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Review article

The emerging translational potential of GDF11 in chronic wound healing

Yuan Li [a], Yucong Li [a], Linlong Li [a], Haixing Wang [a], Bin Wang [c], Lu Feng [a], Sien Lin [a,b,**], Gang Li [a,b,c,*]

[a] Department of Orthopaedics & Traumatology, Stem Cells and Regenerative Medicine Laboratory, Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, SAR, PR China
[b] Shenzhen Research Institute, The Chinese University of Hong Kong, Shenzhen, PR China
[c] Bioland Laboratory, Guangzhou Regenerative Medicine and Health Guangdong Laboratory, Guangzhou, PR China

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ABSTRACT

Chronic skin wounds impose immense suffers and economic burdens. Current research mainly focuses on acute wound management which exhibits less effective in chronic wound healing. Growth differentiation factor 11 (GDF11) has profound effects on several important physiological processes related to chronic wound healing, such as inflammation, cell proliferation, migration, angiogenesis, and neurogenesis. This review summarizes recent advances in biology of chronic wounds and the potential role of GDF11 on wound healing with its regenerative effects, as well as the potential delivery methods of GDF11. The challenges and future perspectives of GDF11-based therapy for chronic wound care are also discussed.

The Translational Potential of this Article: This review summarized the significance of GDF11 in the modulation of inflammation, vascularization, cell proliferation, and remodeling, which are important physiological processes of chronic wound healing. The potential delivery methods of GDF11 in the management of chronic wound healing is also summarized. This review may provide potential therapeutic approaches based on GDF11 for chronic wound healing.

1. Introduction

The process of cutaneous skin healing includes four phases: hemostasis, inflammation, proliferation, and remodeling. There is a cascade of factors involved in wound healing along with local and systemic responses including oxygenation, inflammation, ischemia etc. [1]. Characters associate with chronic wounds include prolonged inflammation phase, antibiotic resistance and failure of skin cells responding to reparative signals [2]. Over the past decades, chronic wounds have imposed immense suffer and economic burden to both patients and health care system. There are burning needs to study and develop methods to promote chronic wound healing.

Skin wound care includes standard therapies such as disinfection and dressing changes, and advanced therapies such as negative pressure, biophysical stimulation, cell therapy, and biological dressings, with pros and cons on different aspects [3]. Among the biological factors, growth differentiation factor 11 (GDF11), also named as bone morphogenetic protein 11 (BMP11), is an important member of transforming growth factor-β (TGF-β) superfamily. GDF11 was firstly discovered in 1999, then many studies have reported its structure, signaling pathways and role in development and pathology [4]. It is known that GDF11 could modulate a series of physiological events including inflammation, cell proliferation, migration and vascularization that are closely related to wound healing process [5,6]. GDF-11 has been shown to promote wound healing in diabetic rat limb ischemia model [7]. The current review summarizes the recent advances in biology and current treatments of chronic wounds, with particular focus on the potential therapeutic role of GDF11 in chronic wound repair.

2. Skin wound healing physiology

2.1. Normal wound healing process

Wound healing following skin injuries includes four sequential and highly coordinated stages of hemostasis, inflammation, proliferation, and

Abbreviations: EPCs, endothelial progenitor cells.

* Corresponding author. Room 74038, 5/F, Lui Che Woo Clinical Sciences Building, Prince of Wales Hospital, Shatin, NT, SAR, Hong Kong, PR China.
** Corresponding author. Room 904, 9/F, Li Ka Shing Medical Sciences Building, Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, NT, SAR, Hong Kong, PR China.
E-mail addresses: sienlin@cuhk.edu.hk (S. Lin), gangli@cuhk.edu.hk (G. Li).

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Abbreviation

GDF11	growth differentiation factor 11
BMP11	bone morphogenetic protein 11
TGF-β	transforming growth factor-β
ECM	extracellular matrix
PDGF	platelet-derived growth factor
EGF	epidermal growth factor
FGF	fibroblast growth factor
MSCs	mesenchymal stem cells
GDF8	growth differentiation factor 8
PCSK5	protein convertase subtilisin/kexin type 5
ActRIs	activin type I receptors
ActRIIs	activin type II receptors
ALK4/5/7	activin receptor-like kinases 4/5/7
R-Smads	receptor-Smads
MAPK	mitogen-activated protein kinase
GASP-1/2	GDF-associated serum protein 1/2
HDACs	histone deacetylases
TNF-α	tumour necrosis factor-α
iNOS	inducible nitric oxide synthase
IL-6	interleukin-6
IL-1β	interleukin-1β
TLR2	toll-like receptor 2
NF-κB	nuclear factor-κB
RA	rheumatoid arthritis
BMDMs	bone marrow-derived macrophages
rGDF11	recombinant GDF11
NSCs	neural stem cells
BM-EPCs	bone marrow EPCs
ICY	intracerebral hemorrhage
PLGA	poly(lactic-co-glycolic) acid
NHS	N-hydroxysuccinimide
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
MAP	mussel-adhesion protein
PDGF-BB	platelet-derived growth factor BB

remodeling. The hemostasis phase is activated immediately upon injury to prevent blood loss through blood clotting and formation of fibrin matrices [2]. The degranulated platelets serve as the earliest promoter of inflammation and recruit immune cells, fibroblasts to the lesion by releasing chemoattractants and mitogens [8]. The recruited neutrophils and macrophages then coordinate for the hereafter healing process. Neutrophils create a favorable microenvironment to kill bacteria and remove cellular debris at the injury sites. Then large amounts of monocytes migrate from vasculature into the wound areas, differentiate into macrophages that orchestrate the healing process [9]. Macrophages that exert pro-inflammatory functions are defined as "M1 phenotype responsible for phagocytosis, cytokines production to initiate healing. The activated macrophages are referred as "M2 phenotype", which stimulate epithelialization, angiogenic, cell proliferation and facilitate granulation tissue formation [10]. In the proliferation phase, keratinocytes proliferate and migrate towards the wound to form a new epithelial coverage. Other cells, such as fibroblasts and endothelial cells, also participate in synthesis of extracellular matrices (ECM) and vascular network formation in the wound [11]. Once wound has been re-epithelialized, remodeling occurs that ECM generally matures and undergoes certain changes to increase apoptosis of myofibroblasts and forming a collagen-rich region, hence the tensile strength, and function of new skin tissue [12].

2.2. Chronic wound pathophysiology

Chronic wound refers to the disrupted healing process and does not heal in a timely and orderly manner, despite the use of current wound management methods. Chronic wounds have imposed immense suffers and economic burden to patients and health care system. A study in U.S. reported that nearly 8.2 million patients suffered chronic wounds and related complications in 2014, with the estimated cost of US$28.1 to US$96.8 billion [13]. Many factors attribute to chronic wounds. Local factors such as infection, oxygenation, necrosis, circulation and systemic factors including overall health status, age, obesity, smoking [14] may determine the fate of wound healing.

Infection is a common factor leading to chronic wound. On the infected wound surfaces, biofilms were often found as aggregated bacterial or fungal colonies attached and embedded into ECM network which trigger extensive inflammation such as massive neutrophilic infiltration and M1 macrophage accumulation [15]. Overactive or prolonged inflammatory responses lead to release abundant proteases that degrade the ECM and impede keratinocyte migration [16]. Pro-inflammatory M1 macrophages accumulate in response to local environmental stimuli which do not allow their transformation towards M2 phenotype. As a result, increased levels of pro-inflammatory cytokines and matrix metalloproteinases were accumulated in the wound, leading to ECM degradation and impaired tissue repair [17]. In the chronic wound, skin resident cells (fibroblasts, keratinocytes, etc.) have impaired proliferation and migration ability and respond poorly to stimulating growth factors [18].

Diabetes is one of the major contributors to non-healing skin wounds. Diabetic ulcers are usually accompanied with neuropathy, infection, and impaired blood supply. Peripheral nerve damage causes sensation loss loses and increased incidents of skin lesion, combined with ischemia and impairment of repair capacity, eventually leading to non-healing wounds [19,20]. In diabetic ulcers, neutrophils have impaired anti-bactericidal activities and monocytes become less responsive to chemokines. However, inflammation phase in diabetic wounds can last up to 2 weeks or longer. Aberrant polarization of macrophages also exist in diabetic wounds [21]. Fibroblasts from diabetic ulcers significantly reduced proliferation and collagen synthesis and delayed apoptosis, owing to a lack of growth factors and impairment of endothelial cells functions [22].

In addition to diabetic ulcers, bedsores, which is also called pressure ulcers and usually appeared in patients with prolonged hospital stay after receiving surgery. Risk factors contributing to bedsores include poor nutrition, aging, affected blood circulation and so on. Similar to diabetic ulcers, bedsores are associated with numerous complications, nerve damage, persistent infection, long-term inflammation and so on. Besides, there have been numerous studies indicating that patients with diabetes have higher risk of developing bedsores than non-diabetic patients [23,24].

3. Current therapy

3.1. Basic wound management

There are a series of well-established wound care guidelines with favorable outcomes. However, chronic wounds often require extra multidisciplinary approaches because of the complexity [14]. For instance, wound infection has long been treated empirically through applying antibiotics and through debridement to remove bacterial biofilms and non-viable tissues [25]. Besides, different types of wound dressings were used to prevent infection and promote chronic wounds healing [26,27]. In the meanwhile, surgical offloading, vacuum therapy, and topical oxygen therapy have been proven to be effective as well [2,28,29].

3.2. Advanced therapies

There were a plenty of advanced wound care technologies available now, including hyperbaric oxygen and negative pressure therapy, biophysical stimulation, novel debridement devices, biological agents for anti-inflammatory response and promoting angiogenesis [30–32]. Biological therapies mainly refer to growth factors application, skin substitutes, and cell therapies. Commercially available products for chronic wounds management include platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and fibroblast growth factor (FGF) [33]. Skin substitutes are dermal decellularized matrices for facilitating dermal cell infiltration [34]. Stem cell therapy uses bone marrow or placental tissue derived mesenchymal stem cells (MSCs) which have been reported as an alternative therapy for non-healing wounds [35,36].

4. The potential of GDF11 in chronic wound healing

4.1. The discovery, structure, synthesis and localization of GDF11

In 1997, McPherron et al. firstly identified growth/differentiation factor-8 (GDF8 or myostatin), a novel TGF-β family member [37]. In 1999, they reported a gene closely related to GDF8 as GDF11 (also named BMP11) [38]. In the same year, Nakashima et al. cloned and characterized GDF11 from rat and they found that GDF11 was first strongly expressed at 8.5 days post coitus and showed the highest expression level in the tail bud during embryogenesis [39]. Subsequently Gamer et al. cloned human and mouse GDF11 successfully [40].

The GDF11 gene was located at human chromosome 12q13.2 (GenBank AF100907) with the genomic sequence (GRCh38). It encodes GDF11 protein containing 407 amino acids, displaying all the identified features of BMP family proteins, such as an RXXR proteolytic processing site, a signal sequence for secretion, and a carboxyl terminal region containing a highly conserved pattern of cysteine residues. However, GDF11 sequence is more close to TGF-β proteins in the C-terminal domain [40]. The GDF11 protein is cleaved and activated by pro-protein convertase subtilisin/kexin type 5 (PCSK5) [41]. Ge et al. reported that the precursor 50 kD GDF11 was cleaved between residues gly119 and asp120 through proteolytic process, and then released as a 37 kD pro-domain and a 12.5 kD mature GDF11 [42]. The GDF11 protein is possibly processed in rough endoplasmic reticulum and Golgi apparatus, the protein is then translated into lysosomes and peroxisomes respectively or directly secreted into extracellular microenvironment, which still needs to be further clarified [4].

GDF11 is widely expressed in embryonic tissues such as limbs, tail bud, and nervous system as well as in adult retina, epithelium, odontoblasts, spleen, skeletal muscle, and specific regions of the brain [4,43,44]. The expression level of GDF11 varies widely in mRNA and protein level in different tissues. The mRNA level is high in human seminal vesicle, cerebral cortex, endometrium, and cervix, while the GDF11 protein is high in cerebral soft tissue, cortex, adrenal gland, testis, caudate, and hippocampus [45].

4.2. The signaling pathway and function of GDF11

Similar to other members of TGF-β family, GDF11 transmits signals through type I and type II receptors, both of which belongs to transmembrane serine/threonine kinases. Firstly, GDF11 binds to primary ligand binding receptors, activin type II receptors (ActRIIs) containing ActRIIA and ActRIIB, then GDF11 recruits activin type I receptors (ActRIs) including activin receptor-like kinases 4,5,7 (ALK4, ALK5 and ALK7) to form complexes with ActRIIs [46]. GDF11 activates Smad and non-Smad signaling pathways after binding to its receptors, known as canonical and non-canonical signaling pathways, and downregulate other TGF-β family proteins. In canonical pathways, GDF11 phosphorylates receptor-Smads (R-Smads) including Smad2/3 and Smad1/5/8, and then R-smads recruit co-mediator Smad, Smad4 to translocate into the nucleus and regulate the target genes transcription together with nuclear cofactors [47]. It is known that GDF11 activates smad2/3 signaling pathway and non-canonical MAPK (p38, JNK, ERK1/2) pathways to decrease the size and function of the nucleolus, reduce cellular anabolism and protein synthesis [48].

Table 1
The effects of GDF11 on inflammation.

Cell type/animal model	GDF11 application (dose)	Effects	Possible mechanisms
Mouse rheumatoid arthritis (RA)/ BMDMs (bone marrow-derived macrophage) [6]	In vitro: 50 ng/mL	In vitro: inhibited inflammatory reaction induced by TNF-α in BMDMs	Suppressed NF-κB signaling pathway
	In vivo: 0.1 mg/kg every 2d, tail vein injection	In vivo: • Protected against development of arthritis • Inflammatory factors in joints greatly reduced after rGDF11 treatment	
BEAS-2B cells/ Acute lung injury [59]	In vitro: overexpressed GDF11 in BEAS-2B cells via lentiviral transfection	In vitro: significantly reduced the expression of inflammatory factors induced by LPS	Reduce the activity of TLR2/ HMGB1/NF-κB signaling pathway
	In vivo: 100 μg/kg, subcutaneously injection	In vivo: attenuated LPS-induced lung inflammatory response in mice	
RAW264.7 macrophages/ Psoriasis-like skin inflammation (IMQ-induced mice model) [60]	In vitro: 50 ng/mL	In vitro: inhibited TNF-α-mediated inflammatory reaction in macrophage	Suppressed NF-κB Signaling pathway
	In vivo: 0.1 mg/kg every day for 1 week	In vivo: • inhibited inflammatory factors after rGDF11 treatment • inhibited the infiltration of inflammatory cells and thickening of epithelium	
High fat diet-induced obesity [61]	In vivo: Hydrodynamically injected with 25 μg (dose: 1 mg/kg) of pLIVE-GDF11 plasmid DNA to overexpress GDF11 in mice, tail vein injection	In vivo: prevented HFD-induced inflammation and macrophage infiltration	Activated TGF-β/Smad2, AMPK, and PI3K/AKT/ FoxO1 signaling pathways

As a critical regulator of numerous physiological processes, endogenous GDF11 in the central nervous system suppresses the proliferation of adult neural progenitor through the ALK5 receptor [49]; And GDF11 expressed in embryonic pancreatic epithelium regulate $NGN3^{+}$ islet progenitor cell differentiation in parallel or downstream of the Notch pathway [50]; Besides, studies has shown that Cor-1 cells express a TGFβ receptor complex containing ActRIIB/ALK5 subunits, which was regarded as natural ligand for GDF11, providing transcriptional basis for GDF11 regulation in neural stem cell transcription [51]. GDF11 also shows impact in cancer biology. For example, GDF11 expressed in triple-negative breast cancer cells plays a tumor-suppressive role, however, bioactive GDF11 generally failed to mature due to PCSK5 deficiency

Table 2
The effects of GDF11 on cell viability, proliferation & migration.

Cell type/animal model	GDF11 Dose	Effects	Possible mechanisms
C17.2 neural stem cells [62]	In vitro: 12.5–100 ng/mL	In vitro: slightly increased cell viability	—
Mouse heart-derived MSCs [63]	In vitro: 50 ng/mL	In vitro: enhanced viability of MSCs	TGF-β receptor/Smad2/3/YME1L-OPA1 signaling pathway
Endothelial progenitor cells [64]	In vitro: 40 ng/mL	In vitro: increased migration	Smad2/Smad3 pathway
Neural stem cells (NSCs) in old mice (22–23-month-old) [5]	In vivo: 1 mg/kg, systemic administration	In vivo: pro-proliferation effects	—

Table 3
The effects of GDF11 on angiogenesis & neurogenesis.

Cell type/animal model	GDF11 dose	Effects	Possible mechanisms
Bone marrow EPCs (BM-EPCs)/ Diabetic Limb Ischemia [7]	In vitro: 50 ng/mL In vivo: injected daily with 0.1 mg/kg rGDF11 for 2 weeks, intraperitoneally	In vitro: improved tube formation and migration of EPCs In vivo: improved vascularization, increased numbers of $CD31^+$ vessels	Activated TGF-β/Smad and AKT/HIF1α Signaling pathway
Rat stroke [67]	In vivo: 0.1–0.3 mg/kg/day rGDF11, tail vein injection	In vivo: promoted angiogenesis and subsequently increased function of cerebral microvessels	Activated cerebral ALK5/Smad2/3 pathways
Intracerebral hemorrhage (ICY) in elderly rats [68]	In vivo: 0.1 mg/kg, intraperitoneal injection	In vivo: enhanced the neurogenesis and attenuated neurological behavior impairment after ICY	—
Primary brain capillary endothelial cell/aging mouse [70]	In vitro: 40 ng/mL In vivo: 0.1 mg/kg/day for 4 weeks	In vitro: improved tube formation and migration of EPCs In vivo: • Enhanced vascular remodeling in aging mouse brain • Increased $Sox2^+$ neural stem cell populations	Increased the phosphorylation of $smad2/3^+$ cells
Aging mouse [69]	In vivo: 1 mg/kg, intraperitoneal injection	In vivo: increased neuroblasts migration and neurogenesis in subventricular zone	—
Mouse BM-MSCs [89]	—	In vitro: lower expression of GDF11 in MSCs reduced their differentiation into endothelial-like cells In vivo: promoted MSCs differentiation into endothelial-like cells	

in triple-negative breast cancer cells [52]. Apart from functioning in embryonic development, nervous system, and cancer endogenously, circulating GDF11 may also be a good candidate for the prevention of age-related heart hypertrophy and skeletal muscle dysfunction.

Multiple proteins have inhibitory effects on GDF11-mediated signaling pathways. For example, GDF-associated serum protein 1/2 (GASP-1/2) could block the binding of GDF11 to type II receptor [53]. Some proteins form inactive complexes with GDF11 to antagonize its functions [54]. In addition, some inhibitory proteins such as Smad7 are also capable of inhibiting GDF11 activity [55]. Transcription factor histone deacetylases (HDACs) have also been found to reduce GDF11 gene expression [56].

4.3. The potential effects of GDF11 on wound healing processes

There haves been a wide range of studies demonstrating that GDF11 has important roles in aging, cardiovascular health and muscle function, etc. [57–59]. Despite only a few studies addressed the direct effects of GDF11 on wound healing, GDF11 has positive effects on physiological processes relating to wound healing, such as inflammation, angiogenesis, neurogenesis, cell proliferation, migration as detailed below.

4.3.1. The effects of GDF11 on inflammation

Normal wound healing requires an appropriate degree of inflammation, with balanced pro- and anti-inflammatory factors. In contrast, chronic wound has sustained pro-inflammation phase that disrupts the healing process and leads to delayed healing. GDF11 has immunomodulatory effects on pro- and anti-inflammatory aspects during tissue repair, as summarized in Table 1. Recombinant GDF11 has been shown to significantly inhibit TNF-α-induced inflammation in macrophages and reduce pro-inflammatory factors production, such as TNF-α, iNOS, IL-6, IL-1β via inhibiting NF-κB signaling pathway [6,59,60]. Overexpression of GDF11 gene in BEAS-2B cells also significantly attenuated the levels of inflammation and apoptosis in the cells and inhibited the activity of TLR2/HMGB1/NF-κB signaling pathway, which is an important mechanism in LPS-induced acute lung injury [59]. Consistently, systemic administration of GDF11 suppressed inflammation and prevented the development of arthritis and relieved acute lung injury damage [6,59], and GDF11 reduced the infiltration of proinflammatory cells, inhibited TNF-α-mediated inflammatory responses and thickening of epithelium in Psoriasis-like skin inflammation [60]. Besides, GDF11 gene transfer through hydrodynamic injection of pLIVE-GDF11 plasmid in mice prevented high fat diet-induced inflammation and macrophage infiltration, which is achieved through TGF-β/Smad2 and PI3K/AKT/FoxO1 pathways [61].

4.3.2. The effects of GDF11 on cell viability, proliferation & migration

In the proliferative phase of wound healing, dermal fibroblasts and keratinocytes rapidly proliferate and migrate to cover the wounds while cells from chronic wounds are less active. GDF11 has shown the capacity to promote cell viability, proliferation, and migration of certain cell types as listed in Table 2. For example, Wang et al. reported GDF11 could slightly increase C17.2 neural stem cells viability after 24 h treatment by adding 12.5–100 ng/mL GDF11 in vitro [62]. MSCs showed a significant increase in cell viability when cultured with 50 ng/mL recombinant GDF11 (rGDF11) or transduced with lentiviral vector carrying GDF11 gene ($MSCs^{LV-GDF11}$) via TGF-β receptor/Smad2/3/YME1L-OPA1 signaling pathway [63]. In addition, Finkenzeller et al. demonstrated that GDF11 promoted cell migration in culture media without FBS, resulting in strong activation of the Smad2/Smad3 pathway [64]. Ozek et al. concluded GDF11 showed pro-proliferation effects on neural stem cells (NSCs) after systemic administration of GDF11 in vivo [5].

4.3.3. The effects of GDF11 on angiogenesis & neurogenesis

Both angiogenesis and neurogenesis are important biological events in wound healing. Following injury, angiogenic capillaries sprout and gradually invade the ECM proteins-rich wound clot, forming a

microvascular network throughout the granulation tissues within a few days [65]. The newly formed blood vessels also highly associated with neurogenesis, which in turn contributes to skin regeneration and it is known that vasculopathy and neuropathy lead to impaired healing in chronic wounds [66].

As listed in Table 3, GDF11 has shown promising effects on angiogenesis as well as neurogenesis during tissue repair. Systematic replenishment of GDF11 improved angiogenic function of endothelial progenitor cells (EPCs) and subsequently promoted angiogenesis and enhanced blood flow in diabetic rats with hind limb ischemia via TGF-β/Smad and AKT/HIF1α signaling pathway [7]. In rats stroke model, GDF11 increased numbers of $CD31^{+}$/$Ki67^{+}$ vascular EPCs, promoting angiogenesis and functional recovery through activation of cerebral ALK5/Smad2/3 pathways [67]. In addition, GDF11 showed neuroprotective effect and ameliorated neurological behavior impairment in the intracerebral hemorrhage model in elderly rats [68]. Similarly, GDF11 promoted neuroblasts migration and neurogenesis in subventricular zone of aged mice [69]. What's more, systemic administration of recombinant GDF11 induced a rejuvenating effect on the aging brain by increasing not only vascular remodeling but also neurogenesis in mice. Evidence showed that GDF11 significantly promoted tube formation and migration of EPCs through an increase in SMAD phosphorylation cascade in vitro and improved vascular remodeling in old mice. Additionally, GDF11 also increased $Sox2^{+}$ neural stem cell populations in vivo [69,70]. Therefore, GDF11 holds a great potential in modulating vascular and neurogenic functions.

5. The potential delivery methods of GDF11 in chronic wound model

Over the past two decades, there has been numerous wound models successfully developed, including in vitro, ex vivo, in vivo and *in silico* models. Even though in vitro models are standardized, easily controlled and fewer ethical concerns, they have limitations in mimicking complex physiological process and representing underlying mechanism in chronic wound healing. Based on these, ex vivo and in vivo models are commonly used and serve as gold standard tools for experimental studies of chronic wound healing [71].

In published studies, GDF11 was usually administered through intraperitoneal or intravenous injection to attain its systemic effects. There is very few report on the tropical application of GDF11 for skin chronic wound healing study. Effective and sustained delivery of GDF11 in chronic wound healing are needed.

Many functionalized biomaterials have been developed to improve protein retention, stability, and enable controlled delivery. Engineered biomaterials that can adapt to complex microenvironment of chronic wounds may prevent protein degradation and maximize their biological functions in the repair process. The potential drug delivery strategies for the application of GDF11 in the treatment of chronic wound are also proposed in this review.

5.1. Ex vivo and in vivo models of chronic wounds

Ex vivo models are typically collected skin samples from human, mouse, rat, pig, rabbit, etc. and created wounds by biopsy punch, burning, etc., and then cultured under artificial conditions. Ex vivo model can provide an alternative and relatively robust and method for early screening of the efficacy of multiple treatments. As the most frequently used models, in vivo models have been developed from the simplest excisional wounds to the much more complex ones (burn, diabetic ulcers, pressure ulcers, venous leg ulcers, etc.) to help mimic the complicated pathophysiology of chronic wound healing. Based on the previous studies, each of these models provides valuable comprehension for potential innovative treatments such as GDF11 related therapeutics for chronic wounds [72].

5.2. Covalent coupling strategies for GDF11

In contrast to physical encapsulation, covalent coupling tethers proteins to a biomaterial via irreversible chemical bonds, which can prolong local protein presentation and controlled release. Covalent coupling strategies can be applied when long-term protein presentation for continuous cellular responses is needed. Protein retention can be achieved using polymers such as PLGA through carbodiimide crosslinker chemical reaction, specifically through N-hydroxysuccinimide (NHS) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) coupling [73]. Wang et al. recently reported the increased retention of VEGF on mussel-adhesion protein (MAP)-coated stents via carbodiimide chemistry [74]. However, covalent linking may cause protein denaturation and impairment of overall bioactivity. Hence covalently immobilizing GDF11 to biomaterials may achieve sustained protein retention in chronic wound, whereas the possible reduction of protein bioactivity shall be taken into consideration. Methods of site-specific protein modification that can recall functional groups of proteins without losing their bioactivities may be adopted [75].

5.3. Physical encapsulation of GDF11

Physical encapsulation of proteins may protect the proteins from rapid degradation and achieve controlled release, based on matrix porosity and degradation kinetics of materials. For example, both the mesh size and degradation rate of hydrogel can be controlled by adjusting the polymer molecular weight. Jain et al. reported a PEG-based hydrogel platform for sustained release of platelet-rich plasma proteins by modulating mesh size and hydrolytic degradation [76]. Biomaterial properties such as elasticity and swelling ability related to their mesh sizes and influence the release rate of proteins. Modifying the ratio of comonomers will alter the degradation kinetics of biomaterials. For instance, increasing hydrophobicity through increasing the lactic acid to glycolic acid ratio led to the reduction of hydrolysis rate and degradation rate of biomaterials [77]. It is worth noting that physical encapsulation of proteins may have burst release pharmacokinetics in vivo, for example, poly(lactic-co-glycolic) acid (PLGA) nanoparticles, a commonly used materials, always exhibit burst release of cargoes which may reduce the therapeutic effects of the agents [78].

GDF11 protein is cleaved to active mature ligands that are ≈25 kDa in total but the active mature ligand may be reduced to ≈12.5 kDa under reducing conditions [79]. Considering the chronic wound healing process is slow, the burst release of GDF11 shall be avoided through double encapsulation, such as encapsulating PLGA nanoparticles into PEG microspheres or hyaluronic acid/methylcellulose hydrogel to prevent burst release happening [80].

5.4. ECM-based graft materials

ECM mainly consists of collagens, glycoproteins and hydroxyapatite which is the most popular scaffold for promoting skin chronic wound healing. Acellular dermal ECM promotes skin cells infiltration and migration during healing process [34]. ECM-based materials mimic the natural affinity between proteins and ECM through electrostatic payload-vehicle interactions, and achieve controlled protein release. The affinity interactions between protein and ECM can be adjusted through modifying sulphate content of ECM [81], adding binding peptides to the protein [82] or synthesizing fusion proteins that consist of peptide- or ECM-binding domains [83].

ECM-based biomaterials are skin friendly, which can facilitate skin cells infiltration, migration, and vascularization as natural bio-scaffolds. Moreover, the electrostatic interactions between proteins and ECM-based biomaterials show high affinity and prolong retention of incorporated proteins [61]. However, caution is needed that the binding and release of GDF11 to ECM in vivo may be disrupted since many proteins can also interact with ECM molecules, and the non-specificity may lead to

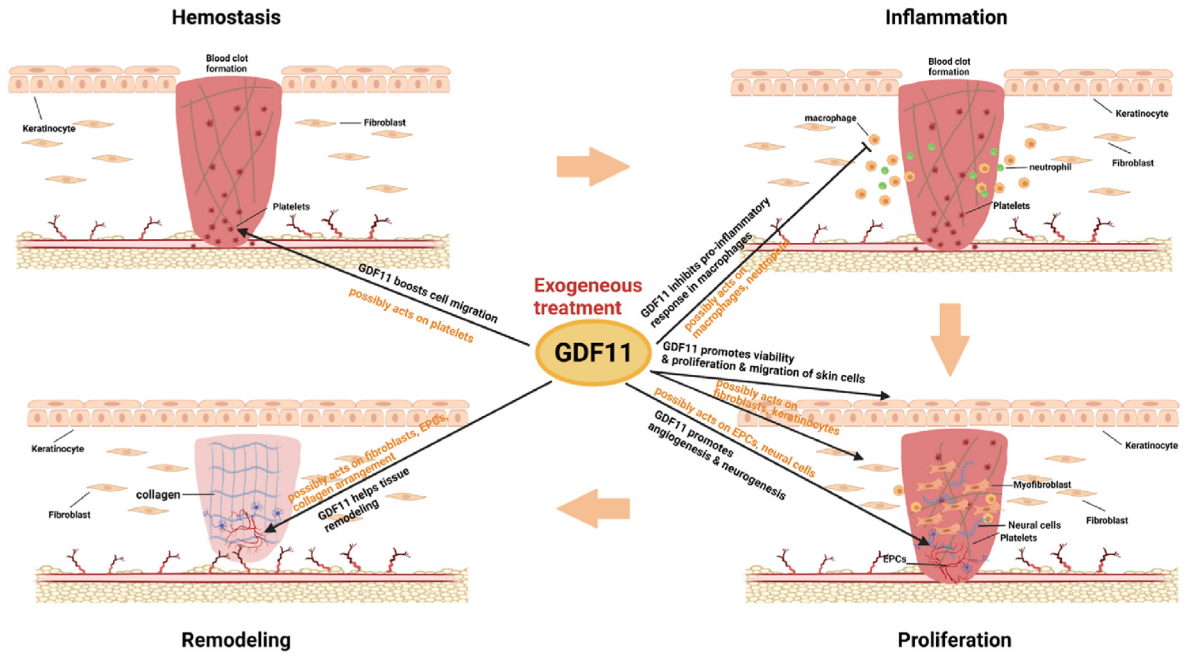

Fig. 1. The potential role of GDF11 in physiological and pathological processes during wound repair in four physiological phases, including hemostasis, inflammation, proliferation, and remodeling. At hemostasis stage, GDF11 possibly regulates platelets migration. At inflammation stage, GDF11 has potential to inhibit pro-inflammation via modulating macrophages or neutrophils. At proliferation stage, GDF11 possibly regulates proliferation and migration of fibroblasts and keratinocytes. Besides, GDF11 also promotes angiogenesis and neurogenesis through acting on EPCs and neural cells. At remodeling stage, GDF11 may continue regulate fibroblasts, EPCs, etc., to help collagen arrangement and angiogenesis.

off-target effects and unpredictable protein release [84].

5.5. Biomaterials for capturing endogenous GDF11

Biomaterials that provide specific protein depots may be applied to encapsulate endogenous proteins or biomolecules at the targeted sites aiding tissue repair. Rinker et al. reported the use of heparin-based biomaterials to sequestrate endogenous heparin-binding growth factors such as FGF-2 and IGF, which can significantly promote chondrogenic differentiation and cartilage repair in the localized area [85]. It is still unknown whether GDF11 is expressed during wound repair. The protein level of GDF11 is hardly detected in normal skin [45], and to design a biomaterials to attract or enrich GDF11 in wound site is a challenge, requiring further careful exploration.

6. Clinical prospect of GDF11 in chronic would healing

Due to the pivotal roles in multiple biological processes, GDF11 has been regarded as potential therapeutic target to several diseases, such as muscular dystrophy and sarcopenia in the elderly, anemia caused by dyserythropoiesis, colorectal cancer, etc. [56,86,87]. For the management of chronic wounds, GDF11 also has broad clinical prospects based on the effects of inhibiting pro-inflammation and enhancing cell proliferation and angiogenesis like PDGF-BB. Similarly, GDF11 would be also applied in the treatments of chronic wounds, such as diabetic ulcers, venous leg ulcers and periodontal defect with topical administration. However, there is still a long way to go in the translation of GDF11, more preclinical studies including safety and efficacy of GDF11 are required before moving to clinical trials in the future [88].

7. Conclusion

Here we reviewed the biology of skin chronic wound healing and the current treatments. Skin chronic wound is still a huge clinical challenge. The potential role of GDF11 in physiological and pathological processes during wound repair, its involvement in inflammation, cell proliferation, migration, angiogenesis, and neurogenesis has been reviewed (Fig. 1). In conclusion, GDF11 has a great translational potential to become a new biological factor to promote chronic wound healing. Methods for GDF11 preparation, encapsulation and controlled release are discussed. However, there are only a few studies reported the promotive effect of GDF11 in wound healing. Investigations are needed to verify its efficacy and determine the best timing (which phase), dosage, duration for GDF11 delivery in chronic wound healing. The cellular source and distribution of GDF11, the active domain of GDF11 structure in skin wound shall be also carefully explored. The use of biomaterials for GDF11 local sustained release will maximize its therapeutic effects, which may lead to a translational bioactive material for chronic wound treatment.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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