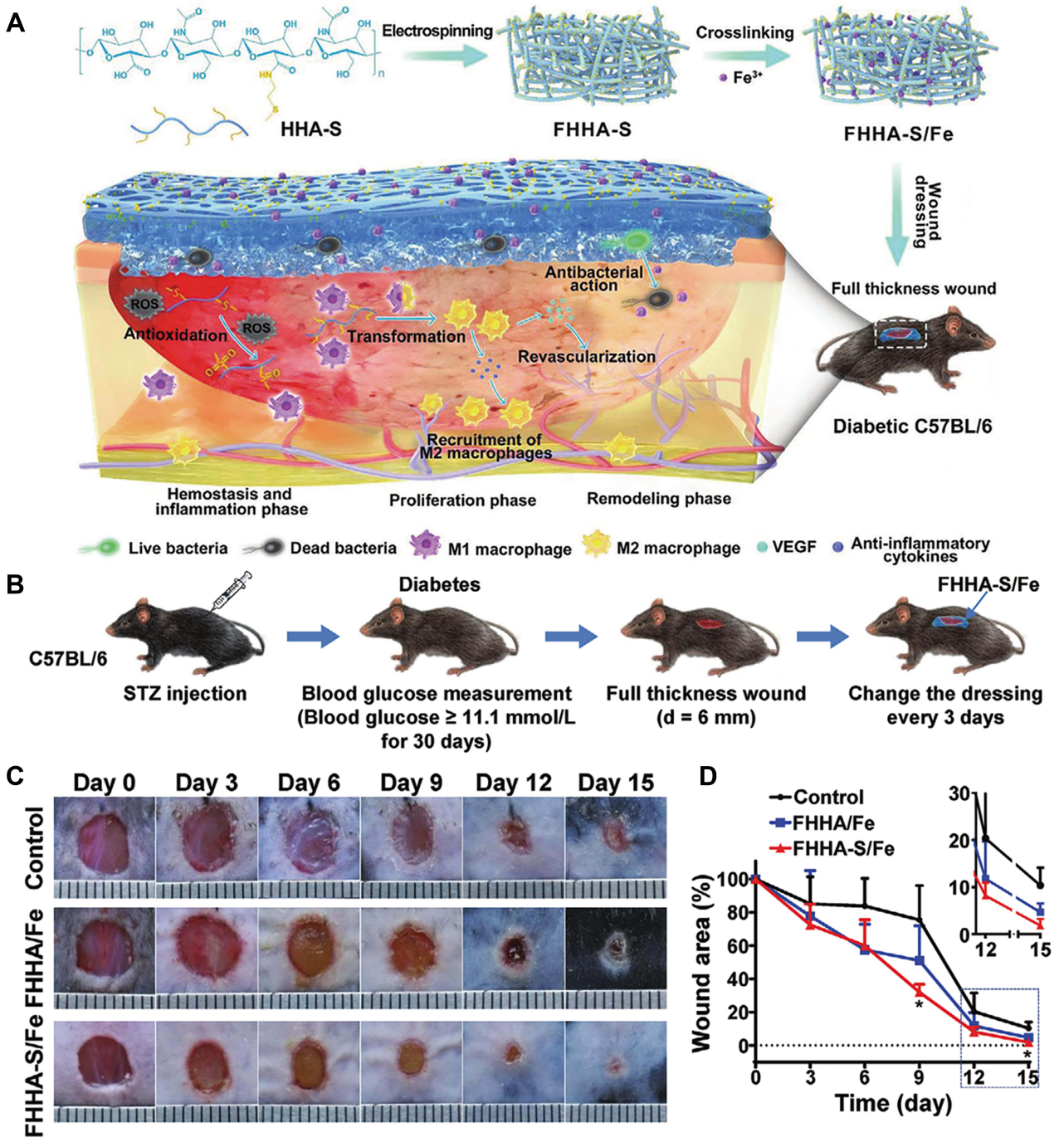

Figure 6 Absorbable thioether grafted hyaluronic acid nanofibrous hydrogel for synergistic modulation of inflammation microenvironment to accelerate chronic diabetic wound healing. (**A**) Illustration of the preparation procedure of FHHA-S/Fe, dressing of FHHA-S/Fe on full-thickness wound model in diabetic C57BL/6 mouse, and the mechanism of FHHA-S/Fe for enhanced chronic wound healing effect. (**B**) Schematic of the establishment and treatment of a chronic diabetic wound model. (**C**) Representative photographs of wounds at indicated days with nanofibrous hydrogel treatment. (**D**) Quantitative analysis of wound area at the indicated days in comparison with the original wound.

Notes: Reprinted with permission from: Liu S, Zhang Q, Yu J, et al. Absorbable Thioether Grafted Hyaluronic Acid Nanofibrous Hydrogel for Synergistic Modulation ofInflammation Microenvironment to Accelerate Chronic Diabetic Wound Healing. *Adv Healthc Mater.* 2020;9(11):e2000198. doi:10.1002/adhm.202000198.[149] © 2020 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Enhanced Angiogenesis

Wound angiogenesis refers to the process of angiogenesis on the original microvessels after skin tissue injury under the stimulation of various factors. Neovascularization plays an important role in wound healing by providing oxygen, nutrition and bioactive substances to the wound site. People with diabetes develop hyperglycemia, which can cause the walls of blood

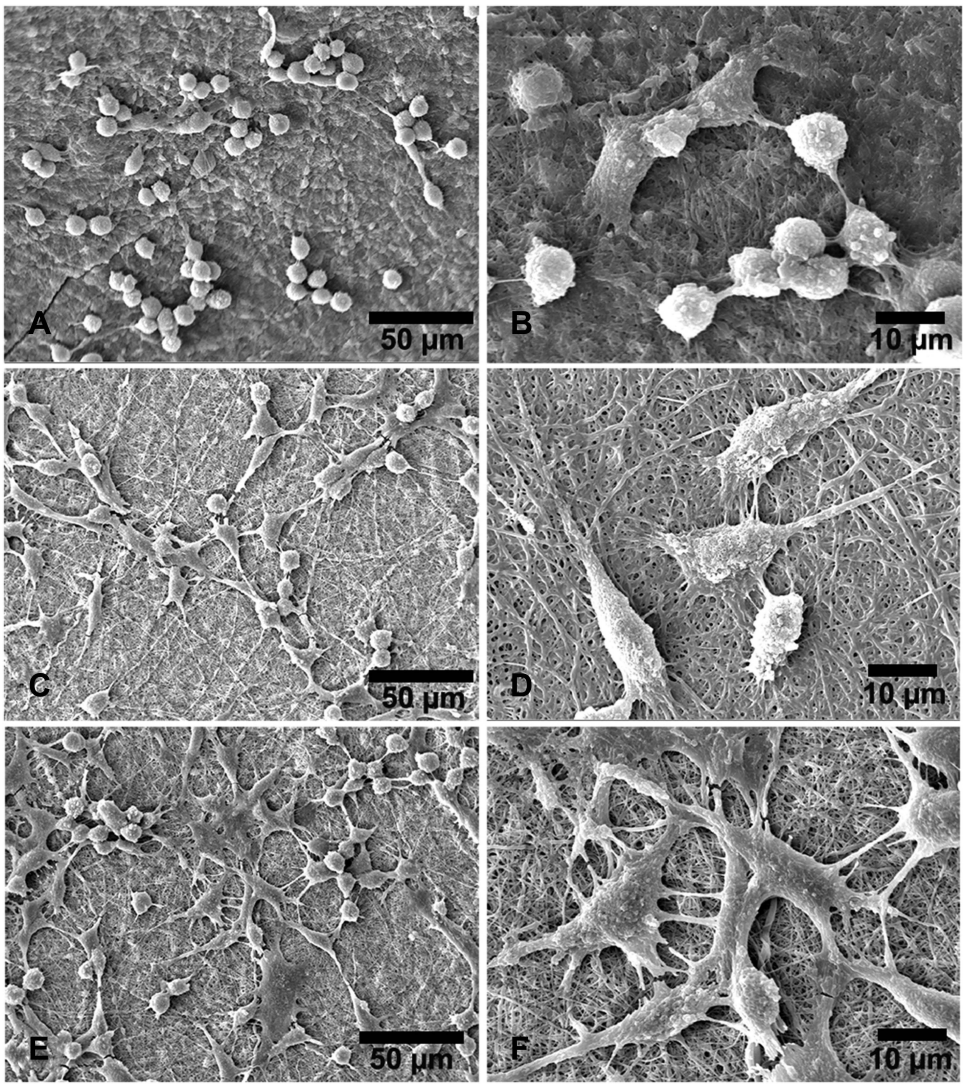

Figure 7 SEM images of L929 cells cultured on alginate hydrogel-electrospun silk fibroin fibers. (**A** and **B**) SF-ALG, (**C** and **D**) SF-ALG-AF1, and (**E** and **F**) SF-ALG-AF2 after 24 h.
Notes: Reprinted from: Ghalei S, Nourmohammadi J, Solouk A, Mirzadeh H. Enhanced cellular response elicited by addition of amniotic fluid to alginate hydrogel-electrospun silk fibroin fibers for potential wound dressing application. *Colloids Surf B Biointerfaces*. 2018;172:82–89. doi:10.1016/j.colsurfb.2018.08.028.[144] Copyright 2018, with permission from Elsevier.

vessels to harden, lowering blood flow and depriving the wound site of much-needed oxygen and nutrients, thereby reducing angiogenesis and hindering the healing of diabetic wounds.[145] Promoting angiogenesis is a promising function of wound dressings.[146,147] Mulholland et al investigated the delivery of siFKBPL nanocomplexes with RALA peptides as a novel gene therapy to reduce endogenous levels of FKBPL, thereby promoting angiogenesis and wound healing.[148] The RALA/siFKBPL complex was added to electrospun alginate/chitosan/PVA nanofibers to enhance the drug delivery effect. In vivo wound healing studies in mice showed a significant increase in angiogenesis when RALA/siFKBPL nanoparticles were delivered from nanofibers, with a 326% increase in vascular density observed compared with untreated wounds.

Conclusions and Future Perspectives

The superior biological characteristics of natural polysaccharides, such as good biocompatibility and biodegradability, can maintain the moist microenvironment for wound healing, and the chemical structure of natural polysaccharides is similar to that of the natural cytoplasmic matrix, which has the function of promoting wound healing. Therefore, natural polysaccharides have been widely used as wound dressing materials. Electrospun nanofibers have a large specific surface, high porosity, good mechanical properties, and excellent biocompatibility, which are beneficial to wound moisturizing,

cell growth and respiration, and skin regeneration. Electrospun polysaccharide nanofibers combine the characteristics of polysaccharide and electrospun nanofibers. They have the functions of hemostasis, absorption, breathability, bacteriostasis, anti-inflammation, and promotion of cell proliferation and tissue remodeling when used as a wound dressing. Therefore, electrospun polysaccharide nanofibers are ideal wound dressings. This article reviewed the preparation of polysaccharide nanofibers by electrospinning and their application in the field of wound healing. A variety of polysaccharide nanofibers, including chitosan, starch, hyaluronic acid, and alginate, were introduced.

Electrospun polysaccharide nanofibers have significant advantages as wound dressings. However, there are only a few types of polysaccharides that can be prepared by electrospinning technology, and the range of properties that can be obtained for wound dressings and the types of wounds that can be treated are limited. For example, electrospun alginate nanofibers have a strong liquid absorption capacity, and are suitable for wounds with a large amount exudate. Once applied to the wound with a little exudate, they will make the wound too dry, uncomfortable and scar. Most importantly, alginate nanofibers have no bacteriostatic properties. The electrospun chitosan nanofiber membrane can inhibit bacteria, but it has poor absorbability and moisture retention, which cannot ensure the moist environment required for wound healing. Therefore, the applicability of polysaccharide nanofibers in wound treatment can be improved by combining a variety of polysaccharide materials.

There have been many studies on polysaccharide electrospinning, but the preparation of polysaccharide nanofibers by electrospinning is still a challenge. This is mainly because polysaccharides are prone to form strong hydrogen bonds, which leads to extremely high viscosity or gelation of electrospinning solutions, resulting in unsatisfactory morphology and performance of nanofibers. This makes it difficult to transfer the production stage of polysaccharide nanofibers from the laboratory to commercial and industrial scales. The effective measures to solve this problem are to constantly try to adjust the solvent, material and structural design of polysaccharide electrospun nanofibers so as to improve the spinnability of polysaccharide wound dressings. Experiments with different solvent combinations can change the swelling and entanglement states of polysaccharide molecules and thus affect the nanofiber morphology. Blending polysaccharides with other electrospinning-friendly polymers, such as polyvinyl alcohol (PVA), polylactic acid (PLA), and polyethylene oxide (PEO), can also improve the spinning performance of polysaccharide nanofibers, which is a common method for preparing electrospun polysaccharide nanofibers. More importantly, the structural design of wound dressings with polysaccharide nanofibers is becoming increasingly complex, which leads to its increased difficulty in preparation technology and poor reproducibility, thus making it difficult to carry out industrial production. Polysaccharide nanofiber dressings with relatively simple structures, low production technology requirements, and excellent wound healing ability are attractive and feasible for commercial development. The addition of electrospun jet devices can also effectively increase the jet flow of the nozzle, which will improve the formation of fibers in the spinning process; thus, increasing the yield of polysaccharide nanofiber wound dressings is of great significance for their commercialization.

Disclosure

The authors declare no conflicts of interest in relation to this work.

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