International Journal of Nanomedicine

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REVIEW

Potential Applications of Nanomaterials and Technology for Diabetic Wound Healing

This article was published in the following Dove Press journal:
International Journal of Nanomedicine

Que Bai[1,*]
Kai Han[1,*]
Kai Dong[1]
Caiyun Zheng[1]
Yanni Zhang[1]
Qianfa Long[2]
Tingli Lu[1]

[1]School of Life Sciences, Northwestern Polytechnical University, Xi'an, Shaanxi 710072, People's Republic of China; [2]Mini-Invasive Neurosurgery and Translational Medical Center, Xi'an Central Hospital, Xi'an Jiaotong University, Xi'an 710003, People's Republic of China

*These authors contributed equally to this work

Abstract: Diabetic wound shows delayed and incomplete healing processes, which in turn exposes patients to an environment with a high risk of infection. This article has summarized current developments of nanoparticles/hydrogels and nanotechnology used for promoting the wound healing process in either diabetic animal models or patients with diabetes mellitus. These nanoparticles/hydrogels promote diabetic wound healing by loading bioactive molecules (such as growth factors, genes, proteins/peptides, stem cells/exosomes, etc.) and non-bioactive substances (metal ions, oxygen, nitric oxide, etc.). Among them, smart hydrogels (a very promising method for loading many types of bioactive components) are currently favored by researchers. In addition, nanoparticles/hydrogels can be combined with some technology (including PTT, LBL self-assembly technique and 3D-printing technology) to treat diabetic wound repair. By reviewing the recent literatures, we also proposed new strategies for improving multifunctional treatment of diabetic wounds in the future.

Keywords: hydrogels, nanoparticles, nanotechnology, diabetic wound healing

Introduction

Diabetes mellitus is a complex metabolic disorder that affects the health of millions of people around the world. The world of diabetes among adults (aged 20–79 years) are 285 million adults, which will increase to 439 million adults by 2030.[1,2] Diabetics will lead to high glucose condition as well as a variety of complications, including cardiovascular disease, nerve damage (neuropathy), kidney damage (kidney disease), eye damage (retinopathy), hearing impairment, dementia, and especial the delayed wound healing which is one of the most serious complications of diabetes impaired wound healing.[3–9] Severe diabetic wounds could lead to amputation.[10] Diabetes can be divided into four main types: Type Ⅰ diabetes is caused by the autoimmune be destroyed of β-cells in the pancreas, eventually leading to reduction of insulin production;[11,12] Type Ⅱ diabetes is closely associated with insulin resistance and subsequent decompensation of pancreatic β-cells (including pancreatic β-cell mass loss and β-cell dysfunction);[13] Gestational diabetes occurs during pregnancy and causes glucose intolerance;[14] other diabetes are resulted by specific genetic defects of beta-cell function, illness of the pancreas, drugs or chemicals, etc.[15]

Correspondence: Qianfa Long; Tingli Lu
Tel +86 029-88460332
Email lonva@live.cn;
lutinglixinxin@nwpu.edu.cn

Normal Wound Healing

Wound healing is a complex and ordered biological process, including four classical stages: hemostasis, inflammation, proliferation and remodeling,[16–18] involving

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http://doi.org/10.2147/IJN.S276001

different cell types releasing many cytokines and growth factors (GFs).[19,20] Hemostasis lasts 2–3 hours, the fibrin plug is formed, and aggressive platelets release pro-inflammatory mediators such as cytokines and growth factors. Cytokines recruit neutrophils and monocytes to the wound area, triggering an inflammatory period of wound healing that lasts from hours to days.[21] The inflammatory phase begins immediately after injury and can last from hours to days in acute wounds, while in chronic wounds it can last for weeks or even months due to the effects of the underlying disease (eg, diabetic foot ulcers).[16] Injury results in the rupture of vessels, and form clots and temporary extracellular matrix (ECM), which closes the wound, reduces blood loss, and helps guide cell migration.[22] Platelets secrete and activate cellular mediators that attract inflammatory cells (multinucleated cells and macrophages), fibroblasts, and endothelial cells.[23] In the proliferation, endothelial cell and fibroblast proliferation and migration promote angiogenesis and new ECM formation.[16] As the new ECM is reconstructed, the old matrix is degraded by proteases (matrix metalloproteinases, MMPs), MMPs promote autolytic debridement and cell migration in wounds.[16,17] The level of MMPs in wounds increases after tissue damage and decreases with remission of inflammation, but increases abnormally in chronic wounds.[17] Epithelial cells migrate from the edge of the wound, initiating epithelialization.[24] Keratinocyte differentiation helps restore the barrier function of the epidermis.[25] Remodeling can last for months and eventually an eschar (scab) has formed on the surface of the wound.[17] The matrix is constantly reconstructed by myofibroblasts.[16] The microfilaments attached to the ECM densify the collagen network and contract the wound.[26] At the same time, new components are secreted to increase matrix density and stability.[26,27] The proportion of different types of collagen began to change: the proportion of type I collagen increased (80%–90%) and the proportion of type III collagen decreased (10%–20%).[28] Apoptosis reduces the density of myofibroblasts, making room for fibroblasts, further strengthening the ECM, and increasing its resistance to mechanical forces.[26]

Diabetic Wound Healing

Under normal physiological conditions, the injured tissue will initiate the acute wound healing process.[16–18] However, when the healing process is disturbed by the underlying pathological mechanism or microbial invasion, the wound cannot heal and become a chronic wound (such as diabetic wound)[29] (Figure 1). Hypoxia is a major cause of diabetic wound damage caused by two factors: limited oxygen supply and high oxygen consumption in the wound.[30] In diabetic patients, oxygen supply to the wound is limited due to vascular dysfunction and neuropathy.[30] In addition to inadequate oxygen supply, high oxygen consumption by wound cells during inflammation also induces hypoxia in wounds.[30] In diabetic patients, the imbalance between angiogenic factors (eg, transforming growth factor-β, TGF-β; fibroblast growth factor 2, FGF2; vascular endothelial growth factor, VEGF; angiopoietins) and angiostatic factors (eg, thrombospondins, endostatin, angiostatin) may lead to angiogenic imbalance and aggravate wound hypoxia.[31] Likewise, hypoxia can amplify the inflammatory response, thereby prolonging injury by increasing the levels of oxygen radicals.[32] Two main events for effective wound healing involve an inflammatory response and migration of keratinocytes, fibroblasts, and endothelial cells. However, diabetic wounds did not undergo a normal healing process rather trapped into a chronic inflammatory stage characterized by excessive accumulation of uninhibited M1 macrophages.[33] Moreover, the fibroblast proliferation, function, and differentiation into myofibroblast also significantly reduced with suppressed expression of tumor growth factor β type II receptor and decreased collagen synthesis, which hindered the tissue remodeling stage.[34] The high glucose levels mediated-induction of matrix metalloproteases-9 (which is responsible for collagen degradation and regulates keratinocytes migration) overexpression in diabetic models impaired keratinocyte migration.[35,36] High glucose could also reduce the activity of VEGF and hypoxia-inducible factor 1α (HIF-1α), and increases the non-enzymatic glycation of many important proteins, leading to abnormal cellular and ECM function, thereby inhibiting angiogenesis in diabetic wounds.[37]

General wound clinical therapies include restoration of skin perfusion, treatment of infection, metabolic control, treatment of co-morbidity and local wound care.[38] Although these standard treatments may achieve the goal of symptom control, but the effective treatment of diabetic wound healing remains limited. Moreover, traditional treatment mainly use dressings, the treatment process is long, easy to cause secondary injury, psychological and physiological adverse effect on diabetic patients. Currently, there are some technologies of wound healing treatment for diabetes, namely topical drug treatment (eg,

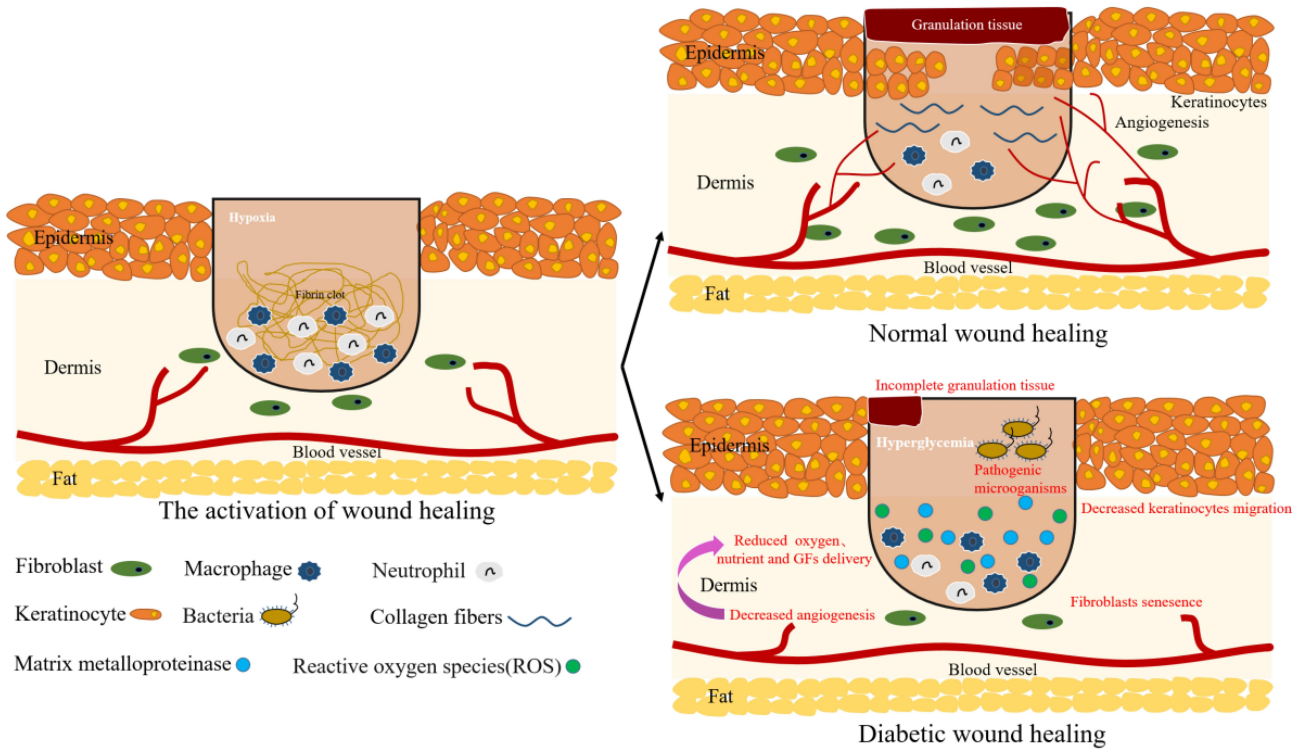

Figure 1 The physiological process of normal wound and diabetic wound. Unlike normal wounds, diabetic wounds are characterized by impaired angiogenesis, excessive inflammatory macrophages. Excessive production of matrix metalloproteinases (MMPs) at the wound site, and hyperglycemia leads to an increase ROS that prevent the formation of healthy tissue.

drugs, peptides and growth factors), cellular therapies (eg, stem cells and fibroblasts) and biomaterial-based treatment.[39] Biomaterials with controlled-release of signaling molecules can be combined with other therapeutic methods, which is a promising treatment method for diabetic wound healing.[40] In this review, we will summarize biomaterials and their potential applications in diabetic wound repair. In addition, we have also reviewed the challenges and application prospects of biomaterials in diabetic wound healing.

Substances Applied in Diabetic Wound Healing

Diabetic wounds often require a longer healing period due to persistent inflammation, bacterial infections, and degradation or diminished expression of growth factors.[41] In addition, chronic hyperglycemia makes new vessel formation is difficult, thus limiting the access of oxygen and nutrients to the wound site.[42] Therefore, some substances need to be delivered from the outside to promote the healing of diabetic wounds. At present, a variety of bioactive molecules (such as growth factors, genes/proteins/peptides, stem cells/exosomes, etc.) and non-bioactive substances (metal ions, oxygen, nitric oxide, etc.) are widely used to promote diabetic wound healing (Figure 2).

Bioactive Molecules

Signaling Molecules

It is well known that chemokines can directly promote angiogenesis, ECM remodeling or formation and re-epithelialization.[43,44] These chemokines play a crucial role in the migration of inflammatory cells and mesenchymal stem cells.[45] Moreover, the chemokines (interleukin-8, IL-8; macrophage inflammatory protein-3α, MIP-3α) that possess the ability to recruit bone marrow-derived mesenchymal stem cells (BMSCs) for articular cartilage repair.[46] In addition, IL-8 is also known to be a potent promoter of angiogenesis.[47] Previous studies have shown that horseradish peroxidase triggered in-situ cross-linked gelatin-hydroxyphenyl propionic acid (GH) hydrogels can be used as an injectable carriers for tissue engineering and regenerative medicine.[48,49] Therefore, two types of chemokines (IL-8 and MIP-3α) could be loaded into GH hydrogel.[50] IL-8/MIP-3α was released through GH hydrogel within 7 days, and endogenous cells were able to attract chemokines to the wound. The incorporation of chemokines did

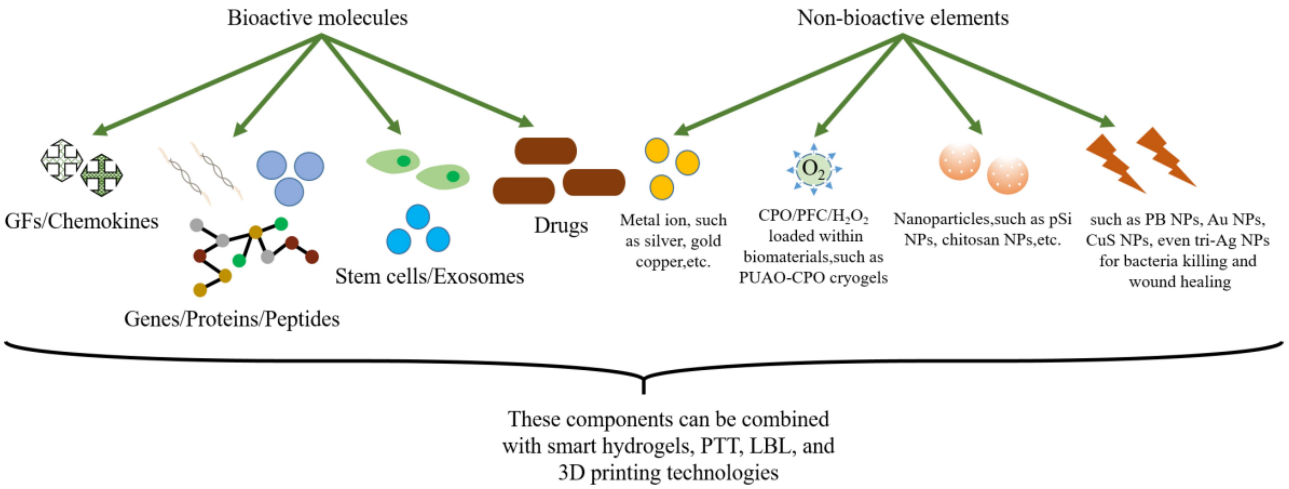

Figure 2 Schematic illustration of the categories of biomaterials used on diabetic wounds. Biomaterials are loaded with bioactive molecules (including GFs, genes/proteins/peptides, stem cells/exosomes, etc.) and non-bioactive substances (including metal ions, oxygen, etc.) to promote diabetic wound healing.

not affect hydrogels' properties (including swelling ratio and mechanical stiffness), and the bioactivities of IL-8 and MIP-3α were stably maintained in GH hydrogel. GH/IL-8 and GH/MIP-3α hydrogel dressings promote diabetic wound regeneration, enhance re-epithelialization/neovascularization and collagen deposition.[50] GH hydrogel can be used as a delivery platform for various therapeutic proteins for wound healing in the future.

Various growth factors are important function in mediating, coordinating and controlling cellular interactions during normal wound healing.[51] But in diabetic wounds, the balance of many growth factors is upset, damaging angiogenesis, disrupting the ECM, and ultimately delaying wound healing (Figure 3). A strategy of mediating the diabetic wound cell signaling is to locally administering endogenous therapeutic growth factors.[52] However, repeated high doses of growth factors are needed to achieve therapeutic effects.[53] And the proteases in the cells cause growth factors to degrade rapidly. Therefore, a delivery system is required not only to maintain growth factor activity, but also to enable sustained and controlled release of growth factors to the target. Currently, various systems (including nanoparticles, hydrogels and nanofibers) have been used for growth factors delivery in diabetic wound[54–61] (Table 1).

Previous studies have shown that VEGF-A is the primary pro-angiogenic factor in normal healing wounds.[62] Its expression reached a peak at 2–3 days after injury and continued to rise for about a week.[63] However, compared to normal mice, the increase of VEGF in db/db diabetes mice is transient, rather than sustained, and rapidly decreases to almost undetectable levels when granulation tissue is formed.[64] The results of clinical trials showed that single-dose application of VEGF to wounds alone has limited success due to its short half-life.[65] Repeated local delivery of VEGF-165 promoted rapid re-epithelialization and enhanced angiogenesis of diabetic wounds.[66–68] In order to overcome the disadvantages of short half-life and repeated delivery of VEGF, delivering VEGF by gene activation strategy should be effective. Physical encapsulation of nucleic acid-carrier complexes in a hydrogel can protect the carrier from degradation and provide more sustained, localized transfection compared with rapid delivery of growth factors or genes.[69] Hyaluronic acid (HA), the main component of the ECM, is a highly biocompatible biomaterial, which can also promote angiogenesis.[70] Porous HA hydrogel with encapsulated proangiogenic (pVEGF) plasmids for local gene therapy in diabetic wound healing.[70] These researches have shown that porous hydrogels did not degrade and provided a mechanical barrier to wound healing. However, transfection levels of pVEGF did not appear to be high enough to enhance angiogenesis by increasing vascular density or size.[70] Devalliere et al recombined keratinocyte growth factor (KGF) and cytoprotective peptides into a protein polymer with the aim of increasing their activity in vivo (enhancing anti-proteolytic ability), thereby accelerating chronic wound healing (increasing wound bed angiogenesis).[71] Previous studies have shown that two or more growth factors are more effective at stimulating angiogenesis and subsequent tissue repair than a single growth factor.[72,73] For example, co-

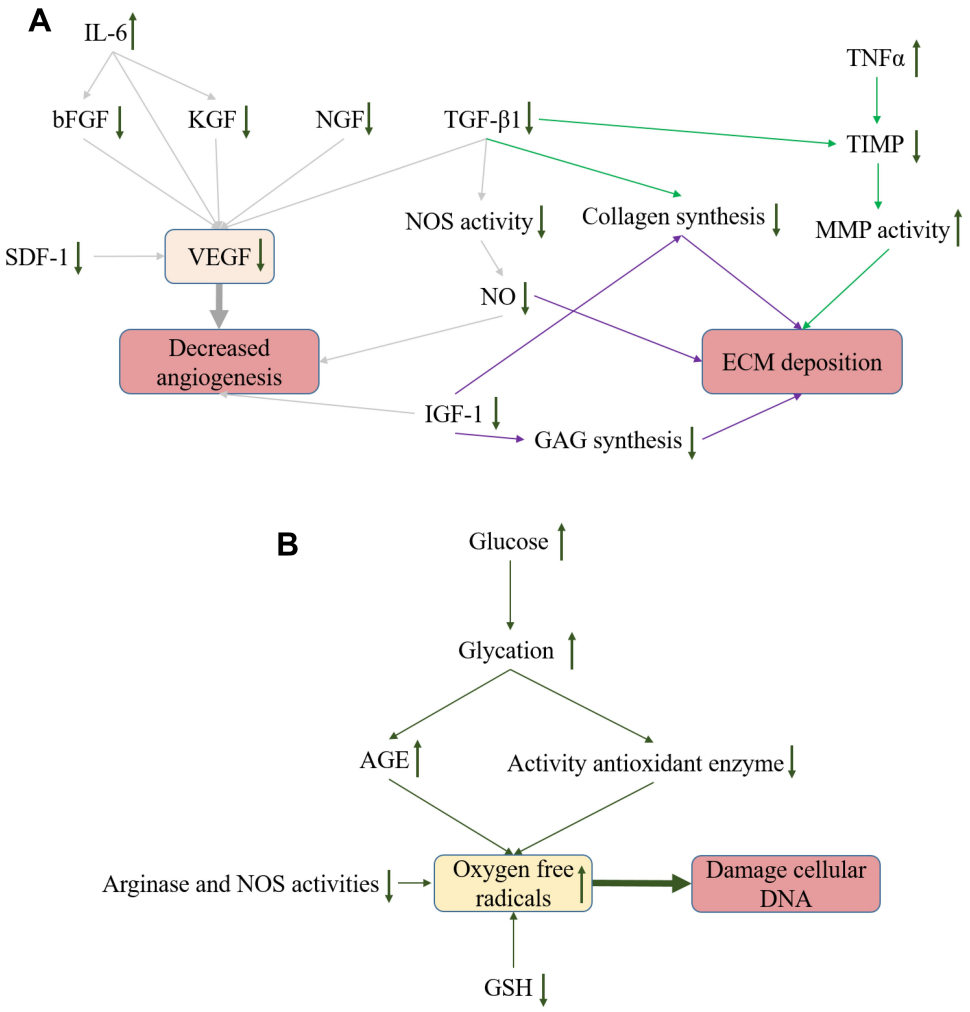

Figure 3 Changes in GFs in diabetic wounds. (**A**) Changes in growth factors in diabetic wounds and their effects on angiogenesis and ECM. (**B**) Hyperglycemia leads to the production of oxygen free radicals.

stimulation of VEGF-A and fibroblast growth factor 2 (FGF-2) significantly improves cell migration and angiogenesis in vivo compared to single angiogenic growth factor.[74] In addition, the delivery of bFGF and VEGF as dual factors immediately restored the vascular network.[75]

In the future, local controlled delivery of multiple GFs by the combination of nanoparticles and hydrogels. At the same time, determine the optimal degradation rate of the hydrogel and reduce the toxicity of the nanoparticles to allow for overall faster wound closure.

Genes/Proteins/Peptides

Targeting disease-related miRNA may be an effective therapeutic strategy in comparison with single-target angiogenic growth factors, since an individual miRNA with its pleiotropic effects can regulate multiple different genes and processes[76] (Table 2). Recently, miR-26a has been identified as a key negative regulator of angiogenesis in diabetic wounds, inhibition of this miRNA may be an effective treatment for diabetes.[76] Wu et al developed a redox-modulatory ceria nanozyme-reinforced self-protecting hydrogel (PCN-miR/Col).[77] PCN-miR/Col not only remodeled the oxidative wound microenvironment, but also ensured the structural integrity of the encapsulated pro-angiogenic miRNA in the oxidative microenvironment.[77] The design adopted the "seed-and-soil" concept in the regenerative medicine field with the aim to reshaping the oxidative wound microenvironment into a proregenerative one (the "soil"), and providing proangiogenic miRNA cues for diabetic wound repair and regeneration (the "seed"). The proposed "seed-and-soil" strategy is applicable to the repair and regeneration of a wide range of damaged tissues, which exposed to highly oxidative diseased microenvironments and dysfunctional biomacromolecules.[77] So, it is a new direction of treatment

Table 1 Growth Factors in Nanoparticles/Hydrogels/Scaffolds Used in Experimental Diabetic Wound Healing Studies

GFs	System	Results	Characteristic	References
IL-8 and MIP-3α	Gelatin hydrogels	Enhanced reepithelialization and increased collagen deposition.	Stable bioactivity; in situ cross-linking.	[50]
bFGF and NGF	Heparin-poloxamer hydrogel	Facilitating schwann cell proliferation, enhanced axonal regeneration and remyelination.	Good affinity; controlled GFs release.	[54]
VEGF and bFGF	PLGA nanoparticles	Induced complete re-epithelialization, with enhanced granulation tissue formation and collagen deposition.	Control release of multiple GFs.	[58]
VEGF, PDGF, bFGF and EGF	Col–HA–GN nanofibrous membrane	Elevated collagen deposition and enhanced maturation of vessels.	A stage-wise release pattern of multiple angiogenic factors.	[59]
pVEGF plasmids	HA hydrogels	Promoted wound closure and induced an enhanced angiogenic response.	Local gene delivery.	[56,70]
SDF-1	PPCN hydrogel	Exhibited accelerated granulation tissue production, epithelial maturation, and the highest density of perfused blood vessels.	Antioxidant thermoresponsive.	[55]
KGF	Elastin biopolymers	Increasing angiogenesis in the wound bed and accelerating healing.	Increasing GFs proteolytic resistance, thus improve their activity in vivo.	[71]
rh-aFGF	Carbomer hydrogel	Remarkable promotion of skin wound healing in diabetic rats with full-thickness injuries.	Good biostability.	[57]
PDGF	Sheath-core nanofibrous PLGA scaffolds	Sustainably released PDGF, vancomycin, and gentamicin for three weeks.	Biodegradable sheath-core nanofibers.	[60]
EGF	OHA and SCS hydrogels	Promotion of fibroblast proliferation and tissue internal structure integrity, as well as the deposition of collagen and myofibrils.	pH-responsive hydrogel.	[61]

for diabetic wounds. Li et al had developed a β-CD-$(D_3)_7$ as the gene carrier to carry siRNA, which effectively interfered with the expression of MMP-9, accelerated wound healing and could not cause organ damage and accumulation.[78] The results suggest that this gene carrier might be developed as a novel topical agent for the diabetic wound treatment. See (Table 2) for other systems.[79–81]

Although genes and growth factors are intended to improve angiogenesis and re-epithelialization, cost and safety issues remain in their application.[82] Introduction of peptides into hydrogels or scaffolds has been widely used to confer these tissue-engineering substrates with bioactivity[83–90] (Table 2). Carrejo et al prepared a multidomain peptide hydrogel that can rapid cell infiltration and elicit a mild inflammatory response, thereby promoting angiogenesis and accelerating wound closure in diabetes.[91] A therapeutic integrin-binding pro-survival peptide-engineered silk fibroin nanosheet that can regulate angiogenesis and promote diabetic ulcer healing.[92] Nanofibrous mats of *Antheraea assama* silkworm silk fibroin are coated with various recombinant spider silk fusion proteins through silk–silk interactions to fabricate multifunctional wound dressings.[93]

We recently reviewed the roles of peptides in diabetic wound healing. Research spans the use of native proteins, recombinant proteins, and engineered peptides with integration in a diverse set of substrates from conjugation to hydrogel matrices. While the current studies have demonstrated the benefits of these strategies, the key consideration should be how to promote diabetic wound repair. A large number of clinical trials should be carried out to conduct an overall evaluation of the efficiency and safety of peptides in diabetic wound healing.

Stem Cells/Exosomes

Stem cells can produce various bioactive substances (such as growth factors) to restore tissue/organ function, so stem

Table 2 Genes/Proteins/Peptides Used in Diabetic Wound Healing are Summarized. Most of the Genes are miRNA, and There are Both Natural and Synthetic Peptides

Gene/Proteins/ Peptides	Carrier System	Function	References
siRNA	β-CD-$(D_3)_7$; nanometer-scale coatings.	Decreasing MMP-9 expression.	[78,79]
Keap1 siRNA	Lipoproteoplex delivers	Activate Nrf2-mediated endogenous antioxidant mechanisms, normalize the ROS imbalance.	[81]
miR-26a	PCN hydrogel	Offer the proregenerative wound microenvironment and proangiogenic miRNAs.	[77]
Plasmid DNA encoding VEGF	Ga-BDEs	Enhance sustained expression of VEGF.	[80]
Heparin mimetic peptide amphiphiles	Nanofibers	Enhance production and activity of major angiogenic growth factors (VEGF).	[84]
DMOG	PCL fiber meshes	Reducing the expression of pro-inflammatory factors (IL-1β,IL-6, and TNF-α), increasing anti-inflammatory factors (TGF-β1 and IL-4) and GFs (IGF-1, HB-EGF, NGF, and bFGF), and promoting angiogenesis (CD-31 and VEGF-α).	[86]
$K_2(SL)_6K_2$	MDP hydrogels	Allowing rapid cellular infiltration, and thus are ideal for tissue engineering strategies.	[91]
Proline	IKFQFHFD hydrogel	Eradicate MRSA biofilm.	[85]
Spider silk fusion proteins	Nanofibrous mats of AaSF	Efficient matrix remodelling of wounds.	[93]
Heparin or bemiparin	CS hydrogels	Improved diabetes-associated impaired wound healing.	[87]
Nucleic acids	tFNAs	Antioxidant activity via the Akt/Nrf2/HO-1 signaling pathway.	[88]
Integrin	Silk fibroin nanosheets	Regulate angiogenesis and promote diabetic ulcer healing.	[92]
Laminin mimetic peptide SIKVAV	CS hydrogels	Significantly promoted BMSCs adhesion and proliferation.	[89]
MMP-9 inhibitor (R)-ND-336	Linezolid	Inhibiting the detrimental MMP-9, mitigating macrophage infiltration to diminish inflammation	[90]

cell therapy is one of the most promising methods for diabetic wounds[94–101] (Table 3). Epidermal growth factor (EGF)-loaded microcapsules and human adipose-derived stem cells (ADSCs) are integrated into the collagen hydrogel and facilitate tissue regeneration and effectively restore blood perfusion.[102] Moreover, acrylated hyaluronic acid (AHA) hydrogels load pluripotent stem cells (hiPSCs) treat type-1 diabetic wounds.[103] In addition, gingival mesenchymal stem cells (GMSCs) loaded into the chitosan/silk hydrogel sponge effectively promote the skin wound healing.[104] With the capacity to protect and regulate immune function during the healing process, macrophages (MΦ) especially MΦ2, contribute to reduce inflammation and promote proliferation and angiogenesis by releasing anti-inflammatory cytokines and growth factors (such as TGF-β and VEGF).[97] Although the pullulan −collagen composite hydrogel has been reported to deliver monocytes or macrophages to the wound bed, the interaction between immune cells and the material is unclear. Liu et al have reported a 0.5Cu-HHA/PVA@MΦ2 hydrogel to provide and regulate MΦ2 for synergistic improvement of immunocompromise and impaired angiogenesis to

Table 3 Summary of Stem Cell/Exosomes Towards Effective Control of Diabetic Wounds

Cell Types	Systems	Characteristic	References
SMSC exosomes	CS Wound Dressings	Overexpression microRNA-126-3p exosomes.	[118,119]
AMSCs exosomes	OHA hydrogels	Bioactive multifunctional properties (injectability, self-healing, antibacterial activity, stimuli-responsive exosomes release).	[116]
GMSCs Exosomes	CS/Silk hydrogel sponge	Combination of GMSC-derived exosomes and hydrogel.	[114]
ASCs exosomes	FEP dressing	Injectable adhesive thermosensitive multifunctional dressing.	[117]
hASC exosome	hASC-exos carrying miR-21-5p as a cargo by electroporation	Combination of ASC-exos with miR-21 to achieve synergetic therapeutic.	[115]
hiPSCs	AHA hydrogels	Engineering vascularized constructs.	[103]
ASCs	PEG-gelatin hydrogel	Delivery of allogeneic ASCs in vivo.	[95]
MSCs	RGO nanoparticles	Acellular dermal composite scaffold.	[96]
ADSCs	GSL cryogels	Delivering ADSCs on antioxidant GS scaffolds coated with GSL, an endothelial basement protein to improve angiogenesis.	[98]
M2 phenotype macrophages	HHA hydrogel	Multiple modulation mechanisms of immunocompromise and angiogenesis.	[97]
Decellularized ECM	dECM hydrogels	Hydrogels derived from genetically engineered.	[100,101]
ECM-biomimetic cell-free nanofibrous	Bone ECM-biomimetic nanofibrous scaffolds	Without additional growth factors.	[99]

accelerate the diabetic chronic wound healing phase transition from inflammation to proliferation and remodeling.[97] Hydrogels facilitate the adhesion, growth, migration and regeneration of immune cells.

Exosomes are nanoscale membrane vesicles (30–150nm in diameter) that can be identified by the expression of exosome-related markers (such as *Alix, Tsg101, CD9, CD63* and *CD81*) and carry functional complexes of proteins, lipids and nucleic acids.[105–108] Therefore, exosomes are considered as drug delivery carriers, and natural RNA carriers for the treatment of diseases.[109–111] And exosomes are considered as one of the most important secretory products of bone marrow mesenchymal stem cells, which can mediate intercellular communication and promote wound healing.[112–115] Polypeptide-based FHE hydrogel (F127/OHA-EPL) contains adipose-derived mesenchymal stem cell exosomes (AMSCs-exo),[116] FHE@exo hydrogel has multifunctional properties of biological activity, including injectability, self-healing, antibacterial activity, and exosome release. And it can significantly improve the proliferation, migration and angiogenesis of human umbilical vein endothelial cells (HUVECs). FHE@exo hydrogel promotes neovascularization and cell proliferation, leading to faster granulation tissue formation, re-epithelialization, and collagen remodeling at wound sites, thus accelerating the healing process of diabetic wounds.[116] Wang et al developed an injectable thermosensitive multifunctional polysaccharide-based dressing (FEP) with sustained pH-responsive exosome release that promotes angiogenesis and diabetic wound healing.[117] Moreover, hydroxyapatite/chitosan or chitosan hydrogel incorporating microRNA-126-overexpressing synovium mesenchymal stem cells (SMSC-126-Exos) can accelerate re-epithelialization, stimulate the proliferation of human dermal fibroblasts, and activate angiogenesis.[118,119] Exosome-based hydrogels hold great promise in the treatment of chronic wounds (especially diabetic wounds) and skin regeneration. Therefore, it may become a treatment means in the future.

Drugs

Under the framework of pharmaceutical and clinical challenges of drug delivery in diabetic wound infections, an ideal drug delivery system must deliver the drug in deep layers of skin. The nanoscale local drug delivery system, combined with hydrogel/nanoparticles properties, can stabilize the long-term release of drugs to the wound and promote healing.[120] At present, a variety of complex delivery systems have been developed to extend drug delivery time[121–126] (Table 4). A multi-responsive composite polydopamine/nanocellulose hydrogel with the ability of drug

Table 4 Delivery of Drug/Natural Macromolecular Bioactive Substances Systems with Effective Control of Chronic/Diabetic Wounds

Drugs/	Drug Delivery Systems	Functions	References
Deferoxamine(DFO)	TDDS; multifunctional hydrogels; nanofibrous/scaffolds.	Increases HIF-1α expression; upregulate VEGF expression.	[132–134]
Statins	Tissue engineering scaffold	In situ eNOS/NO up-regulation.	[121]
Insulin	Injectable hydrogels	pH and glucose dual-responsive hydrogels.	[137]
Curcumin	Gelatin microspheres; chitosan nanoparticles.	MMP9-responsive drug-release system; anti-inflammatory and antioxidant.	[139–141]
Dimethyloxalylglycine (DMOG)	Porous electrospun fibrous membrane	Controllable released DMOG drugs	[138]
Ciprofloxacin	CS and cyclodextrin polymer sponges	local drugs release without risk of toxicity to the body.	[122]
Snail glycosaminoglycan	Sulfated polysaccharide	Accelerated the healing of full-thickness wounds in diabetic mice skin.	[123]
Kirenol	Diterpenoid	Encourage angiogenesis, fibroblast propagation	[124]
Quercetin	Collagen-nanomaterial-drug hybrid scaffold	Promoting collagen deposition and angiogenesis in diabetic wound repair.	[125]
Herbal extract of didymocarpus pedicellatus	pDMAEMA–HA hydrogel	Enhanced cutaneous wound repair as well as high level of cellular repair.	[126]

(tetracycline hydrochloride) release and wound healing.[127] The drug can be released continuously for more than 24 hours, and no explosive drug release occurs at the beginning of the release process. The maximum drug release ratio reached 77%, with long-term drug delivery properties.[127] Desferrioxamine (DFO) is used as a hypoxic-mimetic agent, and has been used for the induction of HIF-1α accumulation.[128–130] And HIF-1α has been shown to play an important role during the wound healing.[131] DFO-loaded hydrogel/scaffolds by upregulating HIF-1α that rapidly promote angiogenesis for diabetic skin regeneration[132–134] (Figure 4). In addition, mixed

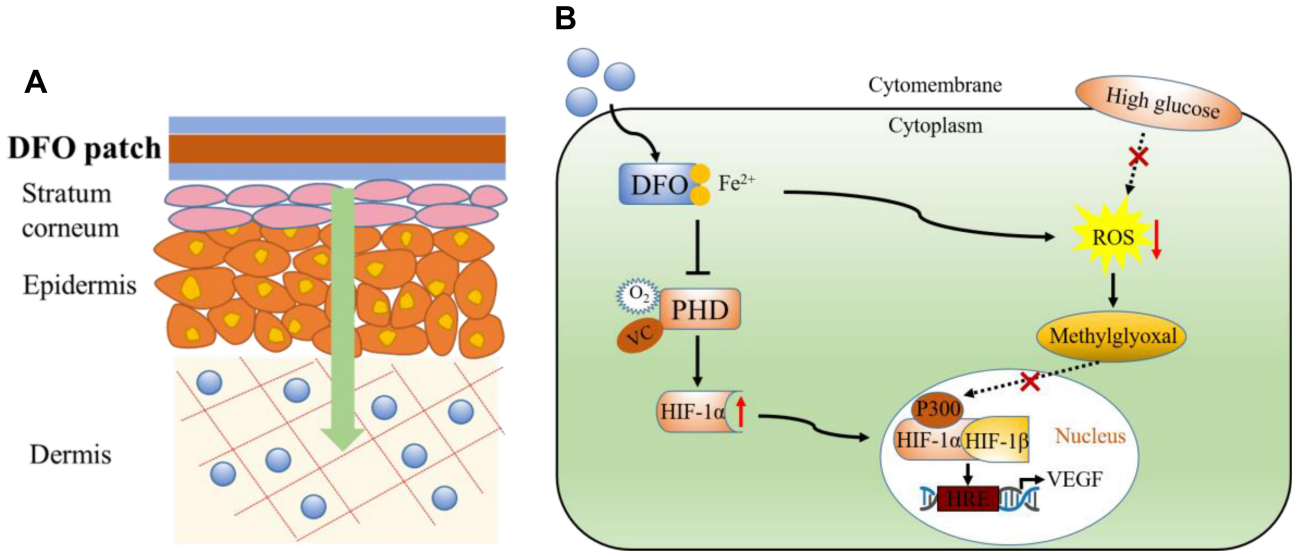

Figure 4 Development of a transdermal drug delivery system for DFO. (**A**) DFO patch is administered through transdermal drug delivery system into the dermis to perform its functions. (**B**) Functional diagram of DFO and its regulation in the HIF-1a signaling pathway.

DFO and bioglass (BG) in sodium alginate hydrogel, BG and DFO could synergistically upregulate HIF-1α and VEGF expression, and subsequently vascularization in the wound sites, and better facilitate diabetic skin wound healing.[135] Insulin is a universal drug for treating diabetes because it is a physiological glucose-lowering agent. The use of topical insulin became of greater interest as a healing agent in diabetic foot ulcers.[136] However, the use of topical insulin presents a great challenge due to the instability of the molecule. In order to ensure molecular stability of insulin, it is incorporated into hydrogels to maximize its effect. Recently, the drug- and cell-loaded hydrogels have promising potential in wound healing. Protein drugs (insulin) and live cells (fibroblasts L929) can be encapsulated in the pH and glucose dual-responsive injectable hydrogels, this hydrogel dressing could promote neovascularization and collagen deposition and enhance the wound-healing process of diabetic wounds.[137] The combination of drugs and cell/growth factors hydrogel may be a promising approach to enhance wound healing and can also be used for the regeneration of other vascularized tissues. A kind of aligned porous poly (L-lactic acid) electrospun fibrous membranes loaded mesoporous silica nanoparticles that release dimethyloxalylglycine for diabetic wound healing.[138] Encapsulation of curcumin nanoparticles with MMP9-responsive and thermos-sensitive gelatin microspheres hydrogel improves diabetic wound healing.[139–141]

Improving some properties of composite scaffolds/hydrogels can increase drug load and control drug release. When scaffolds/hydrogels are subjected to certain stimulation (near infrared laser irradiation or pH), drugs are released in "on-off" mode without explosive drug release at the beginning of the release process, and has long-term drug delivery performance. In the future, our research direction should be precise administration, which can be achieved gradually at different stages of wound healing. Wound-healing research will need to incorporate hydrogels, which can deliver more DNA, growth factors, peptides and drugs, increasing angiogenesis and wound healing. It is also important to determine the optimal hydrogel degradation rate and water content for faster wound healing, while maintaining complex release and mechanical support to the wound bed. However, emerging drug resistance and physicochemical characteristics require the design of more accurate topical drug delivery systems which could be combined with 3D technology to achieve high functional efficiencies in terms of permeability, stability and therapeutic efficacy.

Non-Bioactive Elements

Metal Ion

Currently, the antibacterial nanoparticles used in wound healing are silver nanoparticles, gold nanoparticles, copper nanoparticles, nano-bioactive glass particles, etc.[142–147] Among different metal nanoparticles, AgNP is the most active nanoparticle due to its unique anti-inflammatory properties and antibacterial activity against natural and nosocomial strains of multidrug-resistant (MDR) microorganisms, promoting wound healing.[148] The mechanisms of antimicrobial action of AgNPs are of two types, (a) the inhibitory action and (b) the bactericidal action.[15] Such as NIR laser-excited silver triangular nanoparticles (Tri-Ag) can eradicate multidrug-resistant bacteria and promote wound healing.[149] Tong et al constructed a combinational antibacterial system by loading AgNPs on the polydopamine-modified prussian blue NPs(PB@PDA@Ag), the bactericidal mechanism of this system can be attributed by damaging cell integrity, producing ROS, the reducing ATP and disrupting bacterial metabolism.[150] Likewise, Zhao et al used polydopamine decorated silver nanoparticles, and then loaded into conductive hydrogel to inhibit bacterial growth and control diabetic wound infection.[151] Gold NPs (AuNPs) can perform gene transfer, drug delivery, as biosensors and cancer cell imaging, angiogenesis as well as wound healing.[152–155] AuNPs could inhibit the lipid from peroxidation and prevents the formation of ROS to restores antioxidant discrepancies.[15] AuNP combines with epigallocatechin gallate (EGCG) or alpha-lipoic acid (ALA) or both (EA) to achieve synergistic effects and enhance diabetic wound healing by modulating angiogenesis and anti-inflammatory effects.[156,157] Wang et al optimized a novel gene delivery system based on antimicrobial peptide (LL37) grafted ultra-small gold nanoparticles for the topical treatment of diabetic wounds with or without bacterial infection.[158] Copper nanoparticles (CuNPs) have been gained increasing attention due to its antibacterial activity in diabetic foot ulcer infections[159,160] (Table 5). Bhadauriya et al focused on the synthesis of the yeast extract-immobilized and copper nanoparticle-dispersed carbon nanofibers as a potential diabetic wound dressing material.[161] Copper-based metal −organic framework nanoparticles can be modified to slowly release Cu^{2+}, which reduces toxicity and improves wound healing in diabetes.[147,159,160] However, rapid oxidation and agglomeration of copper nanoparticles are key problems during their use, and needs to control the stability of CuNPs by using biocompatible stabilizer such as chitosan and folic acid.[159–161]

Table 5 Metallic and Metal Oxide Nanomaterials are Used in Diabetic Wound Repair

Metal Ion	Delivery Systems	Relative Merits	References
Silver	PB@PDA@Ag nanosystem; PDA@Ag NPs/CPHs hydrogels	1.Eradicating MRSA assisted with NIR; 2.Epidermal sensors	[145,146,150,151]
Copper	HKUST-1 NPs; Cu-CNF-YE nanofiber; BSA-CuS nanoparticles	1.Decrease copper ion toxicity and apoptosis; 2.Simultaneous control of bacterial infections; 3.As a controllable NO-releasing vehicle.	[147, 159–161, 213]
Gold	AuNPs@LL37	1.A novel gene delivery system; 2.Topical treatment of diabetic wounds with or without bacterial infection	[158]
Rubidium	Rb−CA gel hydrogel	Rb−CA gel exhibited a strong anti-inflammatory effect on the wound.	[208]
Si and Ca ions	BG/AA hydrogel; BG/PEM membrane;	1.BG particles stimulated macrophage proliferation; 2.Improve the angiogenic condition of the wound area.	[163,164,167,168]
Iron −Copper	Bimetallic Fe−Cu nanocomposite	1.Antimicrobial activity; 2.wound healing property	[165]
nCeO	PHBV membrane	Enhance cell proliferation and vascularization	[210]
MoS2	MoS2-BNN6 nanovehicle	MoS2-BNN6 nanovehicle can precisely control NO release, generating oxidative/nitrosative stress.	[212]
NAGEL particles	PCL/gelatin nanofibers scaffold;	1.Released Si ions; 2.Synergetic effect on the improved efficiency of diabetic wound healing.	[162,169]

In recent years, bimetallic/polymetallic composite nanomaterials have great potential in diabetic wound repair.[162–164] Das et al reported a bimetallic (Fe-Cu) wound healing dressing material that exhibited antimicrobial activity against methicillin-resistant *Staphylococcus aureus* and displayed in vivo diabetic wound healing property.[165] Bioactive glass (BG), which is typically composed of Na_2O, SiO_2, CaO and P_2O_5, is considered to be a classical material for hard tissue regeneration.[166] The ionic products of bioglass dissolution stimulate macrophages to secrete anti-inflammatory factors.[167] Zeng et al combined bioglass and sodium alginate for diabetic wound healing.[168] Jiang et al found that the Si ions released by bioactive glass up-regulated the expression of VEGF.[169]

In the future, the reversible swelling-shrinking transition of hydrogels can be utilized to achieve controllable and sustained release of Ag^+, Cu^{2+} and Si^{2+} etc., so as to avoid the explosive ion release causing damage to cells. This system has great potential in tissue repair and antibacterial application.

Oxygen

Chronic diabetic wounds are limited in oxygen supply due to vascular dysfunction and neuropathy.[170] In addition, high oxygen consumption by cells during inflammation also leads to hypoxia in the wounds. Due to the increased utilization of oxygen in some regenerated tissues, there are inevitable differences between the supply and demand of oxygen, and the result is a hypoxic environment with high oxidative stress.[171] In addition, increased oxidative stress in diabetic ulcers is caused by macrophages and neutrophils producing more ROS in a hyperglycemic response.[172,173] Hence the need for multifaceted biomaterials that will simultaneously reduce the oxidative stress, provide oxygen, and induce angiogenesis. To reduce oxidative stress, Zhu et al developed a thermoresponsive antioxidant poly(polyethylene glycol co-citric acid-co -N-isopropylacrylamide) hydrogel (PPCN) that uses the laminin-derived dodecapeptide A5G81 (PPCN-A5G81). A5G81 peptide conjugation to PPCN via the cross-linker N-β-maleimidopropionic acid hydrazide. A5G81 has unique receptor-mediated and antioxidant properties and is beneficial to the diabetic wound repair.[174] Novel nanofibrous mats (chitosan/poly (vinyl alcohol)/ZnO nanofibrous) with antibacterial and antioxidant properties for diabetic wound healing,[175] but the mechanism of the

healing of diabetic wounds caused by nanofiber mats has not been clarified in this study.

Oxygen Containing Nanocarriers

At present, oxygen-producing materials are mainly delivered through some nanoscale systems to relieve wound hypoxia. The main oxygen-producing materials are sodium percarbonate (SPO), calcium peroxide (CaO_2), magnesium peroxide (MgO_2), hydrogen peroxide (H_2O_2), and fluorinated materials.[176–180] It has been shown that the combination of nanomedicine and some oxygen-producing agents can improve the wound healing of diabetes.[30] Recently, Shiekh et al developed a porous cryogels (polyurethane polymeric material-calcium peroxide, PUAO-CPO), PUAO-CPO cryogels can not only continuously release oxygen, but also supplement with adipose-derived stem cell (ADSCs) exosomes[181] (Figure 7B). Nanoperfluorocarbon (nano-PFC) has been widely studied as an oxygen-carrying system to overcome hypoxia-associated resistance in cancer therapies due to its high oxygen affinity and good biocompatibility.[182–184] In addition, PFC has been approved by the USA Food and Drug Administration (FDA) to improve myocardial oxygenation and prevent ventricular dysfunction.[185,186] Therefore, nano-PFC can be used as a nano-drug delivery system (NDDS) to deliver molecules, such as drugs and oxygen to target tissues, and release the contents under the stimulus of external conditions.[187,188] Wang et al combined the radial extracorporeal shock wave therapy (rESW) with oxygen-carrying nano-PFC to provide targeted oxygen supply, improving blood microcirculation of DFUs and accelerating wound healing.[189] And when nano-PFC is injected into the blood circulation, the nanodroplets triggered by rESW can reversibly release oxygen within the tumor tissue[189] (Figure 8C). This strategy offered a great potential for further clinical trials. However, the potential safety problems of PFC-based micro/nanomaterials cannot be ignored. Therefore, a large number of experiments are needed to further prove its reliability. In addition, Zehra et al developed a polycaprolactone (PCL)-based oxygen-releasing electrospun wound dressings. The dressing can produce oxygen continuously for up to 10 days and stimulate angiogenesis.[190] These oxygen-loading nanomaterials can improve wound healing efficiency. Therefore, oxygen-producing biomaterials are essential to cure chronic diabetes wounds in the future[191–194] (Table 6).

Hydrogen Sulfide Containing Nanocarriers

Besides, the synthesis and levels of circulating hydrogen sulfide (H_2S) are reduced in diabetic mellitus.[195] Studies have shown that H_2S can stimulate cell proliferation and migration and regulate ECs assembly into capillary structures.[196] Therefore, exogenous H_2S supplementation is a promising treatment method to promote refractory wound healings in diabetic. Lin et al used emulsion technique to prepare NaHS particles (NaHS@MPs), which could be used as in situ depot for continuous release of exogenous H_2S under physiological conditions.[197] The sustained release of H_2S from NaHS@MPs promotes several cell behaviors, including epidermal/endothelial cell proliferation and migration, as well as angiogenesis, by extending the activation of cellular ERK1/2 and p38,

Table 6 Summary of Current O_2 Delivery Systems

Materials	Delivery Systems	Functions	References
Perfluorocarbon	Nano-PFC	The targeted release of oxygen into the wound from oxygen-loaded Nano-PFC	[189]
MNs with oxygen carrying	GelMA tips	Oxygen carrying and controllable oxygen delivering ability for wound healing	[191]
Calcium peroxide	OxOBand; PGS/PCL nanofibers; scaffolds; OGA hydrogel	Delivering oxygen, inducing angiogenesis, and management of oxidative stress and infection	[181,192–194]
Sodium percarbonate	PCL nanofibers scaffolds	Continuously generating oxygen for up to 10 days	[190]
Sodium hydrosulfide	NaHS@MPs	NaHS@MPs sustained release of exogen-ous H2S under physiological conditions	[197]
Nitric oxide	DNICs	Continuous release of nitric oxide	[201]

accelerating the healing of full-thickness wounds in diabetic mice.[197]

Nitric Oxide Containing Nanocarriers

NO is an antibacterial agent effective against a broad range of bacteria, including biofilm forming microorganisms, through an oxidation process involving free radical superoxide (O2*−) to form peroxynitrite (−OONO).[198] Nitric oxide (NO) plays a key role in the physiological regulation of vascular function, but in diabetic patients, NO synthesis and bioavailability decrease as well as NO consumption increases.[199,200] A direct and effective strategy for promoting diabetic skin ulcer healing is exogenous supplement of NO. Chen et al activated the NO-sGC-cGMP pathway by inducing long-term NO release (t= 27.4±0.5 h at 25°C and 16.8±1.8 h at 37°C) and maintaining the angiogenesis process.[201]

Technology

Nanoparticles

Nanoparticle (NP) is a basic component of nanostructure and has its unique size and characteristics.[202] NPs applications mainly include drug and gene delivery, tissue engineering and fluorescent biological labels, etc.[203–206] (Figure 5). Currently, the NPs used in diabetics wound healing mainly include metallic and metal oxide nanomaterials, nonmetallic nanomaterials (Table 7). NPs and nanotechnology allow them to achieve high local drug concentrations with relatively few side effects compared to traditional drug delivery systems, so drug therapy is more effective. There are two main criteria of nanomaterials used in wound healing (1) nanomaterials that are beneficial to wound healing; (2) nanomaterials as delivery vehicles.

Metallic and Metal Oxide Nanomaterials

The antibacterial mechanism of silver is realized by blocking the respiratory enzyme pathways and altering the microbial DNA and cell wall.[15] Tong et al promoted diabetic wound healing through the antibacterial of silver ions.[150] Copper ions can also stimulate angiogenesis and collagen deposition processes in addition to antibacterial effects, thus improving diabetic wound healing.[159–161] Rubidium (Rb) is an important microelement for the human body. Rb+ has been reported to inhibit or kill bacteria by affecting membrane potential.[207] He et al loaded rubidium into calcium alginate hydrogel to achieve antibacterial and promote diabetic skin wound healing.[208] The intrinsic antibacterial properties of zinc oxide nanoparticles (nZnO) prompt the use of these nanomaterials in several hydrogel-based wound dressings.[209] Cerium oxide nanoparticle incorporated electrospun membranes for diabetic wound healing.[210] However, despite the high potential of metallic nanoparticles in treating drug-resistant bacteria, the high toxicity of these materials limits their use in wound healing.[211] In addition, Gao et al have reported a new near-infrared 808nm laser-mediated nitric

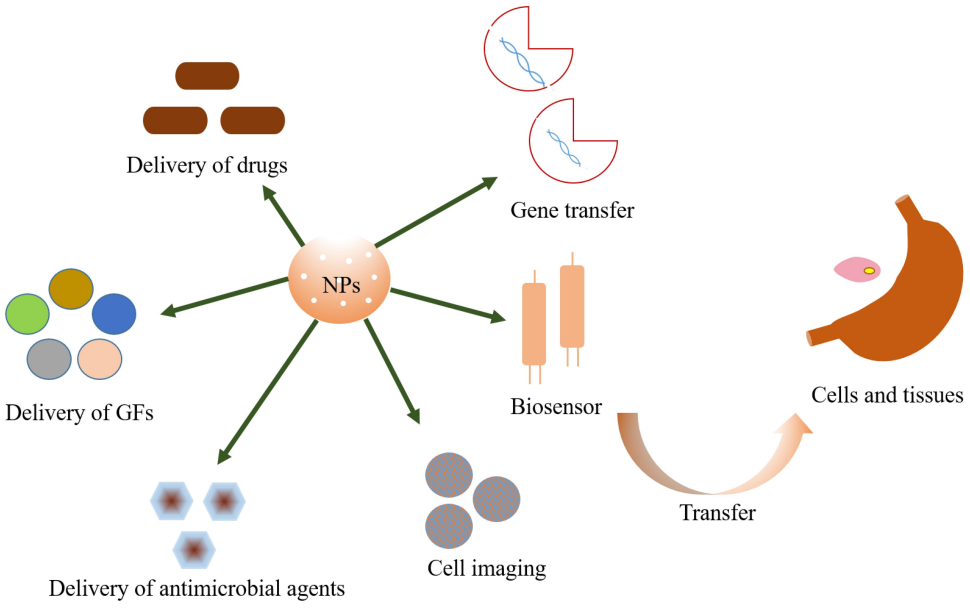

Figure 5 The major applications of nanoparticles.

Table 7 Other Approaches for Diabetic Wound Repair

Technology	Systems	Results	References
NPs	Chitosan/PVA Nano fiber; CW/NPs/HBC-HG hydrogel; MEL-NPs; CS/PVA/ZnO nanofibrous membranes.	Substrate does not have any recognized cytotoxicity; antibacterial properties.	[175,222–224]
	rGO; ADM-GO-PEG/Que.	Enhanced angiogenesis, collagen synthesis, and deposition in treated wounds.	[125,214]
	pSi NPs.	FnAb-loaded pSi NPs treated with proteases show intact and functional antibody for up to 7d post-treatment.	[220]
3D printing	A top layer made of silver-loaded gelatine cryogel; a bottom layer made of PDGF-BB-loaded 3D printed Gel scaffold.	The substrate was able to promote reepithelialization, granulation tissue formation, collagen deposition and angiogenesis in vivo.	[248]
	Satureja cuneifolia-loaded SA/PEG scaffolds.	3D printed scaffolds have shown an excellent antibacterial effect	[262]
	Microneedle patches.	Regulated the blood glucose levels of diabetic mice in normoglycemic ranges for up to 40 h	[263]
	Radially or vertically aligned nanofibers in combination with BMSCs.	Enhancing the formation of granulation tissue, promoting angiogenesis, and facilitating collagen deposition.	[249]
	PCL hydrophobic outer layer; Gel-pio inner layer.	Exhibit excellent ability to waterproof and prevent bacterial adhesion.	[250]
	Four-layer composite dressing (PU and dCA).	Not only allows wound exudates transport from wound bed to the dressing, but also enables controlled backflow of bioactive ion containing fluid to the wound bed for stimulating angiogenesis.	[251]

oxide-releasing nanovehicle (MoS_2-BNN6), MoS_2-BNN6 can effectively inhibit the growth of ampicillin-resistant *Escherichia coli*, heat-resistant *Escherichia faecalis*, and *pathogen Staphylococcus aureus*.[212] Zhao et al used bovine serum albumin stabilized-CuS (BSA-CuS) NPs to propose that PTT could kill bacteria in the field of diabetic wound infection[213] (Figure 6). See Table 5 for detailed description of metal ion nanoparticles.

Nonmetallic Nanomaterials

A recent study reported that the use of graphene oxide (rGO)-isabgol nanocomposite dressings for enhanced vascularization and accelerated wound healing in normal and diabetic rats.[214] Furthermore, a study has shown that the different adhesion and bioactivity properties of GO can prevent bacterial adhesion and biofilm formation. Therefore, there is a growing interest in studying the potential of graphene-based materials in biomedical applications, such as drug delivery, tissue engineering, imaging, biosensing and wound healing.[125,215,216] Porous silicon (pSi) is a biological material widely used in vivo and in vitro.[217] pSi has the ability to store and release a variety of small molecular drugs, oligonucleotides, and even protein therapeutics.[218,219] The use of porous silicon nanoparticles (pSi NPs) is demonstrated for the controlled release of Flii neutralizing antibodies (FnAb) to diabetic wounds.[220] The use of nanotherapeutic drugs alone may cause rapid degradation and cannot reach the target tissue quickly and effectively, thus reducing the biological effect.[58] Xie et al used a dual-growth factor releasing nanoparticle-in-nanofiber system, encapsulated platelet derived growth factor in NP, embedded into VEGF nanofiber, and delivered VEGF quickly and PDGF in a relayed manner. Nanofiber/nanoparticle scaffolds significantly accelerate wound healing by promoting angiogenesis, increasing reepithelialization, and controlling granulation tissue formation.[221]

Naturally occurring polymers, such as chitosan nanoparticles, have been studied for their antibacterial activity and pro-wound healing properties.[222,223] Correa et al reported a melatonin loaded lecithin-chitosan

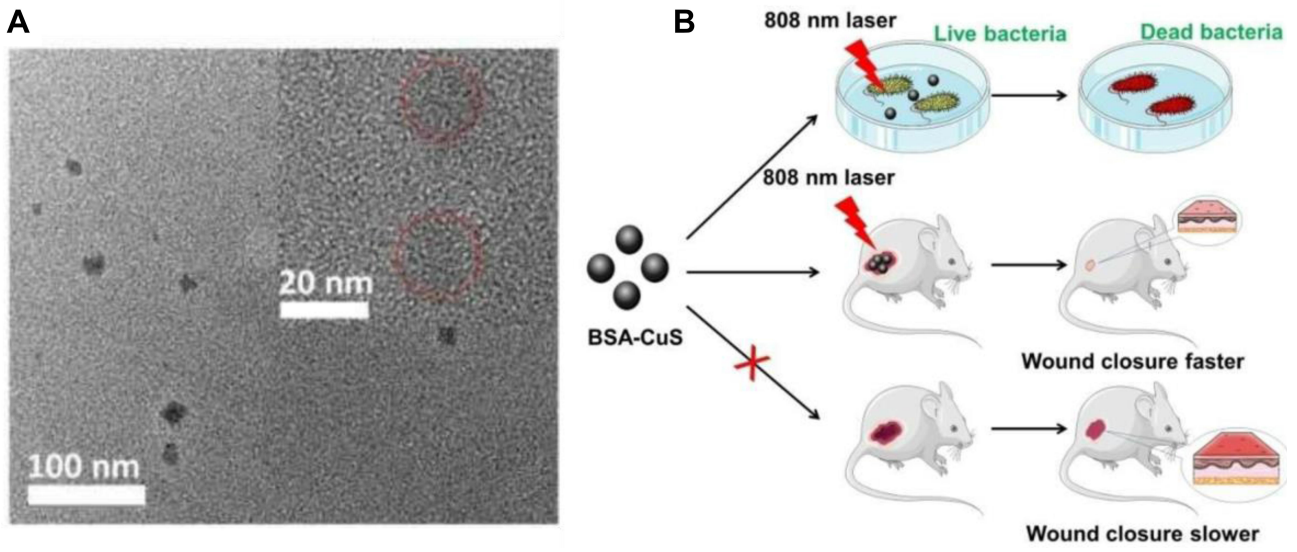

Figure 6 Schematic diagram of BSA-CuS antibacterial therapy. Reprinted with permission from Zhao Y, Cai Q, Qi W, et al. BSA-CuS nanoparticles for photother- mal therapy of diabetic wound infection in vivo. *Biol Chem ChemBiol*. 2018;3:9510–9516. Copyright 2018, John Wiley and Sons.[213] (**A**) HRTEM image of the BSA-CuS nanoparticles. (**B**) Schematic illustration of BSA-CuS nanoparticles as photothermal agent for photothermal antibacterial therapy in vitro and in vivo.

nanoparticles improved the wound healing in diabetic rats.[224] Chitosan composites usually exhibit unique properties that are not individually displayed by chitosan or the incorporated materials.[175,225]

Currently, nanocarriers have been validated in vitro and offered potential therapeutic applications that require to be further tested in vivo. At the same time, several nano-therapeutic agents are used in combination with NPs (loaded copper, which is helpful for wound healing) to provide synergistic effect and accelerate wound healing.

Smart Hydrogels

Hydrogels are considered to be three-dimensional nanofiber materials composed of cross-linked hydrophilic polymer networks.[46] Due to the presence of chemical or physical cross-links, they are able to swell and retain large amounts of water, and preserving their structural and dimensional constrained integrity.[47] Hydrogels are biocompatible and biodegradable materials and have been used in cell therapy, drug delivery, biosensing, tissue engineering and wound healing[226–229] (Table 8).

Injectable Hydrogels

In recent years, injectable hydrogels have favored among researchers due to its nonsurgical treatment to the patients for the purpose of mini-invasive medicine, especially for deep, irregular injuries.[230,231] To enable injection, most in situ forming hydrogels are delivered in a liquid form that will subsequently solidify in the body.[232,233] Typically, the injected precursor gel solution forms a hydrogel via chemical (eg, michael-type addition reaction, disulfide bond formation, click chemistry, radical polymerization) or physical (eg, ionic interactions, hydrogen bonding, hydrophobic interactions) crosslinking.[234,235] Chen et al developed injectable self-healing and antibacterial hydrogel, the multi-functional hydrogel featured manageable, resistant to mechanical irritation, antibacterial and angiogenic properties. Hydrogel would show great promise in the physiological dysfunction and bacterial infection wounds.[236] However, further studies are needed on the release and cytotoxicity of silver ions. Wang et al developed multifunctional hydrogel (injectable, self-healing, and adhesive) that simultaneously eliminated MRSA infection, reduced hyperglycemia, improved oxidative stress, and continuously provided oxygen.[237] In addition, Kong et al loaded desferrioxamine and bioglass into injectable sodium alginate hydrogel to synergistic promote diabetic wound healing.[135]

There have been many reports on wound dressing with bioactive/non-bioactive substances (growth factors, stem cells/exosomes and oxygen, etc.) for diabetic wound, but few studies have considered the specific physiological environment (such as acidic pH, ROS and high glucose levels) of diabetic wounds. Li et al reported a pH and glucose dual-responsive injectable hydrogel by in situ crosslinking of modified chitosan and oxidized dextran, and then Zhao et al incorporated insulin and fibroblasts into the hydrogel, which could not only respond to pH and glucose, but also promote wound healing in diabetic wounds.[137,238] Zhu et al used zwitterionic hydrogel to monitor pH value and glucose concentration in diabetic

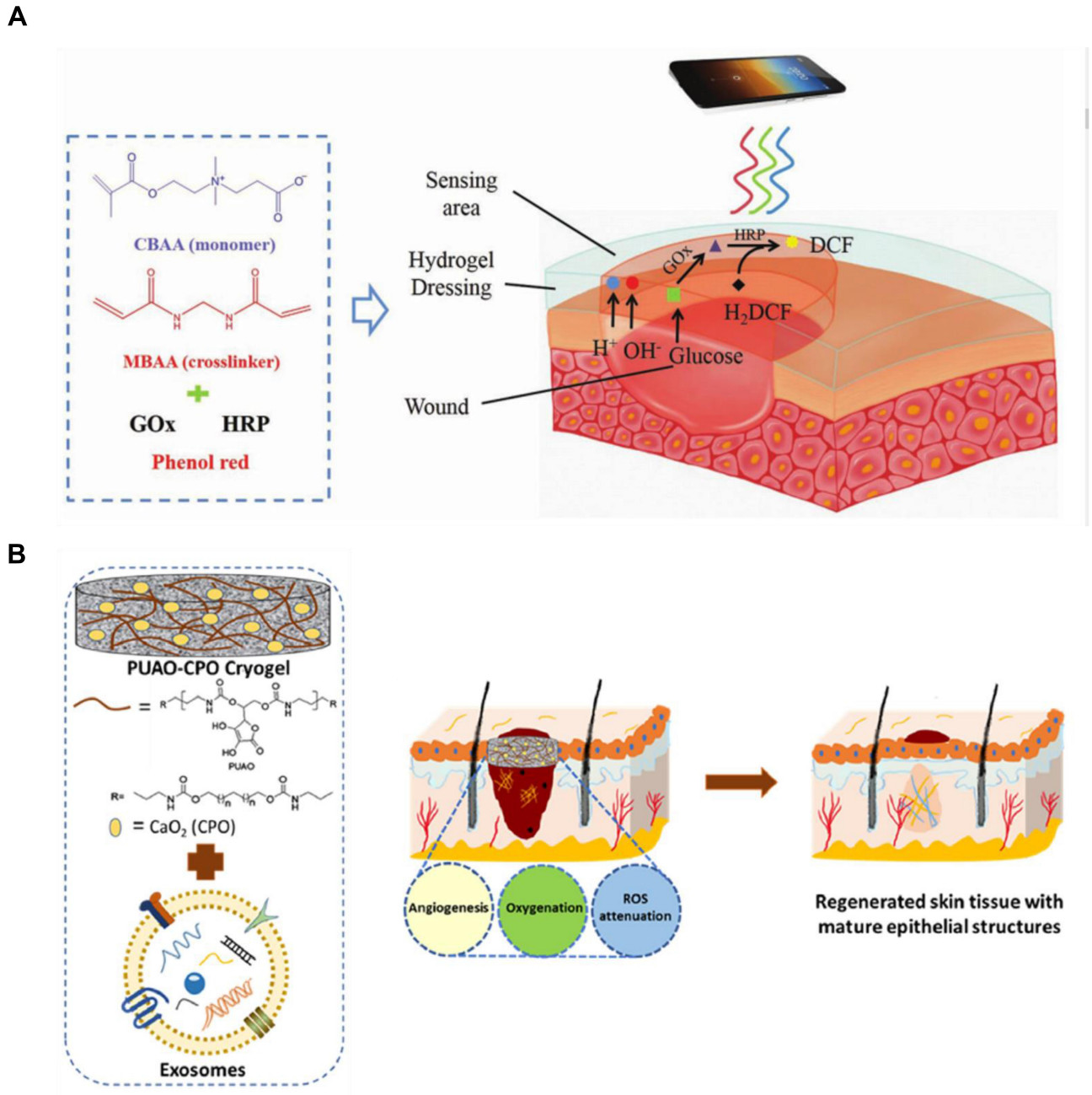

Figure 7 Schematic diagram of hydrogel synthesis. (**A**) Scheme of poly-carboxybetaine (PCB) hydrogel dressing for the detection of pH value and glucose concentration in wound exudate. Reprinted with permission from Zhu YN, Zhang JM, Song JY, et al. A multifunctional pro-healingzwitterionic hydrogel for simultaneous optical monitoring of pH and glucose in diabetic wound treatment. *Adv Funct Mater.*2019:1905493. Copyright 2019, John Wiley and Sons.[239] (**B**) The formation of OxOBand from PUAO-CPO cryogels with ADSC-exos. Reprinted with permission from Shiekh PA, Singh A, Kumar A. Exosome laden oxygen releasing antioxidant and antibacterial cryogel wound dressing OxOBandalleviate diabetic and infectious wound healing. *Biomaterials.*2020;249:120020. Copyright 2020, Elsevier.[181]
Abbreviations: HRP, horseradish peroxidase; DCF, dichlorofluorescein; GOx, glucose oxidase; H_2DCF, 2′,7′-dichlorofluorescein-diacetate.

wounds, and these two parameters are converted into visible images, which were collected by smartphones and monitor changes in wounds at any time[239] (Figure 7A). This multifunctional wound dressing may open vistas in chronic wound management and guide the diabetes treatment in clinical applications.

Conductive Hydrogels

In recent years, conductive hydrogels have also been widely used in health recording electrodes, biomedical patches, wearable/implantable bio-devices, and electronic skin.[240–244] Conductive hydrogels are stimulated by external electrical signals, which are converted to bioelectrical stimulation after

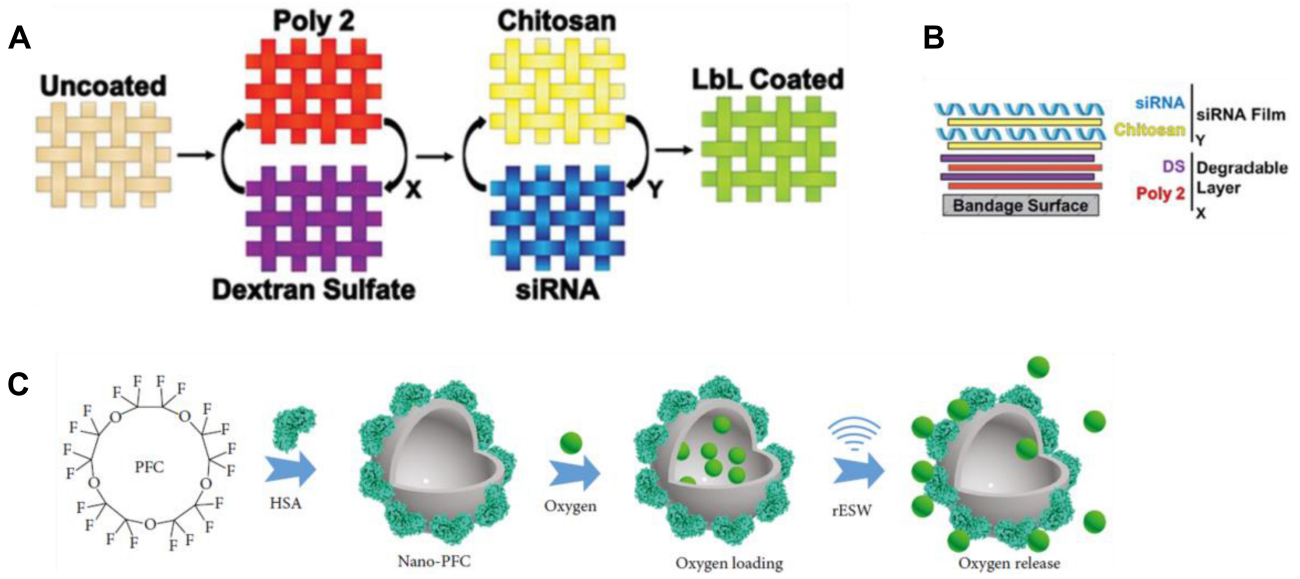

Figure 8 Schematic diagram of material synthesis. (**A**) Schematic of the hierarchical structure of LbL films into a single coating. The first (X) film is a hydrolytically degradable undercoating, while the second (Y) film contains the siRNA to be delivered. (**B**) Side-on schematic of hierarchical LBL film architecture. Reprinted with permission from Castleberry SA, Almquist BD, Li W, et al. Self-assembled wounddressings silenceMMP-9 and improve diabetic wound healing in vivo. *Adv Mater.* 2016;28:1809–1817. Copyright 2016, John Wiley and Sons.[79] (**C**) Schematic illustration of the synthesis procedure and rESW-responsive oxygen release from Nano-PFC. Adapted from Wang S, Yin C, Han X, et al. Improved healing of diabetic footulcer upon oxygenation therapeutics through oxygen-loading nanoperfluorocarbon-triggered by radial extracorporeal shock wave. *Oxid Med Cell Longev.* 2019;2019:5738368. Creative Commons license and disclaimer available from: http://creativecommons.org/licenses/by/4.0/legalcode.[189]

reaching the skin to achieve the purpose of treatment. Zhao et al developed a conductive hydrogels (good self-healing ability as well as repeatable adhesiveness), which can promote angiogenesis, collagen deposition, inhibit bacterial growth and control diabetic wound closure.[151] Zhang et al designed conductive hydrogels based on polyvinyl alcohol and chitosan, the conductivity can enable hydrogels to perceive temperature and strain.[245] The hydrogels are expected to build flexible sensory systems and the next generation of intelligent biomedical products in the future.[245] Researchers are now focusing

Table 8 To Summarize the Role of Multifunctional Hydrogel in Diabetic Wound Healing

Smart Hydrogels	Peculiarity	References
Phenylboronic-modified CS, PVA and benzaldehyde-capped poly(ethylene glycol) hydrogels.	pH and glucose dual-responsive injectable hydrogels.	[137,238]
PDA@Ag NPs/polyaniline, and PVA hydrogels.	Skin-inspired antibacterial conductive hydrogels; good self-healing ability as well as repeatable adhesiveness.	[151]
Calcium silicate nanowires, SA, and OPO hydrogel scaffolds.	Excellent and controlled photothermal ability.	[247]
SH-PEG and silver nitrate hydrogel.	Injectable self-healing coordinative dynamic multifunctional hydrogel.	[236]
EPL-coated MnO_2 nanosheets and insulin-loaded FCHO hydrogel.	Injectable multifunctional hydrogel.	[237]
Polypyrrole or Zn-functionalized CS PVA hydrogel.	Highly stretchable and conductive self-healing hydrogel.	[245]
PCB hydrogel.	Multifunctional pro-healing zwitterionic hydrogel; simultaneous optical monitoring of pH and glucose.	[239]
SA hydrogel.	Bioactive injectable hydrogels.	[135]
PVA-based hydrogel.	ROS-scavenging hydrogel.	[246]

on developing smarter hydrogels that not only contain "sensor" moieties that can respond to wound environmental pH, ROS levels, glucose concentrations, etc., but also are easy to operate and safe, this smart drug delivery system can promote diabetic wound healing.[246,247]

Although significant progress has been made in injectable hydrogels, more research is needed to address some of the current technical challenges. A major limitation of injectable gels is the rapid release of low molecular weight compounds such as drugs and biomolecules. One way to slow down the kinetics of drug release is to hybrid the hydrogel with drug-loaded nanoparticles. Furthermore, the interaction between cells-matrix should be enhanced. All of these methods in combination with 3D cryoprinting. Additionally, the size of injectable hydrogels could be a barrier when moving from preclinical studies into clinical practice, where larger scaffolds are often required for humans. In the future, designing more compressible or self-healing injectable intelligent hydrogels should broaden their biomedical applications and accelerate their clinical translatability.

Other technology

Currently, various technologies, especially multifunctional systems (including photothermal therapy (PTT), layer-by-layer (LBL) self-assembly technique and 3D-printing technology), are widely used in diabetic wound repair.[248–251]

Photothermal Therapy

PTT is based on near infrared (NIR) laser triggered therapy, widely used in cancer treatment. It combines near-infrared laser and light-absorbing nanomaterials to achieve local high temperature around NPs, leading to cancer cell death. Huang et al synthesized BSA-CuS nanoparticles by biomineralization method of bovine serum albumin (BSA) and copper sulfide (CuS), it showed strong killing bacterial ability under NIR.[213,252] PB@PDA@Ag NPs can accelerate the healing of diabetic wounds under NIR.[150] In addition, MoS_2-BNN6 can effectively inhibit the growth of ampicillin-resistant *Escherichia coli*, heat-resistant *Escherichia faecalis*, and *pathogen Staphylococcus aureus*.[212] Although nanoparticles based PTT has great potential for treating diabetic wound infections, local heat can also severely damage surrounding healthy tissue, so precise research and specific clinical trials are needed for PTT therapy.

Layer-by-Layer Self-Assembly Technique

Some biomaterials can improve their biomedical properties through many simple methods, such as layer-by-layer (LBL) self-assembly technique.[253] LBL self-assembly technique is widely used in biomedical for delivery from a broad range of material surfaces.[254] And LBL modified composite material has good stability, mechanical properties and hydrophilicity.[255,256] LBL self-assembly technique is favored by many people because it can alternately deposit the electrostatic force with opposite charge on the surface of polyelectrolyte matrix, improving the continuous release of drugs, and is easy to operate, controllable and economical without potential complications.[257] Natural rubber latex (NRL) can be used to treat chronic skin wounds, but because of their low integration, most applications of NRL biomembranes are external, short-term implants, or as delivery matrices.[258,259] Davi et al can increase the membrane formation speed by 10 times by spraying LBL technology.[260] In addition, self-assembled nanometer-scale coatings can incorporate and release therapeutically relevant quantities of siRNA in a controlled fashion to yield rapid diabetic wound closure[79] (Figure 8A and B). Thus, the use of LBL to alter localized protein expression levels has significant implications for the treatment of site-specific diseases, including cardiovascular disease, DFUs, cancers, and transplant rejection.

3D-Printed

3D-printed scaffolds for wound dressings have many advantages, such as the ability to adjust the dimensional characteristics of wound dressings (such as area, thickness, or pore size), simple drug loading, the use of a variety of materials, and oxygen penetration due to pore design.[261] Sodium alginate/polyethylene glycol (SA/PEG) scaffolds were prepared by adding different concentrations (1, 3 and 5 wt.%) of PEG to SA using 3D-printing technology. 3D-printing scaffolds had good antibacterial effect, especially against gram-positive bacteria. In addition, using 3D-printing technology, ideal porosity and properties were obtained, enabling cells to grow on/within the scaffold.[262] Wu et al used extrusion-based 3D printing and post stretching to fabricate a microneedle patch system for minimally invasive and glucose-responsive insulin delivery for diabetes treatment.[263]

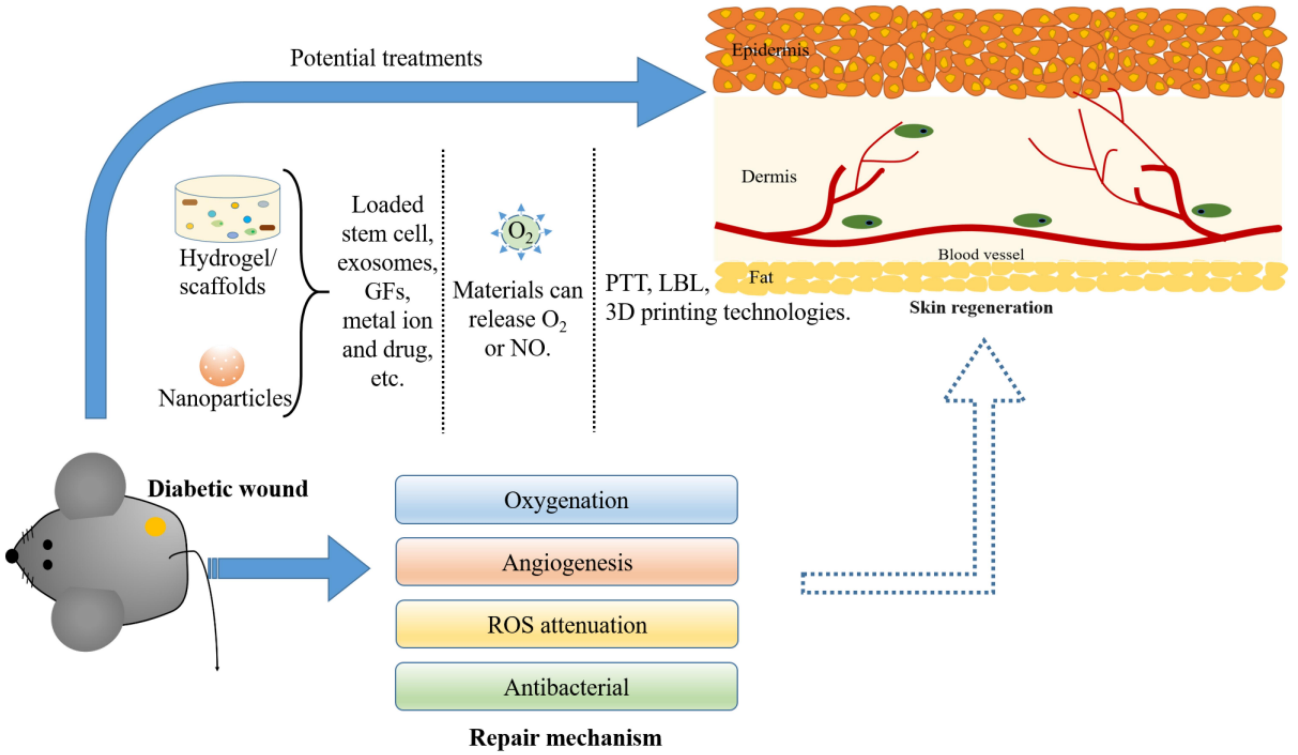

Figure 9 Potential therapies for diabetic wound repair. Strategies for manipulating the regeneration of diabetic wounds include the use of hydrogels (loaded with small molecules and stem cells, etc.), photothermal therapy, and materials that release oxygen. All of these elements have been demonstrated to have an effect on in vitro and in vivo models of wound healing. These repair mechanisms include vascularization, less ROS production, oxygen release, and antimicrobial resistance. Therefore, combining these strategies will undoubtedly change the result of diabetic wound healing.

Conclusions and Perspectives

The treatment of diabetic wounds is complex and challenging due to its pathophysiology, resulting in impaired function of different cells and in unbalanced levels of key biochemical healing mediators. Based on the characteristics of diabetic wounds and the mechanism of tissue repair, nanoparticles/hydrogels loaded with bioactive molecules (such as growth factors, genes, proteins/peptides, stem cells/exosomes) and non-bioactive substances (metal ions, oxygen and nitric oxide), as well as nanotechnology (eg, PTT, LBL self-assembly technique and 3D printing) have been applied to diabetic wound healing (Figure 9). The etiopathogenesis of diabetic ulcers is too complex, one or two substances are not enough to accelerate wound healing, so a variety of substances can be combined to release in different stages of wounds to accelerate diabetic wound healing. Overall, the future direction may be the development of new biomaterials with multiple roles (including improve hypoxia, enhance angiogenesis, reduce oxidative stress and prevent infection) that may regulate wound healing at all stages and provide a balanced environment throughout the wound healing process, thereby reducing potential complications.

In recent years, people are interested in using various technologies to prepare some multifunctional nano-systems for diabetic wound healing. However, enough information about the physicochemical properties of nanoscale systems and their expected behavior and toxicity in human body remains unclear. In the long term, further studies are indispensable to provide insights into how research findings about technology-based therapies can be applied in the clinical arena. In the future, we are sure to design exciting intelligent nanotechnology platforms for the diagnosis and treatment of various chronic diseases.

Abbreviations

IL-6, Interleukin 6; TGF- β1, Transforming growth factor-β1; NGF, Nerve growth factor; KGF, Keratinocyte growth factor; VEGF, Vascular endothelial growth factor; IGF-1, Insulin-like growth factor; bFGF, basic Fibroblast growth factors b; AGE, Advanced glycation end-product; GF, Growth factor; LBL, Layer-by-layer; NO, Nitric oxide; NOS, Nitric oxide synthase; ECM, Extracellular matrix; MMP, Matrix metalloproteinases; TIMP, Tissue inhibitors of metalloproteinases; TNFα, Tumour necrosis factor α;

GAG, Glycosaminoglycan; SDF-1, Stromal cell-derived factor 1; MIP-3α, Macrophage inflammatory protein-3α; DFO, Desferrioxamine; PB, Prussian blue; NP, Nanoparticle; ADSCs, Adipose derived stem cells; GSH, Reduced glutathione; PTT, Photothermal therapy; HIF-1α, Hypoxia-inducible factor 1α; MΦ, Macrophages; MRSA, Methicillin-resistant staphylococcus aureus; BG, Bioglass; nano-PFC, Nanoperfluorocarbon.

Acknowledgments

We acknowledge funding by the Innovation Capability Support Program of Shanxi (Program No. 2020TD-042), Jointly funded by Department of Science and Technology of Shaanxi Province and Northwestern Polytechnical University (No. 2020GXLH-Z-021), the National Natural Science Foundation of China (No. 81803491), the Natural Science Foundation of Shaanxi Province (No. 2019JQ-320), and the Fundamental Research Funds for the Central Universities (No. 3102019smxy002). We would like to thank the Analytical & Testing Center of Northwestern Polytechnical University for supporting our research on diabetic wound repair materials.

Disclosure

The authors declare that there are no competing interests.

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