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Therapeutic role of growth factors in treating diabetic wound

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Abstract

Wounds in diabetic patients, especially diabetic foot ulcers, are more difficult to heal compared with normal wounds and can easily deteriorate, leading to amputation. Common treatments cannot heal diabetic wounds or control their many complications. Growth factors are found to play important roles in regulating complex diabetic wound healing. Different growth factors such as transforming growth factor beta 1, insulin-like growth factor, and vascular endothelial growth factor play different roles in diabetic wound healing. This implies that a therapeutic modality modulating different growth factors to suit wound healing can significantly improve the treatment of diabetic wounds. Further, some current treatments have been shown to promote the healing of diabetic wounds by modulating specific growth factors. The purpose of this study was to discuss the role played by each growth factor in therapeutic approaches so as to stimulate further therapeutic thinking.

Key Words: Growth factor; Skin; Diabetic wound; Therapy; Biomaterial; Delivery system

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Core Tip: This review summarizes the main causes of poor wound healing in diabetes and the role of various therapeutically available growth factors in wound healing. In terms of treatment, it summarizes the treatment methods and drug delivery systems of various growth factors, and discusses the therapeutic effects of different methods and the special properties of drug delivery systems. We hope these discussions will provide the basis for more effective treatments, advance growth factor research, and help more people with diabetes heal their wounds.

INTRODUCTION

The prevalence of diabetes continues to increase at an alarming rate worldwide[1,2]. According to a recent analysis, the global prevalence of diabetes among adults aged 20-79 years is currently at 536.6 million and is projected to rise to 783.2 million by 2045[3]. As of 2015, diabetes was a direct cause of death for about 1.5 million people worldwide (WHO. Accessible at http://www.who.int/diabetes/en, accessed on 26 November 2022). Complications such as cardiovascular disease, nephropathy, retinopathy, neuropathy, and diabetic wounds occur in patients with diabetes. Diabetic wounds are one of the consequences having a lasting impact on patients with diabetes. Diabetic foot ulcer (DFU) is the most common type of diabetic wounds, which has a recurrence rate of 30%-50%[4,5]. Currently, no effective means of foreseeing the development of diabetic sores exist. Thus, the primary goals of treating diabetic wounds include identifying them early, performing a thorough examination, debriding and cleansing the wounds, and preventing or controlling the spread of infection.

One of the trickiest aspects of managing diabetes is dealing with wounds. Normal wound care is insufficient for diabetic wounds due to the differences in blood composition, vascular development, nerve survival, and inflammatory processes[6,7].

Many therapies have been developed for diabetic wounds in recent years[4,8], but those involving growth factors (GFs) have gained the maximum attention. GFs govern most of the processes involved in wound healing[9]. Although several GFs have been shown to be useful in treating diabetic wounds, only a few have been authorized for use in clinical practice. Among the three GF products available, only Regal Maltose has been approved by the Food and Drug Administration for treating neuropathic diabetic ulcers. The limitations in trial design, poor patient compliance, risk of immunogenicity, protein degradation, and variation in the responsiveness and healing support supplied by surrounding tissues are only a few of the many obstacles that stand in the way of the therapeutic application of GF products. It is essential, therefore, to have a firm grasp on the specifics of diabetic wounds, the healing effects of various GFs, and the provision of a dependable and efficient GF delivery system to propose a GF therapy.

In this review, we summarized the major factors contributing to impaired wound healing in patients with diabetes, and the significance of several GFs currently available for therapeutic use. We also conducted illustrative GF treatment experiments to explore various delivery mechanisms and facilitate an understanding about the therapeutic effects of various strategies.

WHY IS THE HEALING OF DIABETIC WOUNDS DIFFICULT?

Vascular complications

Intermittent claudication, ischemia-induced rest discomfort, skin ulcers, and avascular necrosis are all symptoms of peripheral arterial disease (PAD), a group of disorders caused by arterial stenosis distal to the aortic arch. A strong correlation exists between diabetes and PAD; however, determining the true frequency of PAD in patients with diabetes is challenging due to the many complicating factors[10]. One cross-sectional study indicated that 43.87% of patients with DFU also had peripheral artery disease[11]. The most immediate effect of PAD, whether it affects local micro or macro vessels, is a disruption in blood flow or even ischemia[12]. Further, a number of negative consequences occur due to microcirculatory dysfunction. The microcirculation of

patients with diabetes differs from that of patients without diabetes in several important ways, including increased vascular permeability, poor autoregulation, and unresponsiveness to vasodilatory stimuli[10,13]. The endothelial dysfunction due to hyperinsulinemia or hyperglycemia is the primary cause of these characteristics[14,15]. Capillary damage and oxidative stress are two complications of diabetes that can be exacerbated by microcirculatory perfusion problems[16].

Tissues surrounding diabetic wounds may suffer from hypoxia and anemia due to circulatory abnormalities triggered by PAD. The activity and gene expression in cells of injured tissues may be affected by hypoxia[17]. The combination of vascular damage and increased tissue oxygen consumption can lead to hypoxia in diabetic wounds, just as it does in regular wounds. However, hypoxia triggers hypoxia-inducible factor-1 (HIF-1) to enhance wound repair in healthy individuals, but hyperglycemia inhibits HIF-1 and hence slows wound healing in patients with diabetes[18-20]. Since hypoxia is detrimental to healing rather than serving as positive feedback that accelerates diabetic wound closure, it is no longer a factor in promoting wound closure. Lower oxygen levels in DFU were linked to slower wound healing in a study on flow-mediated skin fluorescence monitoring[21]. Furthermore, anemia can inhibit the healing process by inhibiting the metabolic pathways in injured tissues. Patients with diabetes often suffer from anemia, and those with severe foot ulcers are particularly at risk[22-24]. Patients with severe anemia have a higher likelihood of experiencing adverse malignant outcomes, according to a number of studies. These outcomes include a more severe disease-free interval, a more severe infection, and even death[23,25-27]. The impact of anemia on DFU is still debatable, as some studies have shown that it is not significantly linked to the severity or prognosis of DFU[28,29].

Moreover, diabetic wounds frequently exhibit impaired angiogenesis, which results in reduced vascularity and capillary density[30]. Inhibiting the death of important cells in damaged tissue, providing proliferative support activity, facilitating the remodeling phase of repair, and promoting healing growth are all facilitated by oxygen and nutrients provided by angiogenesis[31-33]. However, in diabetic wounds, many factors

that promote angiogenesis are disrupted due to hyperglycemia and chronic inflammation, for example, the release of vascular endothelial growth factor (VEGF)[34] and platelet-derived growth factor (PDGF)[35] and the composition ratio of Ang1/Ang2/Tie2 complex[36,37]. Moreover, the unique internal environment of diabetes may also contribute to the effects of various anti-angiogenic factors, such as the anti-angiogenic factor pigment epithelium-derived factor[38]. These factors interfere with inflammation-mediated angiogenesis and delay the transition from inflammation to proliferative remodeling in wound healing.

Hyperglycemia

Hyperglycemia can delay the healing of diabetic wounds and even exacerbate DFU through the impaired function of various skin cells and peripheral neuropathy. In patients with diabetes, hyperglycemia is an important factor causing dysfunction or reduction of endothelial cells[39-44], which are essential for the healing of diabetic wounds[45,46]. Further, hyperglycemia affects protein synthesis and migration and proliferation of keratinocytes and fibroblasts, which disrupts important processes of re-epithelialization[47-49], for instance, the altered expression of cytoskeletal keratin proteins (K2/K6/K10) and a laminin-5 α3 chain precursor protein (LM-3A32) in DFU keratinocytes[50]. Also, the fibroblasts from DFU exhibit morphological changes, GF energy, extracellular matrix (ECM) deposition, and reduced proliferation and migration of fibroblasts[51-54]. In the pathogenesis of neuropathy, hyperglycemia can damage nerves through the polyol pathway, hexosamine pathway, oxidative stress, advanced glycation end-products (AGEs) pathway, PARP pathway, NF-κB pathway, and so forth[55].

Hyperglycemia can also induce a delay in diabetic wound healing *via* free radicals or reactive oxygen species (ROS). In patients with diabetes, hyperglycemia can induce excessive ROS production through several pathways[56]: (1) reactions in mitochondria[57,58]; (2) impairment of intracellular antioxidative defense systems[59,60]; (3) glycosylation and subsequent signal transduction[61,62]; (4) lipid peroxidation[55,63]; (5)

activation of free radical generator enzymes[64,65]; (6) polyol pathway[66]; (7) protein kinase C pathway[67,68]; and (8) hexosamine pathway[69]. These pathways have been verified in patients with diabetes and are abnormally active and hence disrupt the metabolism of ROS in hyperglycemia. Although the presence of ROS can, sometimes, promote wound healing (*e.g.*, bacterially infected wounds)[70,71], excessive release of ROS can lead to cell and tissue damage and delayed wound healing in DFU[72].

Neuropathy

More than 90% of patients with DFU also have diabetic neuropathy[73]. The most common types of neuropathy are sensory, motor, and autonomic neuropathies of the periphery[74]. Diabetes can cause neuropathy in numerous ways, the most common of which are: (1) autoimmunity; (2) microvascular dysfunction; and (3) various humoral variables (hyperglycemia, hyperinsulinemia, and so on)[75-79].

An important risk factor for wound formation in neuropathy is the deterioration of subjective sensation[80-82]. The selective targeting of C and Aδ fibers by neuropathy in diabetes can lead to neuropathic pain and/or sensory loss[83]. Studies have shown reduced cutaneous innervation in the biopsies of patients with diabetes based on reduced immunoreactivity of protein gene product 9.5 (PGP9.5) (detecting sensory neurons) and various neuropeptides, specifically calcitonin gene-related peptide, substance P (SP), and neuropeptide Y[84,85]. Reduced nerve density, a more fragmented distribution across the dermis[86,87], and reduced nerve afferents in the epidermis[88-91] and dermal papillae[92] are found in the skin of patients with diabetes, even in the absence of clinically detectable sensory neuropathy[93]. Moreover, patients with diabetes may show a significant reduction in amplitude and nerve conduction velocity associated with nerve fiber loss[94]. Patients may have trouble deciphering the severity of their sores or ulcers in the limbs, especially if their pain threshold has been drastically lowered[95]. These variables increase the likelihood of diabetic wound development and may also contribute to the progression of existing wounds. The upper-body paralysis from autonomic neuropathy reduces perspiration production, leading to dry, cracked

skin that can increase susceptibility to irritation and infection while slowing the healing process[72,78]. In dull pain, the increased pressure on the plantar surface of the foot caused by motor neuropathy can cause ischemia and possibly death of tissues in the affected area[78].

Skin innervation is important for normal wound healing and can impact wound healing processes such as keratinocyte proliferation[96], wound re-epithelialization[97], wound contraction[98], and production of granulation tissue[99]. However, in diabetic wounds, neuropathy can impede these steps, delaying the healing of wounds[100]. Further, SP stimulates leukocyte chemotaxis to promote wound healing during the inflammatory phase of a wound[101]. However, reduced SP levels in denervated tissues in patients with diabetes may lead to delayed wound healing[102,103]. Denervation leads to delayed protein extravasation and cell migration[104,105]. Animals exposed to capsaicin have no vasodilation and plasma protein extravasation at the time of injury[106]. A similar delay in inflammatory cell migration was observed in mice with diabetes[107-109]. Chemical and surgical denervation can reduce small nerve fibers in the skin by at least 70%, which leads to poor wound repair[110]. The reduction in skin sensory nerves by subcutaneous injection of capsaicin in mice and rats without diabetes delayed re-epithelialization, reduced epidermal stem cell migration, and inhibited angiogenesis and VEGF expression[111-113].

In fact, many types of neuropathy are complicated by diabetes, and not every neuropathy affects the efficiency of wound healing[78,114]. The neuropathy discussed in this study refers to the ubiquitous disorders of the cutaneous nerves and dysregulation of neuropeptide secretion.

Microbial infection

The wounds in patients with diabetes are highly susceptible to microbial invasion, often leading to life-threatening infections that delay wound closure. The damage of the skin barrier, such as increased trans epidermal water loss and decreased secretion of antimicrobial peptides,[115,116] has been linked to an increased risk of infection.

Neuropathy and chronic inflammation have been proposed as possible causes of this damage[72,117]. Furthermore, the microbial composition of patients with diabetes differs from that of healthy individuals[118-120]. *Staphylococcus aureus* and *S. epidermidis*, for example, are more likely to colonize the skin of patients with diabetes[119,120]. Diabetic wounds have a more restricted microbiome than healthy skin and are home to bacteria such as *Klebsiella* sp., *Abiotrophia* sp., *Escherichia coli*, and *Peptoniphilus* sp.[121-123]. Notably, *S. aureus* and *Streptococcus genera* predominate among the harmful microorganisms in infected wounds[124,125]. The increased release of pro-inflammatory cytokines and a prolonged inflammatory phase due to bacteria and endotoxins in an infected wound are two factors that prevent the wounds from healing[126]. Additionally, the pathogenic bacteria or their secretions continuously damage the wound's tissue and cells, slowing the healing process.

Inflammation

Unlike nondiabetic acute wounds, DFUs have a nonlytic inflammatory phase, with numerous neutrophils and macrophages identified in the wound[127-129] and persistent release of pro-inflammatory cytokines such as leukocyte interleukin (IL)-1, tumor necrosis factor-α (TNF-α), plasma C-reactive protein, and others[128,130,131]. Poor phagocytic activity and dysfunctional leukocytes are also common in patients with diabetes[132-134]. However, in DFU, M1 macrophages continue to dominate the wound milieu and perpetuate inflammation, whereas, in normal wounds, M2 macrophages (promote tissue repair) progressively replace M1 macrophages (promote inflammation)[135-137]. Because of the ongoing inflammatory response, neutrophils remain activated and secrete proteases, which indiscriminately destroy the wound microenvironment[138]. However, inflammation can stifle angiogenesis by limiting VEGF production[139,140]. Diabetic wounds cannot heal properly because chronic inflammation continues to cause harm to tissue cells even after the remodeling phase has begun[109].

Diabetic wound healing requires specific treatment

Normal wound healing can be divided into four stages: hemostasis, inflammation, hyperplasia and remodeling (Figure 1). But for diabetic wounds, the injuries, infections, and other consequences can all be exacerbated by diabetes, which slows recovery time[141] (Figure 2). Excessive formation of AGEs, insufficient neovascularization, insufficient concentration of GFs, imbalance between metabolism and nutrient delivery, abnormal regulation of gene expression, and impaired vascularization are just some of the factors making the healing of diabetic wounds difficult[142]. Therefore, common treatment measures cannot effectively improve the condition of diabetic wounds. Currently, many treatments exist for diabetic wounds, such as oxygen therapy, negative-pressure wound therapy, platelet-rich plasma, stem cells, and cell- and tissue-based products[4,143-150]. Among these, GF therapy has been regarded as an important means to treat diabetic wounds due to its ability to participate in promoting various stages of healing.

ROLE OF GFS IN THE HEALING OF DIABETIC WOUNDS

GFs execute an important role in impaired wound healing, especially in diabetic wounds. They affect many processes, such as the growth and movement of different types of cells, endothelial cell stimulation, angiogenesis, fibroblast chemotaxis, and changes in inflammatory cells. GFs that accelerate and promote wound healing through their physiological effects mainly include VEGF, PDGF, epidermal growth factor (EGF), fibroblast growth factor (FGF), transforming growth factor β (TGF-β), hepatocyte growth factor (HGF), and so forth (Table 1)[108,151-197].

VEGF

The VEGF family consists of a variety of GFs, among which VEGF-A and VEGF-C are mainly involved in wound healing[161]. VEGF-A is produced by endothelial cells, keratinocytes, fibroblasts, smooth muscle cells, platelets, neutrophils, and macrophages[198-200]. It binds to the tyrosine kinase surface receptors Flt-1 (VEGF

receptor 1) and kinase insert region receptor (KDR) (VEGF receptor 2) located on the endothelial surface of blood vessels[201-203]. By acting on these receptors, VEGF-A can participate in the chemotaxis of endothelial cells and promote endothelial cell proliferation, differentiation, and regulation of vascular permeability[204-206]. VEGF-A levels are elevated in nondiabetic wounds[152,207]. Other GFs that can enhance VEGF-A expression include TGF-β1, EGF, TGF-α, KGF, bFGF, and PDGF-BB[208,209]. VEGF can promote angiogenesis to restore tissue perfusion, re-establish microcirculation, and increase oxygen tension in the wound[153]. In diabetic wounds, VEGF-A can promote early angiogenesis, especially the migration of endothelial cells, and improve the re-epithelialization and granulation tissue formation of diabetic wounds[210,211]. *In vivo*, the wounds in mice with diabetes exhibited accelerated re-epithelialization and contraction of wound area after treatment with VEGF mRNA delivery[212,213]. Many drugs and stem cells promote diabetic wound healing through VEGF[214-216].

VEGF-C is released primarily by macrophages and acts through VEGF receptor 3, which is expressed on lymphatic endothelial cells, pore endothelial cells, and monocytes/macrophages[217-219]. The proteolytically processed mature form of VEGF-C can also bind to KDR in the vascular endothelium to increase vascular permeability[220]. The proteolytically processed mature form of VEGF-C can also bind to KDR in the vascular endothelium to increase vascular permeability[220,221]. The administration of VEGF-C *via* an adenoviral vector to diabetic wounds accelerated healing in animal models of diabetes[222].

PDGF

Many different homologous and heterodimeric GFs exist in the PDGF family. Platelets, macrophages, vascular endothelium, fibroblasts, and keratinocytes are the primary cell types responsible for PDGF production in wounds[223-225]. PDGF is required for the majority of wound healing processes. It is found in wound fluid and secreted from the degranulated plate following injury[176,226]. It promotes the proliferation and migration of inflammatory cells such as neutrophils, fibroblasts, macrophages, and smooth muscle

cells[227-229]. Furthermore, it promotes tissue debridement and granulation tissue development *via* macrophages by increasing the production and secretion of GFs such as TGF-β[223]. Further, PDGF plays a crucial role in developing mature blood vessels[230]. It promotes myofibroblast differentiation to rescue delayed wound healing after a diabetic wound penetrates subcutaneously and causes muscle damage[231]. The combination of PDGF-BB, VEGF, and EGF has been shown to increase cell composition and promote wound healing in diabetic wounds, and the use of PDGF-BB alone has been approved for treating diabetic wounds[232]. PDGF-D was also found to be highly effective when applied to wounds in patients with diabetes and ischemia[233]. PDGF is often used in combination with VEGF, which has a significant positive effect on angiogenesis and recovery in diabetic wounds[234-236]. *In vivo*, PDGF-BB can improve the healing quality of full-thickness excision wounds in rats with diabetes; promote angiogenesis, cell proliferation, and epithelialization; and led to thicker and more organized collagen fiber deposition[237]. For clinical trials, the application of PDGF can significantly reduce the healing rate of diabetic wounds and improve the probability of complete healing[238-241].

EGF

Many members of the EGF family aid in wound healing, such as heparin-binding EGF (HB-EGF) and TGF-α[161]. The binding of these ligands to the EGF receptor (EGFR) causes the receptor to dimerize and autophosphorylate, which in turn triggers the tyrosine phosphorylation of downstream proteins inside the cell[191]. Studies *in vitro* demonstrated that EGFR activation facilitated re-epithelialization by increasing keratinocyte proliferation and migration in wounds[242-246].

The paracrine action of EGF on keratinocytes is primarily mediated by its secretion from platelets, macrophages, and fibroblasts[247]. Wound re-epithelialization and tensile strength were both remarkably improved by post-injury EGF upregulation in nondiabetic patients[195]. However, EGF levels were found to be lower in diabetic wounds, and a majority of EGFRs were found to be translocated to the cytoplasm rather

than localized on the cell membrane[161,197]. The addition of topical EGF to diabetic wounds has been shown in clinical trials to improve epithelialization and speed up healing[248,249]. Various attempts have been made to load EGF into various delivery systems for treating diabetic wounds[250,251]. *In vivo*, the application of EGF balances collagen distribution, increases granulation formation, and accelerates wound healing[251-253]. In a clinical trial of 68 patients treated with combined EGF and dressings, 52 had diabetic wounds, which healed completely within 2-14 wk with a low recurrence rate[254].

TGF-α is mainly secreted by platelets, keratinocytes, macrophages, fibroblasts, and lymphocytes[255-258]. It has been shown to increase keratinocyte migration and proliferation and induce the expression of K6 and K16[194,259,260]. In *in vivo* studies, TGF-α played a role in early stimulation and maintenance of wound epithelialization in partial-thickness wounds[261]. *In vivo*, TGF-α can be combined with PDGF-BB to make the wound healing speed in mice with diabetes close to that of nondiabetic mice[262]. However, TGF-α has not been applied to the clinical treatment of wounds so far.

HB-EGF is also upregulated in nondiabetic wounds and secreted by keratinocytes[199,263]. HB-EGF can promote re-epithelialization by binding to the EGFR subtypes HER1 and HER472[264,265]. *In vivo*, HB-EGF is thought to play a role in promoting keratinocyte migration, showing its importance in the early stages of re-epithelialization[189]. At present, HB-EGF has been widely regarded as one of the targets for treating skin wounds and carried in various delivery systems[266]. In a rodent diabetic wound model, HB-EGF improved re-epithelialization and increased collagen content and wound contraction *via* a heparin-based cohesive delivery system[267]. *In vivo*, HB-EGF can promote the proliferation and migration of epidermal keratinocytes in full-thickness excision wounds of mice with diabetes and accelerate epithelialization[267].

FGF

FGF family is a cell signaling protein family comprising 23 members. The members of this family mainly involved in skin wound healing are FGF2, FGF7 (or KGF1), and

FGF10 (or KGF2). FGF2, the basic FGF, is mainly involved in granulation tissue formation, re-epithelialization, and matrix formation and remodeling in wounds[161,182]. FGF7 and FGF10 stimulate keratinocyte proliferation and migration, promote re-epithelialization, and increase the transcription of factors involved in ROS detoxification[268,269]. FGF2 is deficient in diabetic wounds, and wound closure is accelerated following the topical application of FGF2[183,184].

TGF-β

The TGF-β superfamily comprises many members playing essential roles in development and repair. TGF-β1 and TGF-β2 are significant players in wound repair, and can be potent stimulators of extracellular matrix protein and integrin expression[168,270,271]. TGF-β1 is abundantly released from platelets immediately after injury[272]. Latent TGF-βs in the wound matrix also allow the sustained release of proteolytic enzymes. This combination of different cell sources ensures a continuous supply of TGF-β throughout the repair process[273]. Additionally, some researchers have reported the presence of TGF-βs in wound fluid[274,275]. At the cellular regulatory level, TGF-β has many cellular regulatory functions, such as attracting macrophages and fibroblasts to the wound area to improve healing[276,277]. Also, TGF-β can promote re-epithelialization mainly by enhancing keratinocyte migration *via* regulatory factor forkhead box-1 after binding to receptors on the cell surface[277,278]. Moreover, studies show the involvement of TGF-β in scar formation, later wound repair, angiogenesis, and granulation tissue formation[163,169,172,273,279]. In diabetic wounds, TGF-β also promotes wound healing[162]. Compared with other reduced GFs, TGF-β showed a lack of upregulation in diabetic wounds, which might be a factor delaying the healing[279,280]. *In vivo*, the TGF-β/Small mothers against decapentaplegic (Smad) pathway is often activated as an important factor in promoting diabetic wound healing, for example, WDR74 and Baicalin[281,282].

HGF

HGF is a GF capable of regulating the growth, motility, and morphogenesis of various types of cells[283-285]. In wounds, HGF is mainly derived from fibroblasts, acts on epithelial cells, keratinocytes, and endothelial cells, and participates in healing processes such as suppression of inflammation, granulation tissue formation, angiogenesis, and re-epithelialization[155,177,179,180]. Although no changes in HGF levels have been reported in diabetic wounds, the delayed healing process appears to be associated with an imbalance in the activation and inactivation of the HGF/c-Met pathway[9,178,286]. Moreover, HGF can assist other GFs in promoting healing in diabetic wounds[287].

Nerve growth factor

Nerve growth factor (NGF) is a neurotrophic factor essential for the development and survival of some sympathetic and sensory neurons in the central and peripheral nervous systems[288]. NGF levels increase when wounds appear. NGF mRNA is detected in newly formed epithelial cells and granulation tissue fibroblasts at the wound edge[289], with exceptionally high expression in granulation tissue myofibroblasts[290]. Additionally, NGF in wounds can also originate from salivary gland secretion and be transported *via* serum[289]. In wound healing, NGF mainly involves keratinocyte proliferation; proliferation, differentiation, and migration of epidermal stem cells; angiogenesis; fibroplasia; and peripheral nerve regeneration[291-297]. NGF levels are much lower in diabetic wounds and surrounding tissue than in normal skin wounds[298,299]. When NGF was applied explicitly to diabetic wounds, the healing and efficacy rate significantly improved[300,301].

Insulin-like growth factor

Insulin-like growth factors (IGFs) are anti-catabolic and anabolic drugs having two isoforms: IGF-1 and IGF-2[302]. They can regulate the growth and differentiation of cells throughout the body[303]. In normal skin, only a few cells express this protein. However, all epidermal cells and some inflammatory cells were found to produce IGF in the initial

1-3 d after injury[304]. IGF-1 may be involved in granulation formation in wounds, inhibit apoptotic pathways, and attenuate pro-inflammatory cytokine production[142]. In diabetic wounds, the expression of IGFs is markedly decreased and is absent in the basal layer of the epidermis and fibroblasts[305-307].

Connective tissue growth factor

The connective tissue growth factor (CTGF) is a member of the cellular communication network family[308], also known as CCN2. It can stimulate the proliferation and differentiation of fibroblasts in the skin[309]. Further, CTGF is involved in promoting cell adhesion, inflammatory cell chemotaxis, and cell differentiation[310,311]. The specific role of CTGF in nondiabetic wound healing has yet to be definitively concluded. However, the application of recombinant human CTGF in diabetic wounds did show better collagen IV accumulation and macrophage infiltration. Also, it increased α-smooth muscle actin level and healing rate in diabetic wounds compared with nontreated diabetic wounds[312]. In rats with diabetes, individuals treated with CTGF exhibited increased aggregation of type IV collagen, α-smooth muscle actin level, and macrophage infiltration; the rate of diabetic wound healing was also significantly accelerated in these individuals[312].

Colony-stimulating factor

Colony-stimulating factor (CSF) family has many isoforms, but the CSFs involved in wound healing are mainly granulocyte-macrophage CSF (GM-CSF) and granulocyte CSF (G-CSF). GM-CSF primarily stimulates cell proliferation and differentiation in wound healing and stimulates stem cells to produce granulocytes and monocytes[7]. However, the effectiveness of GM-CSF in promoting wound healing appears to be only somewhat recognized at present[313]. G-CSF is mainly involved in the inflammatory process of wounds and is related to the formation of neutrophils[314]. The ability of G-CSF to promote healing and resist infection has been verified in randomized clinical trials of diabetic wounds[315,316].

Prolonged healing results from GF deficiency in diabetic wounds

GFs are essential for healing diabetic wounds, as outlined earlier, because of their pro-healing effects. However, it is challenging to observe normal GF-regulated healing events in nontreated diabetic wounds due to the absence of GFs[157,161,192]. This prevents the healing process of hemostasis, inflammation, granulation tissue formation, wound contraction and re-epithelialization, and remodeling from functioning correctly. Moreover, it further leads to prolonged inflammation, tissue hypoxia, wound infection, and chronic healing[141]. Although this does not imply that the missing GF is the source of the lack of healing function, supplementing the wound with the required GFs has an excellent healing-promoting effect.

GF-RELATED THERAPY FOR DIABETIC WOUND HEALING

The application of exogenous GFs is considered a promising approach for treating diabetic wounds. The reason for using GFs is their ability to stimulate and regulate complex cellular and molecular events to alleviate the specific adverse effects of vascular complications, neuropathy, and inflammation in diabetic wounds, which are essential for good and rapid diabetic wound healing[142,317]. So far, a series of GFs, including PDGF, VEGF, EGF, FGF, TGF-β, KGF, and IGF, has shown the potential to accelerate diabetic wound healing[225,257]. Therefore, introducing appropriate GFs into diabetic wounds effectively promotes chronic healing (Table 2)[237,262,280,319-349].

The standard methods of introducing GFs can be divided into direct or biomaterial-based delivery (Figure 3). Direct delivery is achieved *via* topical application or intradermal injection but with only short-term bioactivity due to proteolysis and destabilizing support. For example, a large injection of multiple GFs is insufficient to maintain angiogenesis[318]. Biomaterial-based delivery is achieved by incorporating GFs into ECM-like hydrogels, scaffolds, or particles, which can provide proteolytic protection and structural support to maintain the bioactivity of GFs[141]. Furthermore, the increase in the levels of GFs in diabetic wounds can also be achieved by gene-

mediated delivery methods, which can be divided into plasmid DNA delivery, transfection with nonintegrating viral vectors, chemical carrier delivery, and gene-eluting biomaterial constructs[317].

GF-loaded delivery therapy

This treatment method requires suitable biological materials that maintain the structure and biological activity of GFs, high encapsulation efficiency, and bioavailability, ensuring the complete release of GFs. Moreover, it is necessary to consider the biocompatibility, degradation, and absorption characteristics of the delivery system. Typically, synthetic polymers of the polyester family, such as polyglycolic acid, poly (lactic-*co*-glycolic acid) (PLGA), polycaprolactone (PCL), or polymers of natural origins, such as collagen, gelatin, fibrin, hyaluronic acid, dextran, alginate, and chitosan, are common delivery materials[141] (Table 3)[319,343,347-349,352-372]. Attempts to improve the feasibility of clinical treatment through innovative delivery systems have attracted much attention (Table 4)[240,241,373-380].

Biodegradable polymer particles are site-specific controlled-release therapeutic systems. Chu *et al*[330] used a double-emulsion method to develop recombinant human EGF (rhEGF)-loaded PLGA nanoparticles and applied them to diabetic wound management. The results showed that the group treated with rhEGF PLGA nanoparticles had the best sustained GF release and the fastest wound healing compared with the group treated with rhEGF or PLGA alone[330]. Another study that used the intradermal route to deliver VEGF-loaded PLGA nanoparticles found that PLGA nanoparticles could sustain VEGF release for 30 d and showed a promoted healing response[341]. Further, another study pointed out that using PLGA-alginate microspheres as the GF carriers could significantly reduce the frequency of administration while maintaining the therapeutic effect[337].

Therapeutic polymer nanofiber mats are new carriers for GF-loaded dressings. This material has the characteristics of high porosity and large surface area to facilitate the penetration of GFs and the circulation of body fluids. rhPDGF-mixed PLGA nanofiber

could release rhPDGF for 21 d and significantly induce the complete closure of diabetic wounds in rats with diabetes[346]. The PCL or PCL-polyethylene glycol (PEG) nanofibers implanted with rhEGF also exhibited effective promotion of wound re-epithelialization *via* increasing keratinocyte proliferation and phenotypic expression in diabetic wounds[326]. Hence, the production of carrier materials and loading of various GFs can be adjusted to achieve better wound healing ability[339]. Moreover, a research group experimented with a polymeric fiber mat different from electrospinning, namely a hydrolytically degradable four-layer structure consisting of polyacrylic acid, poly-β-amino acid ester, VEGF or PDGF, and heparan sulfate. In this structure, GFs could be stacked between each layer of materials to promote the complementary effects on wound healing[342].

The three-dimensional biomaterial is a typical structure used to make dressings with GFs. Both sponges and foams are used as standard wound dressings due to their high absorbency and permeability to moisture and oxygen[350]. Collagen is a new material that can be used to develop biomimetic scaffolds. The collagen base can act as a scaffold and bind other natural polymers, such as gelatin, hyaluronic acid, and chitosan, or other synthetic materials[323,327,333,335,351]. Collagen combined with other polymers to generate composite scaffolds can provide resistance to collagenase digestion and sustained slow release of GFs[327]. Further, a study showed that hydrophilic polyurethane (PU) formed by the copolymerization of polyethylene glycol can serve as a dressing material with good moisture conditions in the wound bed [water vapor transmission rate of approximately 3000 g/(m^2 × day)]. The PU dressing loaded with rhEGF sustained the release of rhEGF for 7 d and eventually promoted re-epithelialization and complete recovery of diabetic wounds in rats[344].

GF gene-targeted therapeutic delivery

Gene-mediated therapeutic delivery at diabetic wounds is primarily the local transfection of therapeutic transgenes or complementary DNA into cells to increase the

transcription of GF messenger RNAs and maintain high concentrations of local GFs[381] (Table 5).

Naked plasmids are the most basic vector form that can accommodate large amounts of genomic DNA. Early research on diabetic wound therapy focused on forcing pDNA into cells by intradermal injection, with higher pDNA infusions achievable with the aid of electroporation[162,382-385]. Furthermore, Yoon *et al* used an ultrasonic microbubble agent (SonoVue) to assist in the ultrasonic puncture delivery of VEGF165-encoded microplastics in diabetic wounds of mice. Their results showed significantly increased cutaneous blood perfusion, accelerated wound closure, and complete recovery of normal wound tissue in mice undergoing ultrasonic portion[386,387].

Viral vector transfection has excellent freedom of improvement and can efficiently integrate *GF* genes into wound cells for expression, thus having significant advantages in delivering therapeutic genes. The most commonly used viral vectors during diabetic wound care include lentivirus (LV), adenovirus (AV), and adeno-associated virus (AAV). The transfection of the *VEGF*^{165} gene with replication-defective AV has been reported to induce and accelerate early wound healing responses, including angiogenesis and granulation tissue formation, in mice with diabetes[388,389]. Furthermore, Galeano *et al*[390] found that viral transfection could release VEGF in diabetic wounds for 4 mo (even after wound healing). Furthermore, de Felipe proposed that a single viral vector capable of transfecting multiple genes could be used for treatment to address the issue that the transfection of a single GF or GF isoform gene only activated a single corresponding signaling pathway rather than promoting multiple stages of wound healing[391]. Jazwa *et al* demonstrated the simultaneous delivery of *VEGF-A* and *FGF4* genes *via* bicistronic AAV, and the results showed that the therapeutic effect of multiple gene delivery was better than that of single GF[392].

Substances such as cationic polymers and lipids are emerging chemical carriers due to their ability to form electrostatic complexes with anionic biomolecules such as pDNA[393]. The advantage of this type of chemical carrier is that it can avoid the use of potentially immunogenic viruses, improve the biostability of pDNA, and facilitate

cellular uptake[394]. For example, a single subcutaneous injection of rhPDGF-B loaded with complexing integrin receptor ligand-conjugated lipopeptide or a complex consisting of arginine-grafted dendrimers loaded with minicyclic VEGF can accelerate the induction of complete wound closure in mice with diabetes[395,396].

Gene-eluting biomaterial scaffolds are similar to GF-loaded scaffolds and focus on improving the stability of the vector. Lee *et al*[280] developed a thermosensitive hydrogel synthesized from PEG, PLGA, and PEG that enabled the controlled release of encapsulated plasmids (containing the *TGF-β1* gene) and the acquisition of accelerated re-epithelialization. The customizable properties of hydrogels bridge the gap between conventional gel-based systems and solid scaffolds, and the porosity of hydrogels provides a large area for released polymers to come into contact with infiltrating cells. However, the contribution of angiogenesis in transfected cells to wound closure is insignificant as the release of polymers is thought to be extremely slow[340]. Nevertheless, this characteristic based on the electrostatic interaction of positively charged polymers in an anionic hyaluronic acid hydrogel matrix provides the basis for developing more controllable polymer delivery systems. For instance, Yang *et al*[334] showed in 2012 that the molecular weight and content of PEG in the copolymer matrix could be changed to regulate the release of polymers (plasmid bFGF/polyethyleneimine) from the core of core-sheath emulsion electrospun fibers. However, such an approach appears to be flawed in diabetic wounds. The problem of low cell availability at the wound edge and reduced cell migration may increase the difficulty of regulating transfection efficiency *in vivo* with this system[397-399].

CONCLUSION

Diabetic wounds are encompassed by various factors (*e.g.*, vascular system abnormalities, neuropathy, and inflammatory process stagnation) induced by the underlying disease and various concomitant diseases that impede normal wound healing. Furthermore, GFs that govern numerous healing processes are rarely detected in diabetic wounds compared with normal healing. The effects of GFs are particularly

specific and have been shown to be beneficial in addressing the discussed diabetic wound features. As a result, GFs can be regarded as a direct and effective agent in managing and treating diabetic wounds. Nonetheless, it is disheartening that only a handful of products have entered clinical trials thus far[141]. We discussed the peculiarity of diabetic wounds and provided a theoretical basis and potential of GFs in treating diabetic wounds and optimizing therapeutic techniques. Combining GF with other therapies such as stem cell transplant, cytokine therapy, and anti-inflammatory drugs can be a promising treatment for diabetic wounds, albeit extensive studies are warranted to further examine the efficacy of this combination treatment strategy.

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