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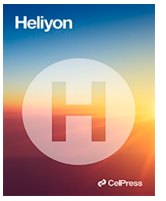

Review article

Mechanism of damage of HIF-1 signaling in chronic diabetic foot ulcers and its related therapeutic perspectives

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A B S T R A C T

Diabetic foot ulcer (DFU) is a chronic complication of diabetes. Wound healing in patients with DFU is generally very slow, with a high recurrence rate even after the ulcer healed. The DFU remains a major clinical challenge due to a lack of understanding of its pathogenesis. Given the significant impact of DFU on patient health and medical costs, enhancing our understanding of pathophysiological alterations and wound healing in DFU is critical. A growing body of research has shown that impaired activation of the HIF-1 pathway in diabetics, which weakens HIF-1 mediated responses to hypoxia and leads to down-regulation of its downstream target genes, leading to incurable diabetic foot ulcers. By analyzing and summarizing the literature in recent years, this review summarizes the mechanism of HIF-1 signaling pathway damage in the development of DFU, analyzes and compares the application of PHD inhibitors, VHL inhibitors, biomaterials and stem cell therapy in chronic wounds of diabetes, and proposes a new treatment scheme mediated by participation in the HIF-1 signaling pathway, which provides new ideas for the treatment of DFU.

1. Introduction

Diabetes mellitus (DM) is a chronic disease, characterized by high blood sugar, caused by the body's inability to produce or use insulin properly. Poorly managed diabetes can cause damage to tissues and organs, such as the kidneys, heart, and nerves. Patients with DFU often have challenging healing processes and are susceptible to infections, leading to an increased risk of amputation [1,2]. Diabetic foot ulcers is one of the most common complications of diabetes, with a high mortality rate and morbidity rate, due to reduced blood circulation and diabetic neuropathy [3]. Approximately 19–34 % of people with diabetes develop DFU, and even if the ulcer is successfully treated, approximately 40 % relapse within 1 year, nearly 60 % within 3 years and 65 % within 5 years, which makes DFU treatment very challenging [4]. So DFU poses a serious health and economic burden worldwide.

Wound recovery in DFU patients typically occurs at a sluggish pace. In some cases, wounds do not even completely heal, and the situation can be further complicated by infections [5]. At present, conventional treatment measures for diabetes mainly include: debridement, change of wound dressing, reduction of lesion pressure, anti-infection measures, management of peripheral vascular lesion and strict glycemic control. Although these methods have been relatively mature, the effect of DFU treatment is still unsatisfactory and the main reason is that the pathogenesis of diabetes is currently unclear [6]. According to numerous research studies, the

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stabilization of HIF-1 is a critical factor in improving the healing process of wounds in diabetic wound [7–9]. This review will discuss the regulatory mechanisms of HIF-1α in diabetes mellitus. Gaining a deeper insight into the development of DFU will lead to innovative treatment strategies.

2. Characteristics of HIF-1

HIF-1 was first identified in hypoxic mammalian cells cultured in a hypoxic environment, and the presence of DNase I-hypersensitive sites was found at the 3 ′end of the erythropoietin (*EPO*) gene, and this region was found to act as a hypoxia-inducible enhancer in transient expression analysis [10,11]. HIF-1 is a major regulator of the hypoxic response, and hypoxia-inducible genes regulate a variety of biological processes, including cell proliferation, angiogenesis, metabolism, apoptosis, immortalization and migration [12].

HIF-1 consists of two subunits, HIF-1α and HIF-1β, encoded by the *Hif1a* and *Hif1b* genes, respectively. Both HIF-1α and HIF-1β subunits are constitutively expressed, but only HIF-1α is affected by oxygen levels [13]. HIF-1β is an aryl carbon receptor nuclear translocator (ARNT), which binds to the aryl hydrocarbon receptor, followed by promoting its translocation to the nucleus [14]. Compared with HIF-1α, the biological properties of HIF-1β are more stable, so this paper focuses on the characteristics of HIF-1α.

HIF-1α protein activity is controlled by two families of oxygen-sensing hydroxylases: prolyl hydroxylase domain-containing proteins (PHDs) and factor inhibiting HIF (FIH) [15]. PHD are members of the dioxygenase family, requiring O2, Fe2+ and the TCA cycle intermediate 2-oxoglutarate (2-OG) for catalytic activity, and are the largest family of non-heme oxygenases [16], while FIH1 is a HIF inhibitor that suppresses HIF-1 expression by inhibiting HIF-1 hydroxylation [17].

In normoxia, PHD hydroxylate HIF-1α and targets it for proteasomal degradation, which is facilitated by the binding of VHL (Fig. 1). In hypoxia, due to the oxygen requirement of hydroxylase activity, the enzyme activity of PHD is reduced and HIF-1α cannot be hydroxylated, while unhydroxylated HIF-1α cannot be degraded by the proteasome, resulting in HIF- 1α stabilization [15]. Once stabilized, HIF-1α translocates to the nucleus, where it dimerizes with HIF-1 β to form a heterodimer. Then, the heterodimer binds to p300 to form a transcriptional activation complex, which recognizes the hypoxia response element (HRE) and activates the transcription of target HIF-1 genes, such as vascular endothelial growth factor (VEGF), glucose transporter protein 1 (GLUT1), hormone erythropoietin (EPO), stromal cell-derived growth factor-1(SDF-1) and stromal cell factor (SCF) [8,12,14,18](Fig. 1). An important target of HIF-1 is VEGF, which plays a central role in angiogenesis and neovascularization. VEGF mRNA cannot be induced by hypoxia in HIF-1β mutant cells further validating the important role of HIF-1 in the secretion of VEGF [19]. Although HIF-1 induced adaptive response to hypoxia, which is regarded as a protective way in many diseases, it has also been reported to be associated with distant metastasis and poor survival in many types of tumors [20].

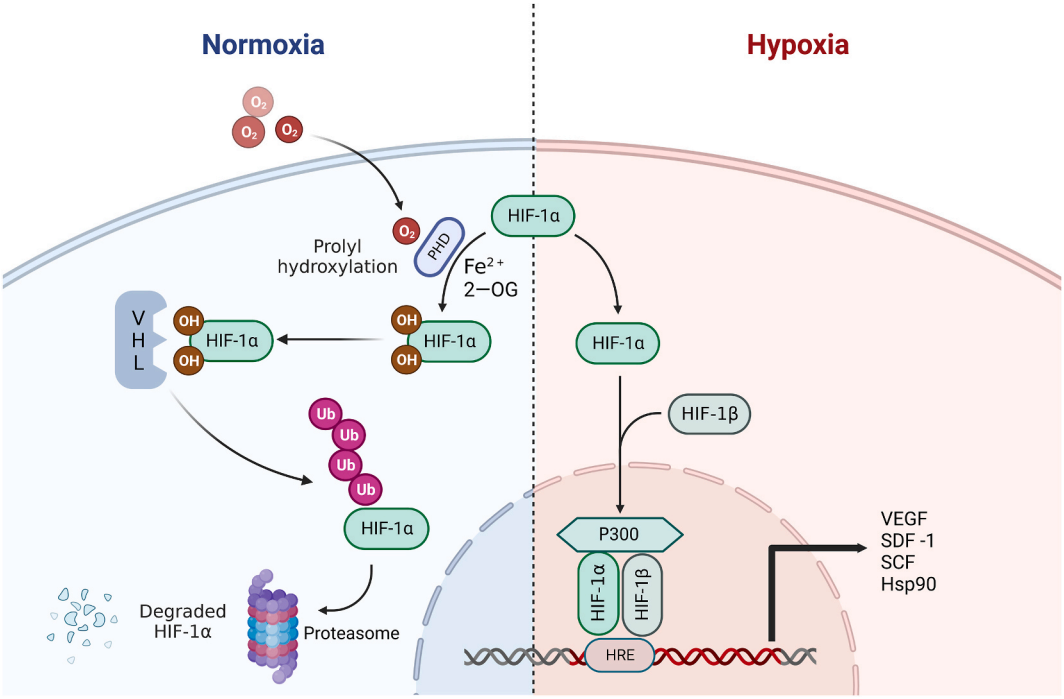

Fig. 1. Regulation of HIF-1 under normxia and hypoxia environment. In normoxia condition, HIF-1α is hydroxylated by PHD in the presence of Fe2+ and 2-OG. Hydroxylated HIF-1α is recognized by VHL, which mediates the ubiquitylation and proteasomal degradation of HIF-1α. In hypoxia, HIF-1α is stabilized and translocates to the nucleus, where it dimerizes with HIF-1β on the HRE of target genes, recruiting coactivators including p300, and activates the transcription of HIF-1 target genes that mediate adaptive responses to hypoxia.

3. Dysregulation of HIF-1 signaling in diabetic wounds

In normoxia, HIF - 1 signaling pathway is induced in response to reduced oxygen levels, leading to hypoxic homeostasis. On the contrary, in diabetic wounds, although tissues are more hypoxic, HIF-1 signaling pathway is inhibited, leading to an impaired adaptive response to hypoxia and thereby decelerating the healing process [21]. A great number of studies have shown that HIF-1 is affected by hyperglycemia under diabetic hypoxic conditions [17,18]. Although the specific mechanism of HIF-1 in DFU is unknown, negative regulation of HIF-1 from hyperglycemia is firm through the following mechanisms (Fig. 2).

3.1. Hyperglycemia promotes PHD-mediated degradation of HIF-1

The degradation of HIF-1α is increased through PHD-mediated degradation in hyperglycemia. Specifically, hyperglycemia promotes hydroxylation of HIF-1α and inhibits HIF-1 in hypoxic cells through a PHD-dependent mechanism [21]. More interesting, Catrina et al. found that hyperglycemia affects hypoxia-dependent stabilization of HIF-1α against proteasomal degradation. To test the hypothesis, the investigators conducted a study of the inhibitory effect of high glucose on HIF-1 protein levels in hypoxic cells, assaying HIF-1 activity in the presence or absence of MG132, a specific inhibitor of proteasome activity. In the presence of MG132, the effect of high concentrations of glucose or mannitol on HIF-1α disappeared, suggesting that this PHD dependent degradation is mediated by proteasome [22].

3.2. MGO aggregation in the high glucose state inhibits the expression of HIF-1

Hyperglycemia leads to intracellular accumulation of methylglyoxal (MGO), a highly reactive oxoaldehyde formed as a by-product of glycolysis [23]. It was found that MGO causes inflammation and delayed healing of diabetic wounds. The mechanism behind this may be that high glucose-induced superoxide increases MGO modification of HIF-1, leading to reduced HIF-1 function [9,24] (Fig. 2).

On the one hand, MGO aggregation inhibited the stability of HIF-1. Unlike the HIF-1 degradation pathway that relies on PHD-mediated and pVHL recruitment. Bento et al. discovered a new pathway for HIF-1α degradation. Hyperglycemia induces the accumulation of MGO, and modification of HIF-1 α contributes to increased binding to the molecular chaperones Hsp 40 and Hsp 70. This, in turn, recruits molecular chaperone-dependent ubiquitin ligase (Carboxy terminus of Hsp70-Interacting Protein CHIP), leading to ubiquitination and proteasome-dependent degradation of HIF-1 α(Fig. 2). This research identifies and demonstrates that this mechanism is independent of pVHL recruitment and does not require PHD-mediated hydroxylation of HIF-1a [23]. This finding also provides a new direction for DFU wound healing.

On the other hand, MGO aggregation in hyperglycemia inhibits the transcriptional activity of HIF-1. First, MGO modify HIF-1α,

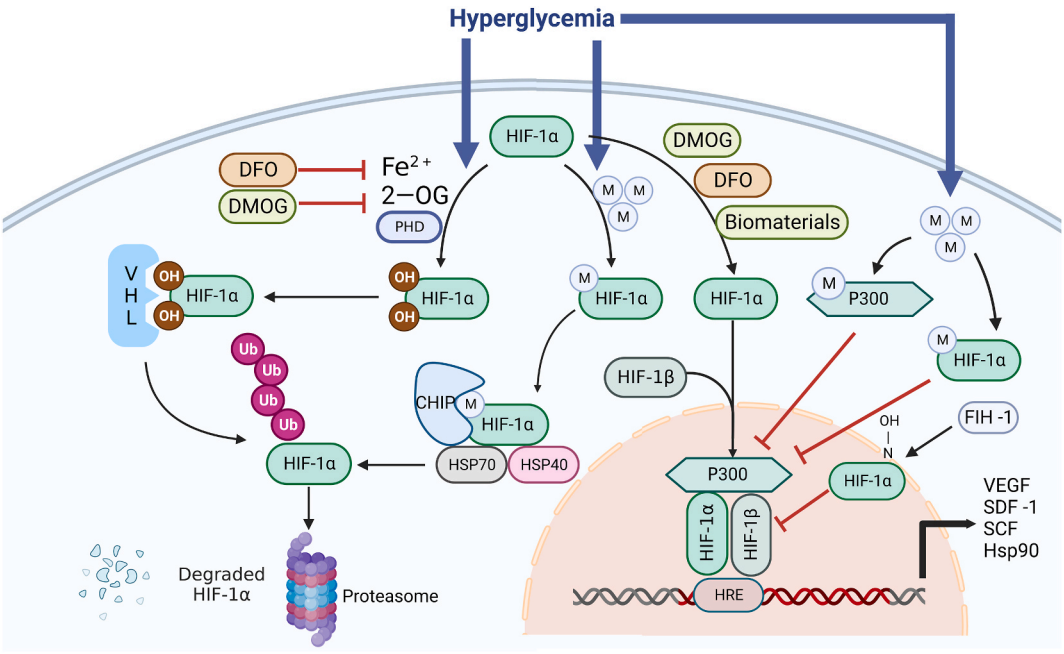

Fig. 2. Hyperglycemia damages Hif-1 signaling pathway. In diabetes, hyperglycemia promotes hydroxylation of HIF-1α and inhibits HIF-1 in hypoxic cells through a PHD-dependent mechanism. Furthermore, Hyperglycemia leads to intracellular accumulation of MGO, which promotes CHIP-mediated HIF-1α ubiquitylation and inhibits the transcriptional activity of HIF-1. Moreover, MGO inhibits HIF-1α dimerization and coactivator recruitment through modification of p300. Elevated blood sugar levels diminish the expression of HIF-1 α and inhibit the gene expression mediated by HIF-1 α, such as *VEGF, GLUT1,* and *EPO*.

preventing the dimerization of HIF-1 α with HIF-1 β, and binding to the promoter of the target gene. Additionally, MGO reduces the binding of coactivators to HIF - 1 α by modifying the coactivator of HIF - 1 α, p300, resulting in reduced transcriptional activity of HIF - 1 α [18]. Likewise, two transactivation domains have been identified, termed the aminoterminal transactivation domain (NTAD) and the carboxy-terminal transactivation domain (CTAD). The negative regulatory effect of hyperglycemia was not only restricted to stability of HIF - 1 α but also targeted both the NTAD and the CTAD of HIF - 1 α, both of which are essential for HIF-1 function [9]. Conclusively, diabetes-induced defects in HIF-1 transcriptional activity were found to result from a combination of disruption of HIF-1α dimerization with HIF1-β and impairment of HIF-1α-p300 binding [25].

3.3. HIF-1 damage leads to downregulation of its target gene

Hyperglycemia leads to downregulation of some HIF - 1 target genes essential for wound healing, such as HSP-90, VEGF - A, VEGF - R1, SDF - 1, and SCF [9] (Fig. 2). In both diabetic patients and animals with ischemic tissues, hyperglycemia caused a decrease in the transcriptional activity of HIF-1, leading to a reduction in VEGF production in response to hypoxia. This inhibition of neovascularization resulted in delayed or nonhealing of chronic diabetic wounds [25]. Furthermore, high glucose-induced PHD-dependent HIF-1 inhibition of HIF-1 has been shown to contribute to overproduction of mitochondrial reactive oxygen species (ROS) in diabetes. This triggers a complex cascade of molecular events that leads to apoptosis and directly induces endothelial damage [26,27]. Endothelial progenitor cells (EPCs) are essential in angiogenesis and wound healing, but their number in circulation and wound levels are reduced in diabetes. Gallagher et al. established in a diabetic mouse model and found that epithelial cells and myofibroblasts in skin wound granulation tissue expressed reduced SDF-1 α, a chemokine that mediates EPC recruitment during ischemia. Furthermore, they demonstrate that impaired EPC homing in diabetic patients is due to reduced levels of SDF-1α [28].

The decrease in the expression of HIF-1 target genes can cause damage to vascular endothelial cells and hinder the formation of new blood vessels, ultimately delaying the healing process of DFU wounds (Fig. 3).

4. Treatment options to regulate theHIF-1 signaling pathway for DFU

We reviewed several drugs in clinical trials and on the market that target the HIF-1 signaling pathway for treating DFU. However, it seems that all these drugs are currently stuck in the clinical trial stage and have not yet been approved for market use (Table 1). Fortunately, these drugs have shown the potential to regulate HIF-1 signaling and demonstrate therapeutic effects on DFU. As

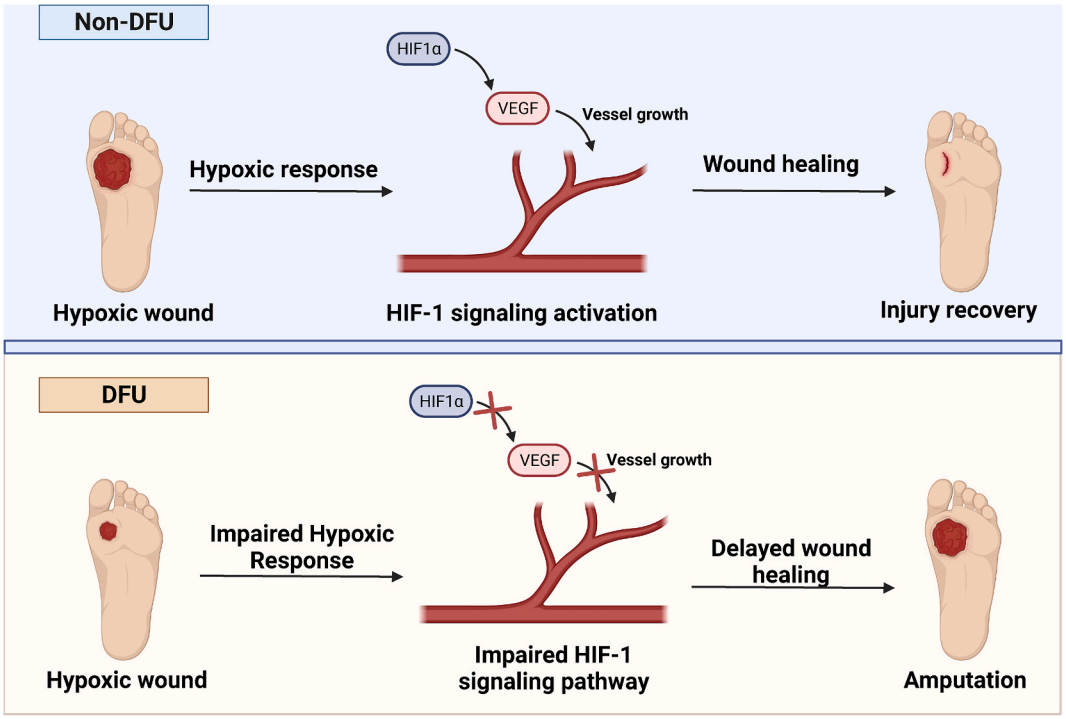

Fig. 3. Impairment in the Hif-1 signaling pathway results in postponed recovery of DFU injuries. In individuals without diabetes who have hypoxic wounds, the activation of the HIF-1 signaling pathway in response to hypoxia leads to an increase in VEGF secretion. This increase facilitates the neovascularization process and promotes wound healing. However, in patients with diabetic foot ulcers (DFU), the impaired HIF-1 signaling pathway hinders the appropriate response to hypoxia, resulting in reduced neovascularization of the wound. As a consequence, wound healing is delayed, and in severe cases, amputation may be required.

additional research is conducted, we can anticipate further discoveries regarding these drugs, and we remain hopeful that they will ultimately benefit patients with diabetic foot ulcers.

There are many treatment options for DFU wounds, and new treatment options such as stem cell therapy, growth factor therapy [29],biomaterials [30]and light therapy, which have opened new doors for the treatment of DFU. We have described above the important mechanisms of the HIF-1 signaling pathway in the development of DFU. This review will continue to summarize the new options for the treatment of chronic diabetic trauma mediated by the participation of the HIF-1 signaling pathway (Table 2).

4.1. Regulation of HIF-1 activity by PHD inhibitors

As mentioned above, hypoxia and impaired adaptive response to hypoxia due to insufficient activation of HIF-1 in diabetes are the underlying pathogenic factors of DFU. Therefore, strategies that aim to increase HIF-1 expression can provide promising therapeutic approaches for the treatment of DFU. In normoxia, PHD regulates HIF-1a activity by targeting HIF-1a degradation, and the use of PHD inhibitors can effectively inhibit HIF-1 degradation to stabilize HIF-1 expression in chronic wounds and promote wound healing [31]. The topical application of common PHD inhibitors such as the 2-ketoglutarate analogue Dimethyloxalylglycine (DMOG), the iron chelator deferoxamine (DFO) [9,32] and $CoCl_2$ [33] has been shown to stabilize HIF-1 α and increase HIF-1 activity.

DFO is a PHD inhibitor approved by the Food and Drug Administration (FDA), and its systemic safety has been proven in clinical use for decades. DFO was found to significantly increase wound regeneration in aged mice by increasing neovascularization and VEGF expression, while also reducing apoptosis [34] The researchers used two different hydroxylase inhibitors, namely DMOG and DFO. Although they are structurally different, both hydroxylase inhibitors can stabilize and activate HIF-1 [9], while Catrina et al. proposed DFO may have potential advantages over other PHD inhibitors as a treatment option for chronic diabetic wounds [18]. Simultaneously, Duscher et al. compared the effectiveness of two small-molecule drugs, DMOG and DFO, to attenuate diabetes-associated cutaneous wound healing deficits by enhancing HIF-1α activation. They proved that both DFO and DMOG can promote wound healing and vascularization in aged mice. DFO stabilized the expression of HIF-1α and increased the transcriptional activity of HIF-1α under hypoxia and hyperglycemia in vitro, while the role of DMOG significantly attenuated under hyperglycemic hypoxic conditions [32]. This illustrates that DFO has a broader clinical application prospect than other PHD inhibitors.

Although DFO plays a key role in the treatment of chronic trauma in mice with diabetes, there is an urgent need for drug delivery systems that target DFO delivery due to its short half-life and the adverse side effects associated with systemic absorption. Duscher et al. designed a transdermal drug delivery system (TDDS) containing small molecule DFO, applied TDDS to the pressure ulcer model of diabetic mice, and found that TDDS can effectively deliver DFO to diabetic wounds. It demonstrated that transdermal administration of DFO significantly improved wound healing. Unexpectedly, prophylactic application of this DFO transdermal drug delivery system DFO also prevented the formation of diabetic ulcers [35]. Later, the team designed enhanced TDDS (eTDDS), which has a better application in promoting wound vascularization, dermal thickness, collagen deposition, and tensile strength than TDDS [36].

4.2. Stabilization of HIF-1 expression in wounds by biomaterials

Recently, an increasing number of studies have shown that biomaterials can accelerate the healing of diabetic wounds, and the study of biomaterials that accelerate chronic diabetic wound healing by activating the HIF-1α signaling pathway has become a hot topic. Since HIF - 1 α is extremely unstable in chronic wounds exposed to air or bacterial infection, the invention of a biomaterial that inhibits the degradation of HIF - 1 α is highly desirable in the management of diabetic ulcers [37]. Biomaterials are mainly divided into three categories: natural materials, synthetic materials and composite material combination. Natural materials encompass a variety of substances such as collagen hydrogels, silk fibroin (SF) films, and hyaluronic acid (HA) hydrogels. Synthetic materials are another category of biomaterials and include substances like polylactide (PLA) nanoparticles, polyphosphate hydrogels, and polycaprolactone (PCL) nanoparticles. Composite materials combine different types of biomaterials to create enhanced properties. Examples of composite biomaterials include PCL-HA Nanofiber scaffold and SF-PCL. Composite materials offer a combination of the desired characteristics of their constituent materials, such as improved mechanical strength or antibacterial properties [38].

4.2. 1. Nanomaterials

Advances in nanomaterials offer new opportunities for the treatment of DFU, and further exploration of nanomaterials will reveal more detailed mechanisms and additional treatment options for diabetic chronic ulcers [39]. Nanomaterials are classified into metallic

Table 1
Summary of drugs for DFU by modulating HIF-1α in clinical trials or market.

Product name	Conditions or diseases	Clinical phases	Status	Clinical trials numbers	Date	Marketed
DFO	DFU	2	In progress	NCT03137966	2017.03–2026.06	No
ALLO-ASC-DFU	DFU	3	In progress	NCT06141811	2023.04–2026.03	No
Electrical stimulation	Diabetic wound	Not Applicable	Completed	NCT02432859	2013.11–2015.02	No
Low Level Laser Therapy	DFU	Not Applicable	Completed	NCT02452086	2013.06–2015.02	No
Pirfenidone Plus MODD	DFU	2	Completed	NCT02632877	2014.01–2015.12	No

ALLO-ASC allogenic adipose-derived mesenchymal stem cells, MODD modified oxide diallyl disulfide.
NCT national clinical trial.

Table 2
Summary of therapeutic options for modulating HIF-1 signaling pathways in DFU.

Therapeutic approaches	Model	Therapeutic Efficacy	Reference
PHD inhibitors	Mice	Stabilized the expression of HIF-1α and increased the transcriptional activity of HIF-1α.	[9]
DMOG	Mice	Enhanced collagen concentration, better neovascularization, and decreased ROS in wounds.	[35]
DFO	Mice	Sustained drug release and increased wound vascularity, dermal thickness, collagen deposition and tensile strength	[36]
DFO-eTDDs			
Biomaterials			
AgNPs	Rats	Improved angiogenesis factors (HIF-1α and VEGF) in diabetic wound models	[41]
PABC scaffolds	Mice	Enhanced HIF-1α/VEGF expression and promoted early angiogenesis and accelerated diabetic	[43]
Cu-DCA NZs	Mice	wound healing.	[55]
Cu-MOF NPs	Mice	Accelerated cellular proliferation, migration and angiogenesis, good antibacterial effect on	[42]
SNP@UCM	Mice	diabetic wounds.	[37]
Hydrogel	Rats	Slowly release Cu^{2+} resulting in induced angiogenesis, promoted collagen deposition and	[46]
DFO-laden hydrogels	Rats	reepithelialization.	[47]
DFO-loaded MMP responsive hydrogel		Improved the secretion of VEGF and cell proliferation and migration and early detection of wound infections. Alleviated inflammation and stimulated angiogenesis in diabetic wound Enhanced angiogenic bioactivity and increased expression of HIF-1α.	
Hydrogel with BG and DFO	Rats	Promoted HIF-1α and VEGF expression and vascularization in the wound sites	[48]
Cell therapy			
HpyADSCs-exo	Nude	Promoted the proliferation and migration of fibroblasts and improve the quality of wound	[52]
ADSCs-hEVs	mice	healing	[5]
ADSCs preconditioned with DFO	Nude	Enhanced the secretion of VEGF and accelerated diabetic wound recovery	[56]
	mice	Improved the neovascularization potential of diabetic rat-derived ADSCs by modulating the	
	Rats	HIF-1α pathway.	

Cu-DCA NZs Copper ions-2,5-dimercaptoterephthalic acid nanozymes, Cu-MOF NPs copper based metal-organic framework nanoparticles, MMP matrix metalloproteinase.

nanomaterials, inorganic nonmetallic nanomaterials, organic nanomaterials, biological nanomaterials, and composite materials.

Recent studies have found that nanoparticles can be effective against human pathogens such as bacteria and even viruses and can be used efficiently to treat a variety of pathological conditions. Certain metals and metal oxides such as silver, copper, cerium oxide and non-metallic nanoparticles such as graphene oxides have been found to have antibacterial and antibiotic properties with a low risk of developing drug-resistant bacteria [40].

Sliver (Ag) is known for its broad-spectrum antimicrobial activity, which is mediated by blocking respiratory enzyme pathways and altering the microbe's DNA and cell walls. Silver nanoparticles (AgNPs) have been reported to be intrinsic therapeutic agents that promote chronic wound healing. AgNPs are capable of removing microorganisms that can interfere with and delay the normal healing phase, potentially promoting diabetic wound healing [39]. Younis et al. showed antibacterial, antioxidant, anti-inflammatory, and pro-angiogenic effects in diabetic trauma animals by cyanobacterial biosynthesis of AgNPs and improved angiogenic factors (HIF-1α, TGF-β1 and VEGF) content in an incision wound model [41].

What's more, copper ion (Cu^{2+}) has excellent antibacterial properties, which can reduce the possibility of wound infection to promote wound healing. However, increased nonphysiological concentrations of Cu^{2+} also increase the risk of ion poisoning [42]. Li et al. developed an injectable self-healing bioactive hydrogel scaffold with robust antibacterial activity and angiogenesis capacity for treating diabetic wound. The nanocomposite scaffold comprises a main network of polyethylene glycol diacrylate (PEGDA) forming scaffolds, with an auxiliary dynamic network formed between bioactive glass nanoparticles containing copper (BGNC) and sodium alginate (ALG) (PABC scaffolds). PABC enhances HIF-1α/VEGF expression to promote early angiogenesis and effectively promotes diabetic wound healing [43].

Compared with traditional nanomaterials, new near-infrared (NIR)-triggered NO nanomaterials offer greater advantages. Yang et al. innovatively invented the HIF - 1 α stable advanced nanomaterial, an intelligent NIR-triggered NO nanogenerator (SNP@UCM). Increased HIF-1α expression in endothelial cells by SNP@UCM enhances angiogenesis at wound sites, promoting the secretion of VEGF and cell proliferation and migration. SNP@UCM also enables early detection of wound infections and ROS-mediated killing of bacteria [37]. Although nanomaterials have developed rapidly in the last decades, translating these basic research results into products that can be applied in the clinic still requires our joint efforts.

4.2. 2. Hydrogel

Hydrogels have become one of the most widely used dressings for diabetic wounds in the clinic. Hydrogel matrices with porous structures and appropriate swelling ratios can absorb large amounts of exudate and provide a moist wound environment for the treatment of diabetic wounds [44]. Hydrogels have variable morphology and adjustable swelling properties. However, its permeability to gases limits its use on infected wounds. Therefore, it is not wise to use hydrogel dressings alone to treat diabetic wounds [38]. Hydrogels combined with drugs also have good potential for application in skin regeneration and wound healing.

There is a growing body of research on DFO combined with hydrogels for the treatment of diabetic chronic wounds, where the hydrogel reshapes the microenvironment to facilitate healing to accelerate wound healing. As a multifunctional adaptive wound dressing of the wound microenvironment, the hydrogel has the potential to treat diabetic wounds and regenerate skin tissue [45]. Ding et al. prepared DFO-loaded silk nanofiber hydrogels to accelerate diabetic wound healing [46], and Li et al. developed a new

DFO-loaded degradable MMP hydrogel for diabetic wounds by incorporating DFO into MMP-cleavable hydrogels to confer enhanced angiogenic bioactivity to composite hydrogels by increasing the expression of HIF-1α [47]. Kong et al. developed an injectable hydrogel containing both bioglass (BG) and DFO for enhanced repair of chronic diabetic skin defects [48]. Numerous studies have shown that the combination of desferrioxamine and hydrogel shows greater advantages in the treatment of diabetic chronic wounds.

4.3. HIF-1α up-regulated stem cells and exosomes for the treatment of diabetic foot

Several studies have previously reported the great potential of stem cells in promoting the repair of chronic skin and diabetic foot and chronic skin wounds [49–51]. Wang et al. found that the survival and proliferation of adipose stem cells (ADSCs) were significantly enhanced after hypoxia induction compared to normal hypoxia, and found that hypoxic adipose stem cell exosomes (HpyADSCs-exo) may accelerate the rate of diabetic wound healing, improve the quality of wound healing whereas inhibit inflammation [52]. The mechanism may be that hypoxia improves the expression of HIF-1α, which in turn promotes the survival and proliferation of adipose stem cells. In subsequent experiments, they confirmed that HIF-1α overexpression in adipose-derived stem cell extracellular vesicles (ADSCs-hEVs) accelerated diabetic wound healing and improved healing quality by inhibiting inflammation and regulating extracellular matrix secretion [5].

Furthermore, HIF-1α overexpression in ADSCs improves their paracrine function under high glucose/low oxygen conditions. Xu et al. demonstrated for the first time that HIF-1α overexpression in ADSCs promotes their paracrine function and survival by reducing ROS production, thus improving their therapeutic role in diabetic wound healing [53]. In addition, Kerstan's study found that hypoxic culture of ABCB5+ mesenchymal stem cells resulted in post-translational stabilization of HIF-1α and upregulation of HIF-1α mRNA levels. Activation of the HIF-1α pathway was accompanied by upregulation of VEGF transcription and increased secretion of VEGF protein [54].

Briefly, transplantation of HIF-1α highly expressing MSCs to the injury site is a promising novel therapeutic strategy for diabetic wound healing and can also be used in combination with other MSC-based therapeutic approaches.

5. Prospective

HIF-1 activity can be stimulated by both PHD inhibitors and VHL inhibitors, however, VHL inhibitors may be more effective in activating HIF. When VHL protein function is abnormal or absent, degradation of HIF protein is hindered, leading to excessive activation of the HIF signaling pathway. This abnormal activation has been linked to tumorigenesis and progression. For instance, a study has shown that approximately 70 % of patients with VHL disease develop renal cell carcinomas during their lifetime [57]. Interestingly, in diabetic patients with tumors, the use of VHL inhibitors promotes the development of diabetes despite their ability to inhibit tumor invasion. Curiously, the administration of VHL inhibitors in diabetic individuals with tumors facilitates the progression of diabetes, notwithstanding their capacity to impede tumor infiltration.

5.1. Limitations of PHD inhibitors

Numerous studies have been conducted to investigate the effectiveness of PHD inhibitors in preventing HIF-1 degradation and enhancing its stability and activity. Despite their potential benefits, PHD inhibitors have been criticized by some scholars because of their limitations, such as poor target selectivity and large side effects. Concerns about their safety and tolerability have been raised due to their off-target effects [8,58]. For instance, Macdougall et al. discovered that PHD inhibitors can cause liver damage. In the phase 2 clinical trial of FG-2216, several patients experienced abnormal liver enzyme test results, and one patient even suffered from fatal liver necrosis [59]. Therefore, inhibition of upstream PHD may not be the optimal approach to stabilizing HIF-1α expression.

5.2. Promising future for VHL inhibitors

Compared with PHD inhibitors, VHL inhibitors have higher activity and higher selectivity, and VHL inhibitors represent an attractive alternative to PHD inhibitors as HIF stabilizers with a different mechanism of action, which can alleviate the potential HIF independent side effects of PHD inhibitors [58]. Stabilizing HIF-1a by preventing downstream interactions between HIF-1a and VHL, preventing independent off-target consequences of HIF-1a, and disrupting protein-protein interactions between VHL and HIF-1a may be a very effective strategy for treating diabetic wounds [60].

As a potent and selective VHL inhibitor, VH298 induces the hypoxia response through a different mechanism, that is, by blocking the VHL, HIF-1a protein-protein interaction downstream of the hydroxylation of HIF-a. In their study, Frost et al. discovered that VH298 interacts with VHL with high affinity and specificity, making VHL its major cellular target. This interaction results in the selective accumulation of hydroxylated HIF-1a in a concentration- and time-dependent manner in various cell lines. As a consequence, there is an upregulation of HIF-target genes at both mRNA and protein levels [58]. Therefore, developing highly active and selective VHL inhibitors could be a promising option for stabilizing HIF as an alternative to PHD inhibitors.

VH298 activates the HIF-1 signaling pathway by stabilizing HIF-1α and hydroxylated HIF-1α. VH298 improves the function of rat fibroblasts, promotes human umbilical vein endothelial cell (hUVEC) angiogenesis, and accelerates wound healing in a rat model of simulated diabetes [61]. Stabilizing HIF-1α by blocking its downstream interaction with VHL has better selectivity compared to PHD inhibitors such as DFO, MOG and COCL2. This is a potential strategy superior to inhibiting upstream strategies for PHDs. However, there are currently few studies on the use of VHL inhibitors in the treatment of diabetic wounds, and more research is needed to

confirm their efficiency.

5.3. Combination therapy

The use of biomaterials is a popular method of treating diabetic wounds, as it promotes wound healing and improves the effectiveness of treatments. Biomaterials such as hydrogels, nanomaterials, and metal scaffolds are commonly used [62–64]. Combining biomaterials with drugs, biologics, or cells has been shown to be a more effective method of treatment. This combination of biomaterials and biologics opens up new possibilities for the healing of chronic diabetic wounds [65].

For example, the team of Li et al. reports the design and synthesis of a cyclometalated iridium (III) metal complex 1a as a stabilizer of HIF-1α, which binds to VHL and inhibits the interaction of VHL–HIF–1α. Furthermore, the compound accumulates HIF-1α levels in cellulose and activates HIF-1α mediated gene expression, including VEGF, GLUT1 and EPO. A significant increase in wound closure was observed in both diabetic and normal mice. The compound significantly accelerated wound closure in diabetic mice compared to controls [8].

Similarly, Wang et al. isolated exosomes or extracellular vesicles (EVs) from epidermal stem cells (ESCs) and loaded them with the HIF-1α stabilizer VH298. Data show that the inclusion of VH298 improves ESC-EV's ability to improve blood vessel and wound healing. The team also developed sustainable delivery vehicles using gelatin methacryloyl (GelMA)as a wound dressing. GelMA hydrogels containing VH-EVs effectively promote wound healing by enhancing local blood supply and angiogenesis, a potential mechanism that may be associated with activation of the HIF-1α/VEGFA signaling pathway [66].

Therefore, the addition of bioactive ingredients, such as drugs, bioactive agents, stem cells, or growth factors, to biomaterials is effective for wound care and treatment in diabetics [65].

5.4. The link between DFU, cancer and HIF-1

Recently, cancer deaths amongst people with diabetes mellitus constitute a larger proportion of deaths among this population in some countries/regions [67]. For example, in England, cancer has overtaken vascular disease as the predominant cause of death in people with diabetes mellitus and is the leading contributor to excess mortality in those with diabetes mellitus compared with those without [68]. Malignant tumor cells employ a variety of strategies to enhance HIF signaling, promote HIF -1α mRNA translation, protein stability and downstream target gene expression during tumor proliferation. On the contrary, in patients with DFU, hyperglycemia leads to impaired HIF-1α signaling pathway and reduced expression of VEGF, resulting in reduced wound neovascularization and increased hypoxia and ischemia on the wound surface, leading to nonhealing or delayed healing. Unfortunately, with the increasing incidence of diabetes and many diabetic patients suffering from tumors, it is necessary to investigate and study whether the topical application of the HIF-1 enhancer interferes with the expression of HIF-1α in tumor cells.

6. Conclusions

The treatment of DFU has been a challenge in the clinic. Hyperglycemia has been found to impair the activation of the HIF-1 pathway, which in turn affects the HIF-1-mediated response under hypoxic conditions. This impairment leads to the downregulation of downstream target molecules such as VEGF, SDF-1, and SCF. This downregulation ultimately results in vascular endothelial damage, reduced neovascularization, and delayed healing of chronic diabetic wounds.

Therefore, improving the stability and transcriptional activity of local traumatic HIF-1 is clinically important for the treatment of DFU. While PHD inhibitors have been developed as HIF-1α stabilizers, they have some drawbacks such as poor target selectivity and off-target effects. Compared with PHD inhibitors, VHL inhibitors are highly active and selective. Potential non-dependent side effects of HIF-1 PHD inhibitors may be mitigated by substituting VHL inhibitors for PHD inhibitors.

At the same time, stem cell therapy has become a significant topic of research due to its potential in promoting DFU repair. Using hypoxia-induced or HIF-1 overexpressing stem cells provides new perspectives in treating DFU. Furthermore, innovations in biomaterial technology have paved the way for biomaterials to become essential tools in treating DFU. Biomaterials such as hydrogels, nanomaterials, and drug carriers possess good biocompatibility and biodegradability, making them excellent clinical drug delivery systems. Incorporating biomaterials with biologics and other treatments such as VHL inhibitors and stem cell therapy may lead to better DFU treatment through modulation of the HIF-1 signaling pathway. Therefore, combining therapies has become an effective strategy for local wound management and has promising potential in DFU treatment.

In summary, this review summarizes the pathogenesis of HIF-1 in DFU and the therapeutic options for treating DFU by modulating the HIF-1 signaling pathway. By analyzing the application of PHD inhibitors, VHL inhibitors, biomaterials and stem cell therapies in chronic diabetic wounds, we conclude that based on the growing development of biomaterials technology and a deeper understanding of the pathogenesis of chronic diabetic wounds, the combined therapeutic strategy of modulating the HIF-1 signaling pathway with biomaterials as carrier will bring hope for chronic wound healing and has a broad potential for application.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CRediT authorship contribution statement

Dong Zhu: Writing – original draft, Conceptualization. **Wuhan Wei:** Writing – review & editing. **Jingyu Zhang:** Writing – review & editing. **Bingkun Zhao:** Writing – original draft, Conceptualization. **Qiang Li:** Supervision, Funding acquisition. **Peisheng Jin:** Supervision, Funding acquisition.

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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References

[1] A. Berbudi, N. Rahmadika, A.I. Tjahjadi, R. Ruslami, Type 2 diabetes and its impact on the immune system, CDR 16 (5) (May 2020) 442–449, https://doi.org/10.2174/1573399815666191024085838.
[2] M. Walicka, et al., Amputations of lower limb in subjects with diabetes mellitus: reasons and 30-day mortality, J. Diabetes Res. (2021), https://doi.org/10.1155/2021/8866126, 2021, pp. 1–8, Jul.
[3] S.A. Bus, et al., Guidelines on the prevention of foot ulcers in persons with diabetes (IWGDF 2019 update), Diabetes Metab Res Rev 36 (2020), https://doi.org/10.1002/dmrr.3269. S1, Mar.
[4] D.G. Armstrong, A.J.M. Boulton, S.A. Bus, Diabetic foot ulcers and their recurrence, N. Engl. J. Med. 376 (24) (Jun. 2017) 2367–2375, https://doi.org/10.1056/NEJMra1615439.
[5] J. Wang, et al., Extracellular vesicles from HIF-1α-Overexpressing adipose-derived stem cells restore diabetic wounds through accelerated fibroblast proliferation and migration, IJN ume 16 (Dec. 2021) 7943–7957, https://doi.org/10.2147/IJN.S335438.
[6] F.M. Davis, A. Kimball, A. Boniakowski, K. Gallagher, Dysfunctional wound healing in diabetic foot ulcers: new crossroads, Curr. Diabetes Rep. 18 (1) (2018) 2, https://doi.org/10.1007/s11892-018-0970-z. Jan.
[7] W.X. Hong, et al., The role of hypoxia-inducible factor in wound healing, Adv. Wound Care 3 (5) (May 2014) 390–399, https://doi.org/10.1089/wound.2013.0520.
[8] G. Li, et al., A small molecule HIF-1α stabilizer that accelerates diabetic wound healing, Nat. Commun. 12 (1) (2021) 3363, https://doi.org/10.1038/s41467-021-23448-7. Jun.
[9] Ileana Ruxandra Botusan, et al., Stabilization of HIF-1alpha is critical to improve wound healing in diabetic mice, Proc. Natl. Acad. Sci. U.S.A. 105 (49) (2008) 19426–19431, https://doi.org/10.1073/pnas.0805230105.
[10] G.L. Semenza, M.K. Nejfelt, S.M. Chi, S.E. Antonarakis, Hypoxia-inducible nuclear factors bind to an enhancer element located 3' to the human erythropoietin gene, Proc. Natl. Acad. Sci. U.S.A. 88 (13) (Jul. 1991) 5680–5684, https://doi.org/10.1073/pnas.88.13.5680.
[11] G.L. Wang, B.-H. Jiang, E.A. Rue, G.L. Semenza, Hypoxia-inducible Factor 1 Is a Basic-Helix-Loop-Helix-PAS Heterodimer Regulated by Cellular 02 Tension, Proc. Natl. Acad. Sci. USA, 1995.
[12] A.L. Harris, Hypoxia — a key regulatory factor in tumour growth, Nat. Rev. Cancer 2 (1) (Jan. 2002) 38–47, https://doi.org/10.1038/nrc704.
[13] R. Cerychova, G. Pavlinkova, HIF-1, metabolism, and diabetes in the embryonic and adult heart, Front. Endocrinol. 9 (2018) 460, https://doi.org/10.3389/fendo.2018.00460. Aug.
[14] C. Yang, Z.-F. Zhong, S.-P. Wang, C.-T. Vong, B. Yu, Y.-T. Wang, HIF-1: structure, biology and natural modulators, Chin. J. Nat. Med. 19 (7) (2021) 521–527, https://doi.org/10.1016/S1875-5364(21)60051-1. Jul.
[15] P.M. Elks, S.A. Renshaw, A.H. Meijer, S.R. Walmsley, F.J. van Eeden, Exploring the HIFs, buts and maybes of hypoxia signalling in disease: lessons from zebrafish models, Disease Models & Mechanisms 8 (11) (Nov. 2015) 1349–1360, https://doi.org/10.1242/dmm.021865.
[16] C.J. Schofield, Z. Zhang, Structural and mechanistic studies on 2-oxoglutarate-dependent oxygenases and related enzymes, Curr. Opin. Struct. Biol. 9 (6) (1999) 722–731, https://doi.org/10.1016/s0959-440x(99)00036-6.
[17] P.C. Mahon, et al., FIH-1: a novel protein that interacts with HIF-1alpha and VHL to mediate repression of HIF-1 transcriptional activity, Gene Dev. 15 (20) (2001) 2675–2686, https://doi.org/10.1101/gad.924501.
[18] S.-B. Catrina, X. Zheng, Disturbed hypoxic responses as a pathogenic mechanism of diabetic foot ulcers: HIF-1 and Wound Healing in Diabetes, Diabetes Metab Res Rev 32 (Jan. 2016) 179–185, https://doi.org/10.1002/dmrr.2742.
[19] J.A. Forsythe, et al., Activation of vascular endothelial growth factor gene transcription by hypoxia-inducible factor 1, Mol. Cell Biol. 16 (9) (Sep. 1996) 4604–4613, https://doi.org/10.1128/MCB.16.9.4604.
[20] E.B. Rankin, A.J. Giaccia, Hypoxic control of metastasis, Science 352 (6282) (2016) 175–180, https://doi.org/10.1126/science.aaf4405. Apr.
[21] S.-B. Catrina, X. Zheng, Hypoxia and hypoxia-inducible factors in diabetes and its complications, Diabetologia 64 (4) (Apr. 2021) 709–716, https://doi.org/10.1007/s00125-021-05380-z.
[22] S.-B. Catrina, K. Okamoto, T. Pereira, K. Brismar, L. Poellinger, Hyperglycemia Regulates Hypoxia-Inducible Factor-1_ Protein Stability and Function, vol. 53, 2004.
[23] C.F. Bento, et al., The chaperone-dependent ubiquitin ligase CHIP targets HIF-1α for degradation in the presence of methylglyoxal, PLoS One 5 (11) (2010) e15062, https://doi.org/10.1371/journal.pone.0015062. Nov.
[24] K. Nickel, U. Wensorra, H. Wenck, N. Peters, H. Genth, Evaluation of immunomodulatory responses and changed wound healing in type 2 diabetes—a study exploiting dermal fibroblasts from diabetic and non-diabetic human donors, Cells 10 (11) (Oct. 2021) 2931, https://doi.org/10.3390/cells10112931.
[25] H. Thangarajah, et al., The molecular basis for impaired hypoxia-induced VEGF expression in diabetic tissues, Proc. Natl. Acad. Sci. U.S.A. 106 (32) (Aug. 2009) 13505–13510, https://doi.org/10.1073/pnas.0906670106.

[26] X. Zheng, et al., Repression of hypoxia-inducible factor-1 contributes to increased mitochondrial reactive oxygen species production in diabetes, Elife 11 (2022) e70714, https://doi.org/10.7554/eLife.70714. Feb.

[27] D.J. Ceradini, et al., Decreasing intracellular superoxide corrects defective ischemia-induced new vessel formation in diabetic mice, J. Biol. Chem. 283 (16) (Apr. 2008) 10930–10938, https://doi.org/10.1074/jbc.M707451200.

[28] K.A. Gallagher, et al., Diabetic impairments in NO-mediated endothelial progenitor cell mobilization and homing are reversed by hyperoxia and SDF-1α, J. Clin. Invest. 117 (5) (May 2007) 1249–1259, https://doi.org/10.1172/JCI29710.

[29] 'Stem Cell-Based Therapy for Diabetic Foot Ulcers', Front. Cell Dev. Biol. 10 (Feb. 2022) 812262, https://doi.org/10.3389/fcell.2022.812262.

[30] M.H. Amer, F.R.A.J. Rose, K.M. Shakesheff, L.J. White, A biomaterials approach to influence stem cell fate in injectable cell-based therapies, Stem Cell Res. Ther. 9 (1) (2018) 39, https://doi.org/10.1186/s13287-018-0789-1. Dec.

[31] A. Dallas, et al., Acceleration of diabetic wound healing with PHD2- and miR-210-targeting oligonucleotides, Tissue Eng. 25 (1–2) (Jan. 2019) 44–54, https://doi.org/10.1089/ten.tea.2017.0484.

[32] D. Duscher, et al., Comparison of the hydroxylase inhibitor dimethyloxalylglycine and the iron chelator deferoxamine in diabetic and aged wound healing, Plast. Reconstr. Surg. 139 (3) (2017), https://doi.org/10.1097/PRS.0000000000003072, 695e–706e, Mar.

[33] K.A. Mace, D.H. Yu, K.Z. Paydar, N. Boudreau, D.M. Young, Sustained expression of *Hif-1α* in the diabetic environment promotes angiogenesis and cutaneous wound repair, Wound Repair Regen. 15 (5) (Sep. 2007) 636–645, https://doi.org/10.1111/j.1524-475X.2007.00278.x.

[34] C.A. Bonham, et al., Deferoxamine can prevent pressure ulcers and accelerate healing in aged mice, Wound Repair Regen. 26 (3) (May 2018) 300–305, https://doi.org/10.1111/wrr.12667.

[35] D. Duscher, et al., Transdermal deferoxamine prevents pressure-induced diabetic ulcers, Proc. Natl. Acad. Sci. U.S.A. 112 (1) (Jan. 2015) 94–99, https://doi.org/10.1073/pnas.1413445112.

[36] D. Duscher, et al., Optimization of transdermal deferoxamine leads to enhanced efficacy in healing skin wounds, J. Contr. Release 308 (Aug. 2019) 232–239, https://doi.org/10.1016/j.jconrel.2019.07.009.

[37] Y. Yang, et al., Ubiquitination flow repressors: enhancing wound healing of infectious diabetic ulcers through stabilization of polyubiquitinated hypoxia-inducible factor-1α by theranostic nitric oxide nanogenerators, Adv. Mater. 33 (45) (Nov. 2021) 2103593, https://doi.org/10.1002/adma.202103593.

[38] S. Ren, S. Guo, L. Yang, C. Wang, Effect of composite biodegradable biomaterials on wound healing in diabetes, Front. Bioeng. Biotechnol. 10 (Nov. 2022) 1060026, https://doi.org/10.3389/fbioe.2022.1060026.

[39] Y. Liu, et al., Emerging theranostic nanomaterials in diabetes and its complications, Adv. Sci. 9 (3) (Jan. 2022) 2102466, https://doi.org/10.1002/advs.202102466.

[40] N.K. Rajendran, S.S.D. Kumar, N.N. Houreld, H. Abrahamse, A review on nanoparticle based treatment for wound healing, J. Drug Deliv. Sci. Technol. 44 (Apr. 2018) 421–430, https://doi.org/10.1016/j.jddst.2018.01.009.

[41] N.S. Younis, M.E. Mohamed, N.A. El Semary, Green synthesis of silver nanoparticles by the cyanobacteria synechocystis sp.: characterization, antimicrobial and diabetic wound-healing actions, Mar. Drugs 20 (1) (Jan. 2022) 56, https://doi.org/10.3390/md20010056.

[42] J. Xiao, et al., Copper metal–organic framework nanoparticles stabilized with folic acid improve wound healing in diabetes, ACS Nano 12 (2) (Feb. 2018) 1023–1032, https://doi.org/10.1021/acsnano.7b01850.

[43] Y. Li, et al., Bioactive antibacterial silica-based nanocomposites hydrogel scaffolds with high angiogenesis for promoting diabetic wound healing and skin repair, Theranostics 10 (11) (2020) 4929–4943, https://doi.org/10.7150/thno.41839.

[44] Y. Qian, et al., Immunoregulation in diabetic wound repair with a photoenhanced glycyrrhizic acid hydrogel scaffold, Adv. Mater. 34 (29) (Jul. 2022) 2200521, https://doi.org/10.1002/adma.202200521.

[45] Z. Shao, T. Yin, J. Jiang, Y. He, T. Xiang, S. Zhou, Wound microenvironment self-adaptive hydrogel with efficient angiogenesis for promoting diabetic wound healing, Bioact. Mater. 20 (2023) 561–573, https://doi.org/10.1016/j.bioactmat.2022.06.018.

[46] Z. Ding, et al., Injectable desferrioxamine-laden silk nanofiber hydrogels for accelerating diabetic wound healing, ACS Biomater. Sci. Eng. 7 (3) (2021) 1147–1158, https://doi.org/10.1021/acsbiomaterials.0c01502.

[47] N. Li, A. Zhan, Y. Jiang, H. Liu, A novel matrix metalloproteinases-cleavable hydrogel loading deferoxamine accelerates diabetic wound healing, Int. J. Biol. Macromol. 222 (2022) 1551–1559, https://doi.org/10.1016/j.ijbiomac.2022.09.185.

[48] L. Kong, et al., Bioactive injectable hydrogels containing desferrioxamine and bioglass for diabetic wound healing, ACS Appl. Mater. Interfaces 10 (36) (2018) 30103–30114, https://doi.org/10.1021/acsami.8b09191.

[49] K.-C. Moon, et al., Potential of allogeneic adipose-derived stem cell–hydrogel complex for treating diabetic foot ulcers, Diabetes 68 (4) (2019) 837–846, https://doi.org/10.2337/db18-0699.

[50] L. Bacakova, et al., Stem cells: their source, potency and use in regenerative therapies with focus on adipose-derived stem cells – a review, Biotechnol. Adv. 36 (4) (2018) 1111–1126, https://doi.org/10.1016/j.biotechadv.2018.03.011.

[51] Q. Li, S. Xia, Y. Yin, Y. Guo, F. Chen, P. Jin, miR-5591-5p regulates the effect of ADSCs in repairing diabetic wound via targeting AGEs/AGER/JNK signaling axis, Cell Death Dis. 9 (5) (May 2018) 566, https://doi.org/10.1038/s41419-018-0615-9.

[52] J. Wang, et al., Hypoxia adipose stem cell-derived exosomes promote high-quality healing of diabetic wound involves activation of PI3K/Akt pathways, J. Nanobiotechnol. 19 (1) (2021) 202, https://doi.org/10.1186/s12951-021-00942-0.

[53] J. Xu, X. Liu, F. Zhao, Y. Zhang, Z. Wang, HIF1α overexpression enhances diabetic wound closure in high glucose and low oxygen conditions by promoting adipose-derived stem cell paracrine function and survival, Stem Cell Res. Ther. 11 (1) (2020) 148, https://doi.org/10.1186/s13287-020-01654-2.

[54] A. Kerstan, et al., Translational development of ABCB5+ dermal mesenchymal stem cells for therapeutic induction of angiogenesis in non-healing diabetic foot ulcers, Stem Cell Res. Ther. 13 (1) (2022) 455, https://doi.org/10.1186/s13287-022-03156-9.

[55] W. Huang, et al., Functional molecule-mediated assembled copper nanozymes for diabetic wound healing, J. Nanobiotechnol. 21 (1) (2023) 294, https://doi.org/10.1186/s12951-023-02048-1.

[56] M. Mehrabani, et al., Deferoxamine preconditioning to restore impaired HIF -1α-mediated angiogenic mechanisms in adipose-derived stem cells from STZ -induced type 1 diabetic rats, Cell Prolif. 48 (5) (2015) 532–549, https://doi.org/10.1111/cpr.12209.

[57] E. Jonasch, et al., Belzutifan for renal cell carcinoma in von Hippel–lindau disease, N. Engl. J. Med. 385 (22) (Nov. 2021) 2036–2046, https://doi.org/10.1056/NEJMoa2103425.

[58] J. Frost, et al., Potent and selective chemical probe of hypoxic signalling downstream of HIF-α hydroxylation via VHL inhibition, Nat. Commun. 7 (1) (2016) 13312, https://doi.org/10.1038/ncomms13312. Nov.

[59] I.C. Macdougall, Novel erythropoiesis-stimulating agents: a new era in anemia Management, Clin. J. Am. Soc. Nephrol. 3 (1) (2008) 200–207, https://doi.org/10.2215/CJN.03840907.

[60] E. M, A novel family of small molecule HIF-1 alpha stabilizers for the treatment of diabetic wounds; an integrated *in silico* , *in vitro* , and *in vivo* strategy, RSC Adv. 12 (48) (2022) 31293–31302, https://doi.org/10.1039/D2RA05364K.

[61] S. Qiu, et al., Von hippel-lindau (VHL) protein antagonist VH298 improves wound healing in streptozotocin-induced hyperglycaemic rats by activating hypoxia-inducible factor- (HIF-) 1 signalling, J. Diabetes Res. (2019), https://doi.org/10.1155/2019/1897174, 1–10, Feb. 2019.

[62] X. Huang, et al., Two-dimensional nanovermiculite and polycaprolactone electrospun fibers composite scaffolds promoting diabetic wound healing, J. Nanobiotechnol. 20 (1) (2022) 343, https://doi.org/10.1186/s12951-022-01556-w. Dec.

[63] L. Pang, et al., In situ photo-cross-linking hydrogel accelerates diabetic wound healing through restored hypoxia-inducible factor 1-alpha pathway and regulated inflammation, ACS Appl. Mater. Interfaces 13 (25) (2021) 29363, https://doi.org/10.1021/acsami.1c07103. –29379.

[64] S. Zhang, et al., Recent advances in responsive hydrogels for diabetic wound healing, Materials Today Bio 18 (2023) 100508, https://doi.org/10.1016/j.mtbio.2022.100508.

[65] H. Cho, M.R. Blatchley, E.J. Duh, S. Gerecht, Acellular and cellular approaches to improve diabetic wound healing, Adv. Drug Deliv. Rev. 146 (2019) 267–288, https://doi.org/10.1016/j.addr.2018.07.019.

[66] Y. Wang, et al., VH298-loaded extracellular vesicles released from gelatin methacryloyl hydrogel facilitate diabetic wound healing by HIF-1α-mediated enhancement of angiogenesis, Acta Biomater. 147 (2022) 342–355, https://doi.org/10.1016/j.actbio.2022.05.018. Jul.
[67] D. Tomic, J.E. Shaw, D.J. Magliano, The burden and risks of emerging complications of diabetes mellitus, Nat. Rev. Endocrinol. 18 (9) (2022) 525–539, https://doi.org/10.1038/s41574-022-00690-7. Sep.
[68] J. Pearson-Stuttard, et al., Trends in predominant causes of death in individuals with and without diabetes in England from 2001 to 2018: an epidemiological analysis of linked primary care records, Lancet Diabetes Endocrinol. 9 (3) (2021) 165–173, https://doi.org/10.1016/S2213-8587(20)30431-9.