R E V I E W

Nanoscale Systems for Local Activation of Hypoxia-Inducible Factor-1 Alpha: A New Approach in Diabetic Wound Management

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Abstract: Chronic wounds in diabetic patients experience significant clinical challenges due to compromised healing processes. Hypoxia-inducible factor-1 alpha (HIF-1α) is a critical regulator in the cellular response to hypoxia, enhancing angiogenesis and tissue restoration. Nevertheless, the cellular response to the developed chronic hypoxia within diabetes is impaired, likely due to the destabilization of HIF-1α via degradation by prolyl hydroxylase domain (PHD) enzymes. Researchers have extensively explored HIF-1α activation as a potential pathway for diabetic wound management, focusing mainly on deferoxamine (DFO) as a potent agent to stabilize HIF-1α. This review provides an update of the other recent pharmacological agents managing HIF-1α activation, including novel PHD inhibitors (roxadustat and daprodustat) and Von Hippel-Lindau protein (VHL) antagonists, which could be potential alternatives for the local treatment of diabetic wounds. Furthermore, it highlights how localized delivery via advanced nanostructures can enhance the efficacy of these novel therapies. Importantly, by addressing these points, the current review can offer a promising area for research. Given that, these novel drugs have minimal applications in diabetic wound healing, particularly in the context of local application through nanomaterials. This gap presents an exciting opportunity for further investigation, as combining these drugs with localized nanotechnology could avoid undesired systemic side effects and sustain drug release within wound site, offering a transformative platform for diabetes wound treatment.

Keywords: nanomedicine, localized delivery, diabetic wound healing, novel prolyl hydroxylase inhibitors

Introduction

Notably, diabetic wounds, including foot and leg ulcers, affect approximately 20% of diabetic patients with high economic burden. Globally, diabetic wounds represent a primary health concern that attracts special clinical attention primarily due to the reported impaired and delayed healing of such wounds, leading to complications, including severe infections and lower limb amputation.[1,2] Of note, hypoxia was reported to show a pivotal role in the hindered healing process of diabetic wounds as decreased oxygen supply to the injured tissues impedes essential cellular repair mechanisms.[3]

As reported, cellular response to hypoxia is essentially regulated by HIF-1. Activation of HIF-1 stimulates a range of mechanisms that enable cells to compensate for oxygen deficiency, including angiogenesis, consequently improving cell survival and promoting tissue regeneration.[4] Therefore, HIF-1 was deemed a crucial factor in initiating and sustaining

Graphical Abstract
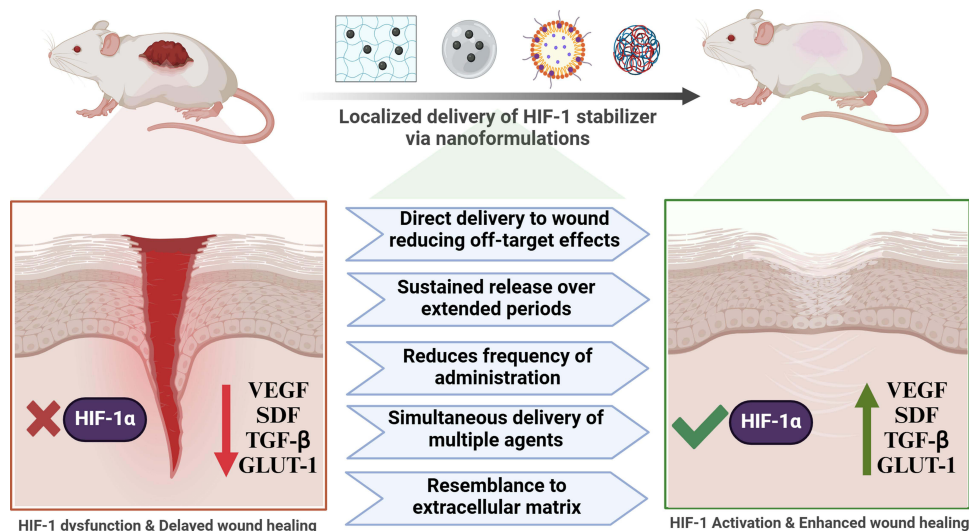
tissue repair mechanisms vital for wound healing. Nevertheless, HIF-1 function is believed to be compromised in diabetic wounds, thus making it a leading target for the development of novel therapeutic modalities for diabetic wounds.

Prolyl hydroxylase domain (PHD) enzymes are accountable for HIF-1 degradation and loss of function. Therefore, PHD inhibitors were recently developed as wound healing promoters where they demonstrated initial success in stabilizing HIF-1 and restoring its function.[5] Meanwhile, the critical obstacle that hinders the clinical application of such recent treatment modality was the systemic severe adverse effects of PHD inhibitors, including excessive erythropoiesis and potential oncogenic risks,[6] that prohibited their systemic administration and urged the development of localized delivery for these drugs to their site of action. Notably, clinical trials have been initiated to investigate the effects of these inhibitors. Daprodustat, a PHD inhibitor, has completed Phase I clinical trials for diabetic foot ulcer treatment (ClinicalTrials.gov: NCT01831804), marking a significant advancement in clinical research. Furthermore, a clinical trial is currently examining the effect of localized DFO delivery on diabetic foot ulcer healing (ClinicalTrials. gov: NCT03137966).

Conspicuously, nanotechnology offers an innovative and valid tool for the precise delivery of HIF-1 stabilizers to the wound site, minimizing systemic adverse effects while maximizing their therapeutic efficacy.[7] The capacity of various nanotechnological platforms, particularly nanofibers (NFs) and nanohydrogels, in improving the delivery and effectiveness of diabetic wound healing promoters has been previously studied.[8–10] Multiple studies have explored strategies to enhance wound healing through the use of nanotechnology. For instance, recent research has demonstrated that nanostructured materials, like nanohydrogels, can support tissue repair by enhancing cell migration and angiogenesis.[11] Additionally, immunomodulatory hydrogels have shown efficacy in modulating the diabetic wound environment by addressing key pathological factors such as hyperglycemia-induced inflammation and excessive reactive oxygen species.[12,13]

The current review provides a concise overview of the HIF-1α role in wound healing and its dysfunction in diabetic wounds. The article then delves into the recent pharmacological agents that target HIF-1α activation in diabetes while examining their potential drawbacks. Moreover, it discusses the role of nanomaterials in overcoming these limitations and enhancing the efficacy of these drugs via local application. Unlike many studies that focus broadly on general wound healing mechanisms, our work distinctly highlights the HIF-1α pathway, a key regulator in tissue repair. By focusing on the stabilization of HIF-1α, we offer a targeted approach to addressing the impaired healing process in diabetic wounds.

Furthermore, this review introduces novel pharmacological agents, including roxadustat, daprodustat, and VHL antagonists, which are relatively underexplored in this context, particularly in terms of their localized application through nanomaterials. We anticipate that these insights will advance the development of innovative therapeutic strategies for diabetic wound management, paving the way for more effective treatments by modulating HIF-1α with nanotechnology.

The Intimate Connection Between Wound Healing and Hypoxia

Tissue repair subsequent to injury constitutes a multifaceted cascade encompassing a coordinated interplay of cellular activities and the reorganization of the extracellular matrix (ECM). The triphasic wound healing model involves inflammation, proliferation, and remodeling (Figure 1). A growing body of evidence underscores the pervasive role of hypoxia throughout the various stages of the wound healing cascade. Fluctuations in oxygen tension trigger precisely regulated signaling pathways that respond to hypoxic conditions. While transient hypoxia is a critical signaling mechanism that initiates essential cellular processes for wound repair, such as fibroblast proliferation and angiogenesis, its transition to a chronic state, particularly in diabetic wounds, can significantly hinder the healing cascade. To fully elucidate this interplay, a comprehensive understanding of the individual stages of wound healing and the corresponding impact of hypoxia on each stage is paramount.
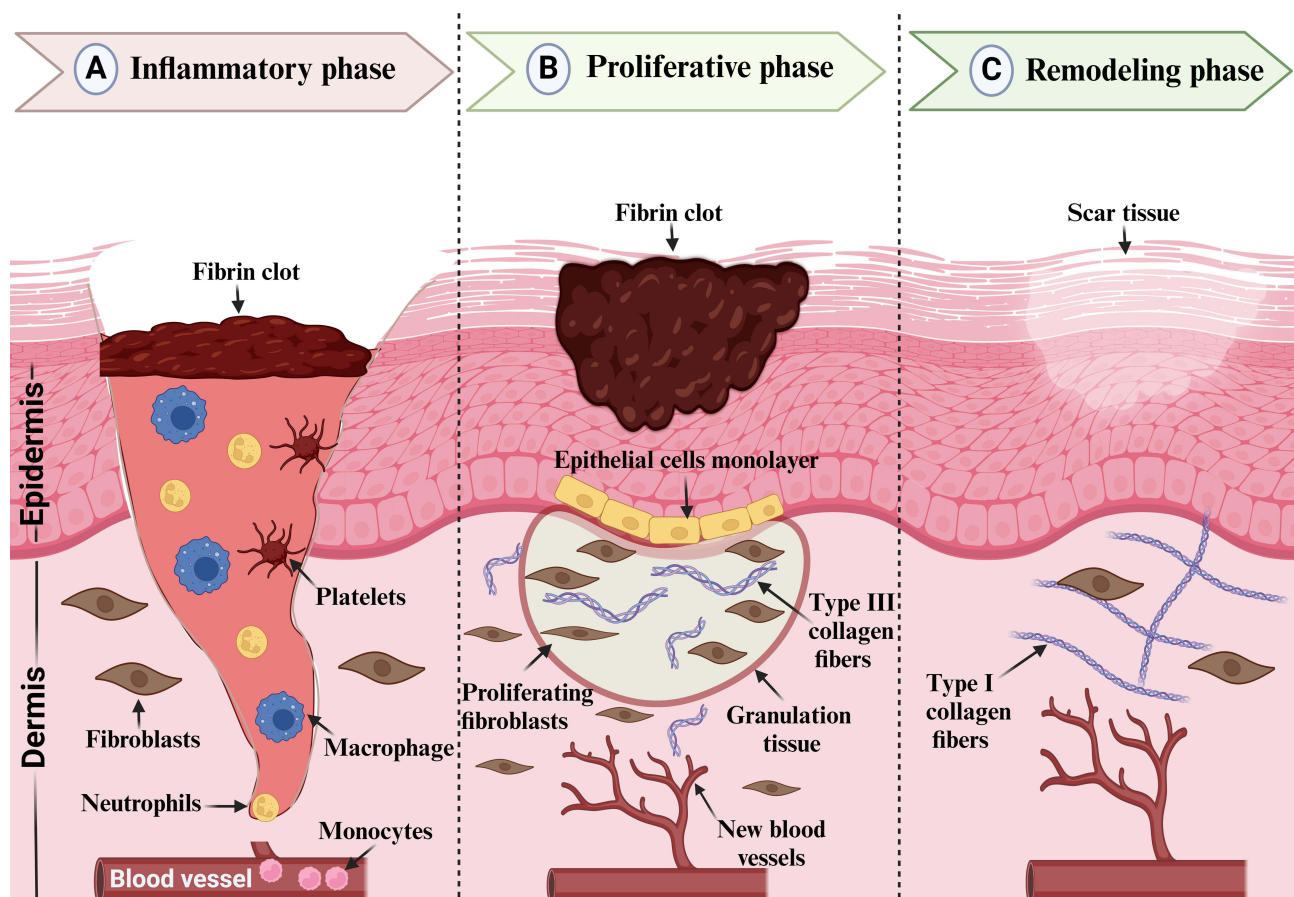
Figure 1 Illustration showing the three phases involved in the wound healing process: (**A**) Inflammatory Phase: characterized by a surge of inflammation and controlled tissue breakdown at the wound site. Platelets, the body's clotting agents, assemble and form a provisional matrix, a temporary scaffold that acts as the foundation for healing. Meanwhile, neutrophils and monocytes are recruited to the area. Neutrophils act as scavengers, clearing away cellular debris and dead tissue. Monocytes, in turn, transform into macrophages, facilitating the proliferative phase. (**B**) Proliferative Phase: Characterized by the growth of new tissue. Fibroblasts proliferate, depositing extracellular matrix (ECM) components and collagen fibers. Angiogenesis supplies the new tissue with oxygen and nutrients, while re-epithelialization aids in wound closure. (**C**) Remodeling Phase: Characterized by the maturation and strengthening of scar tissue. During this phase, the body replaces the less stable type III collagen with the more robust type I collagen, with myofibroblasts aiding in matrix contraction and increased tensile strength, resulting in a more compact and robust collagen matrix. Created in BioRender. Mamdouh, A. (2024) https://BioRender.com/ y77b182.

Inflammatory Phase

The initial phase of wound healing termed the inflammatory phase, commences upon the disruption of the local vasculature and subsequent extravasation of blood due to tissue injury. This event is a key trigger for platelet aggregation and clot formation, culminating in creating a provisional matrix. This temporary scaffold serves a dual purpose: firstly, it facilitates the migration of essential cells to the wound site, and secondly, it contributes to the formation of granulation tissue. In addition, the coagulation cascade and activated and wounded cells coordinate the release of numerous signaling chemicals. These signaling molecules attract inflammatory cells, such as neutrophils and monocytes, to the wound site. Neutrophils are the initial responders and play a crucial role in debridement, which involves removing cellular debris and facilitating tissue healing. Neutrophils play an active role in fighting against invading germs and aiding in the healing process by releasing substances such as matrix metalloproteinases (MMPs) and reactive oxygen species (ROS).[14] These factors facilitate the removal of dead tissue and enhance the transmission of inflammatory signals. Monocytes undergo differentiation and transform into macrophages. At first, macrophages that promote inflammation (M1) emit ROS and cytokines to kill bacteria. Consequently, the growth phase starts when granulation tissue is formed following macrophages' differentiation into anti-inflammatory macrophages (M2).[15]

Proliferative Phase

Approximately three days after the injury, the proliferative phase begins, and it's principally characterized by both macrophage and fibroblast infiltration alongside the formation of granulation tissue in the wound area. Profoundly, macrophages are essential elements of this phase as they release growth factors promoting angiogenesis and fibrous tissue deposition. Moreover, chemotactic attraction of fibroblasts to the site of the wound[16] takes place, triggering ECM deposition, and replacing the temporary matrix formed during the inflammatory stage. Notably, a sufficient supply of oxygen and essential nutrients to the newly formed tissue during the proliferative phase is enabled by stimulating angiogenesis in response to pro-angiogenic signals.[17] Intriguingly, this phase involves restoration of the outermost skin layer with subsequent wound closure in a step known as re-epithelialization, which is achieved through the growth and movement of keratinocytes along the wound's edges.[18]

Remodeling Phase

Eventually, the temporary granulation tissue is replaced by a permanent scar in the so-called remodeling phase, mainly featured in the transformation of the ECM into a stronger and more resilient collagen-based structure. Fibroblasts are crucial in this process as they produce and deposit the collagen fibers.[19] Significantly, the initially prevailing type III collagen, often seen in granulation tissue, is progressively substituted by the more durable and resistant type I collagen. The process of collagen remodeling is carefully managed, ensuring a precise equilibrium between the synthesis and breakdown of collagen. MMPs, secreted by various cell types, including macrophages, endothelial cells, and fibroblasts, are responsible for controlled collagen degradation.[20] Additionally, under the influence of α-smooth muscle actin and growth factors, some fibroblasts differentiate into myofibroblasts. These specialized cells contribute to matrix contraction and enhance the tensile strength of the developing scar tissue. As the robust collagen matrix establishes itself, the fibroblast-rich granulation tissue is progressively replaced by a relatively acellular, mature scar. The duration of this phase varies with the extent of the injury and can span from days to months, ultimately aiming to restore tissue structure and functionality while enhancing tensile strength.[21]

Hypoxia Across Wound Healing Phases

The initial inflammatory phase of wound healing is marked by a hypoxic environment. This phenomenon arises from two main factors: the influx of inflammatory cells with high oxygen demands and disruption of the vasculature around the wound, hindering oxygen delivery. Interestingly, these very inflammatory cells preferentially accumulate in hypoxic regions, suggesting a specific role in processes crucial for healing, such as granulation tissue formation and re-epithelialization.[22] Moreover, the established hypoxic gradient can influence the function of stromal cells. Studies have shown that acute hypoxia substantially enhances the human dermal fibroblast proliferation.[23] Intriguingly, hypoxic conditions significantly enhance the secretory function of fibroblasts, leading to a near tenfold increase in the production of transforming growth factor-β1 (TGF-

β1), a well-established regulator of wound healing. Therefore, acute hypoxia appears to induce a transient upsurge in cellular proliferation, thereby contributing to the launch of the wound-healing cascade.[24]

In a pioneering study, Remensnyder and Majno documented a significant gradient of hypoxia within the wounded cremaster muscle of rats, exhibiting a close correlation with revascularization levels.[25] Building on this, Elson et al subsequently corroborated these findings, demonstrating a coordinated and transient induction of HIF-1α and its downstream target genes, including vascular endothelial growth factor (VEGF), during the process of epidermal wound healing.[26] These foundational studies highlight the paramount importance of HIF-1 signaling activation and regulation within the context of wound healing. Furthermore, they convincingly demonstrate the critical role played by the adaptation of hypoxic cells, encompassing inflammatory cells, keratinocytes, endothelial cells, and mesenchymal stromal cells, to the hypoxic microenvironment established at the wound site. This adaptation is demonstrably crucial for these cell populations to fulfill their respective functions during the wound-healing process.

Hypoxia and Diabetic Chronic Wounds

After discussing how hypoxia can stimulate beneficial responses in acute settings, it becomes evident that chronic hypoxia presents substantial challenges, particularly in conditions like diabetes, where vascular and metabolic disruptions are prevalent.[27] The pathophysiology of diabetic wounds introduces a distinctive set of challenges due to the multifaceted impact of hyperglycemia, peripheral arterial disease (PAD), neuropathy, and related vascular complications (Figure 2). The combination of these variables leads to a consistently low oxygen environment in wounds, significantly hindering crucial healing processes. Recent studies provide mounting evidence that the delayed wound healing observed in diabetic
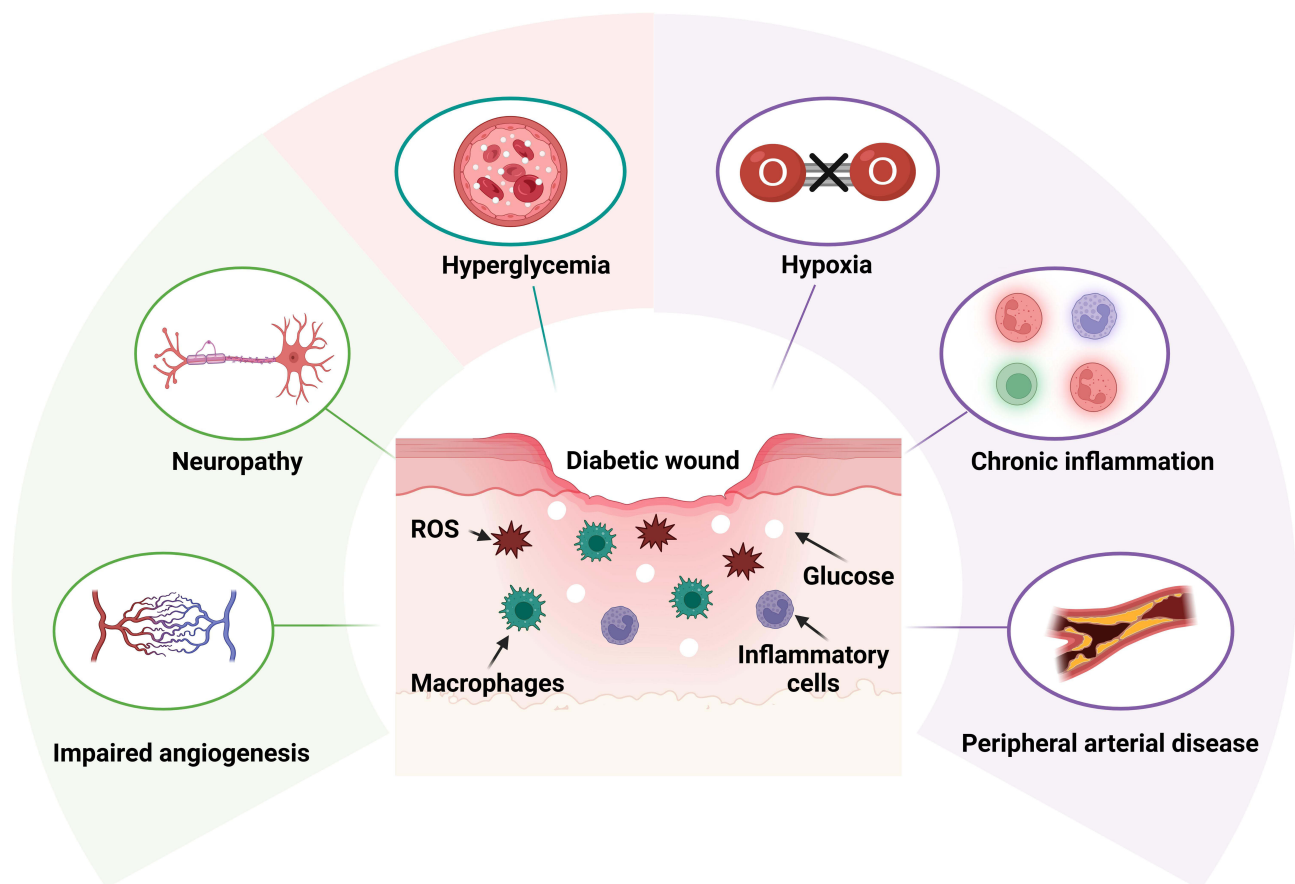
Figure 2 Pathophysiology of diabetic wounds: This diagram illustrates the vicious cycle contributing to chronic diabetic wounds. Hyperglycemia increases glucose levels, resulting in oxidative stress and the production of reactive oxygen species (ROS), which damage blood vessels and nerves. Neuropathy impairs sensation, causing unnoticed injuries. Peripheral arterial disease (PAD), resulting from vascular damage, restricts blood flow, impeding healing. Impaired angiogenesis limits the delivery of nutrients and oxygen to the wound site. Chronic inflammation, driven by persistent hyperglycemia, disrupts healing as dysfunctional macrophages fail to resolve inflammation, perpetuating tissue damage. Created in BioRender. Mamdouh, A. (2024) https://BioRender.com/ x89d650.

patients might be attributed to worsened hypoxic conditions and defective cellular responses to hypoxia. These characteristics are considered key pathogenic factors.[3,28] This section will explore the mechanisms by which hyperglycemia impairs the supply of oxygen and cellular function, how PAD limits blood flow and worsens tissue hypoxia, and how neuropathy impairs sensory perception and vascular regulation, hence sustaining chronic hypoxia in diabetic wounds.

Hyperglycemia

Hyperglycemia, a characteristic feature of diabetes, causes a range of biochemical alterations that interfere with the normal wound healing process. One of these alterations is the reduced supply of oxygen to the tissues. Hyperglycemia causes problems with the cells lining the blood vessels and damages the small blood vessels, which reduces the flow of blood to the wound and affects the supply of oxygen.[29] Consequently, the wound environment becomes hypoxic, exhibiting reduced quantities of oxygen compared to healthy tissue. Furthermore, elevated glucose levels can potentially modify the characteristics of red blood cells, resulting in reduced flexibility and increased susceptibility to aggregation.[30] These modifications decrease the capacity of red blood cells to traverse through microvasculature and effectively transport oxygen to tissues. This impaired oxygen transport exacerbates the hypoxic conditions in diabetic wounds. In addition, high amounts of glucose and the resulting oxidative stress hinder the formation of angiogenic agents, such as VEGF.[31] The wound experiences worsened hypoxia due to insufficient blood flow caused by inadequate angiogenesis.

Peripheral Arterial Disease

Diabetic wounds are characterized by vascular insufficiency, a fundamental pathophysiological characteristic. Individuals with diabetes are especially prone to PAD, which is characterized by a gradual constriction and hardening of the arteries that provide blood to the limbs.[32] This syndrome causes a considerable reduction in blood flow to the extremities and impairs oxygen delivery to the wound site. Hence, the diminished blood flow resulting from PAD plays a significant role in creating the long-lasting oxygen-deprived conditions seen in diabetic wounds.

Neuropathy

Diabetic neuropathy, a common consequence, is identified as an additional significant element that contributes to the pathophysiology of diabetic wounds. This neuropathy interferes with the function of nerves that control the expansion and contraction of blood vessels. This condition of autonomic neuropathy disrupts the normal control of blood circulation, resulting in an inadequate blood supply to the tissues. Without adequate vascular responses, wounds in diabetic individuals suffer from insufficient oxygenation.[33] Neuropathy diminishes the sensation in the extremities, especially the feet, resulting in a heightened susceptibility to undiscovered injury. As a result of ongoing pressure and trauma, these injuries have the potential to progress into chronic wounds.[34] Moreover, neuropathy exacerbates the inflammatory response and following stages of wound healing, impeding the body's ability to maintain the healing process efficiently.[35]

Hypoxia-Inducible Factor-1 Alpha (HIF-1α)

Understanding the multifaceted impact of hypoxia on diabetic wound pathophysiology underscores the critical need to explore molecular responses and adaptive mechanisms that regulate tissue oxygenation. One mechanism that plays a role in wound repair under ischemia conditions involves HIF-1α, a transcription factor responsible for regulating many processes necessary for this process. Within the diabetic wound milieu, persistent hypoxia alters the normal HIF-1α signaling pathway, leading to a defective cellular response to low oxygen supply. As a result, this malfunction hampers the well-known positive effects of HIF-1α, making the process of wound healing more complicated in individuals with diabetes. This section explores the attributes and regulatory processes that control the function of HIF-1α while clarifying the specific mechanisms via which this pathway becomes compromised in diabetes.

The Role of HIF-1α in the Wound Healing Process

HIF-1 is a transcription factor that plays a critical role in helping cells adapt to low-oxygen settings. It acts as a heterodimer, comprising two subunits: an alpha subunit called HIF-1α and a beta subunit called HIF-1β. In response to hypoxic conditions, HIF-1α is stabilized and moves to the nucleus in response to hypoxic circumstances. At that point, it engages with HIF-1β, creating a functional heterodimer. The dimerization event functions as a molecular mechanism that triggers the activation of transcription for several genes (Table 1) involved in wound healing, such as angiogenesis, metabolic adaption, cell survival, proliferation, and migration.[36,37]

The crucial function of HIF-1α in wound healing is supported by the hindered angiogenesis and delayed healing found in mice with reduced HIF-1α activity due to either heterozygous knockout or age-related decline.[47,48] Likewise, targeted inactivation of HIF-1β in endothelial cells also results in defective wound healing.[49] These findings collectively exhibit the multifaceted effects of HIF-1 in promoting tissue repair.

HIF-1α Regulation and Its Dysfunction in Diabetes

Regulation Under Non-Diabetic Conditions

The regulation of the HIF-1α subunit exhibits a tight coupling to oxygen availability, with oxygen levels dictating its fate between degradation or stabilization.[50–52] Under normoxic conditions (Figure 3a), specific proline residues (P402 and P564) within HIF-1α are hydroxylated by PHD proteins. Notably, these hydroxylation reactions require co-substrates such as oxygen, 2-oxoglutarate (2-OG), and iron.[53] This oxygen-dependent hydroxylation is a molecular recognition tag for the VHLE3 ubiquitin ligase. VHL then targets the hydroxylated HIF-1α for ubiquitination, ultimately resulting in its degradation by the proteasome. The remarkably short half-life of HIF-1α in the presence of oxygen (less than 10 minutes) underscores the remarkable efficiency of this regulatory mechanism.[54]

Table 1 Key HIF-1α Target Genes Associated with Wound Healing

Gene	Role in Wound Healing	Reference
VEGF	VEGF is critical for angiogenesis, supplying nutrients and oxygen to the wound site and promoting tissue repair and regeneration.	[38]
iNOS	iNOS produces nitric oxide, which has antimicrobial properties and enhances blood flow to the wound. Nitric oxide also facilitates collagen synthesis and fibroblast activity, enabling wound contraction.	[39]
EPO	EPO promotes angiogenesis and has anti-apoptotic effects, protecting cells in the wound area from programmed cell death. This enhances the survival of endothelial cells and other critical cells involved in tissue repair.	[40]
PDGF	PDGF triggers fibroblast and smooth muscle cell migration to the wound, promoting tissue repair and granulation tissue formation.	[41]
TGF-β	TGF-β controls cell growth, specialization, and production of wound-healing matrix, promoting granulation tissue, contraction, and scarring.	[42]
MMPs	MMPs break down wound debris, paving the way for cell movement and new tissue formation.	[43]
GLUT-1	GLUT1 and GLUT3 facilitate increased glucose uptake, ensuring that cells in the wound area have sufficient energy for repair and regeneration activities.	[26,44]
GLUT-3		
SDF-1	SDF-1 functions as a molecular beacon, recruiting stem cells and progenitor cells to the wound site. This targeted migration of cells fosters tissue regeneration and repair processes.	[45]
HO-1	HO-1 provides cytoprotectants and has anti-inflammatory and antioxidant properties, reducing oxidative stress in the wound area and promoting healing.	[46]

Abbreviations: EPO, Erythropoietin; GLUT1, Glucose Transporter Protein 1; GLUT3, Glucose Transporter Protein 3; HO-1, Heme Oxygenase 1; iNOS, Inducible Nitric Oxide Synthase; MMPs, Matrix Metalloproteinases; PDGF, Platelet-Derived Growth Factor; SDF-1, Stromal Cell-Derived Growth Factor-1; TGF-β, Transforming Growth Factor-beta; VEGF, Vascular Endothelial Growth Factor.
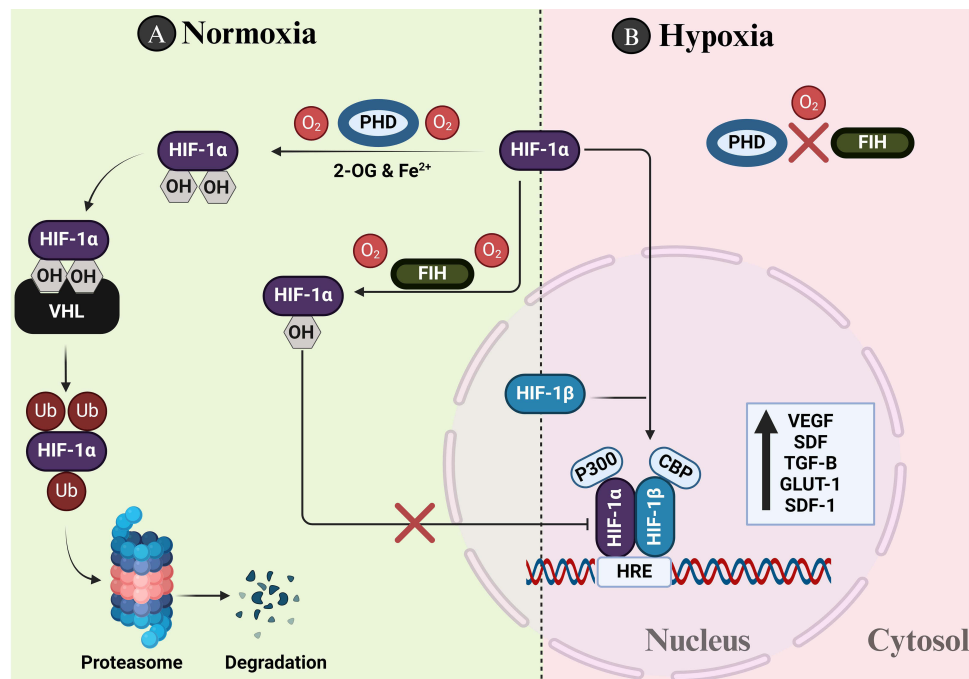
Figure 3 Regulation of HIF-1: Panel (**A**) depicts the normoxic scenario. Under normoxic conditions, prolyl hydroxylase domain (PHD) proteins hydroxylate specific proline residues within HIF-1α. These hydroxylation reactions require oxygen, 2-oxoglutarate (2-OG), and iron (Fe²⁺) as co-substrates. The presence of these hydroxyl groups on HIF-1α serves as a recognition motif for the von Hippel-Lindau (VHL) E3 ubiquitin ligase. Consequently, VHL targets hydroxylated HIF-1α for ubiquitination, ultimately leading to its proteasomal degradation. An additional layer of regulation is provided by a factor inhibiting HIF-1 (FIH). FIH impedes the recruitment of essential coactivators such as CREB-binding protein (CBP) and p300, thereby dampening the transactivation activity of HIF-1α. Panel (**B**) illustrates the hypoxic scenario. In response to hypoxic conditions (low oxygen levels), PHD activity becomes significantly reduced due to limited oxygen availability. This abrogation of hydroxylation by PHDs allows HIF-1α to evade recognition and subsequent degradation by the VHL ubiquitin ligase pathway. Therefore, HIF-1α undergoes stabilization and accumulates within the cell. The stabilized HIF-1α translocates to the nucleus, where it heterodimerizes with its partner, HIF-1β. This functional HIF-1α/β complex exhibits a high affinity for hypoxia response elements (HREs) present in the promoter regions of target genes. The binding of the HIF complex to HREs is further facilitated by the recruitment of coactivators, such as CBP and p300. This coordinated assembly on the promoter region culminates in the transcriptional activation of a multitude of genes essential for cellular adaptation to hypoxia. Created in BioRender. Mamdouh, A. (2024) https://BioRender.com/ i10w859.

Under hypoxic conditions (Figure 3b), the activity of PHD proteins becomes significantly diminished due to the limited availability of oxygen, effectively shutting down the hydroxylation of HIF-1α.[55,56] This abrogation of hydroxylation renders HIF-1α invisible to the VHL E3 ubiquitin ligase, thereby thwarting its recognition and subsequent proteasomal degradation. Consequently, HIF-1α undergoes stabilization and translocates to the nucleus, dimerizing with its partner, HIF-1β. This functional HIF-1α/β heterodimer exhibits a high affinity for hypoxia response elements (HREs) present in the target gene promoters. The binding of the HIF complex to HREs is further facilitated by the recruitment of coactivators, such as CREB-binding protein (CBP) and p300. This coordinated assembly on the promoter region culminates in the transcriptional activation of many genes critical for hypoxia adaptation.

Regulation Under Diabetic Conditions

The pathophysiology of diabetic wounds introduces a distinctive set of challenges due to the multifaceted impact of hyperglycemia, neuropathy, and related vascular complications. Combining these variables leads to a consistently low oxygen environment in wounds. One would logically expect an induction of HIF-1α activation to occur as a compensatory response. However, paradoxically, the function of HIF-1α is impaired, exacerbating the delay in healing typically observed in diabetic wounds.

A substantial body of research indicates that hyperglycemia negatively affects HIF-1α activity under hypoxic conditions characteristic of diabetes.[57,58] One prominent mechanism involves hyperglycemia-induced promotion of PHD-mediated degradation of HIF-1α. Hyperglycemia enhances the hydroxylation of HIF-1α, resulting in its degradation through PHD- and VHL-dependent pathways, even in hypoxic conditions.[59,60]

Another contributing mechanism involves the intracellular accumulation of methylglyoxal (MGO), a reactive by-product of glycolysis. Notably, elevated MGO levels, a hallmark of hyperglycemia in diabetes, are associated with increased inflammation and delayed wound healing. Mechanistically, MGO directly modifies HIF-1α, leading to a decrease in its stability and potentially hindering its transcriptional activity.[61]

Bento et al identified a novel pathway where hyperglycemia-induced MGO modifications enhance HIF-1α binding to molecular chaperones Hsp40 and Hsp70.[62] This interaction facilitates the recruitment of chaperone-dependent ubiquitin ligase (CHIP), leading to ubiquitination followed by proteasomal degradation of HIF-1α, independent of PHD and VHL pathways.

Furthermore, MGO appears to directly modify the coactivator protein p300 directly, thereby hindering its interaction with HIF-1α. This impaired interaction between HIF-1α and p300 likely contributes to the diminished transcriptional efficacy of HIF-1α.[63]

These findings highlight the critical role of HIF-1α dysfunction in the impaired wound healing observed in diabetes. The complex interplay between hyperglycemia-induced oxidative stress, PHD-mediated degradation, and MGO accumulation results in significant impairment of HIF-1α stability and transcriptional activity (Figure 4). Fortunately, these defects have been reported to be partially reversible,[4,63] opening avenues for therapeutic interventions aimed at restoring HIF-1α activity and promoting efficient wound healing in diabetic patients.

Pharmacological Agents for HIF-1α Stabilization

Recent advancements in understanding the mechanisms responsible for impaired HIF-1α function in diabetes offer a compelling rationale for presenting HIF-1α as a promising therapeutic target for developing novel strategies to promote efficient wound healing in diabetic patients. As previously discussed, the PHD enzyme requires the co-substrates 2-OG
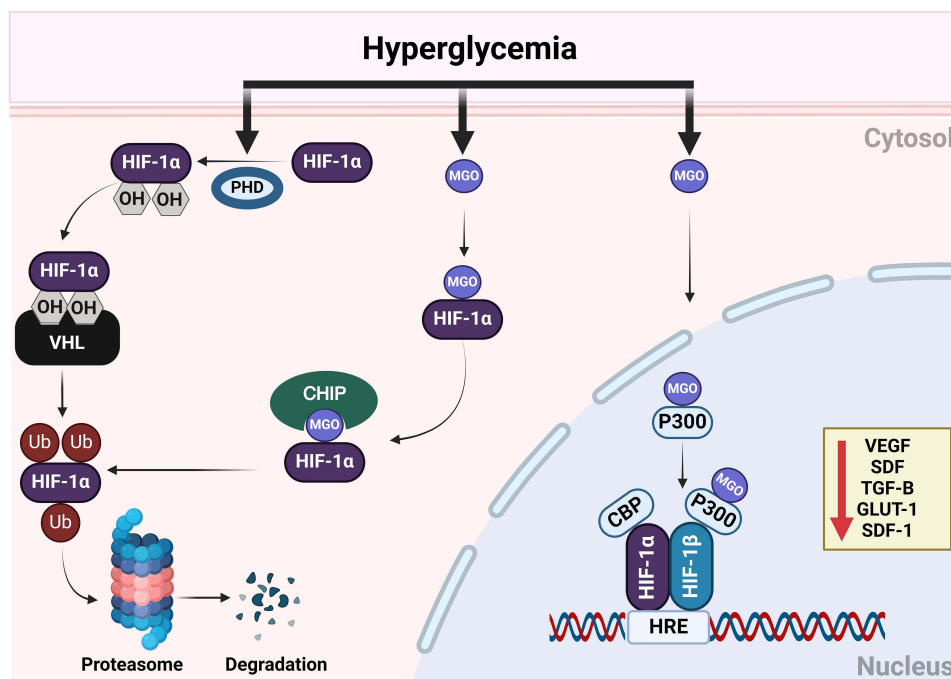
Figure 4 Hyperglycemia-induced dysfunction of HIF-1 signaling in diabetes. This figure illustrates the multifaceted mechanisms by which hyperglycemia disrupts HIF-1α stability and function in diabetes. Elevated blood glucose levels promote the degradation of HIF-1α through two main pathways; VHL-dependent pathway: Hyperglycemia stimulates the activity of prolyl hydroxylase domain (PHD) proteins. Hydroxylated HIF-1α becomes a target for the von Hippel-Lindau (VHL) E3 ubiquitin ligase, leading to its ubiquitination and subsequent degradation by the proteasome. MGO-dependent pathway: Hyperglycemia also contributes to the intracellular accumulation of methylglyoxal (MGO), a reactive by-product of glycolysis. MGO directly modifies HIF-1α, decreasing its stability. This modification recruits chaperone-dependent ubiquitin ligase (CHIP), which tags HIF-1α for ubiquitination and proteasomal degradation, independent of the PHD and VHL pathways. Furthermore, MGO disrupts HIF-1α's transcriptional activity by altering the coactivator protein p300. This modification weakens the interaction between HIF-1α and p300, thereby diminishing HIF-1α's ability to regulate the expression of target genes. Created in BioRender. Mamdouh, A. (2024) https://BioRender.com/ w30u996.

and iron to hydroxylate specific proline residues on HIF-1α, marking it for degradation. Thus, decreasing or inhibiting these co-substrates presents a potential mechanism for PHD inactivation, thereby stabilizing HIF-1α.

As illustrated in Figure 5, various HIF-1α stabilizing agents, including cobalt chloride, DFO, and 2-OG inhibitors such as roxadustat, and daprodustat, inhibit the PHD degradation pathway by interfering with cofactors. The VHL antagonist VH298 also prevents HIF-1α degradation by inhibiting its interaction with VHL, directly stabilizing HIF-1α.

Therapeutic Agents Targeting Iron

Iron (Fe^{2+}) is a critical cofactor for PHD enzyme activity. It binds reversibly to the active site of this metalloenzyme, facilitating the hydroxylation of HIF-1α. Consequently, strategies to reduce iron availability present a promising therapeutic approach. Iron chelation therapy, such as DFO, can directly sequester iron, limiting its accessibility to PHDs. Alternatively, competitive substitution with non-catalytic metal ions, such as cobalt (Co^{2+}), can displace iron from the active site, effectively inhibiting PHD activity.

Cobalt chloride ($CoCl_2$) can mimic hypoxic conditions by inhibiting PHD enzymes via the competition with iron, leading to HIF-1α stabilization.[64] This hypoxia mimetic approach triggers a cellular response similar to that observed under actual hypoxic conditions, promoting wound healing processes. Salts of cobalt have been found to inhibit hydroxylase activity by antagonizing iron.[65,66] Huang et al investigated the potential of $CoCl_2$ to enhance fracture healing in Sprague-Dawley rats.[67] Their study employed intraperitoneal injection (IP) of $CoCl_2$ at a dose of 15 mg/kg and observed a significant acceleration of bone formation and remodeling during the repair process. Mechanistically, the authors attributed these effects to $CoCl_2$-mediated activation of the HIF-1α pathway.

DFO stands out as one of the pioneering discoveries in HIF activation. Notably, it was among the first identified organic compounds capable of inducing HIF activity.[68] DFO exerts its effect by binding to iron, which is a necessary co-factor for the activity of PHD enzymes. By chelating iron, DFO prevents the degradation of HIF-1α, thereby stabilizing it.[69] In diabetic mice, DFO has been shown to counteract the transcription-suppressing effects of high
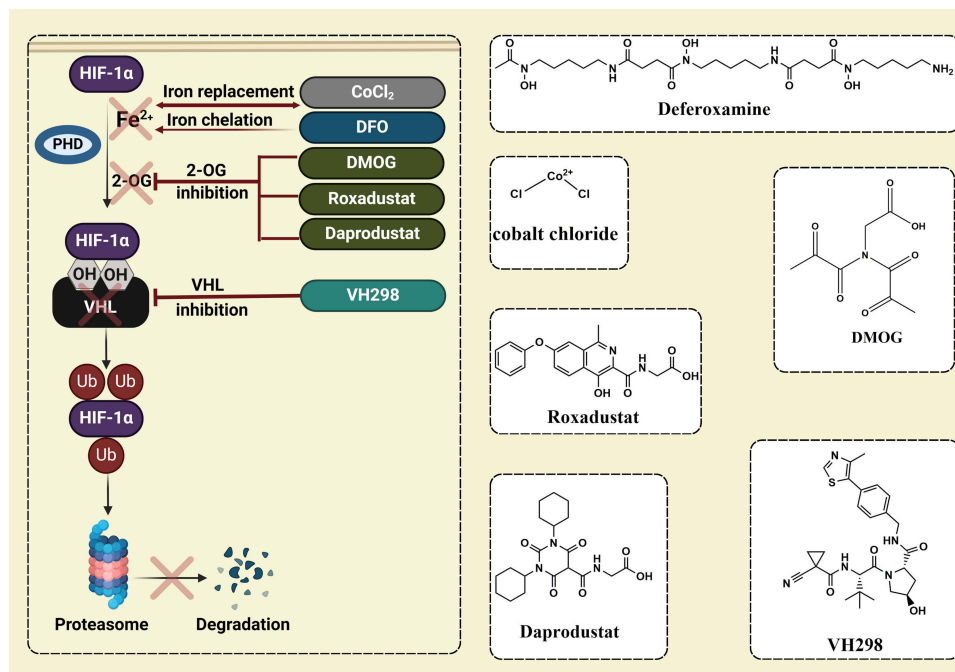
Figure 5 Molecular Structures and Mechanisms of HIF-1 Stabilizing Agents: The diagram illustrates the activation of HIF-1 through various mechanisms. Cobalt chloride ($CoCl_2$) and deferoxamine (DFO) replace iron and chelate iron, respectively, reducing iron availability, a cofactor for prolyl hydroxylase domain (PHD) enzymes, thereby inhibiting the PHD degradation pathway. Additionally, 2-oxoglutarate inhibitors, including dimethyloxalylglycine (DMOG), roxadustat, and daprodustat, inhibit the 2-OG cofactor for PHD, resulting in further inhibition of HIF-1α degradation. The VHL protein antagonist VH298 is also shown, which stabilizes HIF-1α by inhibiting the interaction between VHL and hydroxylated HIF-1α. Unlike PHD inhibitors, VHL antagonists directly target the downstream degradation pathway of HIF-1α. Created in BioRender. Mamdouh, A. (2024) https://BioRender.com/c1lt096.

glucose, thereby restoring neovascularization and promoting efficient wound healing.[70] Beyond its established role in iron chelation, DFO exhibits intriguing antioxidant properties. These properties may extend beyond its ability to bind iron, potentially offering an additional mechanism for promoting wound healing. In particular, research suggests that DFO might prevent MGO-mediated modifications of the coactivator protein p300, thereby enhancing its interaction with HIF-1α.[71]

Therapeutic Agents Targeting 2-OG

2-OG analogs are pivotal in the stabilization and activation of HIF-1; they competitively inhibit PHD enzymes by occupying the 2-OG binding site and preventing the hydroxylation of HIF-1α.[72,73] 2-OG analogs can be broadly categorized into classical inhibitors and novel pharmacological agents.

Classical inhibitors, such as dimethyloxalylglycine (DMOG) and N-oxalylglycine (NOG), structurally mimic 2-OG, thereby competitively inhibiting PHD enzymes. Preclinical research has investigated DMOG and NOG extensively, demonstrating their efficacy in stabilizing HIF-1α.[74] Several studies have consistently shown that DMOG effectively stabilizes HIF-1α across different cell types, including keratinocytes,[75] endothelial cells,[76] and fibroblasts.[77] In a groundbreaking study by Duscher et al, the first to directly compare DMOG and DFO, researchers investigated their effects on wound healing in diabetic mice.[78]

Beyond traditional inhibitors like NOG and DMOG, novel pharmacological agents such as roxadustat and daprodustat have emerged.[79,80] These drugs offer distinct advantages over their predecessors. While mimicking the 2-OG binding site similar to classical inhibitors, roxadustat and daprodustat boast optimized pharmacokinetic and pharmacodynamic profiles, making them more clinically translatable For instance, daprodustat is undergoing early-stage evaluation in a phase I clinical trial, focusing on evaluating its safety and tolerability when applied topically to both healthy subjects and diabetic wound patients.[81] Roxadustat, however, has gone a preclinical investigation, demonstrating its capacity to enhance the healing process of wounds in diabetic rats via HIF-1α activation.[82]

Von Hippel-Lindau Protein Antagonist

Markedly, a different approach for activation of HIF-1α was mediated by VHL antagonists suppressing the interaction between VHL and hydroxylated HIF-1α,[60] with subsequent angiogenesis stimulation and alleviation of diabetic wounds hypoxia.[83] VHL antagonists directly target HIF-1α degradation mechanisms, offering more consistent stabilization of HIF-1α, compared to PHD inhibitors that target upstream PHD enzymes.[84]

As an example of a VHL antagonist, VH298 could be a promising therapeutic agent accelerating wound healing via promoting angiogenesis and tissue regeneration.[60] Qiu et al recently studied the localized delivery of VH298 in a diabetic rat wound-healing model.[85] Compared to control groups, wounds treated with VH298 displayed a demonstrably superior healing pattern via HIF-1α activation. The authors emphasize the need for future research to develop extended-release formulations of VH298 to ensure sustained efficacy within the dynamic wound healing microenvironment.

Side Effects and Consideration

HIF-1α stabilizers, though promising for enhancing wound healing, present several significant challenges after systemic exposure. Most current research on novel agents focuses on their effects via systemic routes, which often results in substantial off-target effects. Tampering with the PHD-HIF pathway raises significant concerns due to potential off-target effects. These concerns stem from the involvement of HIF-1α in various pathological processes.[86] Although VEGF activation via HIF-1α benefits angiogenesis and wound healing, it can cause undesirable effects. Elevated VEGF levels can promote abnormal angiogenesis, increasing the risk of tumor growth.[87,88] Furthermore, systemic VEGF upregulation can lead to vascular leak syndrome, resulting in edema and other complications.[89]

In addition to oncological concerns, continuous activation of HIF-1α signaling has been implicated in worsening pulmonary hypertension and potentially leading to heart failure, especially in patients with pre-existing conditions.[90,91] Also, pharmacological agents that target iron for HIF-1α activation can affect iron metabolism, potentially leading to iron deficiency, which manifests as symptoms in bones.[92,93] Notably, patients who are already iron-deficient may experience exacerbated symptoms.

Localized Delivery of HIF-1α Stabilizer via Nanotechnology

After discussing the numerous negative consequences of systemic exposure to HIF-1α stabilizers, localized delivery via nanomaterials advances a promising solution. The main advantage of this strategy is the achievement of both controlled and localized drug delivery of HIF-1α stabilizers within the injured tissues, minimizing any potential systemic adverse effects. This modality could establish a platform for developing novel and efficient therapies for diabetic wounds by targeting HIF-1α. Moreover, the benefits of nanotechnology extend beyond this application; various nanotechnology-based materials offer numerous advantages, making them a viable strategy to address the current research gaps related to the limited application of novel HIF-1α stabilizers for diabetic wound healing. This section will shed more light on the different types, applications, and theoretical potential benefits of nanotechnology-based platforms for targeted delivery of HIF-1α stabilizers.

Advantages of Combining Nanotechnology with HIF-1α Stabilizers

Nanotechnology-based techniques present significant advantages for the targeted delivery of HIF-1α stabilizers in diabetic wound treatment. One of the main advantages is the ability to deliver the drug directly to the site of the wound.[94] In sharp contrast to the systemic route of administration where the whole body is likely to be exposed to the drug, the local delivery by nanocarriers ensures enough drug concentration at the precise site where it is most needed while lowering the chances of systemic drug adverse effects. Such targeted treatment is vital, considering that diabetic patients are highly susceptible to drug side effects.

Also noteworthy is that nanotechnology-based drug delivery systems have more potential for controlled release.[95] The application of NPs enables the release of HIF-1α stabilizers at a controlled rate, maintaining optimal therapeutic levels over an extended period. Such a release pattern is of great importance in chronic wound management, especially in patients with diabetes, where wound healing is impaired and continuous drug delivery is required. The controlled release further reduces the frequency of drug administration, thus decreasing the persisting need for drug dressing and increasing compliance in patients. Furthermore, this method helps continue a consistent therapeutic effect, thereby enhancing the overall efficacy of the treatment.

Moreover, certain NPs are also well known for their specific properties, such as antibacterial (silver NPs), anti-inflammatory (chitosan NPs), and antioxidant (selenium NPs) ones, that could work on improving the wound healing system by collaborating with HIF-1α stabilizers, targeting many levels of the healing process at the same time.[96–98] Even if the NPs do not have these characteristics, they can still serve as a flexible platform for combining several therapeutic agents in one delivery vehicle. HIF-1α stabilizers are not the only molecules NPs can be designed to carry; other bioactive agents such as anti-inflammatory drugs, growth factors, antibiotics, etc. This gives multiple functions simultaneously, making managing diabetic wounds more effective and faster, thus enhancing the patient's quality of life.

Additionally, a significant advantage attributed to the application of nanoscale materials in wound treatment is that they can act as a surrogate ECM.[99] Specifically, these are types of nanomaterials that are synthesized from polymers or proteins, hence the name biocompatible, that tend to have some similarity with the structure and functioning of the ECM, a characteristic crucial for the attachment, growth, and movement of cells.[100] These NPs promote tissue regeneration while they hasten the healing process because they give specific structural support, which imitates that of normal skin cells.[101] This form of biological support is essential for the management of diabetic ulcers since the normal process of healing is often heavily compromised.

Nanotechnology, in general, has brought new therapeutic strategies that will help to minimize or even overcome such barriers in diabetic wound healing. The next section details the different applications of various nanoparticles, nanohydrogels, NFs, and many other nanotechnologically-based platforms in diabetic wound healing.

Types of Nanomaterials for Diabetic Wound Healing

NPs have a globally debated use and are very efficient in medical therapies, with wound healing being one case in point. NPs typically range in size from 1 to 100 nm and can be synthesized employing a wide range of materials, different structural characteristics, and advantageous properties. The prevalent categories of NPs employed for wound healing include organic NPs, metallic NPs, NFs, and nanohydrogels. Each type has a distinct degree of effectiveness in wound

healing. Utilizing these characteristics enables the design of NPs to address specific healing issues, establishing them as innovative agents in wound therapeutics.

Metallic NPs

Silver, gold, and copper NPs have come into focus as wound-healing metallic NPs due to their unique properties, including antimicrobial activity, antioxidant properties, and enhanced cell proliferation ability.[102] These types of NPs can be designed to facilitate tissue regeneration and accelerate the healing process by addressing infection and inflammation, two of the most common problems in diabetic wounds.

Metallic NPs can accelerate the healing of diabetic wounds in various ways: Silver, copper, and zinc oxide NPs are especially noted for their potent antimicrobial properties, helping to reduce bacterial colonization in chronic wounds.[103,104] Gold and titanium NPs have been observed to decrease inflammatory responses, which is a principal factor in controlling the course of diabetic wounds, as chronic inflammation worsens the healing process.[105,106]

In this context, Li et al developed a hydrogel loaded with DFO and copper NPs as an effective approach to diabetic wound healing.[107] The developed approach exhibited excellent antibacterial activity and effectively decreased the persistent inflammatory reactions in diabetic wounds. Additionally, combining DFO and copper NPs synergistically enhanced the expression of HIF-1α and VEGF. In another study, the combination of DFO with silver NPs synergistically enhanced cell migration angiogenesis, reduced inflammation, and demonstrated remarkable antimicrobial activity, resulting in fast wound healing in a rat model of infected diabetic wound.[108]

Hence, opportunities exist for further investigations of the combining metallic NPs with novel HIF-1α stabilizers. Metallic NPs can stabilize HIF-1α stabilizers, preventing the drug from degrading and ensuring its prolonged activity in hypoxic conditions typical of diabetic wounds. As shown in Figure 6, this combination can synergistically enhance wound healing by the dual action of metallic NPs hindering bacterial colonization and inflammatory responses and HIF-1α stabilizers promoting vascularization in diabetic wounds. Table 2 summarizes the applications of different metallic NPs in wound healing.
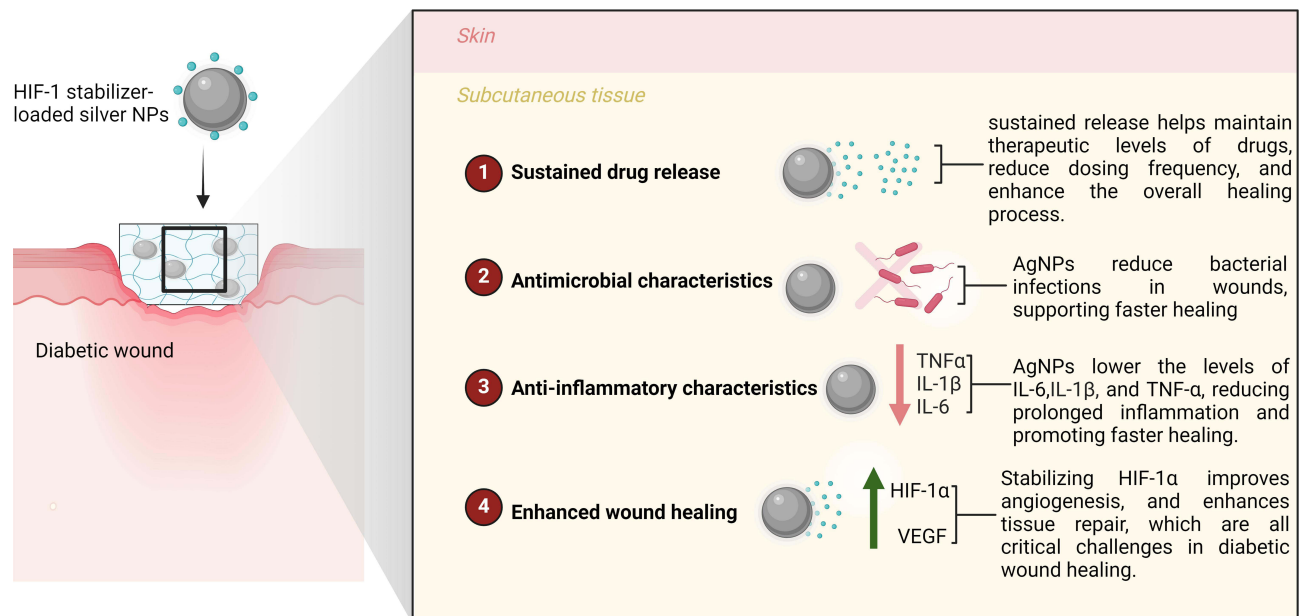
Figure 6 Loading silver nanoparticles (AgNPs) with HIF-1α stabilizer drugs offers a comprehensive approach to diabetic wound healing. This strategy combines sustained drug release with enhanced angiogenesis, tissue regeneration, and reduced chronic inflammation. AgNPs help address the key challenges of wound healing in hypoxic and diabetic conditions by promoting HIF-1α stability, increasing VEGF production, and providing antibacterial effects, ultimately leading to faster and more effective wound repair. Created in BioRender. Mamdouh, A. (2024) https://BioRender.com/ q68h441.

Table 2 Overview of Therapeutic Applications of Metallic NPs in Wound Healing

Metallic NPs	Payloads	Key findings	References
Silver NPs	Quercetin	In an excisional diabetic wound model, the designed system demonstrated synergistic therapy paradigms for diabetic wounds by reducing the wound gap and increasing the percentage of re-epithelialization compared to diabetic control after 18 days of post-treatment.	[109]
Gold NPs	Nerolidol	Topically applying the drug-loaded gold NPs improved the healing of diabetic wounds within 14 days, compared to the control group, which had a longer wound healing time.	[110]
Copper NPs	Curcumin	The synthesized NPs exhibited biodegradability, antibacterial activity, and nontoxicity. The animal model evaluation demonstrated that this nanocomposite significantly enhanced wound healing, resulting in a wound healing rate of 92.25% after 14 days.	[111]
Zinc NPs	Azithromycin	Employing an experimental infection model in rats, the synthesized NPs improved the elimination of bacteria and accelerated the epidermis regeneration, promoting tissue development.	[112]
Titanium NPs	–	The chitosan gel loaded with titanium NPs revealed the remarkable effectiveness of NPs in promoting wound healing, as it resulted in complete epithelization within 10 days in diabetic rats.	[113]

Lipid-Based NPs

Lipid-based NPs, including solid lipid NPs and liposomes, are widely explored in biomedical applications due to their biocompatibility, biodegradability, and ability to encapsulate hydrophilic and lipophilic drugs.[114] These systems are particularly advantageous for diabetic wound healing as they provide controlled and targeted drug delivery, reducing systemic side effects.

Lipid-based NPs can shield labile agents from degradation in the harsh environment of the wound, thereby maintaining their therapeutic effectiveness.[115] In addition, they can be combined with HIF-1α stabilizers and other active substances (antimicrobial peptides, etc)., thereby forming multi-functional systems that cover several aspects of the treatment of diabetic ulcers, from infection prevention to stimulating angiogenesis.

Combining lipid-based NPs and HIF-1α therapies can ensure a controlled and extended release of HIF-1α stabilizers at the site of the wound, enhancing the availability of drugs for a longer time, enabling better angiogenesis and the repair of the tissues. Liposomes can fuse with the cell membranes, allowing drug transport into the target cells.[116] Thus, these properties help improve the penetration and action of drugs in wound healing processes. Solid lipid NPs are beneficial in incorporating a solid core polymeric matrix that can protect drugs from degradation while attaining sustained and controlled release features.[117] They are particularly advantageous in the administration of drugs that are light-sensitive such as, roxadustat or enzyme-sensitive.

In a recent study, a novel HIF-1α stabilizers, roxadustat, has been incorporated into cubosomes, demonstrating a sustained release of the drug for 48 h and effectively developing a conducive environment for tissue repair by promoting angiogenesis, stabilizing HIF-1α, and collagen synthesis.[118] In another study, loading DFO with liposomes significantly enhanced wound healing compared to plain DFO by enhancing drug penetration and sustaining drug release.[119] Additionally, DFO-loaded solid lipid NPs have shown a prolonged sustained release with a higher entrapment efficiency, which is significant for such a hydrophilic drug.[120] Table 3 summarizes the applications of different metallic NPs in wound healing.

Ceramic NPs

Ceramic NPs refer to nonorganic nanoparticles made of silica, calcium phosphate, and other compounds. These NPs are stable, biocompatible, and possess structural integrity.[126] They have paved their way in the biomedical field, particularly in the application of drug delivery vehicles, because they can encapsulate and protect therapeutic entities and provide controlled release.[127]

In the diabetic wound healing context, ceramic NPs' advantages include their ability to assist in tissue engineering, prevent infections, and increase the effectiveness of the agents used in wound healing. Certain ceramic NPs contain

Table 3 Therapeutic Applications of Lipid-Based NPs in Wound Healing

Nanomaterials	Drugs	Key Findings	References
Liposomes	Resveratrol	The liposomal hydrogel's local application greatly enhanced the healing process, wound closure on the ninth day, and decreased infiltration of inflammatory cells at the wound site.	[121]
Niosomes	Diltiazem	Pathological investigations revealed that the wound healing in the group treated with niosomal gel was superior to that in the commercial brand. Among all the preparations examined for cutaneous, the niosomal gel consistently showed non-irritating properties.	[122]
Solid lipid NPs	Retinoic acid	The developed system expedited the wound-healing process in diabetic mice. In addition to reducing leukocyte infiltration in the wound bed, NPs enhanced collagen deposition and decreased scar tissue deposition.	[123]
Nanostructured lipid carriers	Simvastatin	The prepared system presented a controlled release profile and accelerated wound healing, stimulating angiogenesis in damaged tissue and improving the survival and growth of stem cells.	[124]
Nanoemulsion	Linezolid	The wound evaluation showed that using nanoemulsion topically reduced the wound size and greatly enhanced the percentage of wound contraction to about 97% on day 14, compared to the other groups.	[125]

calcium phosphate, a natural bone and tissue replacement that enhances angiogenic growth and tissue restoration, essential to the diabetic wound restoration process. In a recent study, local administration of DFO within a triphosphate calcium scaffold has been found to significantly enhance HIF-1 and VEGF expression, promoting bone regeneration in osteoporotic rats.[128]

HIF-1α stabilizers can be incorporated and released to the wound target by ceramic NPs in a controllable and sustained manner. This increases the local levels and activity duration of HIF-1α, catalyzing faster and improved healing of diabetic wounds. They may also complement the effects of HIF-1α stabilizers, further enhancing the wound microenvironment through promoting neovascularization, decreasing oxidative burden, and expediting tissue repair. The NPs might also play a role in wound healing strategies by interacting with the wound bed and promoting cell proliferation.

In a previous study, DMOG-loaded silica NPs have been shown to exert a synergistic effect on diabetic wound healing.[129] In vitro, combining DMOG drugs and Si ions enhanced the expression of attachment, proliferation, migration, and angiogenesis genes. The in vivo study exhibited that they improved the formation of new blood vessels, regeneration of epithelial tissue, and collagen production while reducing inflammation in diabetic wound beds, promoting successful wound healing.

Another interesting ceramic material is bioglass, which contains Ca and Silica ions. Bioglass itself shows high biological activity and can release products that, upon degradation, support osteogenesis, angiogenesis, and wound healing.[130] In a previous study, the combination of bioglass and DFO accelerated diabetic wound healing by exhibiting a synergistic effect in endorsing HIF-1α expression and revascularization.[131]

Protein-Based Nanomaterials

Biomaterials such as collagen, gelatin, silk fibroin, and other protein-based nanomaterials are seeing an increase in biomedicine applications because of their biocompatibility and biodegradability. Because they are derived from nature, they are degraded into non-toxic components, and hence, the possibility of side effects is minimized. Their compatibility with living tissue avoids any immune responses, which are critical in chronic diabetic wound situations.

Collagen helps increase the number of fibroblasts in the wound area, which is essential for ECM synthesis and tissue repair. Due to its hydrophilic properties, collagen facilitates fibroblast penetrating the wound base.[132] This particular feature is critical in diabetic wounds as padding of fibroblast infiltrates enriches the ability of tissue repair and remodeling of ECM. Also, Collagen aids in the deposition of its fibers, thereby enhancing the quality structure of the healing tissue.[133] Another property of collagen is its ability to enhance cell migration, which is necessary for wound

healing and closure. Collagen-based nanomaterials can act as carriers for HIF-1α stabilizers, providing a synergistic benefit in promoting re-epithelialization, angiogenesis, and overall tissue regeneration.[134]

Gelatin, derived from collagen through partial hydrolysis, is a highly biocompatible and biodegradable material widely used in tissue engineering and wound healing. Since it is quite close in structure to collagen, gelatin has many beneficial characteristics, including easing cell attachment, supporting tissue regeneration, and enhancing wound closure.[135] Gelatin's flexible and stable nature allows it to be easily modified and shaped into various forms, making it an ideal delivery system for HIF-1α stabilizers. In a recent study, DFO-loaded gelatin microspheres enhanced angiogenesis by increasing the expression of HIF-1α and angiogenic growth factors, leading to collagen deposition and fast wound closure in a full-thickness diabetic wound model.[136]

Silk fibroin belongs to the class of natural proteins sourced from silkworms. It has been primarily used in biomedical applications like wound healing because of its excellent physical strength and biocompatibility. Among other proteins like, for instance, gelatin and collagen, SF has better toughness, mechanical performance, and thermal stability.[137] Also, since it has the Arg-Gly-Asp sequence, it helps to expand cell adhesion, proliferation, and migration, critical processes for the successful healing of the skin.[138] This protein has been developed into different forms of nanomaterials, which are highly effective as carriers of HIF-1α stabilizers in wound healing.[139]

Polymeric Nanomaterials

Polymer-based nanomaterials, including hyaluronic acid, chitosan, alginate, and Poly lactic-co-glycolic acid (PLGA), are extensively used in drug delivery due to their tunable characteristics, biocompatibility, and ability for controlled and targeted drug release. These NPs are ideal for diabetic wound healing, as they protect bioactive molecules from degradation, can be engineered to respond to environmental stimuli like pH or temperature, and offer sustained release of therapeutic agents, maintaining a necessary dosage in the wound area for an extended period, reducing the need for dressing changes.

Hyaluronic acid is an abundant glycosaminoglycan present in the ECM of many connective tissues. Its properties of moisture retention, firmness, and supporting cell activity make it critical in diabetic wound healing.[140] Its hydrophilic nature maintains a wet environment that is important for cell migration and population while inhibiting dryness and cell death. Furthermore, hyaluronic acid increases fibroblast movement and proliferation of keratinocytes and aids in granulation tissue.[141] These properties make it an ideal delivery system for HIF-1α stabilizers in managing chronic diabetic wounds.

Chitosan, a naturally occurring polymer obtained from chitin sourced from exoskeletons of crustaceans, contains many properties that are effective for diabetic wound healing. It is biocompatible, biodegradable, and non-toxic. Chitosan's antimicrobial properties help inhibit bacterial growth, forming a protective barrier that minimizes infection risks.[142] Chitosan modulates the immune response, reducing prolonged inflammation helping wounds progress through various healing phases.[97] Its mucoadhesive attribute also assists in localizing the drug at the site of application for a prolonged time.[143] It contributes to sustained therapeutic release, which is paramount for enhancing wound healing processes, especially in diabetic ulcers. When combined with HIF-1α stabilizers, these properties accelerate healing by stimulating angiogenesis and tissue regeneration. In a recent study, Zhang et al fabricated a chitosan/hyaluronic acid hydrogel loaded with DFO NPs and investigated its efficacy for wound healing.[144] The composite nano hydrogel's photothermal response facilitated wound healing by efficiently reducing inflammation through controlled DFO release and regulation of the immunological reaction of injured skin tissue.

Alginate-based nanomaterials are frequently used in wound dressings because they maintain a moist wound environment.[145] Co-delivery of HIF-1α stabilizers within alginate-based nanomaterials can enhance healing by promoting tissue hydration and angiogenesis. Another critical advantage of alginate is its pH-dependent release characteristics,[146,147] which benefit wound healing. Intriguingly, chronic wounds feature alkaline pH, which decreases gradually as the wound healing process progresses. Therefore, utilizing alginate-based nanomaterials that facilitate a higher release of therapeutic agents in an alkaline medium initially, followed by sustained release in an acidic pH, could be highly beneficial. This dual-release mechanism guarantees an initial rapid distribution of the medicine to initiate the healing process, followed by a controlled and continuous release to facilitate ongoing tissue repair and regeneration.

The mucoadhesive nature of alginate allows it to stay in place on the wound bed for extended periods.[148] This extended retention helps maintain a moist environment, critical for wound healing, particularly in chronic diabetic wounds. Recently, Li et al prepared an alginate-based hydrogel loaded with DFO and copper NPs and explored its efficacy in diabetic wound healing.[107] The developed system exhibited a sustained release of DFO for 60 h. The alginate composite shown excellent antibacterial activity and effectively decreased the persistent inflammatory reactions. In vivo, it enhanced angiogenesis and expedited the healing of diabetic wounds while maintaining excellent biocompatibility.

Poly(lactic-co-glycolic acid) (PLGA) is one of the most commonly used copolymers. Its advantages have been demonstrated in various biomedical applications, especially wound healing.[149] Given its adjustable mechanical characteristics and regulated degradation rates, PLGA is suitable for promoting tissue regeneration, particularly in diabetic wounds where the healing process is commonly hindered.[150] A key feature of PLGA is its ability to provide controlled and sustained drug release. This allows therapeutic agents to be delivered over extended periods, which is crucial for promoting wound closure and tissue repair. PLGA's surface modification capabilities also improve drug interaction, increasing its efficacy in diabetic wound care. In a recent study, a HIF-1α stabilizer, DFO, was loaded in PLGA NPs, and the NPs were incorporated into a hyaluronic acid hydrogel.[151] The PLGA NPs demonstrated a prolonged release of DFO over 12 days and reached 15 days after encapsulating in the hydrogel. Moreover, when evaluated in a mouse model of excisional skin wounds, the composite hydrogel enhanced wound healing and stimulated the development of new blood vessels and granular structures.

Nanohydrogels

Nanohydrogels represent a class of drug delivery systems. They are characterized by precise and targeted drug delivery to specific sites followed by a controlled rate of drug release, merging the properties of hydrogels and NPs.[152] As an ideal drug delivery carrier, nanogels exhibit numerous positive characteristics, including exceptional drug loading capacity, enhanced stability, biocompatibility, and remarkable responsiveness to different environmental stimuli.[153]

Nanohydrogels have a 3D highly swollen network structure, which makes them especially effective in medical applications such as wound healing. These hydrogels provide moist wound care in diabetic patients, which prevents excessive dryness, which is detrimental to wound healing. Their porous structure mimics the ECM, supporting cell adhesion, migration, and proliferation, all vital for wound closure.[154] Moreover, Some nanohydrogels are designed to respond to specific stimuli, such as changes in pH or temperature. This responsiveness permits targeted drug delivery and controlled release in response to the wound environment.

Wang et al have developed a novel therapeutic approach aiming to enhance diabetic wound healing by utilizing exosomes loaded with the HIF-1α stabilizer, VH298, and integrating these VH298-loaded exosomes (VH-EVs) into a gelatin methacrylate (GelMA) hydrogel. The study aimed to promote angiogenesis and accelerate wound healing through the sustained release and targeted delivery of VH298 to wound sites.[155] The GelMA hydrogel, synthesized to mimic extracellular matrix properties, demonstrated suitable mechanical strength, porosity, lower swelling ratio, and slower degradation, resulting in a steady release of VH-EVs for 15 days. In vitro experiments revealed that VH-EVs significantly enhanced the proliferation, tube formation, and migration of human umbilical vein endothelial cells (HUVECs) more effectively than free VH298 or EVs alone. These effects were linked to the upregulation of HIF-1α and VEGF, key proteins involved in angiogenesis. In vivo, VH-EVs incorporated into GelMA hydrogel (Gel-VH-EVs) showed superior wound healing in diabetic mice compared to other treatments. Wounds treated with Gel-VH-EVs exhibited complete closure by day 12, with enhanced granulation tissue formation, collagen deposition, and re-epithelialization.

Deng et al recently conducted a study involving a newly developed hyaluronic acid-based multifunctional hydrogel incorporating silver nanoclusters (AgNCs) and DFO-loaded polydopamine/manganese dioxide (PHMD) NPs aimed at enhancing the healing process of infected diabetic wounds.[156] This hydrogel demonstrated several advantageous characteristics: it featured a customizable gelation time ensuring excellent injectability, adjustable mechanical properties with a degradation rate nearing 90% after 3 days at pH 5, pH-responsive behavior facilitating enhanced release of encapsulated AgNCs and DFO in acidic conditions typical of diabetic wounds, superior tissue adherence, and close tissue contact capabilities. The combination of AgNCs and PHMD supplied hydrogel with potent antibacterial activity superior to that of AgNCs alone, demonstrating DFO's dual role owing to its antibacterial action and HIF-1 activation. Notably, the in vivo study using diabetic rats with S. aureus-infected

wounds stated that Hydrogel@AgNCs&PHMD demonstrated a significant ability to accelerate wound closure compared to other treatment groups as evidenced by 80% wound closure by day 7 and almost-complete closure by day 14.

Nanofibers

NFs represent a groundbreaking category of nanomaterials. Electrospun fibers can be created from both natural and synthetic polymers. These fibers are distinguished by a high surface area to volume ratio as well as a remarkable biomimetic structure thus enabling a range of applications, including electronics plus the biomedical field.[157] This biomimetic quality facilitates cellular adhesion, proliferation, and migration stimulating tissue repair.

A remarkable further benefit of NFs over other nanomaterial is their inherent porosity. Such characteristic contributes markedly to improved wound healing as it allows efficient nutrients and gas exchange creating an ideal milieu supporting necessary cellular processes vital for tissue regeneration. Additionally, NFs were reported to accelerate the epithelialization process and minimize scarring. This could be attributed to their significant capacity to absorb wound exudates and necrotic tissue (eschar) owing to their swelling ability.[158,159] Moreover, NFs could be employed to encapsulate bioactive substances (eg, growth factors, antibiotics, and anti-inflammatory medications), and then achieve a controlled release of these substances. The controlled release achieved by NFs ensures both sustained as well as extended bioactive substances action thus decreasing dosing frequency and improving patient compliance. As per diabetic wound management, incorporating HIF-1 stabilizers into NFs, could specifically improve vascularization and accelerate wound closure. Figure 7 displays the key advantages of NFs in wound healing.
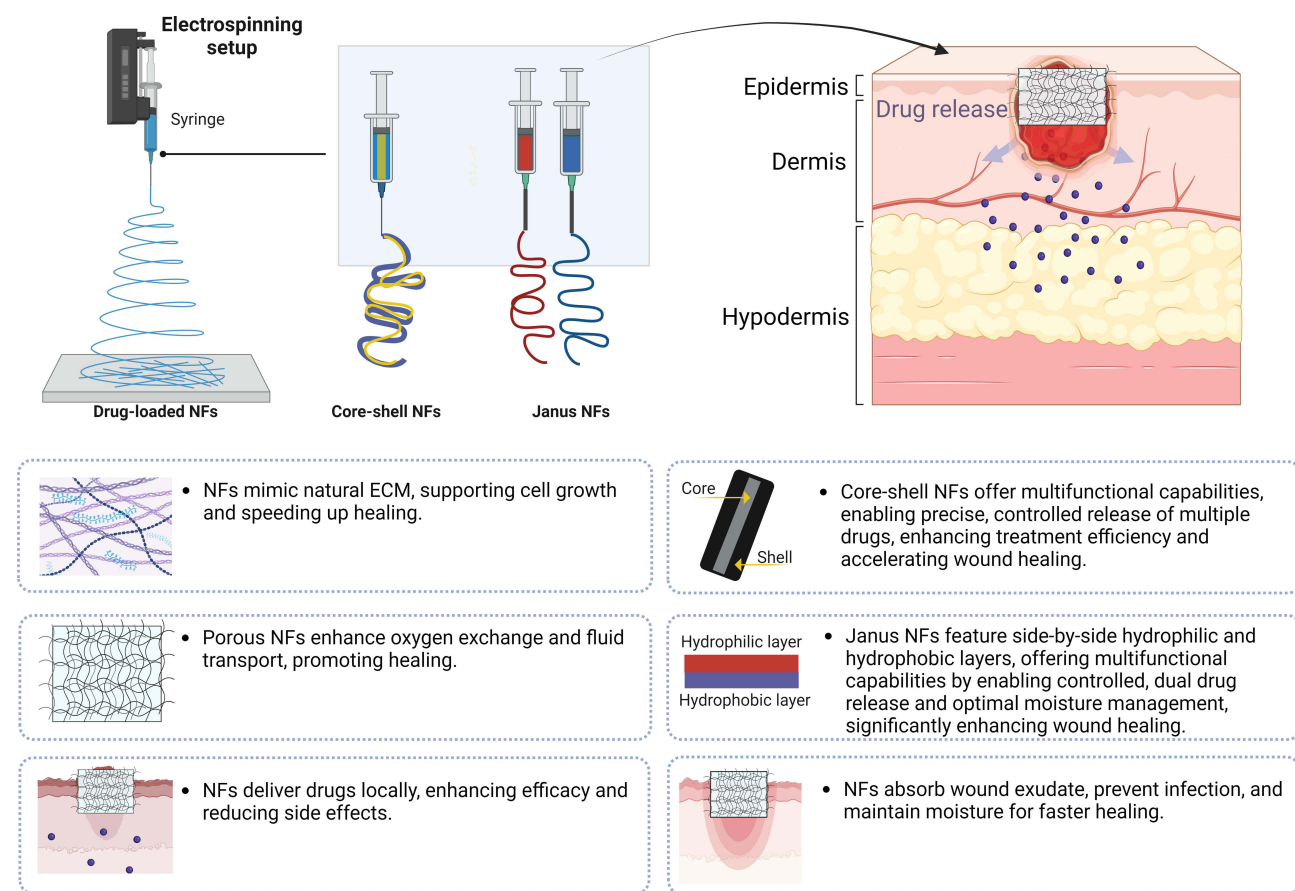
Figure 7 Advanced Nanofiber Dressings for Targeted Drug Delivery: NFs resemble the ECM, providing an ideal environment for cell growth and accelerating healing. Their porous structure enables better oxygen exchange, promoting wound recovery. NFs ensure localized and sustained release of drugs directly to the wound site, maximizing efficacy and minimizing systemic side effects. Additionally, NFs absorb wound exudate, maintaining an optimal moisture balance, which supports faster wound healing. Advanced multifunctional NFs, such as core-shell and Janus nanofibers, offer additional benefits by enabling dual drug loading or sequential release, further enhancing their therapeutic potential. Created in BioRender. Mamdouh, A. (2024) https://BioRender.com/ y72h378.

Recently, Zhu et al established a pioneering design for a wound dressing for diabetic wound healing.[160] This dressing is featured with a distinctive NFs bilayer. The outer layer consists of a mixture of a blend of hydrophilic polycaprolactone (PCL) and polyethylene glycol (PEG) NFs loaded with DFO. This layer offers effective exudate management and enhances angiogenesis. Meanwhile, the inner layer is composed of hydrophobic PCL NFs, with a mesh-like structure. The design of this dressing ensured both mechanical strength and biocompatibility. Moreover, the inner mesh structure of PCL NFs enhanced fibroblast attachment and proliferation, crucial for wound closure. In addition, the release kinetics of DFO from the outer layer showed a sustained release profile over time with a release percentage of 86% for 48 h. In a diabetic full-thickness cutaneous wound model, the NFs accelerated wound closure, achieving near complete closure by day 16 compared to standard treatments, underscoring its efficacy in creating a conducive microenvironment that efficiently managed biofluids and stimulated angiogenesis.

Li et al introduced a creative approach to diabetic wound healing using a combination of advanced materials.[129] Their strategy centers on aligned, porous poly(L-lactic acid) (PLLA) electrospun fibrous membranes. These membranes incorporate mesoporous silica nanoparticles (DS) specifically designed to deliver DMOG. By incorporating DS into the PLLA nanofibrous scaffold (DS-PL), they established a dual cooperative controllable release system. The study demonstrated that DS-PL effectively released DMOG and Si ions over an extended period of 15 days. This controlled release profile significantly enhanced endothelial cell functions, including proliferation and migration, by stabilizing HIF-1α and upregulating VEGF. Moreover, in vivo studies using a diabetic mouse model revealed accelerated wound closure rates with DS-PL scaffolds, reducing wound size by 95% after 15 days. Furthermore, DS-PL scaffolds stimulated collagen deposition, particularly Collagen I, and promoted re-epithelialization in diabetic wounds, critical for tissue regeneration.

Finally, a growing body of research investigates the application of nanotechnology for the localized delivery of HIF-1α stabilizers in the context of wound healing. These investigations further solidify the promising potential of integrating nanotechnology with the HIF-1α activation pathway. A comprehensive overview of these supplementary research endeavors is presented in Table 4.

Table 4 Advances in Nanotechnology for Targeted Delivery of HIF-1α Stabilizers in Wound Healing

Nanomaterials	Key Findings	References
Bioactive CoNZ	CoNZ demonstrates potent enzymatic activity, effectively neutralizing ROS, and significantly aiding both pathological and normal wound healing. CoNZ treatment dramatically enhances healing by reducing inflammation and promoting angiogenesis.	[161]
DMOG/PCL/COL-1 NFs	DMOG-NFs delivered the drug effectively, promoting cell migration and gene activity for healing. In animal studies, they improved blood vessel formation, skin regrowth, and wound closure speed.	[134]
DFO transfersomal gel	The optimized DFO transfersomal gel enhances skin penetration and significantly accelerates wound healing, neovascularization, and collagen production. This formulation improves sustained DFO delivery, restoring the healing process.	[8]
DFO/Niosomes-loaded NFs	The scaffold's biomimetic properties controlled DFO release, and enhanced neovascularization, wound closure, and healing. This biodegradable scaffold synergistically promotes tissue regeneration.	[162]
CS/SA/PVA/DFO bilayer NFs	CS/SA/PVA/DFO NFs demonstrated favorable water vapor transmission rates for gaseous exchange and high swelling capacity for wound exudate absorption. The sustained release of DFO prolonged therapeutic agent delivery exhibited an anti-bacterial effect and accelerated healing in complex chronic wounds.	[9]

(*Continued*)

Table 4 (Continued).

Nanomaterials	Key Findings	References
PGA/SF-DFO scaffolds	In vitro studies showed PGA/SF-DFO scaffolds have a porous, high-surface-area 3D structure with good mechanics and biocompatibility. In vivo, these scaffolds promoted diabetic wound healing through improved blood vessel formation, collagen deposition, and restored wound bed mechanics.	[139]
DFO-Laden silk NF hydrogels	In vitro and in vivo studies demonstrated the hydrogels' ability to dampen inflammation and stimulate vascularization. DFO-Laden silk NF hydrogels proved effective in reducing chronic inflammation and stimulating angiogenesis, leading to accelerated healing and enhanced deposition of ECM	[163]
FSNs@DFO-H@Dex nanogel	This multifunctional nanohydrogel combines photothermal effects for treatment with controlled cell growth and blood vessel formation, promoting wound healing. DFO enhances these effects while Dex reduces inflammation, ultimately accelerating healing.	[144]
DFO-CuNPs/SA hydrogel	The DFO-CuNPs/SA hydrogel combines DFO and copper nanoparticles to boost healing. This synergy elevates growth factors (HIF-1α and VEGF), promotes angiogenesis, and fights infection. Animal studies confirm its effectiveness in accelerating diabetic wound healing with good biocompatibility.	[107]
DFO liposomal gel	DFO liposomal pluronic gel exhibited superior wound healing potential compared to plain DFO in diabetic rats. It promoted multifaceted wound healing by accelerating contraction and influencing growth factor activity, neovascularization, and collagen deposition.	[119]

Abbreviations: CoNZ, cobalt-nanozyme; ROS, reactive oxygen species; DMOG/PCL/COL-1 NFs, Dimethyloxalylglycine-loaded poly(e-caprolactone)/type 1 collagen nanofibers; CS/SA/PVA, chitosan/sodium alginate/polyvinyl alcohol; PGA/SF, Polyglycolic Acid/Silk Fibroin; ECM, extracellular matrix; FSNs@DFO-H@Dex, functionalized silica loaded with deferoxamine as the core and dexamethasone filled hyaluronic acid–chitosan hydrogel as the shell; DFO-CuNPs/SA, deferoxamine-loaded copper nanoparticles incorporated in sodium alginate hydrogel; HIF-1α, hypoxia inducible factor 1 alpha; VEGF, vascular endothelial growth factor.

Future Perspectives

The future of diabetic wound treatment via nanoscale technologies for HIF-1α activation poses several challenges and exciting opportunities. Below are the critical current limitations and potential future research directions.

Clinical Transition

While there are some ongoing clinical applications of HIF-1α stabilizers, their broader clinical use remains limited. For example, a clinical trial is currently investigating the effect of local DFO on the healing process in diabetic foot ulcers (ClinicalTrials.gov: NCT03137966). Similarly, Daprodustat has completed Phase I clinical trials for diabetic foot ulcers treatment (ClinicalTrials.gov: NCT01831804). These trials mark significant steps forward in the clinical translation of HIF-1α stabilizers. However, despite these advancements, the clinical translation of nanomaterials for localized delivery of HIF-1α stabilizers remains a significant challenge. Currently, there are no clinical applications for these nano-based systems. As mentioned, nanomaterials hold the potential to offer several critical advantages that make them particularly suitable for diabetic wound management. However, transitioning these technologies from preclinical studies to clinical practice faces numerous hurdles. First, the scalability of nanomaterial production for large-scale manufacturing remains a significant hurdle, as consistent synthesis methods must be developed. Second, ensuring the long-term safety, biocompatibility, and stability of these materials is crucial, especially for chronic wound treatments. Regulatory approval also poses a challenge due to the novel nature of nanotechnology-based systems, requiring rigorous clinical trials to demonstrate their efficacy and safety.

Bridging the Gap in Preclinical Research

A critical gap in current research is the limited investigation into novel HIF-1α stabilizers beyond DFO and DMOG. To move forward, it is essential to focus on these novel agents, which include PHD inhibitors like roxadustat and

daprodustat and VHL antagonists like VH298. These drugs offer a more refined approach to stabilizing HIF-1α but have yet to be fully explored in the context of diabetic wounds. For instance, roxadustat has been investigated in only two studies focusing on its efficacy in wound healing following systemic application via intraperitoneal injection.[82,164] While these studies provided foundational insights, systemic application can lead to undesirable side effects, limiting its clinical feasibility. Notably, only one study to date has evaluated the localized application of roxadustat through a cubosomal hydrogel delivery system,[118] which successfully avoided systemic side effects, showing a potential direction for future therapeutic interventions. Similarly, daprodustat and VH298 have not been extensively studied in the context of wound healing, representing a significant gap in preclinical exploration.

Moving forward, future research should aim to incorporate these novel agents into advanced nanoscale delivery systems, which can provide localized delivery and minimize systemic exposure. This approach will not only enhance the therapeutic potential of these novel stabilizers but also offer a more controlled and targeted treatment for chronic wounds, particularly in diabetic patients. Additionally, comparative studies evaluating the efficacy of these novel agents are critically needed. Currently, there is only one study comparing the efficacy of DFO and DMOG in wound healing,[78] underscoring the necessity for further head-to-head comparisons with newer drugs like roxadustat, daprodustat, and VH298. Such studies would provide valuable insights into the relative strengths and limitations of each stabilizer and could guide the development of more effective therapeutic strategies for diabetic wounds.

Drug Repurposing

Another area for investigation is drug repurposing. It proposes a remarkably attractive approach for accelerating the development of novel therapies for diabetic wounds. A significant advantage of this approach is the acceleration of clinical translation and reducing potential risks associated with new drug development. Significantly, drug repurposing allows leveraging existing FDA-approved drugs with established safety profiles. DFO serves as a prime example of the potential of drug repurposing in wound healing. Originally approved for the treatment of iron overload disorders, DFO has emerged as a potent activator of HIF-1α, a key regulator in the cellular response to hypoxia, which is critical for wound healing. The safety and pharmacokinetics of DFO are already well understood, making it an ideal candidate for repurposing in diabetic wound management.

Looking ahead, future research should focus on identifying and repurposing additional FDA-approved HIF-1α stabilizers or drugs with angiogenic or anti-inflammatory properties that have been previously approved for unrelated conditions By utilizing the drug repurposing strategy, these compounds could provide new therapeutic avenues with reduced development time and improved safety profiles. Moreover, the integration of drug repurposing with advanced nanotechnology platforms offers a powerful synergy. This strategy not only enhances drug efficacy but also minimizes systemic side effects, a significant concern when repurposing drugs for new therapeutic applications. For instance, incorporating DFO into nanocarrier systems for localized delivery has shown promise in preclinical models, and similar strategies should be extended to other repurposed drugs.

Multifunctional Nanomaterials

The advancement of nanotechnology offers transformative potential for diabetic wound healing by enabling the design of multifunctional nanomaterials capable of addressing multiple aspects of the wound healing process. Among these, core-shell and Janus systems represent cutting-edge innovations in nanoscience that have garnered attention due to their ability to integrate multiple therapeutic modalities within a single platform.[165,166] These complex nanostructures can be engineered to tackle critical challenges in diabetic wounds, such as hypoxia, infection, inflammation, and impaired angiogenesis, simultaneously.

In the future, research should focus on combining HIF-1α stabilizers with these advanced multifunctional nanomaterials to leverage their synergistic benefits. This could involve developing nanomaterial-based systems with dual functions enabling the co-delivery of HIF-1α stabilizers alongside other therapeutic agents, such as anti-inflammatory drugs or growth factors, offering a comprehensive treatment solution for diabetic wound management.

Conclusion

Impaired wound healing in diabetic patients is a significant medical and public health issue globally, associated with poorer prognosis and higher mortality rates. Hypoxia plays a crucial role in normal wound healing processes via HIF-1α activation, which regulates many essential processes for wound repair under ischemic conditions. However, in diabetic wounds, chronic hypoxia disrupts normal HIF-1α signaling, resulting in a dysfunctional hypoxic response. Consequently, the beneficial effects of HIF-1α are diminished, exacerbating wound healing challenges.

Many studies have emphasized the importance of HIF-1α signaling regulation in diabetic wound healing and have explored pharmacological approaches to stabilize and activate HIF-1α. These approaches include iron substitution, iron chelation, 2-OG inhibition, and the novel strategy of using VHL antagonists. Regardless of the promise of HIF-1α stabilizing agents in enhancing wound healing, systemic exposure to these agents presents significant challenges, including abnormal angiogenesis, increased tumor growth risk, and disrupted iron metabolism. These limitations require a localized drug delivery system.

Nanotechnology-based platforms offer a solution by enabling localized, sustained drug release, enhancing drug efficacy at lower doses, and allowing the co-delivery of multiple therapeutic agents such as HIF-1α stabilizers, growth factors, and antibiotics in a single formulation. This approach simultaneously addresses multiple aspects of wound healing, promoting faster and more effective tissue repair, particularly beneficial in diabetic wound treatment. Additionally, the inherent properties of these nanomaterials, such as mimicking the ECM, degradability, biocompatibility, porosity, and swellability, provide further advantages. Recent studies have demonstrated the promising outcomes of nanotechnology-based delivery systems incorporating HIF-1α stabilizers, in experimental animal models, as evidenced by improved vascularization, accelerated wound closure, and enhanced tissue regeneration. This synergistic strategy represents profound progress in developing practical therapeutic approaches for diabetic wounds, leveraging the key biological pathways regulated by HIF-1.

Finally, While HIF-1α activation plays a crucial role in promoting angiogenesis, cell proliferation, and tissue regeneration, its use in therapeutic applications must be approached with caution. Excessive or prolonged activation of HIF-1α can lead to adverse effects such as abnormal angiogenesis, edema, and even potential oncogenesis due to its role in promoting blood vessel growth. Beyond the systemic side effects of HIF-1α stabilizers, other challenges in diabetic wound healing, such as chronic infection, excessive inflammation, oxidative stress, and poor immune response, require more than just angiogenesis promotion. This is where multifunctional nanomaterials become especially valuable because they can address these additional factors by delivering multiple therapeutic agents alongside HIF-1α stabilizers.

Multifunctional nanomaterials offer an innovative solution by co-delivering HIF-1α stabilizers alongside other therapeutic agents that target these complications. For instance, chronic infections in diabetic wounds can be controlled through the incorporation of antibacterial agents in nanomaterials, while anti-inflammatory drugs can be delivered to reduce excessive inflammation that hampers healing. Furthermore, multifunctional nanomaterials can carry ROS scavengers to neutralize oxidative stress, protecting cells from damage and promoting tissue regeneration. By targeting these multiple aspects of wound healing simultaneously, multifunctional nanomaterials provide a synergistic approach that enhances the efficacy of HIF-1α stabilizers and addresses the complex nature of diabetic wounds.

Abbreviations

2-OG, 2-oxoglutarate; CHIP, chaperone-dependent ubiquitin ligase; CBP, CREB-binding protein; DFO, deferoxamine; DMOG, dimethyloxalylglycine; ECM, extracellular matrix; HUVECs, human umbilical vein endothelial cells; HREs, hypoxia response elements; HIF-1α, Hypoxia-inducible factor-1 alpha; MMPs, matrix metalloproteinases; MGO, methylglyoxal; NFs, nanofibers; NOG, N-oxalylglycine; PAD, peripheral arterial disease; PHD, prolyl hydroxylase domain; ROS, reactive oxygen species; TGF-β1, transforming growth factor-β1; VEGF, vascular endothelial growth factor; VHL, Von Hippel-Lindau protein.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Disclosure

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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