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REVIEW

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Progress of microneedle targeted modulation technology in the reconstruction of immune microenvironment in diabetic wounds

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Abstract

Wound healing in diabetic patients is mainly hindered by a combination of long-term glycosylation, persistent inflammatory response, and immunosuppressive state. The interaction of these factors not only results in considerable prolongation of the wound healing process but also elevates the likelihood of recurrent ulcer development, profoundly affecting patients' quality of life. Traditional treatments, including surgical debridement, anti-infection, dressing application, vascular intervention, and glycaemic control, can only relieve some symptoms. However, they are often ineffective in addressing the underlying cause of impaired wound healing. It is of concern that the importance of the immune microenvironment in diabetic wound healing has not yet been fully appreciated and investigated, and the homeostasis of the immune microenvironment is crucial for promoting cell proliferation, angiogenesis, and tissue repair. However, this microenvironment is often dysregulated in the diabetic state. This paper reviews the key factors leading to dysregulation of the immune microenvironment, including immune cell dysfunction, abnormal cytokine expression, and disruption of key signalling pathways, and introduces an innovative silicone-based microneedle drug delivery method, which takes advantage of microneedle's precise targeting and highly efficient drug loading capacity to deliver drugs with immunomodulatory functions directly to the wound in a sustained manner, activate the corresponding signalling pathways, promote the polarization of M1 macrophages into the M2 phenotype, and stimulate neovascularization, providing a low inflammatory and pro-angiogenic immune microenvironment for diabetic wound healing, which provides a new therapeutic idea and means for diabetic wound healing.

Keywords Microneedle, Diabetic wound, Immune microenvironment, Targeted therapy, Drug delivery

Introduction

Diabetes mellitus (DM) represents a pervasive metabolic condition affecting millions worldwide [1]. Diabetic wounds (DW), particularly diabetic foot ulcers (DFUs), are a common complication. In recent years, statistics have shown that the number of DW patients is growing, and about 19% to 34% of people will develop DFUs [2]. These ulcers are prone to recurrently ruptured and are difficult to heal, posing a significant and growing public health problem [3, 4]. In addition, among diabetic patients, the amputation rate associated with DFU is

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29.3% [3], which places a heavy psychological burden on patients and increases the pressure on families and society [5].

Normal wound healing constitutes a dynamic process encompassing four interconnected stages: haemostasis, inflammation, proliferation, and remodelling [6]. Any disruptions in these processes can impede the wound healing process, resulting in refractory wounds [7]. In diabetic patients, impaired glucose metabolism leads to a persistent high glucose (HG) environment, causing abnormal activation of related signalling pathways and triggering complex pathologies such as impaired immune function, poor blood microcirculation, systemic inflammation, and even cancer, which can significantly delay or even halt the wound healing process [8, 9].

Traditional therapies for diabetic wounds encompass debridement, application of wound dressings, reduction of pressure on the lesion, infection control, management of peripheral vascular issues, and rigorous glucose level regulation. While these approaches address both local and systemic factors, they primarily slow disease progression and have limited effectiveness in promoting wound healing [10]. In recent years, the concept of the immune microenvironment has been extensively applied across various fields, including cancer, chronic infections, inflammation, autoimmune disorders, and transplant rejection [11–14]. The concept of immune microenvironment modulation is also vital for treating chronic wounds, especially DFUs [15]. The diabetic immune microenvironment (DIME) is a highly complex system. It is influenced by the hyperglycaemic metabolic milieu induced by diabetes. This milieu leads to conditions such as ischaemia, hypoxia, hyperinflammation, and persistent infection. The DIME consists of inflammatory factor (e.g. tumour necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β)), immune cells (e.g. neutrophils, macrophages, and lymphocytes), and growth factors, all of which collectively control the inflammatory response at the wound site. Despite individual variability among patients with diabetic wounds, the central role of DIME dysregulation in the difficulty of diabetic wound healing is similar. A number of pathological changes induced by diabetes lead to an imbalance in immune homeostasis, mainly manifested by overactivation of M1 macrophages and impaired polarization towards the M2 phenotype, delayed re-epithelialization due to disruption of the extracellular matrix (ECM) structure, and oxidative stress and amplification of the inflammatory response caused by the high-sugar environment, triggering multiple signalling cascades such as IKK/NF-κB, TGF-β/SMAD, and JAK/STAT through the AGE/RAGE axis, delaying the re-epithelialization process [16–18]. Factors such as concurrent bacterial infection further influence the immune microenvironment and determine the course of diabetic wound repair [15, 19–21]. Although the immune system can promote wound healing through the immune cycle, several challenges prolong the healing of DFUs. These challenges include inadequate local tissue perfusion due to diabetic traumatic vasculopathy, the ineffective migration of cells involved in the initial inflammatory response to the wound site, bacterial infection due to prolonged wound exposure, and loss of neurotrophic nutrition to traumatic tissues due to neuropathy [22]. Addressing these issues and creating a suitable local immune microenvironment for diabetic wounds is essential to improve normal tissue healing [23].

Innovative approaches are being explored to address the limitations of traditional therapies. Microneedle (MN), as a minimally invasive, painless platform and scarless healing for transdermal drug delivery, demonstrates significant potential in enhancing wound healing rates [24]. In conventional intravenous drug delivery, significant drug loss occurs due to degradation and first-pass metabolism, resulting in low target site concentration. However, MNs-based drug delivery efficiently penetrates the stratum corneum to deliver the drug into the targeted skin layers (epidermis, superficial dermis, or deep dermis), ensuring a high local concentration at the wound site. This method avoids gastrointestinal degradation and first-pass metabolism, potentially improving patient outcomes [25]. Some MNs are made of various special materials, including PN-Si and chitosan metal nanocomposites [26–28]. The natural antibacterial properties of MNs enable them to promote wound healing [29, 30]. Some functional microneedles also have antioxidant, pro-angiogenic, and antimicrobial functions, which can target and regulate the immune microenvironment of diabetic wounds, providing a new therapeutic modality to promote diabetic wound healing [31–35].

In this review, we first introduce the key factors that lead to the imbalance of the immune microenvironment in diabetic wounds, including the mechanisms of immune cells and growth factors, in the diabetic pathological environment that affect wound healing. Next, omics technologies are used to reveal the complexity of the DIME, with a focus on the interactions between the different pathways involved in regulating wound healing and the regulation of the DIME by gene editing technology. In addition, this article provides an overview of recent advances in microneedle-mediated regulation of the immune microenvironment, focusing on the multifunctional properties of multifunctional microneedles and their potential to promote wound healing. Finally, the limitations of current microneedle-mediated

immune microenvironment regulation are discussed and future research directions for microneedle therapy are projected.

Review

The key pathogenic factors in the dysregulated immune microenvironment of DW

Immune cell dysfunction

Persistent inflammation stands as a pivotal factor impeding diabetic wound healing [20]. Excessive or stalled inflammatory responses can impede the progression of wound healing from the inflammatory stage to the proliferative and remodelling stages, thus impairing effective wound repair [9]. During the typical inflammatory phase of wound repair, neutrophils and pro-inflammatory macrophages are swiftly recruited to the wound site, tasked with eliminating foreign bacteria and necrotic tissue. This process entails the secretion of numerous products, such as reactive oxygen species (ROS), matrix metalloproteinases (MMPs), and cytokines, which facilitate the healing process through various steps, including receptor activation, signalling cascades, gene transcription and translation, and vesicular transport. T lymphocytes play a bridging role in the body's immune response, coordinating and executing the body's defence mechanisms through interactions with other immune cells [36]. However, in wounds of patients with diabetes mellitus, the transition from the inflammatory to the proliferative phase poses a significant challenge, which significantly contributes to the prolonged non-healing of their wounds [37, 38].

In diabetic pathological conditions, the conversion of M1 macrophages to the M2 type is impeded, which manifests itself as a persistent pro-inflammatory macrophage state, and prolonged and refractory wounds are associated with persistent inflammation, which leads to difficulties in wound healing [16, 39]. Many studies have highlighted that the prolonged infiltration of inflammatory cells, particularly neutrophils, which contribute to the release of inflammatory factors within the wound microenvironment, plays a crucial role in delaying wound healing [40]. Modulating the body's normal inflammatory response can effectively promote the transition of diabetic wounds from the inflammatory phase to the proliferative phase, thereby playing a positive role in diabetic foot wound healing. For instance, Zhou et al. employed a biodegradable hydrogel composed of snail glycosaminoglycan and gelatine methacrylate (AFG/GelMA hydrogel) to markedly enhance chronic wound healing in a type 1 diabetic rat model and a db/db mouse model (carrying the diabetes gene, db) following a single application. This hydrogel effectively captures pro-inflammatory cytokines, significantly reduces inflammation, and induces macrophage polarization towards the M2 phenotype by suppressing their expression via inhibition of the NF-κB signalling pathway. Consequently, this promotes the healing of chronic wounds [41]. Ban et al. have demonstrated the pivotal role of miRNA-497 in regulating the inflammatory response during diabetic wound healing. The in vivo application of miRNA-497 results in a reduction of key pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α. Based on these findings, miRNA-497 has been suggested as a promising therapeutic candidate for the treatment of diabetic wounds [42]. During the final stages of wound healing, the majority of inflammatory cells involved in the repair process undergo apoptosis, differentiation, or other, as yet undefined, mechanisms, leading to their disappearance. This process is contingent upon the severity of the injury to the organism and can vary in duration, ranging from weeks to years [40, 43].

In summary, many immune cells, including neutrophils, macrophages, and T lymphocytes, are important components of the wound immune microenvironment and play important and diverse roles in diabetic wound healing, and their dysfunction and dysregulation is an important cause of delayed diabetic wound healing.

Growth factor imbalance

In recent years, with the advancement of our understanding of wound healing mechanisms, numerous growth factors have been identified as crucial players in the repair process. The disruption of normal levels of several growth factors, notably fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), angiogenic factors including vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), and hypoxia-inducible factor-1α (HIF-1α), has been documented to hinder wound healing in individuals suffering from DFUs and other challenging wounds [44].

FGFs, a class of polypeptide growth factors exhibiting diverse biological activities, are ubiquitous in various organs and tissues. They stimulate the proliferation and differentiation of fibroblasts and play a pivotal role in the process of wound regeneration. FGFs, which are secreted by nearly all tissues, play a vital role in the early growth of fibroblasts. By binding to or activating the tyrosine kinase receptor/fibroblast growth factor receptor (FGFR) on the cell surface, FGFs regulate a multitude of intracellular responses. This regulation is crucial for promoting early angiogenesis and wound repair [45]. However, compromised blood flow can impede the migration of leukocytes, keratinocytes, fibroblasts, and endothelial cells to the wound site, thereby adversely impacting wound healing. Furthermore, the use of FGFs in the treatment of DFUs is constrained by their short half-life, which

necessitates frequent administrations to sustain therapeutic effectiveness. Chronic wounds exhibit a highly proteolytic environment, leading to the rapid degradation of these growth factors [46].

Thus, in diabetic wounds, growth factor function and regulation are often affected by microenvironmental changes. For example, factors such as inadequate perfusion, insufficient oxygen, and a high-protein hydrolysis environment can adversely affect growth factor stability and activity. Understanding the dynamics of these growth factors and their role in the wound can help develop more effective therapeutic strategies, such as targeting repair or enhancing the activity of specific growth factors to improve the wound healing process.

Impaired angiogenesis

Acute vaso-occlusive events are one of the adverse outcomes of the diabetic foot, partly due to the failure to develop an adequate compensatory microvascular system in response to ischaemia [21]. Angiogenesis is a pivotal aspect of the proliferative phase of wound healing. The reduced angiogenesis seen in diabetic wounds is primarily attributed to disruptions in the immune microenvironment during this phase [22]. The focus of regulating the DIME is on how to remodel the vasculature of diabetic wounds and restore local blood supply.

Under the co-stimulation of moderate hypoxia, cytokines, and protein hydrolases, endothelial cells, macrophages, and smooth muscle cells are activated and proliferate to form new vascular networks [47]. Increased expression of miR-133 b has been demonstrated to induce downregulation of epidermal growth factor receptor (EGFR) and affect endothelial cell proliferation and angiogenesis in diabetic wounds [48]. MSC exosome therapy enhances vascular function and angiogenesis in situations where wound-associated endothelial dysfunction results in compromised vascular function. Furthermore, it facilitates tissue repair by suppressing inflammation and remodelling the immune microenvironment at the wound site [49]. Nitric oxide (NO) plays a role in collagen remodelling, and the concentration of endothelial nitric oxide synthase (eNOS) in wounds impacts the rate of wound closure, the strength of the wound after rupture, and the inward growth of capillaries. Moreover, M2 macrophages secrete cytokines like VEGF and PDGF, which stimulate angiogenesis and collagen deposition, further contributing to the wound healing process [50]. There is also evidence that applying MSC-derived exosomes to wound surfaces promotes angiogenesis and tissue repair through the production of pro-angiogenic factors [51].

By understanding these mechanisms, potential therapeutic strategies for intervention in diabetic wound angiogenesis can be provided, which may help improve angiogenesis and wound healing in diabetic wounds.

Application of omics analysis to the immune microenvironment in DW

Signalling pathways regulating immune microenvironment

Various signalling pathways participate in the wound healing process, each contributing uniquely to the regulation of different phases of tissue repair. For example, the Wnt/β-catenin pathway primarily enhances re-epithelialization, angiogenesis, and tissue regeneration. Meanwhile, the PI3 K/AKT/mTOR pathway is essential for modulating cell proliferation, migration, and the formation of new blood vessels. The VEGF signalling pathway serves as the primary impetus for angiogenesis, whereas the TGF-β pathway plays a crucial role in regulating cellular proliferation, differentiation, migration, apoptosis, and the synthesis of the ECM (Fig. 1) [52–54].

During the initial stages of diabetic wound formation, the adaptability of cells to hypoxia diminishes, resulting in persistent and excessive inflammation, which significantly delays healing and leads to severe tissue damage [55]. Under hypoxic conditions, HIF-1α is initially activated, predominantly via the PI3 K/AKT/mTOR signalling cascade, which plays a central role in modulating cellular growth, metabolism, and viability. This signalling pathway is elicited by a diverse array of growth factors and cytokines, encompassing interferon-γ (IFN-γ), epidermal growth factor (EGF), TGF-β, VEGF, IL-4, and IL-15. These cell molecules bind to the respective receptor situated on the cell membrane, initiating the activation of phosphoinositide 3-kinase (PI3 K). During this process, PI3 K catalyses the transformation of phosphatidylinositol 4,5-bisphosphate (PIP2) into phosphatidylinositol 3,4,5-trisphosphate (PIP3). Subsequently, PIP3 triggers the activation of protein kinase B (AKT) and phosphoinositide-dependent kinase 1 (PDK1). Through phosphorylation, AKT inhibits the tuberous sclerosis complex 1 and 2 (TSC1/2), relieving the suppression on the Ras homolog enriched in brain (RHEB). Consequently, this activation leads to the stimulation of the mammalian target of rapamycin complex 1 (mTORC1). mTORC1, in its activated state, stimulates the expression of HIF-1α, which dimerizes with HIF-1β to induce the transcription of target genes, including TGF-β, PDGF, and VEGF [56]. This process governs various cellular activities, including mitochondrial metabolism, protein and lipid synthesis, inflammation, and angiogenesis [57, 58].

The JAK-STAT signalling pathway primarily functions to suppress excessive inflammatory responses in wounds [59, 60]. It plays a crucial role in regulating cellular responses to a wide range of cytokines and growth

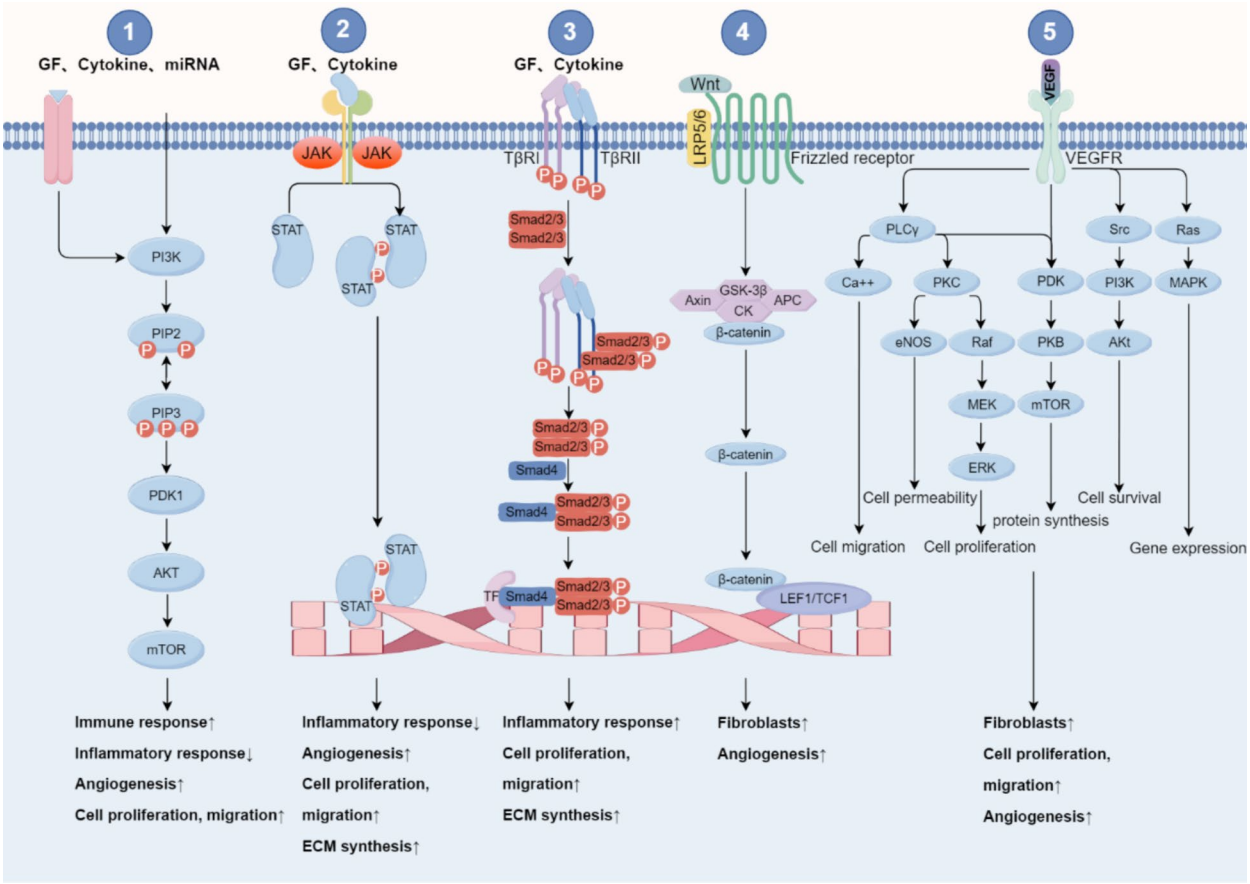

Fig. 1 The role of five signalling pathways in regulating the immune microenvironment of DW. (1) PI3 K/AKT/mTOR pathway: Upregulated cytokines, such as HIF-1α and VEGF, induce the transcription and protein expression levels of target genes through the PI3 K/AKT/mTOR signalling pathway, which regulates cell proliferation, migration, and angiogenesis to accelerate wound healing [56–58]. (2) JAK-STAT pathway: JAK/STAT pathway signalling leads to the upregulation of various proteins to regulate inflammatory response, angiogenesis, cell proliferation and migration, and ECM synthesis [62, 63]. (3) TGF-β/SMAD pathway: TGF-β regulates cell proliferation, differentiation, migration, apoptosis, and ECM synthesis by targeting genes through SMAD transcription factors [66–68]. (4) Wnt/β-catenin pathway: When the Wnt/β-catenin pathway is switched on and activated, the level of β-catenin in the cytoplasm increases and is translocated to the nucleus. It plays a key role in regulating cell proliferation, migration and fibroblastogenesis [73]. (5) VEGF pathway: The VEGF pathway is a key pathway in angiogenesis, signalling through VEGFR to activate multiple downstream pathways that regulate endothelial cell proliferation, survival, migration, and vascular permeability [71, 72]

factors, including interleukins, interferons, colony-stimulating factors, and various other signalling molecules [61]. This pathway is activated when extracellular cytokines or growth factors bind to their respective receptors, leading to receptor dimerization and subsequent trans-phosphorylation of JAK proteins. Once activated, JAK phosphorylates tyrosine residues on both the cytokine receptor and other JAKs, creating docking sites for STAT proteins. JAK then phosphorylates STATs, which dissociate from the receptor and form homo- or heterodimers via SH2 domain–phosphotyrosine interactions. These STAT dimers translocate to the nucleus where they regulate the transcription of target genes [62]. In the process of wound healing, this pathway regulates cell proliferation and migration, inflammation, angiogenesis, and ECM synthesis [63].

The TGF-β/SMAD pathway is predominantly activated during the second phase of wound healing, where it plays a crucial role in substantially augmenting inflammation and collagen deposition. This pathway is particularly important in pathological healing processes, such as those observed in diabetic wounds [64]. This pathway is activated in response to diverse stimuli, encompassing cytokines, growth modulators, and mechanical tension. It engages in intricate crosstalk with other wound repair-related signalling mechanisms, such as the JAK-STAT, RAS/MAPK, PI3 K/AKT/mTOR, and Wnt/β-catenin pathways, to facilitate the healing process [65]. Upon

binding of TGF-β and bone morphogenetic proteins (BMPs) to their respective receptors—TGF-β receptor type II (TβRII) and bone morphogenetic protein receptor (BMPR)—SMAD proteins are activated. Activated SMAD2 and SMAD3 then form a complex with SMAD4 and move into the nucleus, where they associate with transcription factors to create a transcriptional complex that regulates gene expression. Studies have shown that TGF-β-induced Akt phosphorylation in a high glucose environment increases the availability of cell surface TGF-β transmembrane receptors (TGFBRs) for signalling in human keratinocytes (HaCaT) and mouse epithelial fibroblasts, suggesting that TGF-β/SMAD signalling plays an important role in diabetic trauma [66], mainly regulating cell differentiation, proliferation, migration, ECM synthesis, and apoptosis [67, 68].

Li et al. found that extracellular vesicles derived from endothelial progenitor cells (EPC-EVs) have the capability to transfer VEGFR-2. This transfer subsequently activates the VEGF/PI3 K/AKT/eNOS signalling pathway, which promotes tissue repair in soft tissue injuries by fostering angiogenesis and stimulating collagen production in both fibroblasts and keratinocytes [69]. Research has shown that the main pathway involved is the VEGF pathway, which is a key pathway regulating angiogenesis [70]. Upon binding to its receptors (VEGFRs) on endothelial cells, VEGF triggers the activation of several downstream signalling cascades such as Ras/MAPK, PI3 K/AKT, and PLCγ/PKC. These signalling cascades, in turn, exert regulatory effects on a broad spectrum of cellular processes, encompassing cell proliferation, migration, survival, vascular permeability, and angiogenesis [71, 72].

The Wnt/β-catenin pathway occupies a pivotal position in the final stage of wound healing. This highly conserved signalling pathway becomes active when Wnt ligands bind to Frizzled receptors and LRP5/6 co-receptors present on the cell surface. In normal physiological conditions, cytoplasmic β-catenin is constantly degraded by the APC/GSK-3β/Axin destruction complex. However, upon the activation of the Wnt/β-catenin pathway, this degradation is halted, causing β-catenin to accumulate and translocate to the nucleus. Within the nucleus, β-catenin interacts with transcription factors, notably LEF1 and TCF1, which triggers the activation of Wnt-responsive genes essential for various processes, including development, stem cell maintenance, and wound repair [73].

In summary, diabetic wound healing is intricately regulated by a variety of signalling pathways, each of which plays a critical role at different stages of the repair process. The PI3 K/AKT/mTOR pathway is a cornerstone in the regulation of cell proliferation, migration, and angiogenesis, while also acting as a central regulator of cell growth and metabolism. The JAK-STAT pathway fine-tunes the immune and inflammatory responses and supports wound healing by preventing excessive inflammation. In addition, the TGF-β/SMAD pathway plays a critical role in the intermediate and late stages of wound healing, controlling cell proliferation, migration, and ECM synthesis. Aberrant activation of this pathway can interfere with the healing process. The VEGF signalling pathway is primarily involved in promoting angiogenesis, ensuring that wounds receive an adequate blood supply. Finally, the Wnt/β-catenin pathway promotes tissue regeneration and re-epithelialization in the final stages of wound healing. Understanding the function of these pathways and their alterations in diabetic wounds may help develop targeted therapeutic strategies, ultimately improving wound healing outcomes and clinical management.

Gene editing and circRNA-mediated immune microenvironment regulation

The regulation of the immune microenvironment mediated by gene editing technology involves multiple complex gene sequences and subtle changes in gene expression [74]. In terms of DFU, precise regulation of genes related to the immune microenvironment through epigenetic and transcriptional regulation has become a research hotspot. It controls the transcriptional activity of genes without changing the gene sequence itself and affects the expression pattern of downstream proteins, which in turn has a significant impact on the function and behaviour of immune cells [75, 76]. CircRNAs, a class of covalently closed-loop RNA molecules, possess unique structural stability and regulatory potential, enabling them to function as microRNA sponges, RNA-binding protein decoys, and transcriptional regulators. These functions make circRNAs important molecular players in reshaping immune microenvironments and represent a novel direction in gene editing strategies [77–79].

With the advancement of technology and in-depth research, circRNAs are expected to become diagnostic biomarkers and therapeutic targets for DFU [80]. Zhang et al. discovered that HG can trigger an increase in circBPTF expression within human umbilical vein endothelial cells (HUVECs), which regulates endothelial dysfunction through the miR-384/LIN28B axis, including cell apoptosis, inflammation, and oxidative stress, causing irreversible damage to wounds in diabetic patients [81]. Therefore, a key research focus is on mitigating the detrimental effects of a hyperglycaemic metabolic milieu in diabetic patients. Cheng et al. reported that down-regulating hsa_circ_0068087 can alleviate inflammation and endothelial cell (EC) dysfunction that are mediated by the HG-induced TLR4/NF-κB/NLRP3 inflammasome

pathway. This is accomplished by sequestering miR-197, which in turn helps rectify the immune microenvironment imbalance caused by high glucose levels and facilitates the restoration of normal wound healing processes [82]. Similarly, circ_LRP6 enhances the viability and migration of vascular smooth muscle cells (VSMCs) under hyperglycaemic conditions via the miR-545-3p/HMGA1 axis [83]. These regulatory networks highlight the multifaceted role of circRNAs in immune modulation and tissue repair. As expression profiles of certain circRNAs correlate strongly with DFU progression, they offer diagnostic potential and could predict wound healing outcomes or treatment responsiveness. Xiang et al. demonstrated that in the treatment of DFUs with traditional Chinese medicine (Sheng-ji Hua-yu (SJHY) formula), the downregulation of TNF-α, IL-6, and IL-1β protein expression by acting on the circRNA-Krt13/miR-665-3p/Itga3 and circRNA-Krt14/miR-706/Mylk4 pathways plays a key role during the inflammatory and maturation stages, providing clinical evidence for the selection of potential biomarkers that could predict the efficacy of diabetic wound healing treatments [84]. In addition, the downregulation of miR-21-3p and miR-146a and the overexpression of miR-203 in DFU tissues delay the wound healing process, making it more likely to transition into chronic wounds [85–87].

Current researchers are committed to studying the regulatory mechanism of circRNA as a sponge for miRNAs in DFU. However, the expression of circRNAs is dynamic and overlapping during the various stages of DFU wound healing, which is challenging for screening the most critical circRNAs for clinical application [88]. In the clinic, gene modification techniques can be used to alter the expression level of circRNAs for therapeutic purposes, but reliable gene modification techniques are still lacking [89]. In addition, precise delivery of circRNAs to wounds is also a problem that needs to be solved in the clinic [90].

Other ways to modulate the immune microenvironment

In addition to modulating the diabetic trauma immune microenvironment through signalling pathways and gene editing, there are a variety of other approaches, such as the application of topical growth factor analogues, the use of antioxidants to neutralize excess free radicals in order to mitigate oxidative stress, laser therapy, and cellular therapy, among various other modalities [91, 92]. The utilization of mesenchymal stem cells (MSCs), autologous skin stem cells, and other stem cell types has demonstrated considerable efficacy in accelerating wound healing. This is achieved by enhancing the immune microenvironment through the secretion of diverse cytokines and repairing damaged tissues. Additionally, exosome therapy represents a promising approach that modulates inflammatory responses and immune cell functions in wounds. This therapy employs MSC-derived exosomes, which are enriched with miRNAs, proteins, and other biomolecules. Notably, exosome therapy circumvents the adverse effects often associated with traditional stem cell transplantation, exhibiting enhanced stability, reduced immunogenicity, minimized risk of immune-mediated rejection, and decreased potential for malignant transformation [93]. Extracellular vesicles derived from adipose-derived stem cells (ADSC-EVs) play a pivotal role in regulating immune responses and inflammation. These EVs facilitate the enhancement of angiogenesis, expedite skin cell proliferation and epithelialization processes, and exert modulatory effects on collagen remodelling [94, 95]. In a hypoxic environment, HypADSCs-exo have been shown to enhance blood perfusion and improve the survival of transplanted tissues, inhibit inflammatory reactions, which ultimately promotes diabetic wound healing [96]. Wang et al. pretreated fibroblasts with a PI3 K/AKT inhibitor and observed a significant reduction in HypADSCs-exo-mediated fibroblast proliferation after inhibiting PI3 K/AKT signalling, indicating that HypADSCs-exo can promote diabetic wound healing by activating the PI3 K/Akt signalling pathway [97].

The mentioned techniques can be employed either as standalone therapies or in conjunction with other modalities to markedly enhance the immune microenvironment of diabetic wounds, ultimately expediting wound healing and optimizing overall patient prognosis.

Microneedle-based advances in the regulation of the immune microenvironment of DW

Previous research has demonstrated that the modulation of the immune microenvironment in diabetic wounds is closely correlated with the process of wound healing [98]. However, discussions in the literature on how immune microenvironment regulation promotes DFU healing are often fragmented. To make immune microenvironment regulation a potential option for treating DFUs, it is urgently needed to develop improved carriers or delivery methods to target the microenvironmental status of diabetic wounds. Diabetes mellitus profoundly impacts the skin condition due to its characteristic high glucose metabolism, resulting in a notable decrease in the density of epidermal and dermal cells, retarded maturation of collagen fibres, and a diminished number of neurons [99]. In addition, the impairment of the skin's protective barrier due to persistent hyperglycaemia renders the skin more prone to dryness, infections, and hyperkeratosis, thereby diminishing the efficacy of traditional topical treatments [100]. The skin of a healthy individual comprises two main layers: the epidermis, which ranges

in thickness from 50 to 150 μm, and the dermis, with a thickness of 400–2400 μm. The stratum corneum (SC), located at the outermost layer of the epidermis, comprises 15–20 layers of keratinocytes with a thickness ranging from 10 to 40 μm. Serving as a vital component of the skin's barrier and the most durable layer of the skin, the SC exhibits an elastic modulus that spans from 1 to 1000 MPa [101]. How to penetrate the SC with minimal invasiveness, deliver drugs transdermally, and reduce the pain caused by conventional invasive procedures has been a hot topic in the current research [102]. A microneedle represents a minimally invasive and painless transdermal drug delivery system, consisting of an array of needles and a base. It offers excellent biocompatibility, high mechanical strength, and ease of processing, enabling it to swiftly penetrate the diseased skin of diabetic patients, reach deeper layers of the wound, and accurately deliver drugs in a targeted manner [24, 103]. Cheng et al. devised an innovative black silicon microneedle (BSi-MN) patch characterized by substantial drug loading capacity and remarkable antibacterial properties. This patch was produced using a straightforward approach encompassing laser patterning, conventional alkaline etching, and Ag-catalysed chemical etching. Given its uncomplicated preparation procedure and suitability for batch manufacturing, the BSi-MN patch holds considerable promise for applications in the realm of transdermal drug delivery (TDD). Moreover, it provides a valuable instrument for modulating the microenvironment of diabetic wounds [29]. Li et al. designed a superswelling microneedle device that exhibits rapid swelling characteristics, increasing the molecular weight of the loaded drug to 500 kDa [104]. In addition, infection constitutes a primary factor contributing to the delayed healing of diabetic wounds [20]. The current research is focused on developing efficacious strategies to prevent and manage severe bacterial infections in diabetic wounds, with the aim of enhancing the fundamental state of these wounds [105]. Moreover, given the multiple challenges posed by the immune microenvironment of diabetic wounds, single-function microneedle systems often fail to achieve a comprehensive therapeutic effect. Researchers have therefore turned to the development of multifunctional microneedle platforms that integrate immunomodulatory, antimicrobial, and pro-angiogenic effects. The representative system (Fig. 2) illustrates the latest innovations in this field. Li et al. have developed a microneedle patch system (PFG/M MNs) that

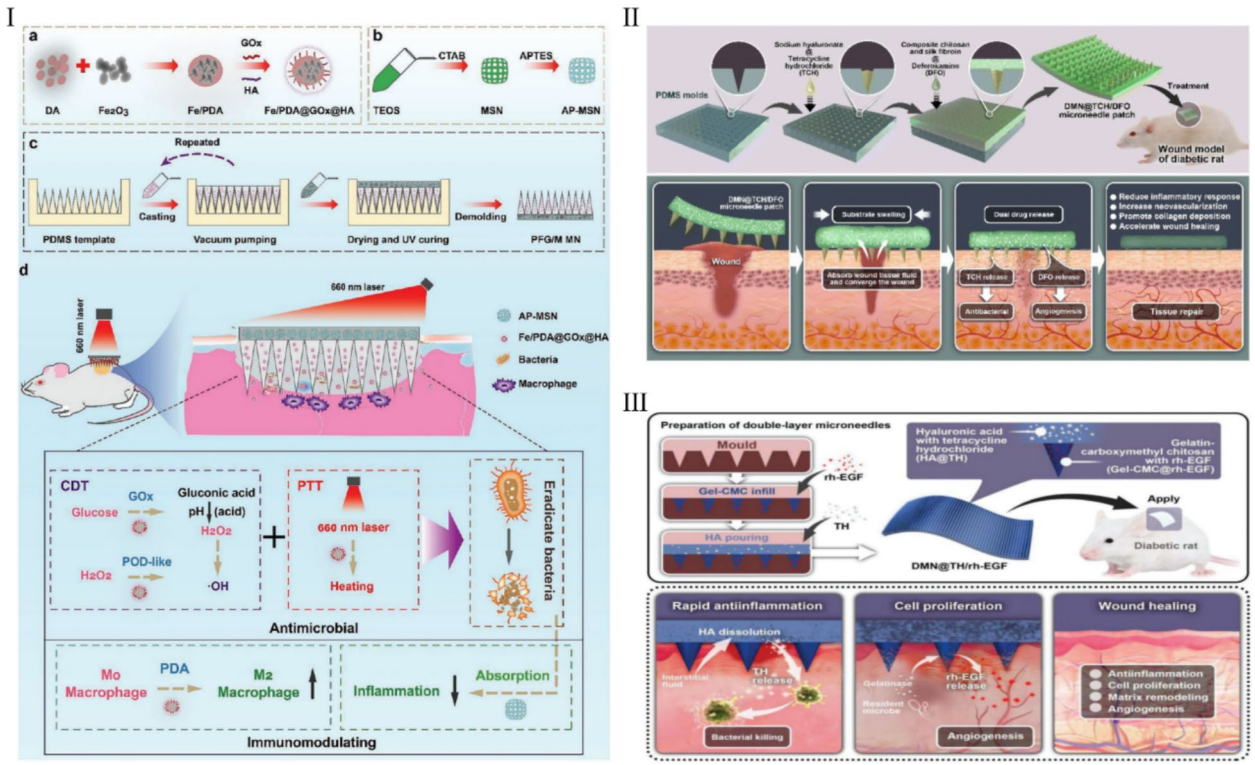

Fig. 2 Representative multifunctional microneedle systems for diabetic wound healing. (I) The mechanism of action of PFG/M MN in the treatment of infected wound healing. Reprinted with permission from [106] (Copyright 2023 by Wiley–VCH). (II) Schematic diagram of DMN@TCH/DFO for acceleration of wound healing in diabetes. Reprinted with permission from [107] (Copyright 2023 by Royal Society of Chemistry). (III) Illustration of DMN@TH/rh-EGF in various stages of diabetic wound healing. Reprinted with permission from [108] (Copyright 2023 by Wiley–VCH)

combines polydopamine (PDA)-encapsulated iron oxide nanoparticles, glucose oxidase (GOx), and hyaluronic acid (HA) at the microneedle tips. This innovative system synergizes the benefits of chemodynamic therapy, photothermal therapy, and M2 macrophage polarization, demonstrating notable antibacterial and immunemodulatory effects, which exerts a favourable influence on modulating the immune microenvironment of diabetic wounds [106]. Gao et al. reported that a dual-layer drug-loaded microneedle system (DMN@TCH/DFO), encapsulating the antimicrobial drug tetracycline hydrochloride (TCH) and the angiogenic drug deferoxamine (DFO), played a significant role in diminishing inflammatory responses and fostering angiogenesis and collagen deposition. These effects notably accelerated the healing process of diabetic wounds [107]. Similarly, Liu et al. devised a novel dual-layer drug-loaded microneedle system (DMN@TH/rh-EGF) by integrating the antibacterial tetracycline hydrochloride (TCH) with recombinant human epidermal growth factor (rh-EGF) at the microneedle tips. This system effectively suppressed inflammatory responses while enhancing angiogenesis, collagen deposition, and tissue regeneration, ultimately accelerating the healing of diabetic wounds [108].

Microneedles can be used to deliver immunomodulatory drugs via exosome-based carriers. A growing number of studies have demonstrated that exosomes and their carriers have significant therapeutic effects on a wide range of diseases, from cancer to cardiovascular disease to diabetic complications [109]. EV-based modulation of the immune microenvironment is achieved by injecting the surface proteins and their carriers (including various cytokines and miRNAs) into the wound site via a microneedle, thereby targeting the signalling pathways that regulate the immune microenvironment of diabetic wounds and play a key role in the various stages of wound healing (Fig. 3) [67, 110]. Extracellular vehicles (EVs) derived from human umbilical cord mesenchymal stem cells (HUCMSCs), enriched with factors like EGF, VEGF, IL-15, or eNOS (UCMSC-exo/eNOS), can activate the PI3 K/AKT/mTOR signalling pathway. This activation modulates neutrophil infiltration and promotes anti-inflammatory macrophage phenotypes by suppressing M1 polarization while enhancing M2 polarization. These effects collectively accelerate angiogenesis, collagen deposition, and the reconstruction of the immune microenvironment at the wound site, thereby promoting the healing of chronic wounds [15, 111]. Targeting specific miRNAs, including miR-222, miR-181c, and miR-let7b, to activate the PI3 K/AKT/mTOR signalling pathway can suppress the production of pro-inflammatory cytokines. This regulation helps mitigate excessive inflammation and facilitates the restoration of the wound's normal healing process [56, 112, 113]. Additionally, delivering anti-inflammatory miRNAs (such as miR-21) from MSC-EVs, which can regulate the JAK-STAT and PI3 K/AKT pathways and promote Ras protein activation, participates in inflammation regulation, cell proliferation, and wound healing processes [114, 115]. The delivery of proteins from MSC-EVs, which regulate the levels of MMPs and the TGF-β signalling pathway, such as tissue inhibitors of metalloproteinases (TIMP-1 and TIMP-2), can also modulate the expression levels of ECM components at the wound site [116, 117]. Furthermore, exosomes loaded onto microneedles, carrying specific miRNAs such as miR-100, miR-125b, and miR-31, can enhance the activation of the Wnt/β-catenin signalling pathway by inhibiting negative regulators, thereby accelerating the wound healing process [73]. In addition to the long-standing research on microneedle-mediated transdermal drug delivery in the field of chronic wounds, microneedles are now widely used in the medical aesthetic industry. By injecting HA and acting as a means to disrupt skin cell structure, they induce the expression and deposition of elastin and collagen, significantly improving the elasticity and hydration of ageing skin [33]. The safe, efficient, and user-friendly transdermal drug delivery characteristics of microneedle injections have even enable their extensive application in both hospital and home environments [104].

In summary, immune microenvironment reconstruction based on microneedle modulation shows remarkable potential in diabetic wound treatment. A detailed comparison of traditional therapy for diabetic wounds with microneedle therapy is summarized in Table 1. Microneedle systems have garnered significant attention in diabetic wound treatment research, owing to their minimally invasive, painless design, and ability to penetrate the impaired skin of diabetic patients, enabling targeted and efficient drug delivery. Research in recent years has continued to explore the combination of microneedles with exosomes to develop a multifunctional microneedle system to further improve the immune microenvironment of wounds, reduce inflammatory responses, and accelerate wound healing. These advances have demonstrated that microneedles can effectively deliver drugs and therapeutic factors, contributing to various aspects such as antimicrobials and promotion of angiogenesis by modulating the immune microenvironment, which accelerates the healing of diabetic wounds.

Conclusion and perspective

In recent years, the DIME has demonstrated significant regulatory potential and plays a critical role in the management of chronic wounds. Systematic reviews have shown that local immune damage caused by DFUs

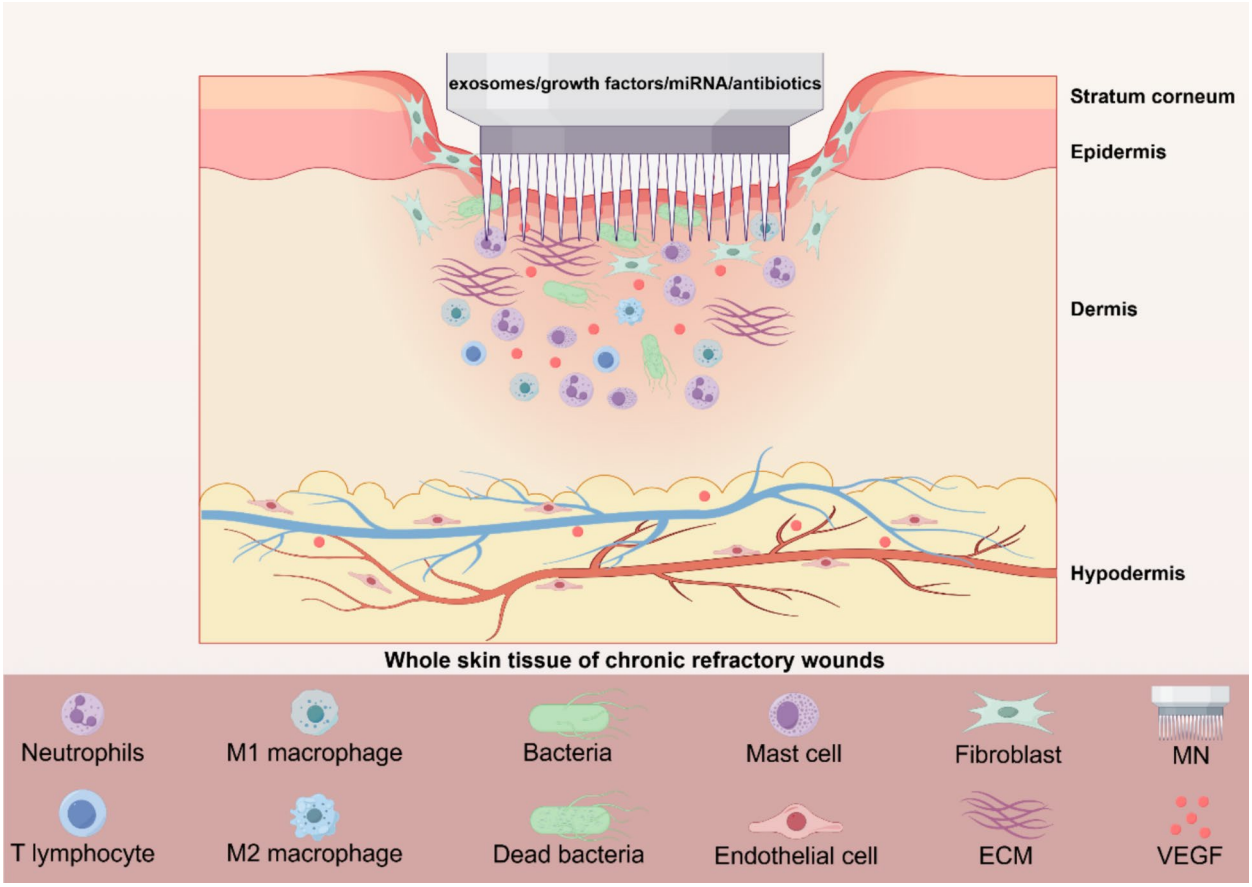

Fig. 3 Schematic diagram of the microneedle-mediated healing process of chronic refractory wounds. (1) Skin puncture using a microneedle device loaded with exosomes, growth factors, antibiotics, and a variety of miRNAs is performed to inject drugs into the lesion site. (2) Neutrophils gathered to the wound surface, M1 macrophages, and T lymphocytes activated cellular immunity through phagocytosis to kill bacteria and phagocytose necrotic tissues, and various immune cells, including mast cells, participated in the early inflammatory response of wound healing, and in the late stage of inflammatory response, M1 polarized to M2 to inhibit the infiltration of neutrophils and terminate inflammatory response in time. (3) Macrophages, fibroblasts, endothelial cells, and various GFs are involved in wound remodelling and angiogenesis

Table 1 Application of traditional therapy and MNs therapy in the treatment of diabetic wounds

Aspect	Applications	Mechanism	Characteristic	Potential benefit	References
Traditional therapy	Surgical debridement Anti-infection Dressing application Vascular intervention Glycaemic control	Symptom control Passive repair	Highly invasive Traumatic	Conventional treatment Low return on health economics	[118–122]
MNs therapy	Interstitial fluid monitoring Wound irrigation Cell transplantation Immune microenvironment regulation	Theranostic function Targeted drug delivery Active intervention	Minimally invasive Painless Targeted Sustained-release medication	Personalized treatment Intelligent management Low cost	[106, 123–126]

can exacerbate wound conditions. Modulation of the immune microenvironment prior to conventional interventions has demonstrated the potential to significantly improve wound healing outcomes. Among emerging therapeutic strategies, immunomodulatory drug delivery via microneedles represents a promising treatment strategy, offering advantages such as painlessness, minimally invasive application, efficient drug loading, and dynamic

regulation. This approach is expected to emerge as a novel strategy to modulate the immune microenvironment in diabetic wounds.

Despite encouraging preclinical findings, the clinical translation of MNs-mediated immunotherapy is still in its infancy. Several limitations need to be addressed before these strategies can be widely adopted in clinical practice. These include standardization of MN production and formulation, scalability of manufacturing processes, and comprehensive evaluation of long-term safety and immunoregulatory efficacy in humans. Future research should focus on optimizing MN design for improved targeting precision, controlled release kinetics, and responsiveness to specific wound microenvironment cues. Integration with advanced bioresponsive materials, real-time biosensing, and circRNA-based gene regulation may further enhance therapeutic precision.

This review presents an innovative therapeutic perspective for repairing DFUs by targeting the regulation of the immune microenvironment. It provides a comprehensive summary of the current research on the role of the immune microenvironment in promoting wound healing and skin regeneration, with the aim of achieving improved clinical outcomes in the treatment of diabetic wounds.

Abbreviations

DM	Diabetes mellitus
HG	High glucose
DW	Diabetic wounds
DFUs	Diabetic foot ulcers
DIME	Diabetic immune microenvironment
TNF-α	Tumour necrosis factor-alpha
IL-1β	Interleukin-1β
MN	Microneedle
ROS	Reactive oxygen species
MMPs	Matrix metalloproteinases
AFG	Biodegradable snail glycosaminoglycan
GelMA	Gelatine methacrylate
NLRP3	NOD-like receptor thermal protein domain-associated protein 3
ECM	Extracellular matrix
VEGF	Vascular endothelial growth factor
TLR4	Toll-like receptor 4
PDGF	Platelet-derived growth factor
FGF	Fibroblast growth factor
IGF	Insulin-like growth factor
HIF-1α	Hypoxia-inducible factor-1alpha
FGFR	Fibroblast growth factor receptor
EGFR	Epidermal growth factor receptor
eNOS	Endothelial nitric oxide synthase
EGF	Epidermal growth factor
IFN-γ	Interferon-γ
PI3 K	Phosphatidylinositol 3-kinase
PIP2	Phosphatidylinositol 4,5-bisphosphate
PIP3	Phosphatidylinositol 3,4,5-trisphosphate
AKT	Protein kinase B
PDK1	Phosphoinositide-dependent kinase 1
TSC1/2	Tuberous sclerosis complex ½
RHEB	Ras homolog enriched in brain
mTORC1	Mammalian target of rapamycin complex 1
JAK	JANUS kinase
STAT	Signal transducer and activator of transcription
SH2	Src homology domain
BMP	Bone morphogenetic protein
TβRII	TGF-β receptor type II
BMPR	Bone morphogenetic protein receptor
TGFBRs	TGF-β transmembrane receptors
HaCaT	Human keratinocytes
EPC-EVs	Endothelial progenitor cell-derived extracellular vesicles
Ras	Small G Protein
MAPK	Mitogen-activated protein kinase
PLCγ	Phospholipase C gamma
PKC	Protein kinase C
VEGFRs	Vascular endothelial growth factor receptors
GSK-3β	Glycogen synthase kinase 3 beta
APC	Adenomatous polyposis coli
Axin	Axis inhibition protein
CK	Casein kinase
LEF1	Lymphoid enhancer-binding factor 1
TCF1	T cell-specific DNA-binding protein
miRNAs	MicroRNAs
HUVECs	Human umbilical vein endothelial cells
SJHY	Sheng-ji Hua-yu formula
SC	Stratum corneum
BSi-MN	Black silicon microneedle
TDD	Transdermal drug delivery
PDA	Polydopamine
GOx	Glucose oxidase
HA	Hyaluronic acid
TCH	Tetracycline hydrochloride
HUCMSC-EVs	Human umbilical cord mesenchymal stem cell-derived extracellular vesicles
UCMSCs-exo/eNOS	ENOS-rich umbilical cord mesenchymal stem cell-derived extracellular vesicles

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SSW and JDS conceived and designed the main ideas of this article. SSW performed the literature review, wrote the first draft of the manuscript, and revised it according to feedback. JDS provided financial support for this article. WC, XW, and ZFW provided feedback and revisions to improve the manuscript. JDS supervised the writing process and reviewed the manuscript several times to determine the final version.

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Declarations

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Not applicable.

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