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The Role of Hypoxia-Inducible Factor in Wound Healing

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Significance: Poor wound healing remains a significant health issue for a large number of patients in the United States. The physiologic response to local wound hypoxia plays a critical role in determining the success of the normal healing process. Hypoxia-inducible factor-1 (HIF-1), as the master regulator of oxygen homeostasis, is an important determinant of healing outcomes. HIF-1 contributes to all stages of wound healing through its role in cell migration, cell survival under hypoxic conditions, cell division, growth factor release, and matrix synthesis throughout the healing process.
Recent Advances: Positive regulators of HIF-1, such as prolyl-4-hydroxylase inhibitors, have been shown to be beneficial in enhancing diabetic ischemic wound closure and are currently undergoing clinical trials for treatment of several human-ischemia-based conditions.
Critical Issues: HIF-1 deficiency and subsequent failure to respond to hypoxic stimuli leads to chronic hypoxia, which has been shown to contribute to the formation of nonhealing ulcers. In contrast, overexpression of HIF-1 has been implicated in fibrotic disease through its role in increasing myofibroblast differentiation leading to excessive matrix production and deposition. Both positive and negative regulators of HIF-1 therefore provide important therapeutic targets that can be used to manipulate HIF-1 expression where an excess or deficiency in HIF-1 is known to correlate with pathogenesis.
Future Directions: Targeting HIF-1 during wound healing has many important clinical implications for tissue repair. Counteracting the detrimental effects of excessive or deficient HIF-1 signaling by modulating HIF-1 expression may improve future management of poorly healing wounds.

SCOPE AND SIGNIFICANCE

Skin serves as a vital protective barrier against infection. Disruption of its integrity can lead to significant disability or even death. Recent advances have increased our understanding of biologic processes underlying wound healing and given rise to improvements in patient care. However, the end goals of wound care—rapid wound closure and an aesthetically satisfactory scar—remain out of reach for a significant number of patients. This review will summarize current knowledge of the biology of hypoxia in wound healing. In addition,

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the role of hypoxia-inducible factor-1 (HIF-1) in wound healing and as a novel therapeutic target will be described.

TRANSLATIONAL RELEVANCE

An important prognostic determinant of wound repair is the presence of hypoxia. While early relative hypoxia has been shown to induce wound healing,[1] prolonged hypoxia conversely leads to delayed healing. Adaptive cellular responses to hypoxia are mediated by HIF-1, which upregulates the expression of many genes that enhance healing in low-oxygen conditions. A better understanding of these molecular processes may lead to improved treatment of patients.

CLINICAL RELEVANCE

An estimated 6.5 million people in the United States each year suffer from chronic nonhealing skin ulcers, most commonly caused by diabetes, venous stasis, and pressure sores.[2] Therapies currently available to patients suffering from abnormal wound healing are often insufficient to ensure satisfactory wound repair. Thus, there is an urgent need for novel therapeutic strategies to address nonhealing wounds and continued investigation into better understanding of the wound healing process.

BACKGROUND

Cutaneous wound healing

Traditionally, skin wound repair has been divided into three overlapping processes: inflammation, proliferation, and remodeling (Fig. 1).[3]

At the initiation of the inflammatory stage, tissue injury causes disruption of local vasculature and extravasation of blood. This leads to platelet aggregation and the formation of a clot. The blood clot forms a provisional matrix that acts as a scaffold for cells at the wound site, and contributes to the eventual formation of granulation tissue. Numerous active signaling factors are generated by the coagulation pathway and by injured or activated cells. These factors serve to recruit inflammatory cells, such as neutrophils and monocytes, to the site. The inflammatory cells then debride the wound while releasing additional factors that stimulate the migration of fibroblasts to the wound to form granulation tissue as part of the proliferative process (Fig. 2A).[4]

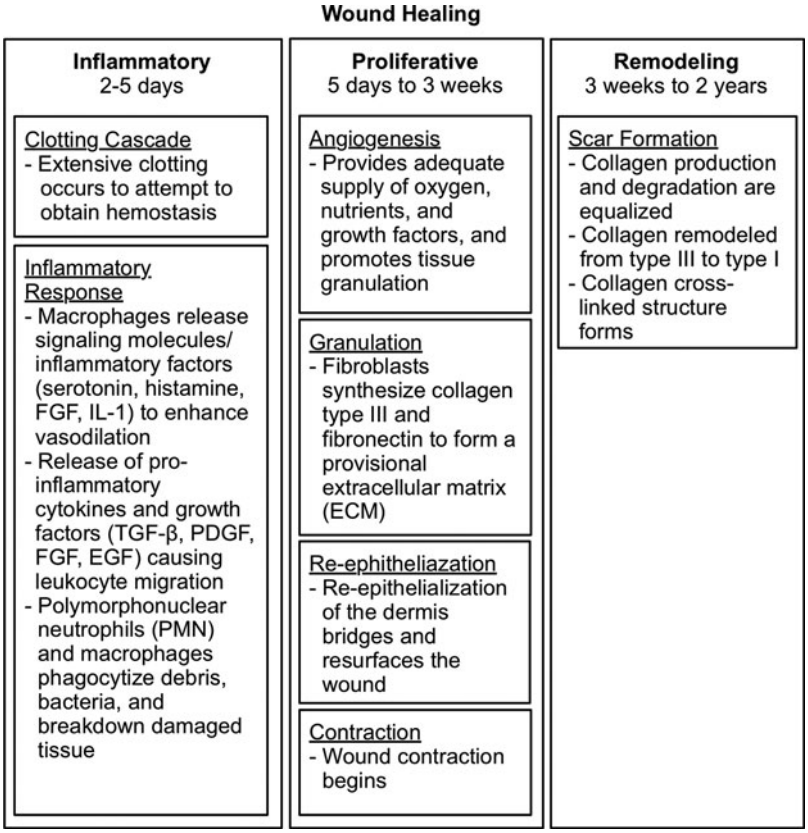

Figure 1. Comparison of the major characteristics of the three phases of wound healing: inflammation, proliferation, and remodeling.

During proliferation the newly formed granulation tissue begins to assemble in the wound. This occurs approximately four days after initial injury. During this process, macrophages, blood vessels, and fibroblasts simultaneously invade the wound area. Macrophages secrete growth factors that stimulate formation of fibrous tissue and angiogenesis while fibroblasts lay down an extracellular matrix (ECM) (Fig. 2B).

In the remodeling stage the ECM is gradually replaced by a collagen matrix, which is also secreted by fibroblasts. Collagen remodeling that occurs during the transition from granulation tissue to scar formation is dependent on a low rate of collagen synthesis and catabolism. The degradation of collagen is controlled by the activity of proteolytic enzymes called matrix metalloproteinases (MMPs). MMPs are secreted by a number of cells, including macrophages, endothelial cells, epidermal cells, and fibroblasts. Once an abundant collagen matrix has been deposited in the wound, the fibroblast-rich granulation tissue is replaced by a relatively acellular scar (Fig. 2C).[3]

Oxygen in wound healing

Oxygen has long been known to play a prominent role in the healing process. As the individual steps of the wound healing cascade are elucidated, the involvement of oxygen at nearly every stage has become increasingly clear. Changes in oxygen concentrations activate precisely regulated pathways that respond to hypoxia by attempting to restore oxygen supply to cells and by modulating cell function under hypoxic conditions.

During the initial inflammatory process, wound sites are often hypoxic. This is due to disruption of vasculature surrounding the wound, leading to impaired oxygen delivery, and exacerbated by a rapid influx of inflammatory cells participating in the healing process with high metabolic demands for oxygen. These inflammatory cells preferentially accumulate in hypoxic areas to play a critical role in granulation, re-epithelialization, and other healing processes.[5] This hypoxic gradient can also affect stromal cell function, as the proliferation of human dermal fibroblasts is greatly enhanced under acute hypoxia.[6] Fibroblasts were found to

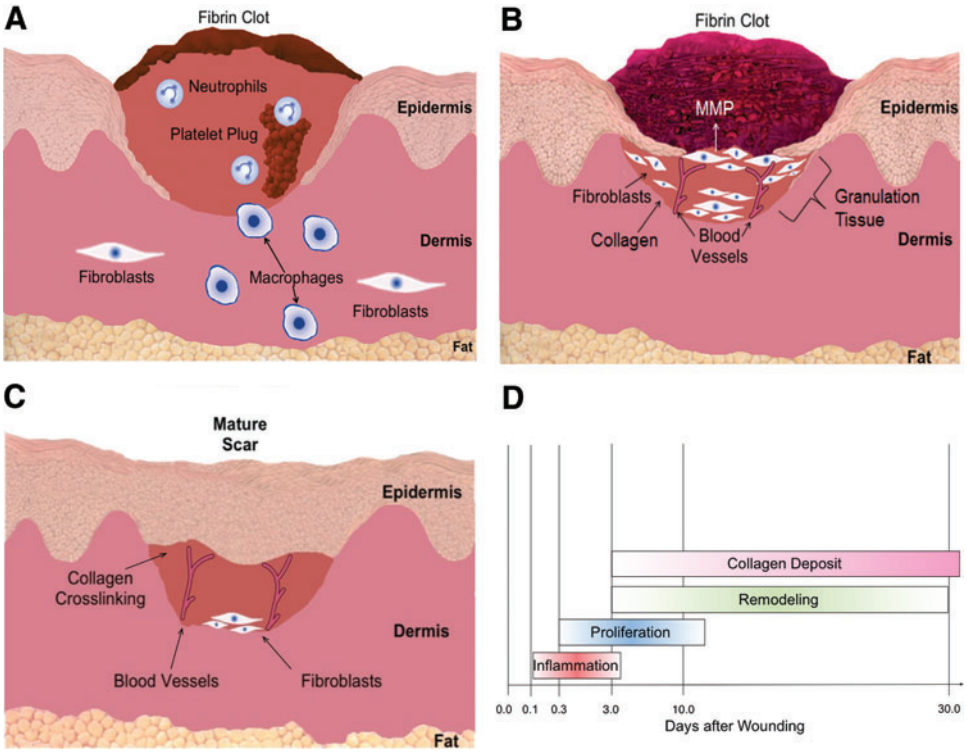

Figure 2. **(A)** Inflammation. Hemostasis and inflammation occur immediately following injury. Extravasation of blood leads to the formation of a clot. Numerous signaling factors are released leading to the recruitment of inflammatory cells, such as neutrophils and monocytes, to the wound. Monocytes then differentiate into mature macrophages at the wound site. Both neutrophils and macrophages are phagocytes and act to debride the wound while releasing additional factors to stimulate migration of fibroblasts to the wound site. **(B)** Proliferation and remodeling. During proliferation, fibroblasts secrete extracellular matrix (ECM) to form granulation tissue. Angiogenesis also occurs simultaneously as endothelial cells migrate to the area of the wound. Collagen secreted by the fibroblasts is concurrently degraded by matrix metalloproteinases (MMPs) as part of the remodeling process. **(C)** Maturation. During maturation, collagen production and degradation equalize. Disorganized collagen fibers are cross-linked and aligned along tension lines, leading to an increase in the tensile strength of the wound. **(D)** Time course of different processes that occur in the wound during healing. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

secrete up to nine times more transforming growth factor-β1 (TGF-β1) when exposed to hypoxic conditions, which demonstrates this increased activity.[7] Acute hypoxia thus induces a temporary increase in cellular replication and contributes to initiation of the healing process.

However, successful wound healing ultimately requires restoration of normoxic conditions through repair of the local microvasculature.[8] For instance, poor fibroblast production of collagen, an oxygen-dependent process, contributes to the inadequate production of ECM seen in many chronic wounds. Molecular oxygen is required for hydroxylation of proline and lysine during collagen synthesis and for the maturation of protocollagen into the stable triple-helical collagen. In the absence of sufficient oxygen, only protocollagen, which does not have the tensile strength of collagen, can be made.[9] Fibroblast proliferation has also been found to be directly related to oxygen availability. Whereas hypoxia initially increases fibroblast proliferation and fibroblast secretion of TGF-β1, this adaptation is transient. Chronic oxygen deprivation severely diminishes fibroblast activity. Further, oxygen is believed to strongly induce fibroblast differentiation into myofibroblasts by turning on specific intracellular signaling pathways.[10] These myofibroblasts in turn contribute to wound closure through contraction.[11]

Nonetheless, more oxygen is not always better for tissue repair. Humans are adapted to respond constructively to the relative hypoxia at the healing edge of many wounds. Hypoxia has been traditionally regarded as an important stimulus for fibroblast growth and angiogenesis. Both adaptive responses occur through the activation of HIF-1, which regulates many processes required for wound repair during ischemia in the damaged tissue.

Hypoxia-inducible factor-1

HIF-1, composed of a dimer of an alpha (HIF-1α) and a beta (ARNT or HIF-1β) subunit, is present in all nucleated cells of metazoan organisms. The subunits of HIF-1 bind together to acquire transcriptional properties, allowing it to regulate the transcriptional activity of hundreds of genes that promote cell survival in hypoxic conditions. Considered to be a master regulator of oxygen homeostasis, HIF-1 acts predominantly under hypoxic conditions. The HIF-1β subunit is constitutively

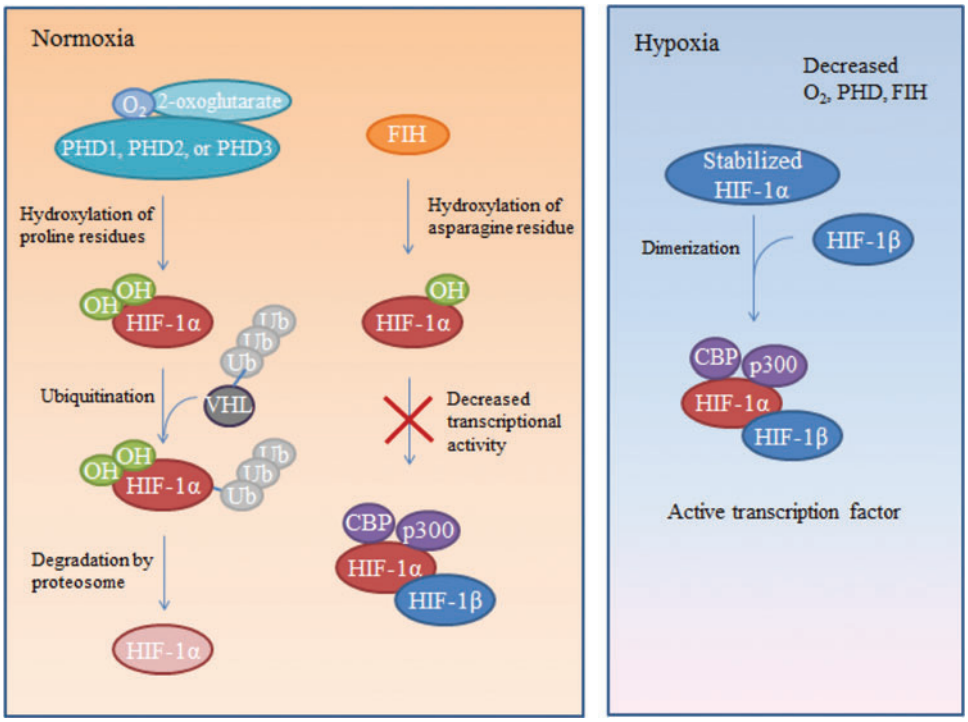

Figure 3. Hypoxia-inducible factor-1 (HIF-1) regulation during hypoxia and normoxia. During normoxia HIF-1α is degraded by a major pathway through PHD1, 2 or 3, and by a minor pathway through FIH. PHD hydroxylates select proline residues on HIF-1α causing a conformational change that allows ubiquitination by a VHL ubiquitin–protein ligase complex followed by proteosomal degradation. FIH hydroxylates asparagine residues within HIF-1α, preventing interaction between HIF-1α and its coactivators. During hypoxia, HIF-1α is stabilized due to reduced oxygen, which is required for PHD binding, and reduced PHD and FIH levels. The stabilized HIF-1α subunit binds to HIF-1β subunit to form an active transcription factor. Active HIF-1 then binds to coactivators CBP and p300 to promote expression of downstream target genes.To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

expressed whereas the HIF-1α subunit is oxygen regulated.[12] Regulation of HIF-1 is thus determined by the rapid posttranslational degradation or stabilization of the HIF-1α subunit (Fig. 3).[13]

In normal tissue oxygen conditions, HIF-1α is rapidly and continuously degraded following translation.[14] Tissue hypoxia, however, induces a sustained increase in the expression of HIF-1α. This is mainly due to oxygen-dependent hydroxylation of HIF-1α amino acid proline residues, Pro402 and Pro564, in a reaction catalyzed by HIF prolyl-4-hydroxylases (PHDs) 1, 2, and 3 in presence of its cofactors, oxygen and 2-oxoglutarate.[15] Hydroxylation of the amino acid residues results in conformational changes that allow HIF-1α ubiquitination by a Von Hippel-Lindau (VHL) ubiquitin–protein ligase complex followed by proteosomal degradation.[15]

In addition to hydroxylation by PHDs, HIF-1α is also regulated by factor inhibiting HIF-1 (FIH) in an oxygen-dependent manner. HIF-1α has two transactivation domains, TAD-N and TAD-C, which bind to coactivators, such as CREP-binding protein (CBP) and p300.[16] In the presence of oxygen, FIH hydroxylates an asparagine residue within TAD-C, preventing interaction between HIF-1α and the transcriptional coactivators.[17] This results in decreased transcriptional ability of HIF-1. Regulation by FIH is believed to be a secondary regulatory mechanism for HIF-1α proteins that evade the primary PHD-mediated regulation.[18]

Levels of HIF-1α protein increase exponentially as oxygen concentration declines.[19] Under hypoxic conditions, HIF-1α degradation is limited by reduced presence of oxygen cofactor and by the depletion of PHDs and FIH. Stabilized HIF-1 is then activated by phosphorylation, allowing dimerization of HIF-1α with HIF-1β. The active transcription factor translocates to the nucleus where it binds to the *cis*-acting hypoxia regulatory element in the promoter region of HIF-inducible genes along with transcriptional coactivators p300 and CBP.[20]

DISCUSSION

HIF-1 in wound healing

In normal cutaneous wounds, HIF-1 is important for enhancement of appropriate inflammatory and angiogenic responses (Fig. 4).

In line with its role in mediating adaptation to hypoxia, HIF-1 plays a key role in modulating inflammatory responses, one of the most common causes of tissue hypoxia.[21] Inflamed tissues and

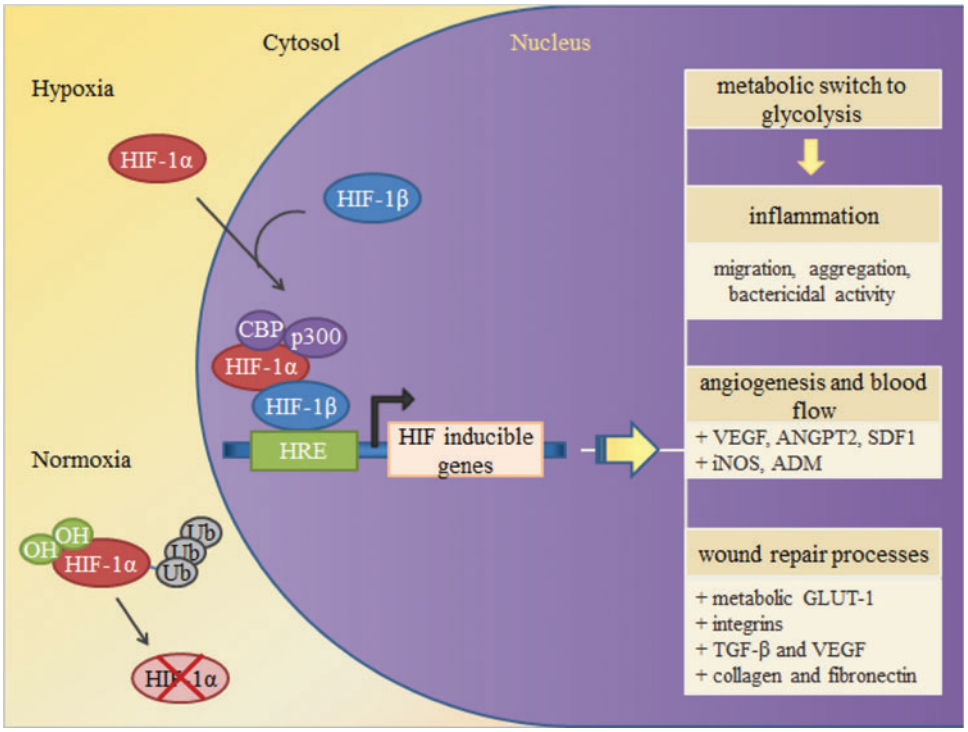

Figure 4. Activation of HIF-1. Under hypoxia, HIF-1α is stabilized and binds to the HIF-1β subunit to form the active transcription factor HIF-1. HIF-1 translocates to the nucleus where it binds to hypoxia regulatory elements (HREs) within the promoter region of HIF-1-inducible genes along with coactivators p300 and CBP to promote expression of HIF-1 target genes, such as *VEGF* and *SDF-1*. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

the areas surrounding external wounds are characterized by low concentrations of oxygen. Effector cells of the innate immune system must be capable of responding to these difficult conditions in order to maintain activity and viability. Many studies have shown that neutrophils and macrophages are highly reliant on anaerobic glycolysis for adenosine triphosphate production.[22] Neutrophils utilize different glucose sources for different cellular functions; motility, chemotaxis, and aggregation are fueled by the glycolytic pathway.[23] Myeloid cells on the other hand rely almost entirely on anaerobic respiration and typically maintain anaerobic respiration even in highly oxygenated environments. Not surprisingly, HIF-1 can influence the cellular inflammatory response through its control of the metabolic switch to glycolysis.[24] Results from studies that employ HIF-1α-gene-knockout mice have demonstrated that HIF-1α is an essential regulator of energy metabolism, migration, aggregation, and bactericidal activity in inflammatory cells.[11] Functional inactivation of HIF-1α results in greatly decreased motility, invasiveness, and adhesion in isolated macrophages.[22] In addition, it has been shown that HIF-1α expression plays a pivotal role in promoting the differentiation of myeloid cells into monocytes and macrophages.[25]

HIF-1 activation is also a primary stimulus of angiogenesis, the formation of new blood vessels from pre-existing vessels, in both physiological and pathological conditions.[26] Angiogenesis is regulated by a balance between stimulatory and inhibitory growth factors and by physiological stresses such as alterations in oxygen levels.[27] Hypoxia stimulates the growth and remodeling of the existing vasculature. This enhances blood flow to oxygen-deprived tissues through the activation of several HIF target genes. These include vascular endothelial growth factor (*VEGF*), a potent angiogenic factor, as well as other angiogenic growth factors, such as angiopoietin 2 and stromal cell-derived factor 1 (*SDF-1*).[28] *VEGF* acts in a paracrine manner to stimulate differentiation of angioblasts, proliferation and survival of endothelial cells, and sprouting of new blood vessels.[29] In addition, hypoxic stabilization of HIF-1 causes the expression of genes that control vascular tone and blood flow, such as inducible nitric oxide synthases and adrenomedullin.[27] The overall result of the activation of these genes is stimulation of neovascularization and remodeling to enable adequate oxygen delivery to hypoxic tissues. Regulation of angiogenesis by HIF-1 is thus critical for reinstatement of oxygen and nutrient delivery to the healing site, and enhances cell survival. Without HIF-1 activation, continued vascular disruption can lead to cessation of blood flow, ischemia, hypoxia, and tissue necrosis.

In addition to the genes mentioned, HIF-1 also transcriptionally upregulates expression of many other genes that enhance the wound repair process, such as metabolic proteins (*GLUT-1*), adhesion proteins (integrins), soluble growth factors (*TGF-β* and *VEGF*), and ECM components (type I collagen and fibronectin) (Table 1). For these reasons, HIF-1 is generally viewed as a positive regulator of wound healing and a potential regulator of tissue fibrosis.

Pathological wound healing

Wound healing inherently involves a complex series of interactions between cells, chemical signals, ECM proteins, and microenvironments. Any alteration to these precise events can lead to defective wound healing and abnormal scar formation. Clinically, abnormal wound healing falls into two main categories: fibroproliferative disorders and chronic wounds. Both can be caused by abnormal HIF-1 expression. In fibroproliferative disease, overexpression of HIF-1 correlates to an increase in the expression of profibrotic factors associated with excessive production of collagenous matrix. Conversely, HIF-1 deficiency in ischemic wounds commonly found in diabetic or elderly patients correlates with reduced adaptive responses to hypoxia and impaired healing.[1,30]

HIF-1 overexpression

Fibroproliferative disorders, which include keloid and hypertrophic scars, are the result of an excessive fibrogenic response that outstrips remodeling.[31]

Table 1. *Target genes of the hypoxia-inducible factor regulatory pathway*

Angiogenesis	*Erythropoiesis*
Transforming growth factor-beta 3 (*TGF-β3*)	Erythropoietin (*EPO*)
Vascular endothelial growth factor (*VEGF*)	
	Iron Metabolism
Cell Growth and Survival	Ceruloplasmin
Insulin-like growth factor 2 (*IGF-2*)	Transferrin (*Tf*)
Transforming growth factor-alpha (*TGF-α*)	
	Matrix Metabolism
Glucose Metabolism	Collagen prolyhydroxylase
Adenylate kinase 3	Matrix metalloproteinases (*MMP*s)
Aldolase A, C	Plasminogen activator
Carbonic anhydrase 9	receptors and inhibitors
Enolase 1	
Glucose transporters (*GLUT*s) 1, 3	*Vascular Tone*
Hexokinase 1, 2	Adrenergic receptor (α_{1b})
Lactate dehydrogenase A	Adrenomedullin
Phosphoglycerate kinase 1	Endothelin
Phosphofructokinase L	Heme oxygenase 1
Pyruvate kinase M	Nitric oxide synthase 2

Fibroproliferative lesions are often painful, itchy, and prone to contracture development.[32] Keloid and hypertrophic scars are raised skin scars characterized by a constitutively active proliferative phase and by a highly vascular structural make-up, with excessive deposition of mostly type I collagen.[33] Hypertrophic scars contain distinct collagen bundles and high myofibroblast density, an important feature in provoking contractures around areas prone to mechanical stress.[34] Keloids on the other hand deposit large amounts of thick disorganized collagen fibers and seldom provoke contracture. Keloids are further distinguished by aggressive growth and ability to exceed the margins of the original lesion.[35] Keloids are particularly resistant to medical management, and can develop from wounds of all sizes. Hypertrophic scars develop after deep or extensive cutaneous insults, such as burns and surgical incisions, and can be treated through grafting and surgical corrections. Biopsies of these fibroproliferative lesions often demonstrate elevated levels of growth factors and upregulation of their receptors.[36] Consistent elevation of HIF-1α protein levels resulting from increased transcription and translation, followed by stabilization of the HIF-1α subunit, is observed in keloid and scleroderma tissues compared with normal skin and has been linked with increases in expression of factors that may help to drive fibrosis, such as TGF-β1, thrombospondin-1, PAI-1, and VEGF.[37]

HIF-1 deficiency

Chronic wounds on the other hand are characterized by persistent inflammation, lack of a proliferative phase, and increased proteolytic activity preventing the sufficient deposition of matrix components.[38] The vast majority of cutaneous chronic wounds present clinically as diabetic, venous, and pressure ulcers.[39] In contrast to acute hypoxia, chronic ischemia has a net inhibitory effect on a number of pivotal fibroblast functions in the skin. Using an ischemic limb model, persistent hypoxia was shown to reduce production of collagenous matrix and retard granulation tissue formation as well as reduce contraction in a cutaneous wound.[40] On the other hand, defective granulation tissue formation and delayed dermal regeneration in diabetic mice wounds were improved by increasing the stabilization of HIF-1.[1] Additionally, HIF-1α gene transcription was found to be impaired in dermal fibroblasts of aged mice resulting in delayed angiogenic responses in ischemic wounds.[41] Lastly, constitutive expression of HIF-1 through gene therapy has been found to improve wound healing in aged diabetic mice.[42] Results from these and other studies suggest that impaired healing in chronic ischemic wounds is partly caused by defective HIF-1 signaling and a reduced ability to respond to local tissue hypoxia.[1]

Both aberrant scarring and chronic wounds lead to significant complications for patients, who suffer from chronic pain, permanent functional loss, and reduced quality of life. Therapies currently available to address aberrant wound healing are often insufficient to ensure satisfactory wound healing. There is thus an urgent need for further investigation into novel therapeutics.

There is considerable evidence that HIF-1α signaling is impaired in diseases that are characterized by impairments in wound healing, such as diabetes and aging.[43–45] In human cells and preclinical models of diabetes this defect can be traced to a specific methylglyoxalation event on an arginine residue in the transcriptional cofactor p300 that prevents assembly of the transcriptome and activation of all HIF-1α responsive genes, such as VEGF, SDF-1, or GLUT-1.[43] Conversely in aging, constitutive upregulation of all three prolyl hydroxylases results in the robust degradation of HIF-1α and impaired activation of the hypoxia response.[45] In either case the end result is the same, namely, a failure of the wound to upregulate VEGF or convert to anaerobic metabolism, leading to impaired wound healing. Importantly these defects appear to be partially reversible, which provides therapeutic opportunities to improve wound healing in these conditions.[43] However, other studies have indicated that HIF-1 stabilization may actually lead to delayed wound healing. For instance, published studies have shown that HIF-1α stabilization in ischemic wounds leads to induction of miR-210, which in turn silences its target, E2F3. Downregulation of E2F3, a key regulator of cellular proliferation, in keratinocytes has been shown to lead to impaired re-epithelialization and delayed wound closure.[46] These results attest to the complexity of the HIF signaling pathway and to the need for further investigation in order to develop targeted and clinically effective therapies.

HIF-1 therapeutics

Wound care strategies currently available to patients remain far from ideal, owing mostly to our limited understanding of the complex mechanics involved in the healing process. A better understanding of the complex role of hypoxia in scarring tissues and chronic wounds will aid in the development of pharmaceutical agents that can redress the detrimental outcomes often seen in insufficient repair and scarring.

Both positive and negative regulators of HIF-1 provide important potential therapeutic targets for drugs that can be used to manipulate HIF-1 expression in pathological conditions where overexpression or deficiency in HIF-1 correlates with pathogenesis. For instance, PHD inhibitors can stabilize HIF-1 and subsequently drive expression of downstream HIF-1 target genes.[1] These inhibitors have been useful in improving healing of diabetic ischemic wounds in mice and are now currently undergoing clinical trials for treatment of several human-ischemia-based conditions.[47] Drugs that inhibit HIF-1 hydroxylation have also been found to be beneficial in improving wound healing in diabetic mice.[48] Lastly, correction of HIF-1 deficiency with electroporation-facilitated gene therapy has been shown to improve wound healing, enhance angiogenesis, and increase circulating angiogenic cells in diabetic aged mice.[49] However, it is important to note that none of these targeted therapies, such as the PHD-based compounds, have yet made the full transition to clinical use. One of the major challenges in developing clinically effective PHD-based therapies lies in developing a sufficiently selective compound. This endeavor is complicated by the complexity of the HIF signaling system, in which multiple HIF and PHD isoforms are involved in regulating the expression of a large variety of genes.[47]

TAKE-HOME MESSAGES

- There is an urgent need to improve therapeutic options for the 6.5 million Americans suffering from chronic wounds.
- HIF-1 plays a major role in wound healing through its role as the main regulator of oxygen homeostasis.
- HIF-1 is a transcription factor that is stabilized during hypoxia to induce the expression of hundreds of downstream target genes, many of which have important roles in the wound healing process.
- Deficiency of HIF-1 can lead to nonhealing chronic wounds whereas overexpression of HIF-1 can contribute to fibrosis and excessive scarring.
- Modulation of HIF-1 expression through both positive and negative regulators may provide a promising avenue for novel therapeutics aimed at improving wound healing.
- However, the complexity of the HIF signaling pathway and existence of multiple HIF and PHD isoforms present a continuing challenge to the development of clinically effective targeted HIF therapies.

In addition, whether stabilization of HIF-1 and upregulation of downstream effectors translate to functional improvements in wound closure also depends on whether other fundamental prerequisites, such as a threshold level of tissue oxygenation, are present to fuel the healing process. This is of particular concern for patients with wounds that are afflicted by extreme chronic hypoxia. Chronic ischemia has several important consequences for wound healing including reduced cell responsiveness to growth factors.[50] Treatment with hyperbaric (HBOT, hyperbaric oxygen therapy) or topical oxygen is one of multiple approaches currently being utilized to improve healing of these wounds. HBOT, the systemic delivery of oxygen, has been found to benefit wound healing in certain conditions.[51] Further, HBOT may work synergistically with growth factors to improve wound healing outcomes. Studies have shown that HBOT in conjunction with growth factors (PDGF and TGF-β1) improves healing of ischemic wounds.[52] However, as susceptibility to oxygen toxicity is variable and dependent on individual expression of genes that encode antioxidant proteins, it is possible that certain patients are predisposed to respond poorly to the massive increase in tissue pO_2 following HBOT. In those patients the increased oxidative stress could result in molecular responses such as growth arrest and decreased wound healing. Therefore, it has been suggested that topical oxygen is a better alternative to HBOT. Not only is topical oxygen potentially less toxic, but unlike HBOT, topical oxygen can be given at home and is less expensive.[53] As topically applied oxygen is able to modestly increase the pO_2 of superficial wound tissue, it may prove beneficial in cases where hypoxia of the superficial wound tissue is a key hurdle to repair processes. However, the effects of supplemental oxygen therapy in wound healing are not fully understood outside of its general beneficial effects on impeding wound infection (Table 2). Not much is known about how supplemental oxygen affects wound healing systemically or through local perfusion near the wound site. Elucidating the precise role of oxygen in tissue repair is complex and further investigation is required.

Table 2. *Comparison of topical versus hyperbaric oxygen therapy*

Topical Oxygen	*Hyperbaric Oxygen*
Direct delivery of oxygen to superficial wound tissue	Oxygen is delivered by vascular system
Oxygen delivery is independent of vasculature	Oxygen delivery dependent on good vasculature
Reduced risk of multiorgan oxygen toxicity	Multiorgan oxygen toxicity may occur
Oxygenates wound tissue at 1 atm	Oxygenates blood at 2–3 atm
Portable devices are available	Specialized facilities and personnel required
Less expensive	Higher cost
Limited research on outcomes	Greater number of studies into outcomes
Limited understanding of mechanism	Limited understanding of mechanism

SUMMARY

Hypoxia influences every aspect of wound healing, from fibroblast proliferation to tissue growth and remodeling. Local oxygen gradients and HIF-1 in normal healing are likely to be important for maintaining good angiogenic responses and granulation tissue formation by potentiating cell migration,[54] proliferation, survival, growth factor release, and matrix synthesis in the early phases of healing. A failure to respond to hypoxic stimuli due to HIF-1 deficiency has been shown to propagate chronic hypoxia, which appears to contribute to the formation of chronic wounds, though high levels of HIF-1 have also been found in ischemic wounds. In contrast, consistent HIF-1 accumulation in fibrotic disease leads to increased myofibroblast differentiation and excessive matrix production. Based on all of the discussed points, it is strongly suggested that targeting HIF-1 has several important clinical implications for tissue repair, but that the immense intricacy of the HIF-1 pathway presents a considerable challenge to any such endeavor.

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Abbreviations and Acronyms

ADM = adrenomedullin
ANGPT2 = angiopoietin 2
ARNT = aryl hydrocarbon receptor nuclear translocator
cAMP = cyclic adenosine monophosphate
CBP = CREB-binding protein
CREB = cAMP response element-binding protein
ECM = extracellular matrix
EGF = epidermal growth factor
EPO = erythropoietin
FGF = fibroblast growth factor
FIH = factor inhibiting HIF-1
GLUT = glucose transporter
HBOT = hyperbaric oxygen therapy
HIF = hypoxia-inducible factor
HRE = hypoxia regulatory element
IGF = insulin-like growth factor
IL-1 = interleukin 1
iNOS = inducible nitric oxide synthase
MMP = matrix metalloproteinase
PAI-1 = plasminogen activator inhibitor-1
PDGF = platelet-derived growth factor
PHD = prolyl-4-hydroxylase
PMN = polymorphonuclear neutrophil
SDF-1 = stromal cell-derived factor 1
TAD = transactivation domain
Tf = transferrin
TGF = transforming growth factor
VEGF = vascular endothelial growth factor
VHL = Von Hippel-Lindau