Review Article

Microenvironment of diabetic foot ulcers: Implications for healing and therapeutic strategies

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Diabetic foot ulcers (DFUs) are a common yet serious complication in individuals with diabetes, often presenting as chronic, nonhealing wounds that significantly impair quality of life. The healing process of DFUs is largely influenced by the local microenvironment, which encompasses factors such as hypoxia, inflammation, and the involvement of various cell types. Poor blood circulation in the affected area results in hypoxia, compromising cellular function and restricting nutrient supply, thereby delaying wound healing. In addition, chronic inflammation disrupts immune system balance, with excessive pro-inflammatory cytokines not only failing to facilitate tissue repair but also exacerbating tissue damage. Moreover, key cell types, including fibroblasts, keratinocytes, and macrophages, play crucial roles at different stages of the healing process, contributing to collagen production and skin regeneration. A comprehensive understanding of the complex dynamics within the DFU microenvironment is essential for developing more precise therapeutic approaches, such as advanced drug delivery systems and bioactive materials, aimed at promoting wound healing and reducing the risk of recurrence.

Key words: Diabetic foot ulcers, hypoxia, inflammation, microenvironment, wound healing

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INTRODUCTION

Diabetic foot ulcers (DFUs) pose a significant health challenge for individuals with diabetes, resulting in a considerable burden on healthcare systems.[1] These chronic wounds often lead to serious complications, such as infections, prolonged hospitalization, and even lower limb amputation. The prevalence of DFUs is alarming, with studies suggesting that up to 25% of diabetic patients will develop a foot ulcer during their lifetime.[2] The multifactorial nature of DFUs makes them particularly challenging to treat, as various intrinsic and extrinsic factors interplay to impede the healing process.[3]

A critical determinant of healing outcomes in DFUs is the local microenvironment, which is markedly different from that of acute wounds.[4] In contrast to acute wounds, which typically progress through a well-defined healing cascade, DFUs often exhibit a persistent inflammatory response characterized by elevated levels of pro-inflammatory cytokines and immune cell infiltration.[5] This prolonged inflammation results in a cycle of tissue damage and repair that can become dysregulated, ultimately delaying healing.

Another significant aspect of the DFU microenvironment is hypoxia, which arises from inadequate blood flow and perfusion.[6] Hypoxia not only limits the availability of oxygen and essential nutrients but also disrupts the normal functioning of key cellular players involved in healing, including fibroblasts and keratinocytes.[7] Furthermore, impaired angiogenesis – the formation of

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new blood vessels – exacerbates the hypoxic conditions and hinders the delivery of healing factors to the wound site.[8,9]

The cellular composition of the DFU microenvironment is complex and includes various cell types, such as fibroblasts, keratinocytes, macrophages, and endothelial cells.[10] Each of these cells plays distinct yet interconnected roles in the healing process. For instance, fibroblasts are responsible for collagen deposition and extracellular matrix (ECM) remodeling, while keratinocytes are essential for re-epithelialization. Macrophages, on the other hand, not only mediate inflammation but also orchestrate the transition from inflammation to repair by secreting growth factors that promote tissue regeneration.[11]

Biochemical factors, including growth factors and cytokines, further modulate the healing process by influencing cell proliferation, migration, and ECM synthesis.[12] The ECM itself provides a structural framework that supports cellular attachment and migration, facilitating the healing process. Dysregulation of these biochemical signals can lead to a failure in the proper healing response, prolonging the ulcerative state.[13,14]

In this review, we focus on the intricate local microenvironment of DFUs, aiming to elucidate how these cellular and biochemical factors interact to contribute to delayed healing. We will explore the specific cellular components present in the DFU microenvironment, the impact of chronic inflammation and hypoxia, and the critical role of the ECM in wound healing. By understanding these dynamics, we can identify potential therapeutic targets that may enhance healing and improve outcomes for patients suffering from DFUs.

CELLULAR COMPOSITION OF THE DIABETIC FOOT ULCER MICROENVIRONMENT

The cellular landscape of DFUs is intricate and multifaceted, composed of a diverse array of cell types that interact dynamically to mediate the healing process.[10] Fibroblasts are pivotal in synthesizing and remodeling the ECM, which provides structural support and regulates cellular behavior.[11] They produce key ECM components, such as collagen, elastin, and proteoglycans, which are essential for maintaining tissue integrity and facilitating cell migration during the healing process.[15] In DFUs, fibroblast activity is often diminished due to the hostile microenvironment characterized by chronic inflammation and hypoxia, leading to inadequate ECM deposition and impaired wound closure.[16]

Keratinocytes, which are primarily responsible for re-epithelialization, also play a critical role in DFU healing.[17] They migrate across the wound bed to cover the defect, and their proliferation is influenced by growth factors present in the microenvironment.[18] In the context of DFUs, keratinocyte function can be impaired by the persistent inflammatory milieu and the lack of appropriate signaling cues, which can delay the re-epithelialization process.[19]

Macrophages, another key cellular component, have a dual role in the healing process.[20] These cells can exist in different polarization states: M1 macrophages, which are pro-inflammatory, and M2 macrophages, which promote tissue repair and resolution of inflammation. In DFUs, an accumulation of M1 macrophages can perpetuate inflammation, leading to tissue damage and impaired healing.[21] Conversely, M2 macrophages facilitate the transition to a regenerative state through the secretion of growth factors and cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which are essential for tissue repair and angiogenesis.[18] The ability to modulate macrophage polarization within the DFU microenvironment could therefore provide a novel therapeutic strategy to enhance healing by promoting the shift from the pro-inflammatory to the reparative phase.[22]

Endothelial cells are also integral to the healing process, as they are critical for angiogenesis—the formation of new blood vessels. In DFUs, impaired angiogenesis often results from chronic hypoxia and inflammation, further limiting oxygen and nutrient supply to the healing tissue.[23,24] The interplay between endothelial cells and macrophages is significant; for example, macrophages can secrete angiogenic factors that stimulate endothelial cell proliferation and migration, thereby facilitating new blood vessel formation.[25,26] Table 1 summarizes the roles of different cell types involved in the healing process of DFUs.

Impact of inflammation on wound healing

Inflammation plays a fundamental role in the wound healing process, yet its impact can be a double-edged sword. Acute inflammation is necessary for clearing debris, preventing infection, and initiating the healing cascade.[27] In contrast, chronic inflammation, which is frequently observed in DFUs, can significantly hinder the healing process. Persistent inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6) are elevated in DFUs, disrupting the normal healing cascade.[28] These cytokines can delay re-epithelialization, inhibit fibroblast function, and impede angiogenesis, ultimately leading to prolonged wound healing and an increased risk of complications.[29]

Research indicates that targeting inflammatory pathways may improve healing outcomes in DFUs. For instance, the

Table 1: Cellular dynamics in the healing process of diabetic foot ulcers

Cell type	Role in healing	Challenges in DFUs	Key interactions
Fibroblasts	Synthesize and remodel the ECM Produce collagen, elastin, and proteoglycans for tissue integrity and cell migration	Activity often diminished due to chronic inflammation and hypoxia Leads to inadequate ECM deposition and impaired wound closure	Interacts with keratinocytes and macrophages to regulate healing processes
Keratinocytes	Responsible for re-epithelialization Migrate to cover the wound defect; proliferation influenced by growth factors	Function can be impaired by persistent inflammation and lack of signaling cues Delays the re-epithelialization process	Influenced by growth factors secreted by fibroblasts and macrophages
Macrophages	Dual roles: M1 (pro-inflammatory) and M2 (promoting tissue repair) M2 macrophages secrete growth factors (e.g., IL-10, TGF-β) essential for tissue repair and angiogenesis	Accumulation of M1 macrophages perpetuates inflammation and tissue damage Need for modulation of polarization to enhance healing	M1 macrophages can inhibit endothelial cell function; M2 macrophages promote angiogenesis and recruit fibroblasts
Endothelial cells	Critical for angiogenesis (formation of new blood vessels)	Impaired angiogenesis due to chronic hypoxia and inflammation Limits oxygen and nutrient supply to healing tissue	Interacts with macrophages, which can secrete angiogenic factors to stimulate endothelial cell proliferation and migration

ECM=Extracellular matrix; TGF-β=Transforming growth factor-beta; DFUs=Diabetic foot ulcers

use of anti-inflammatory agents such as corticosteroids or novel biologics could potentially modulate the inflammatory response, promoting a shift toward a more regenerative environment.[30,31] In addition, the application of localized therapies that can reduce inflammation at the wound site, such as cytokine inhibitors or mesenchymal stem cells, may facilitate a transition from the chronic inflammatory phase to the proliferative phase of healing.[32]

Furthermore, the concept of inflammation resolution is gaining traction as a critical aspect of wound healing. Effective resolution of inflammation involves the transition from pro-inflammatory signals to anti-inflammatory signals, allowing for the restoration of tissue homeostasis. Strategies that enhance the resolution phase of inflammation, such as the administration of resolvins or protectins, may hold promise for promoting healing in chronic wounds.[33]

Hypoxia and its role in diabetic foot ulcers

Hypoxia is a prevalent feature of DFUs, primarily resulting from reduced blood flow and impaired angiogenesis.[34] Oxygen is crucial for cellular metabolism, and it plays a significant role in the production of essential growth factors that drive the healing process. Under hypoxic conditions, the expression of hypoxia-inducible factor 1-alpha (HIF-1α) is increased, which orchestrates a range of adaptive responses, including angiogenesis and glycolysis.[35,36] While HIF-1α is essential for initiating reparative processes, chronic hypoxia can lead to maladaptive responses, promoting fibrosis and inhibiting effective healing.[37]

This chronic hypoxia presents an even greater challenge in DFUs, as it negatively affects the function of key cellular players that are essential for healing. For example, fibroblasts, which are responsible for collagen production and ECM remodeling, show reduced functionality under prolonged low-oxygen conditions, leading to inadequate ECM deposition and impaired wound closure.[38] Moreover, hypoxic conditions can exacerbate the inflammatory response by promoting the recruitment of inflammatory cells to the wound site, further complicating the healing process.[39,40]

Strategies aimed at alleviating hypoxia may offer promising avenues for enhancing healing in DFUs. For example, hyperbaric oxygen therapy has been shown to improve tissue oxygenation and stimulate angiogenesis, leading to accelerated wound healing in chronic ulcers. In addition, the application of oxygen-releasing materials or the use of topical agents that enhance oxygen delivery to the wound site may also improve healing outcomes by restoring oxygen levels and promoting a more favorable microenvironment for cellular activities.[41]

Extracellular matrix dynamics

The ECM is fundamental to wound healing, providing structural support and regulating cellular behavior.[42] In DFUs, the composition and organization of the ECM are often disrupted, contributing to impaired healing.[43] Key components of the ECM, such as collagen and glycosaminoglycans, are essential for maintaining tissue integrity and facilitating cellular migration.

In DFUs, the deposition of collagen is frequently inadequate, leading to the formation of weak and disorganized scar tissue.[44] Moreover, the degradation of the ECM is frequently accelerated due to elevated matrix metalloproteinases and reduced levels of tissue inhibitors of metalloproteinases, resulting in a net loss of ECM components. This imbalance contributes to a dysfunctional healing response and increases the risk of ulcer recurrence.[45]

To address these ECM-related challenges, modulating ECM dynamics through the application of biomaterials

or growth factors may provide a potential therapeutic approach to enhance tissue regeneration. For instance, the use of collagen-based dressings or scaffolds can provide a supportive environment for cell attachment and migration while delivering bioactive agents to the wound site.[46] Recent advances in tissue engineering, including the use of three-dimensional (3D) bioprinting and smart biomaterials, hold promise for creating an optimal ECM environment conducive to healing.[47] These technologies allow for the fabrication of personalized scaffolds that mimic the native tissue architecture and biochemical composition, thereby enhancing the regenerative potential of the wound-healing process.

Therapeutic approaches targeting the microenvironment

Given the complexity of the DFU microenvironment, multifaceted therapeutic approaches are necessary to promote effective healing. Strategies such as local delivery of growth factors can enhance specific aspects of the healing process. For example, the administration of vascular endothelial growth factor (VEGF) can stimulate angiogenesis, while fibroblast growth factor can promote fibroblast proliferation and ECM deposition.[48,49]

Nanotechnology also offers innovative solutions for targeted drug delivery in DFUs.[48] Nanocarriers can encapsulate therapeutic agents, facilitating controlled release at the wound site and enhancing bioavailability. By modifying the surface characteristics of nanocarriers, it is possible to achieve selective targeting of specific cell types within the microenvironment, improving the efficacy of treatment.

Advanced wound dressings play a crucial role in maintaining a moist environment, which is essential for promoting healing and preventing desiccation of the ulcer.[50] These dressings can incorporate bioactive agents, such as antimicrobial peptides or growth factors, to further enhance their therapeutic properties.[51] In addition, incorporating smart materials that respond to changes in the wound microenvironment (e.g. pH or temperature) can optimize drug release profiles, ensuring that therapeutic agents are delivered precisely when and where they are needed.

Furthermore, stem cell therapy has emerged as a promising option to replenish damaged tissue and modulate the microenvironment.[13] Stem cells possess the ability to differentiate into various cell types involved in wound healing and can secrete a range of bioactive factors that promote tissue regeneration.[15,52] Future research should focus on integrating these therapeutic modalities to develop comprehensive treatment plans tailored to individual patient needs. Personalized approaches that consider the unique characteristics of each DFU, including its size, depth, and surrounding microenvironment, will be essential for optimizing healing outcomes and reducing recurrence rates. Table 2 summarizes the intricate relationship between inflammation, hypoxia, and ECM dynamics in DFUs, highlighting potential therapeutic approaches for improved wound healing.

DISCUSSION

The local microenvironment of DFUs is multifaceted and critical for determining healing outcomes.[53] A comprehensive understanding of this microenvironment, encompassing cellular components, biochemical factors, and physical characteristics, is essential for developing effective therapeutic strategies. DFUs represent a unique challenge due to their chronic nature, where the interplay between various factors often leads to delayed healing and increased risk of complications, such as infections and amputations.[54]

The cellular composition of the DFU microenvironment is a fundamental aspect that dictates healing trajectories.[55] Fibroblasts and keratinocytes are integral for ECM synthesis and re-epithelialization, respectively, while macrophages

Table 2: Impact of inflammation, hypoxia, and extracellular matrix dynamics on wound healing in diabetic foot ulcers

Aspect	Description	Key points
Inflammation	Inflammation plays a crucial role in wound healing, with acute inflammation being beneficial while chronic inflammation hinders the process	Chronic inflammation in DFUs is marked by elevated cytokines (e.g., TNF-α, IL-1β) Anti-inflammatory therapies may improve healing outcomes
Hypoxia	Hypoxia, due to reduced blood flow and impaired angiogenesis, hampers the wound healing process by affecting key cellular functions	Chronic hypoxia can lead to maladaptive responses and exacerbate inflammation Strategies to alleviate hypoxia include hyperbaric oxygen therapy and topical agents
ECM	The ECM is vital for providing structural support and regulating cellular behavior, with its dynamics significantly impacting healing outcomes	Impaired collagen deposition and accelerated ECM degradation occur in DFUs Modulating ECM dynamics with biomaterials and growth factors may enhance healing
Therapeutic approaches	Multifaceted strategies, including growth factor delivery, nanotechnology, advanced dressings, and stem cell therapy, are necessary to optimize healing in DFUs	Local delivery of VEGF and FGF can stimulate angiogenesis and fibroblast activity Smart materials and nanocarriers enhance treatment efficacy

VEGF=Vascular endothelial growth factor; ECM=Extracellular matrix; DFUs=Diabetic foot ulcers; FGF=Fibroblast growth factor; TNF=Tumor necrosis factor

serve as central regulators of inflammation and tissue repair.[56] The dual role of macrophages is particularly noteworthy; the transition from pro-inflammatory M1 macrophages to reparative M2 macrophages is critical for moving the wound from a chronic inflammatory state to a regenerative phase.[57] Research shows that manipulating macrophage polarization can significantly impact healing outcomes, suggesting that therapies aimed at promoting this shift could enhance the reparative process.[58] For instance, the application of M2-inducing cytokines or the use of nanocarriers to deliver these factors locally could be explored as potential therapeutic avenues.[59]

Inflammation is a double-edged sword in the wound-healing process.[60] While acute inflammation is necessary for clearing debris and preventing infection, chronic inflammation, as seen in DFUs, impedes the healing cascade.[61] The persistent presence of inflammatory cytokines such as TNF-α, IL-1 β, and IL-6 has been implicated in delaying re-epithelialization and angiogenesis. These cytokines not only activate pro-inflammatory pathways but also inhibit key processes such as fibroblast proliferation and angiogenesis. Innovative anti-inflammatory strategies, such as the use of monoclonal antibodies or small molecule inhibitors targeting specific inflammatory pathways, may prove beneficial in curtailing excessive inflammation. Furthermore, understanding the precise timing of intervention is crucial; interventions should be tailored to the specific phases of wound healing to maximize their efficacy without compromising necessary inflammatory responses.[62] For example, early-phase inhibition of TNF-α may enhance the transition from inflammation to the proliferative phase, while later-phase treatments could focus on modulating M2 macrophage function to accelerate tissue repair.

Chronic hypoxia in DFUs exacerbates the healing challenge by hindering cellular metabolism and growth factor production.[63] HIF-1α activates a network of genes involved in angiogenesis, metabolism, and cellular survival under hypoxic conditions. Strategies that enhance tissue oxygenation, such as hyperbaric oxygen therapy, are promising; however, their implementation needs to be evaluated in well-designed clinical trials to ascertain efficacy and safety. Furthermore, the development of oxygen-releasing biomaterials could provide localized solutions to hypoxia, offering a controlled release of oxygen at the wound site.[64,65]

The ECM is essential for providing structural integrity and biochemical signals necessary for cellular behavior during healing. In DFUs, the ECM is often disorganized, leading to inadequate support for cellular migration and function. Advances in biomaterials and tissue engineering, particularly the use of 3D bioprinting technologies, could revolutionize DFUs treatment by creating personalized scaffolds that replicate the native ECM.[66] These scaffolds could incorporate bioactive molecules that promote angiogenesis and cellular proliferation, ultimately enhancing the healing process. Research exploring the interactions between ECM components and cellular signaling pathways is vital for developing effective ECM-targeting strategies.

Given the complexity of the DFU microenvironment, multifaceted therapeutic approaches are necessary. Localized delivery systems that utilize nanotechnology can enhance the precision of drug delivery, allowing for targeted treatment of specific cellular populations within the wound. In addition, combining growth factors with advanced wound dressings that maintain a moist environment can significantly improve healing outcomes. The use of stem cell therapy to replenish damaged tissues and modulate the microenvironment also shows promise, although the logistics of implementing such therapies in clinical practice require further exploration.

In conclusion, understanding the complexities of the DFU microenvironment is paramount for developing innovative and effective therapeutic strategies. By addressing the interplay between cellular dynamics, inflammatory processes, hypoxia, and ECM integrity, researchers can pave the way for novel interventions that not only enhance healing outcomes but also improve the overall quality of life for patients suffering from DFUs. Further investigations into the molecular mechanisms regulating each of these factors, along with the development of targeted therapies, will be key to overcoming the challenges presented by DFUs and advancing clinical care in this area.

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Conflicts of interest

There is no conflict of interests.

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