Epigenetic regulatory mechanism of macrophage polarization in diabetic wound healing (Review)

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Abstract. Diabetic wounds represent a significant complication of diabetes and present a substantial challenge to global public health. Macrophages are crucial effector cells that play a pivotal role in the pathogenesis of diabetic wounds, through their polarization into distinct functional phenotypes. The field of epigenetics has emerged as a rapidly advancing research area, as this phenomenon has the potential to markedly affect gene expression, cellular differentiation, tissue development and susceptibility to disease. Understanding epigenetic mechanisms is crucial to further exploring disease pathogenesis. A growing body of scientific evidence has highlighted the pivotal role of epigenetics in the regulation of macrophage phenotypes. Various epigenetic mechanisms, such as DNA methylation, histone modification and non-coding RNAs, are involved in the modulation of macrophage phenotype differentiation in response to the various environmental stimuli present in diabetic wounds. The present review provided an overview of the various changes that take place in macrophage phenotypes and functions within diabetic wounds and discussed the emerging role of epigenetic modifications in terms of regulating macrophage plasticity in diabetic wounds. It is hoped that this synthesis of information will facilitate the elucidation of diabetic wound pathogenesis and the identification of potential therapeutic targets.

Contents

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1. Introduction

In the contemporary era, diabetes has emerged as a pervasive and critical chronic illness. The global prevalence of diabetes is projected to increase to 643 million by 2030 and 783 million by 2045, representing a significant threat to human life and health (1). Chronic diabetic wounds represent a significant complication of diabetes that also presents a substantial global public health challenge. When patients with diabetes develop foot ulcers, they are often at risk of subsequent osteomyelitis, amputation and even mortality (2). The global prevalence of diabetic foot is 6.3% and the risk of developing foot ulcers ranges between 19-34% among patients with diabetes (3). Owing to the challenges associated with wound healing in patients with diabetes, as well as the elevated morbidity and mortality rates in the population, this problem has received increasing attention in the biomedical field.

A growing body of evidence indicates that macrophages play a crucial role in the process of diabetic wound healing. During normal wound healing, there is a gradual transition in the macrophage phenotype, shifting from the initial M1 phenotype associated with the acute response, to the later M2 phenotype that promotes healing. However, in diabetic individuals, this phenotypic macrophage imbalance hinders the resolution of inflammation, resulting in persistent nonhealing of wounds (4). Accordingly, the modulation of macrophage polarization has become a key objective in the management of diabetic wounds.

The advent of novel high-throughput technologies has revealed epigenetic mechanisms governing gene expression in macrophages, which play a pivotal role in modulating their plasticity (5). The present review aimed to elucidate the mechanisms behind macrophage involvement in diabetic wounds and

the epigenetic factors that govern macrophage polarization in diabetic wounds, with the aim of furthering our understanding of the pathogenesis behind diabetic wounds and identifying potential targets for clinical interventions.

2. Macrophage polarization

Macrophages, a vital element of the immune system, are instrumental in maintaining homeostasis, preserving tissue integrity and regulating inflammatory processes (6-8). The distinguishing features of macrophages include their functional plasticity and diversity (9). Macrophage polarization is characterized by distinct functional and phenotypic characteristics in response to local microenvironmental stimuli. Macrophages can be conventionally categorized as M1 or M2 (10-12). M1 macrophages represent a pro-inflammatory phenotype. They are also referred to as classical macrophages, can initiate inflammation and possess potent antimicrobial properties. However, they also carry the potential to induce tissue damage. By contrast, M2 macrophages, also known as alternatively activated macrophages, exhibit an anti-inflammatory phenotype and facilitate a state that is conducive to anti-inflammatory responses and tissue repair (13,14). Macrophage polarization determines the fate of organs and tissues during inflammation or injury. In the preliminary phases of an inflammatory response, macrophage polarization into the M1 form is initiated through the classical pathway by lipopolysaccharide (LPS), a key outer membrane component in gram-negative bacteria. Moreover, cytokines such as interferon (IFN)-γ, tumor necrosis factor (TNF) and granulocyte-macrophage colony-stimulating factor also contribute to macrophage activation. M1 macrophages actively secrete a variety of pro-inflammatory cytokines, including interleukin (IL)-6, TNF, IL-1β, IFN-β, IL-12 and IL-23 and nitric oxide. These substances work in conjunction to facilitate rapid and efficient physiological responses to infection and tissue damage (15,16). It is also noteworthy that M1 macrophages can regulate immune response with the help of Th1 and Th17 cells. Through complex cell signaling and molecular interactions, they can help to efficiently eliminate pathogens and maintain the immune balance within the body. Prolonged polarization of macrophages in the M1 state may lead to tissue damage (17). In the advanced stages of the inflammatory response, M2 macrophages are activated through alternative pathways, resulting in the production of various anti-inflammatory cytokines. This facilitates the amelioration of inflammatory responses and promotes tissue damage repair (18). Based on the corresponding functions induced by various stimulants, M2 macrophages can be categorized into four distinct subtypes: M2a, M2b, M2c and M2d. T-helper (Th)2 cells and M2 macrophages can engage in reciprocal interactions to maintain immune homeostasis. Stimulated by the IL-4 and IL-13 secreted by Th2 cells, M2a macrophages, also known as wound-healing macrophages, express markers such as the mannose receptor (MR or CD206) and decoy IL-1 receptor (IL-1R). They secrete anti-inflammatory factors including IL-10, transforming growth factor (TGF)-β, arginase-1 (Arg-1), C-C motif chemokine ligand (CCL)17, CCL18, CCL22 and CCL24 to facilitate the resolution of chronic inflammation and accelerate the process of wound healing (19-22). Specifically, M2a macrophages secrete IL-10, which in turn can suppress the activity of Th1 cells and other pro-inflammatory cells, indirectly maintaining the relative advantage of Th2 cells and promoting Th2-type immune responses, thus playing a role in wound healing and tissue remodeling (23). M2b macrophages, which have also been described as regulatory macrophages, are primarily triggered by the presence of immune complexes, Toll-like receptor (TLR) agonists, LPS, or IL-1β. They express various surface protein markers, including CD86, IL-10R, IL-12R and TNF superfamily member 14 (TNFSF14) (24-26). M2b macrophages have been observed to exhibit dual regulatory functions characterized by the production of pro-inflammatory factors (IL-1β, IL-6 and TNF-α), as well as high expression of the anti-inflammatory factor IL-10 and low expression of IL-12. Consequently, they can also serve to inhibit immune-inflammatory responses (20,23,25). M2c cells, also known as inactivated macrophages, are primarily stimulated by glucocorticoids, IL-10 and TGF-β. Their main surface protein markers include CD163, CD206, TLR-1 and TLR-8. These macrophages secrete IL-10, TGF-β, CCL13, CCL16, CCL18 and other cytokines that contribute to immunosuppression and the phagocytosis of apoptotic cells (27,28). Tumor-associated M2d macrophages can be induced by IL-6 or a combination of TLR ligands and A2a adenosine receptor agonists. Their surface markers include IL-10R and IL-12R. M2d macrophages are capable of secreting cytokines that facilitate angiogenesis and tumorigenesis, including IL-10, IL-12, TNF-α, TGF-β and vascular endothelial growth factor (VEGF) (29-32). Despite their opposing functions, M1 and M2 macrophages can transition from one phenotype to the other in specific states to collectively maintain the dynamic equilibrium of the immune system. Additionally, changes in extracellular matrix (ECM) composition, signaling by other immune cells and metabolic state changes can affect macrophage plasticity. Changes in ECM components such as collagen and fibronectin can interact with macrophage cell surface receptors to regulate their activation states (33). Other immune cells, such as B cells and dendritic cells, release signaling molecules that can influence the polarization direction and function of macrophages. Metabolic state changes such as hypoxia and nutrient imbalance can prompt macrophages to adjust their metabolic pathways, thereby affecting their phenotypes and functions (34). These factors enable macrophages to play different roles in complex environments, thus assisting in both immune regulation and tissue repair (6).

3. Macrophages in normal wound healing

The process of wound healing is a complex biological phenomenon that occurs in four distinct, overlapping and highly regulated stages: Hemostasis, inflammation, proliferation and remodeling (35,36). Each requires a particular sequence, timing and duration at an optimal intensity to achieve effective wound healing. Disruption of any of these stages can result in delayed wound healing. Hemostasis, the initial phase, involves three processes: Vasoconstriction, primary hemostasis and secondary hemostasis. Following injury, blood vessels in the vicinity quickly constrict to minimize the bleeding caused by damage to the microvascular system. Primary and secondary hemostasis occur via two parallel and mechanically linked

pathways (37). After a wound is sustained and blood vessels rupture, the endo-subcutaneous thrombotic matrix is exposed, which initiates primary hemostasis. This process includes platelet aggregation and the formation of platelet thrombi (38). Secondary hemostasis entails activation of the clotting cascade, which culminates in the conversion of soluble fibrinogen into insoluble fibrin chains that collectively constitute the fibrin network. The platelet plug adheres to the fibrin network, forming a clot that stops bleeding and releases complement and growth factors, including TGF-β, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) and epidermal growth factor (EGF). Furthermore, it serves as a provisional scaffold for infiltrating cells, which are vital for the process of wound healing (39-41). It has been identified that macrophages play a critical role in this part of wound healing (42). Although not directly involved in the hemostatic phase, they are essential for coordinating various transitions that take place among the subsequent phases of inflammation, proliferation and remodeling.

Inflammation. Once hemostasis is achieved, the wound enters an inflammatory phase characterized by persistent infiltration of neutrophils, macrophages and lymphocytes (43). Neutrophils are of particular importance during the initial stages of inflammation, primarily functioning in an anti-infective capacity (44). Macrophages are critical regulatory cells involved in inflammatory responses. Following tissue injury, resident dermal macrophages are the earliest responders, initiating an inflammatory response by releasing hydrogen peroxide that leads to the sequential recruitment of neutrophils and monocytes to the site. The recruited monocytes then further differentiate into macrophages (45). The TLR family plays a pivotal role in macrophage polarization, with particular emphasis on TLR2 and TLR4. TLR2 recognizes diverse pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns, whereas TLR4 predominantly identifies LPS. Upon binding to their respective ligands, TLR2 and 4 recruit myeloid differentiation primary response 88 (MyD88), leading to its activation, as well as the subsequent activation of TNF receptor-associated factor 6 (TRAF6). TRAF6 activation results in nuclear translocation of NF-κB, which initiates the transcription of pro-inflammatory cytokines and other genes, as well as activation of the MAPK pathway (46-48). These pro-inflammatory cytokines and their associated transcription factors collectively drive macrophage polarization toward the M1 phenotype, resulting in an early-stage inflammatory response involving pathogen clearance and tissue repair. Owing to their unique recognition mechanism, M1 macrophages can accurately identify PAMPs on the surface of bacteria or fungi, thereby forming phagocytic lysosomes. M1 macrophages then release potent antibacterial mediators such as reactive oxygen species (ROS) and active nitrogen into the surrounding environment to effectively eliminate pathogens (49,50). The excessive and uncontrolled release of inflammatory cytokines has a significant detrimental effect on the ability of the body to repair damaged tissues. These cytokines exacerbate the effects of ROS on tissues and prolong the inflammatory response, which should have resolved itself, thus impeding essential tissue regeneration processes (51,52). Macrophages are also involved in the clearance of cellular debris and apoptotic neutrophils (53). In the later stages of the inflammatory response, TLR-induced inflammation is gradually attenuated, allowing for continued wound healing (48). At this stage, macrophages typically undergo a gradual transition to the M2 phenotype and secrete substantial amounts of anti-inflammatory cytokines, which strongly facilitate the gradual resolution of inflammation and tissue healing.

The neuroimmune axis plays an important role in the healing process. Complex interactions occur between neurotransmitters released by nerve fibers and immune cells. For example, neuropeptides such as Substance P (SP) can increase the levels of inflammatory factors such as TGF-β, TNF-α, IL-1β, IL-2, IL-8 and IL-6 that are released by dendritic cells, T cells, neutrophils and macrophages (54). SP also ensures extravasation, migration and subsequent accumulation of white blood cells at the site of injury, thereby creating an inflammatory microenvironment that further ensures the proliferation and angiogenesis of endothelial cells and promotes wound healing (55).

Proliferation. The transition from M1 to M2 macrophages indicates the onset of the proliferative phase of wound healing, which involves angiogenesis and re-epithelialization (40,41). A prominent characteristic of this phase is the extensive activation of endothelial cells, fibroblasts, keratinocytes and macrophages (56). As mesenchymal cells, fibroblasts are widely distributed throughout a range of tissues and play a pivotal role in the promotion of granulation tissue formation and the replacement of transient stroma during the proliferative process (57). Fibroblasts derived from different sources are mobilized to the wound site, where they proliferate to bridge gaps in the wound and facilitate the generation of new ECM (58). Initially, vascularized ECM transforms into granulation tissue and keratinocyte-represented epithelial cells undergo proliferation and migration toward the granulation tissue, thereby facilitating re-epithelialization. The anti-inflammatory and proliferative characteristics of M2 macrophages have been well documented. M2 macrophages possess the capacity to increase levels of anti-inflammatory factors, lower levels of pro-inflammatory ones and produce a considerable quantity of growth factors, including PDGF, EGF, VEGF, TGF-β1 and insulin-like growth factor 1. These growth factors facilitate cell proliferation, the formation of granulation tissue and angiogenesis (59-62). M2a macrophages not only effectively inhibit the inflammatory response and reduce inflammation-induced tissue damage but also actively promote the normal development and functional maintenance of blood vessels, thereby providing the necessary conditions for wound healing (63). It has also been demonstrated that M2c macrophages can facilitate the migration of vascular endothelial cells and enhance angiogenesis (64). Additionally, M2c macrophages secrete matrix metalloproteinase (MMP)-9 to recruit blood vessels and blood-derived stem cells to the injury site. This promotes angiogenesis, phagocytosis of wound debris and the deposition of ECM components (63,65).

Remodeling. The final stage of wound healing, known as remodeling or regression, is a complex and protracted process involving tissue restructuring and the enhancement of wound strength. This phase involves ECM reorganization, wound

contraction and scar maturation (66). Fibroblasts facilitate wound contraction by differentiating into myofibroblasts, which further promote wound contraction. New collagen scaffolds are formed during tissue repair and reconstruction. If the original ECM is not degraded in a timely manner, new tissue formation is impeded. MMPs target the degradation of existing ECM components, thereby creating favorable conditions for the integration of new collagen scaffolds and tissue remodeling. Collagen I replaces collagen III as the primary ECM component, leading to remodeling and increased tensile strength. The main producers of MMPs are macrophages and the naturally occurring tissue inhibitors of metalloproteinases are responsible for controlling their activity (67). During tissue remodeling, the population of macrophages decreases and the remaining ones are involved in regulating collagen and the ECM (9,61,68,69). In addition to MMP release, M2 macrophages also regulate collagen turnover via the mannose receptor (70).

4. Macrophages in diabetic wound healing

The wound-healing process in diabetes is halted at a specific stage, typically the inflammatory phase, and fails to advance further. Dysregulated macrophage phenotypes and functions represent critical factors that contribute to persistent non-healing in diabetic wounds (Fig. 1). These findings indicate that the diabetic microenvironment stimulates an increased production of hematopoietic stem cells in the bone marrow, which then differentiate into a greater number of monocytes entering the peripheral blood. These monocytes then migrate to the wound and transform into M1 macrophages, which are characterized by IL-1β and TNF-α markers. This exacerbates the inflammatory response at the wound site and impedes normal wound healing (71). Barman *et al* (72) corroborate this conclusion, demonstrating a higher number of monocyte infiltrations in the wounds of mice with type 2 diabetes mellitus (T2D) compared with healthy mice. Elevated TLR2 and 4 levels in diabetic wounds have been shown to result in sustained activation of pro-inflammatory signals and the persistence of M1 macrophages, thereby impeding progression to the next healing stage (73-75). Macrophages in diabetic mice display a sustained increase in M1-like macrophage markers, including nitric oxide synthase 2, TNF-α, IL-1β and MMP9, and decreased M2-like macrophage markers such as Arginase 1, CD206 and CD36 (76,77). Similarly, diabetic foot ulcers in humans show increased expression of M1-like markers such as CD68 and IL-1β and decreased expression of M2-like markers such as CD163, CD206 and Arg-1 (76,78). Persistent hyperglycemia and oxidative stress have been shown to synergistically exacerbate the polarization propensity of M1 macrophages, leading to sustained secretion of potent pro-inflammatory mediators that inflict severe damage to wounded tissues (42,56). Therefore, the persistence of the pro-inflammatory M1 phenotype and deficiency of M2-type macrophages in diabetic wounds may contribute to an unbridled pro-inflammatory microenvironment (79). Furthermore, macrophages in diabetic wounds exhibit reduced bactericidal and phagocytic activities, impairing their ability to effectively eliminate dead tissue and pathogens. This results in prolonged inflammation that further complicates the healing process (80,81). Patients with diabetes often have neuropathy and immune dysfunction as well, resulting in disorders in neural-immune interactions that can impair tissue healing. Neuropeptides such as SP and calcitonin gene-related peptide (CGRP) interact with cytokines released by immune cells to form a neural-immune axis. For example, the reduced release of SP by nerve fibers in diabetic wounds may cause a decrease in the levels of pro-inflammatory cytokines released by immune cells, affecting the initiation of the early inflammatory response in wounds (82). Concurrently, the reduction in CGRP levels in the diabetic state may interfere with its ability to polarize macrophages to a pro-repair phenotype, leading to delayed wound healing (83,84).

Initiation of the proliferative phase in diabetic wounds presents a complex challenge and represents a significant factor contributing to the complexity of wound repair progression. In diabetic wounds, macrophages persist in the pro-inflammatory M1 phenotype. This promotes an inflammatory response and inhibits the initiation of tissue proliferation, ultimately leading to impaired wound healing (84-86). A hyperglycemic environment impedes the transition of macrophages from the M1 to the M2 phenotype, resulting in compromised proliferation and migration of endothelial cells and fibroblasts. This ultimately leads to impaired angiogenesis, collagen deposition and wound healing (87). The dysregulation of macrophage activity in diabetic wounds results in a reduction in VEGF-A and VEGF receptor 1 signaling, leading to impaired angiogenesis and delayed wound healing (88,89).

Although the complex process of diabetic wound healing is multifaceted and involves a diverse array of cellular, molecular and physiological mechanisms related to macrophages, it primarily correlates with the hyperactivation of M1 macrophages and impaired transformation from M1 to M2 macrophages (4,79). The modulation of macrophage polarization has proven to be a promising avenue for enhancing diabetic wound healing owing to the pivotal role of macrophages in the process (90).

5. Epigenetic regulation of macrophage polarization in diabetic wounds

Epigenetic modifications are dynamic and inheritable changes that occur in the genome without altering DNA sequences (91). Investigating epigenetics is crucial for understanding the pathogenesis of diseases and the effect of environmental factors on gene expression. These alterations primarily involve DNA methylation, histone modification, chromatin remodeling and non-coding RNAs (ncRNAs) RNAs, all of which contribute to the modulation of gene expression (92). A growing body of research has highlighted the pivotal role of epigenetics in controlling macrophage phenotypes. A number of studies have demonstrated that epigenetic modifications in macrophages are closely associated with the pathogenesis of T2D and its associated complications, such as diabetic wounds (Fig. 2) (93,94).

DNA methylation. DNA methylation is a stable, widespread and abundant form of epigenetic modification that markedly affects gene expression (95). It plays a pivotal role in a number of biological processes and diseases. For example, during cell differentiation and development, DNA methylation

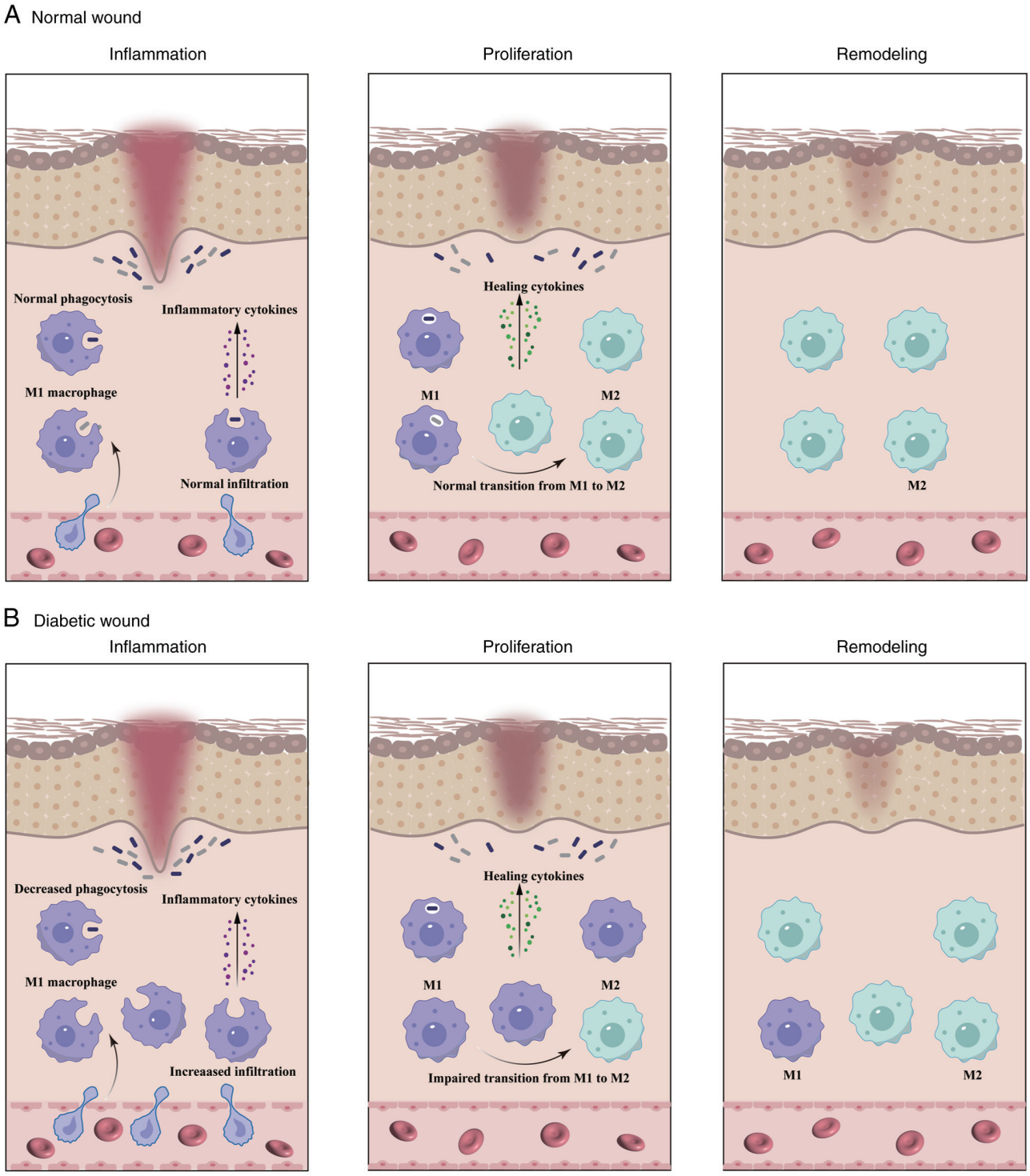

Figure 1. Macrophages in normal and diabetic wounds. (A) In normal wounds, during the inflammatory stage, monocytes in the blood are recruited to the tissue and differentiate into M1 macrophages. Along with the resident tissue macrophages, these then release inflammatory factors and promote the inflammatory response. Meanwhile, macrophages remove cell debris and apoptotic neutrophils. During the proliferative phase, macrophages convert from M1 to M2 and release a large number of growth factors to promote cell proliferation, granulation tissue formation and angiogenesis. (B) In diabetic wounds, monocyte-macrophage infiltration into the peripheral blood and wound tissue is increased, but the bactericidal and phagocytic activities of the macrophages are decreased. In the proliferative stage, there are more M1 macrophages and fewer M2 macrophages and the conversion process from M1 to M2 is impaired.

precisely regulates the expression of specific genes, thereby determining cell fate and function (96). With regard to metabolic regulation, DNA methylation can regulate the expression of genes associated with metabolism, thereby participating in the occurrence and development of metabolic diseases such as obesity and diabetes. This process is primarily catalyzed by DNA methyltransferase (DNMT), which uses S-adenosylmethionine as a methyl donor, selectively adding methyl groups to the cytosines of two DNA nucleotides, predominantly forming 5-methylcytosine and a minor quantity of N6-methylpurine (97-99). The regulation of DNA methylation is primarily governed by the DNMT

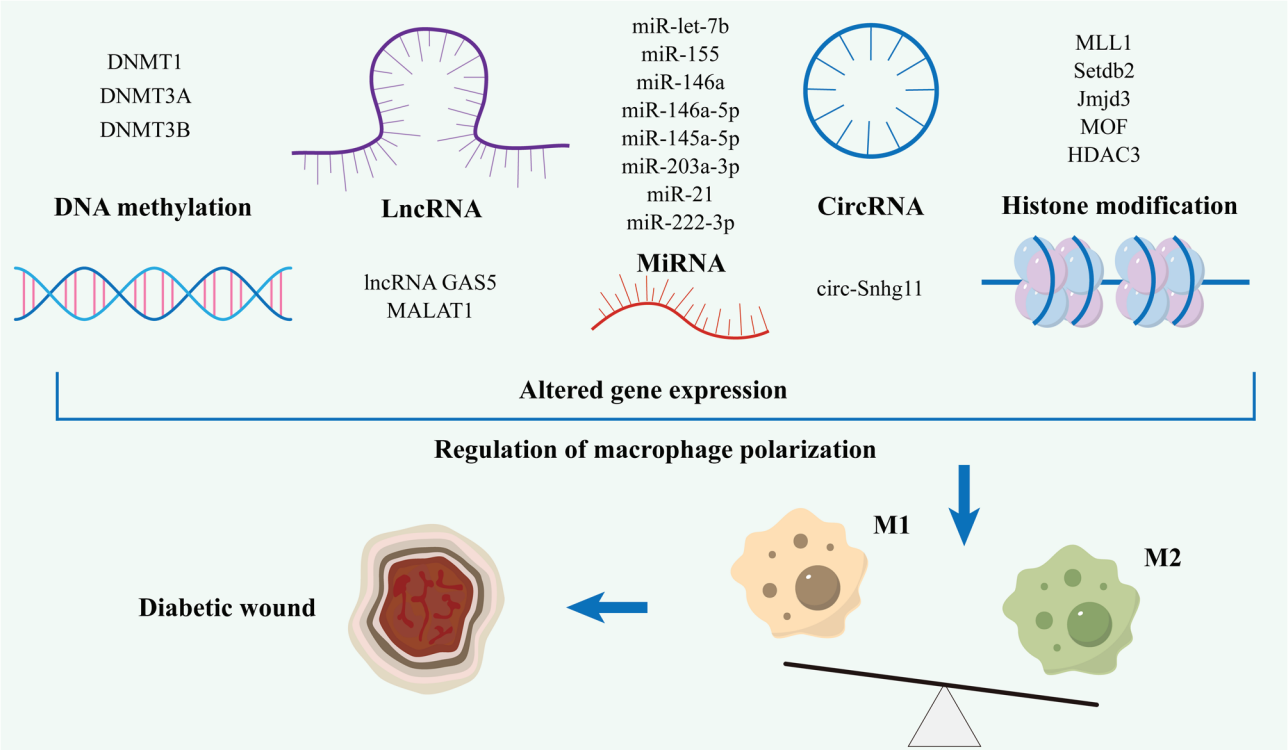

Figure 2. Epigenetic regulation of macrophage polarization in diabetic wounds. Various epigenetic modifications, such as DNA methylation, histone modification and non-coding RNA, can modulate gene expression, thereby influencing the phenotypes and functions of macrophages in diabetic wounds and affecting their healing. lnc, long non-coding; mi, micro; circ, circular; DNMT, DNA methyltransferase; MLL1, mixed-lineage leukemia 1; Setdb2, SET domain bifurcated 2; Jmjd, jumonji domain-containing protein-3; MOF, males absent on the first; HDAC, histone deacetylase.

family, which comprises DNMT1, DNMT2, DNMT3A and DNMT3B (100,101). During cell division, newly synthesized DNA strands contain hemimethylated sites. DNMT1 accurately recognizes these sites and is responsible for maintaining methylation during DNA replication. DNMT3A and DNMT3B are enzymes that participate in *de novo* DNA methylation and are responsible for regulating the methylation patterns of the genome (102-104). Hypermethylation of the promoter prevents the binding of transcription factors or recruits inhibitory complexes, resulting in the shutdown of gene expression, also known as gene silencing. By contrast, hypomethylation promotes gene expression (105,106).

DNA demethylation is a precisely regulated biological process that involves the removal of methyl groups from DNA molecules, thereby modifying their methylation status. There are two types of DNA demethylation in mammals: Active and passive (107). The ten-eleven translocation protein family plays an essential role in active DNA demethylation by catalyzing the oxidation of methylated cytosines. This process is followed by repair via the base excision repair pathway (108). Passive demethylation can be described as a failure of the methylation maintenance mechanism during semi-conservative DNA replication. As a result, DNMT1 is unable to fully methylate the 5-C site on the strand, leading to a reduction in genome-wide methylation over time (109,110). DNA demethylation reverses the methylation pattern, signifying gene activation. DNA methylation and demethylation play equally crucial roles and the dynamic equilibrium between them determines the ultimate epigenetic methylation pattern in the cell (111).

A growing body of research has demonstrated that abnormal DNA methylation patterns regulate macrophage expression and affect diabetic wound healing (Table I). Notch1, PU.1 and Krüppel-like factor 4 are needed to promote monocyte differentiation and macrophage polarization. The hematopoietic stem cells of mice with T2D exhibit NADPH oxidase 2 (NOX-2)-induced oxidative stress, leading to increased expression of DNMT1 via the downregulation of let-7d-3p microRNA (miRNAs/miRs), thereby promoting methylation of the promoters of the three aforementioned genes and inhibiting their expression. This mechanism reduces macrophage infiltration into wounds and enhances the tendency of M1 macrophages to polarize, thereby promoting an inflammatory response while inhibiting wound repair (112). The promoters of M1-specific genes (Cfb, Serping1 and Tnfsf15) in macrophages isolated from the ischemic muscles of hyperlipidemic mice and those with T2D exhibit significant hypomethylation, resulting in the upregulation of M1 gene expression and promotion of M1 macrophage polarization. By contrast, the promoters of M2 macrophage-specific genes (Nrp1, Cxcr4, Plxnd1, Arg1, Cdk18 and Fes) were found to be markedly hypermethylated, leading to downregulation of M2 gene expression and hindering of M2 polarization in macrophages. This demonstrates that changes to DNA methylation can alter the polarization of macrophages in diabetic ischemic muscles, thereby exerting a regulatory effect on gene expression (113). Davis *et al* (114) found that cyclooxygenase-2/prostaglandin E2 (Cox-2/PGE2) was upregulated in macrophages from both human and mouse diabetic wounds and could regulate the downstream macrophage-mediated

Table I. DNA methylation patterns regulating macrophage polarization in diabetic wounds.

First author(s), year	Factor	Regulation of macrophages	DNA methylation/ demethylation status	Related genes	Effects	(Refs.)
Yan, 2018	DNMT1	M1↑	methylation↑	Nox-2, miR-let-7d-3p, Notch1, PU.1, Klf4	Promotes the inflammatory response and inhibits wound repair	(112)
Babu, 2015	- -	M1↑ M2↓	methylation↓ methylation↑	Cfb, Serping1, Tnfsf15, Nrp1, Cxcr4, Plxnd1, Arg1, Cdk18, Fes	Inhibits wound repair	(113)
Davis, 2020	DNMTs	M1↑	methylation↓	COX-2, PGE2	Promotes inflammatory responses and delays wound healing	(114)

DNMT, DNA methyltransferase.

inflammatory response. Their study demonstrated that TGF-β1 was able to induce miR-29b expression in diabetic wound macrophages. Furthermore, miR-29b was able to downregulate the expression of DNMT3b, leading to a hypomethylated state of the Cox-2 promoter that led to increased Cox-2/PGE2 production. This mechanism promotes the polarization of macrophages toward the M1 phenotype, resulting in persistent and unabated local inflammation at the wound site, thereby impeding the tissue repair process following injury (114). Therefore, based on research into epigenetic modifications, the expression of this gene can be inhibited by targeting hypermethylation of the Cox-2 promoter. This intervention has the potential to reverse the inflammatory macrophage phenotype and contribute positively to diabetic wound repair. These findings suggest that aberrant DNA methylation patterns, characterized by both hypermethylation and hypomethylation, may contribute to the increased infiltration of pro-inflammatory macrophages into diabetic wounds, thereby promoting inflammatory responses and impeding wound healing. Consequently, targeting abnormal DNA methylation patterns to reverse the macrophage phenotype holds promise as a potential therapeutic strategy for enhancing diabetic wound recovery.

Histone modification. The nucleosome, composed of ~146 bp of DNA wrapped around histone octamers (H2A, H2B, H3 and H4), serves as the basic structural element of chromatin (115). Histone modifications such as acetylation, methylation, phosphorylation, polymerization and ubiquitination play crucial roles in shaping chromatin structure, maintaining nucleosome stability and regulating gene transcription (116). Histone modification primarily affects arginine, lysine, serine, threonine and tyrosine residues in the N-terminal tails of histone proteins (117). Methylation and acetylation are the most widely studied types of histone modifications. Histone methylation is catalyzed by histone methyltransferases. This modification typically targets lysine and arginine residues on histones and demethylases actively remove the resulting methylation marks. Lysine methylation is a reliable indicator of gene expression control. For example, lysine methylation at position 4 of H3 promotes transcriptional activation, whereas the same modification at positions 9 and 27 tends to inhibit transcription (118). Histone acetylation is a dynamic modification that occurs primarily at the relatively conserved N-terminal lysine positions of H3 and H4. This process is mediated by the coordination between histone acetyltransferases and histone deacetylases. Lysine acetylation often leads to transcriptional activation and deacetylation during gene silencing (119,120). Histone modification has emerged as an attractive target for regulating macrophage phenotypes in a number of diseases. For instance, SET and MYND domain-containing protein (SMYD)3, a histone lysine methyltransferase of the SMYD family, promotes macrophage conversion from M1 to M2 by activating the tricarboxylic acid cycle and regulating the transcriptional activities of metabolic enzymes such as citrate synthase, succinate dehydrogenase complex subunit C and pyruvate carboxylase (121). Enhancer of zeste homolog 2 functions as a histone methyltransferase that induces trimethylation of lysine 27 residue of histone H3 (H3K27) (H3K27me3) to modulate the polarization of liver macrophages from M2 to M1. This process contributes to the development and progression of autoimmune hepatitis and autoimmune reactions (122).

Histone modification has been shown to potentially regulate macrophage phenotypes in diabetic wounds (Table II). Mixed-lineage leukemia 1 (MLL1) serves as a biomarker of inflammation and a key factor in macrophage activation (123). During the early inflammatory phase of normal wound healing, MLL1 is upregulated in macrophages. MLL1 is also a histone methyltransferase specific to the lysine 4 residue of histone H3 (H3K4). MLL1 elevates H3K4me3 at the NF-κB binding site, initiating pro-inflammatory macrophage-mediated wound inflammatory storms that impede wound healing. The timing of MLL1 expression in prediabetic wound macrophages corresponds to the temporal changes in inflammation levels in prediabetic mouse models, with early reduction and late elevation (124). Similarly, research has indicated that MLL1 mediates the alteration of H3K4me3 on the TLR4 promoter in macrophages within diabetic wounds, subsequently activating the transcription of the TLR4 gene and facilitating the

Table II. Histone modification regulating macrophage polarization in diabetic wounds.

First author(s), year	Factor	Regulation of macrophages	Histone modification	Related genes	Effects	(Refs.)
Kimball, 2017	MLL1	M1↑	Histone methylation	NF-κB	Promotes the inflammatory response	(124)
Kimball, 2019	Setdb2	M1↓ M2↑	Histone methylation	NF-κB	Inhibits inflammation and promotes tissue repair	(126)
Davis, 2020	Jmjd3	M1↑	Histone demethylation	NF-κB	Promotes the inflammatory response	(127)
Gallagher, 2015	Jmjd3	M1↑	Histone demethylation	IL-12	Promotes the inflammatory response	(78)
denDekker, 2020	MOF	M1↑	Histone acetylation	NF-κB	Promotes the inflammatory response	(130)
Karnam, 2023	HDAC3	M1↑ M2↓	Histone deacetylation	-	Promotes inflammation, inhibit angiogenesis and delays wound healing	(136)

MLL1, Mixed-lineage leukemia 1; Setdb2; SET domain bifurcated 2; Jmjd3, jumonji domain containing 3; MOF, Males absent on the first; HDAC3, histone deacetylase 3.

polarization of M1 macrophages. This can result in the dysregulation of inflammation and impairment of wound healing in diabetes (74). This suggests that MLL1, a potential therapeutic target for diabetic refractory wounds, plays an essential role in determining the wound macrophage phenotype through histone modifications. SET domain bifurcated 2 (Setdb2) functions as a histone methyltransferase that specifically targets histone H3 lysine 9 (H3K9) for methylation, thereby modulating the chromatin structure and silencing gene expression (125). Kimball *et al* (126) found that Setdb2 can act as a brake on the inflammatory response in normal wounds. By contrast, Setdb2 expression is markedly reduced in diabetic wounds, thus allowing unrestricted expression of inflammatory genes. Following a typical wound injury, the elevation of Setdb2 expression in macrophages results in an augmentation of H3K9me3 levels at the NF-κB binding site on the promoter of the gene that stimulates inflammation. This phenomenon culminates in the suppression of gene transcription, thereby facilitating the attenuation of wound inflammation and the transition to the proliferative stage. The regulation of Setdb2 expression in wound macrophages is controlled by IFN-β, which targets the JAK/STAT1 pathway at the end of the inflammatory phase. However, disruption of the IFN-β-Setdb2 regulatory axis within diabetic wound macrophages results in a failure of the phenotype transition necessary for macrophage repair, which in turn delays wound healing (126). Setdb2, with its powerful function of modulating macrophage plasticity, may represent a promising new target for treating refractory diabetic wounds.

H3K27me3 in the promoter region inhibits gene transcription and effectively represses gene expression. Jumonji domain-containing protein-3 (Jmjd3) is a histone demethylase that is specific to H3K27. Upregulation of Jmjd3 leads to the inhibition of histone methylation and activation of gene transcription. It has been shown that palmitate stimulation can increase the expression of Jmjd 3, thereby inducing macrophages to enter a pro-inflammatory state and upregulating inflammatory cytokine levels by removing the inhibitory H3K27me3 marker on the promoter of the NF-κB regulatory gene. Inhibitors of Jmjd3 may suppress the expression of NF-κB inflammatory genes via histone modification pathways and enhance diabetic wound healing by modulating the macrophage phenotype (127). M1 macrophages secrete pro-inflammatory factors, such as IL-12, to initiate an inflammatory immune response. Gallagher *et al* (78) discovered that a significant increase in Jmjd3 expression on the IL-12 promoters of diabetic wound macrophages results in the specific removal of methyl groups from H3K27me3 by Jmjd3, effectively eliminating the inhibitory function of H3K27me3. This leads to an increased expression of IL-12 and continuous activation of pro-inflammatory macrophages, which keeps wounds in the inflammatory phase and makes the transition to the proliferative phase more difficult, resulting in delayed wound healing. However, the H3K27 demethylase inhibitor GSK-J4 enhances H3K27me3-mediated inhibition of the IL-12 promoter and effectively reverses IL-12 expression in the macrophages (78). Given these mechanisms, targeting histone demethylases to regulate macrophage-mediated inflammation may represent a novel approach to correcting diabetic wound healing.

Males absent on the first (MOF) is a histone acetyltransferase that selectively acetylates H4K16 to enhance gene transcription (128,129). High expression of inflammatory cytokines mediated by NF-κB in diabetic wound macrophages leads to chronic inflammation and impedes transition to the proliferative phase. MOF has been shown to be overexpressed in macrophages within diabetic wounds, where it facilitates the expression of inflammatory genes by acetylating histone H4K16 on NF-κB-mediated inflammatory gene promoters, thereby contributing to the delayed healing of diabetic

Table III. Non-coding RNAs regulating macrophage polarization in diabetic wounds.

First author(s), year	Factor	Regulation of macrophages	Target	Effects	(Refs.)
Hu, 2020	lncRNA GAS5	M1↑	STAT1	Promote inflammation	(143)
Kuang, 2023	MALAT1	M2↑	miR-1914-3p, MFGE8, TGFB1, SMAD3	Promote diabetic wound healing	(144)
Ti, 2015	miR-let-7b	M2↑	TLR4/NF-κB/STAT3/AKT	Improve inflammation	(171)
Moura, 2019; Ye, 2017	miR-155	M1↑	-	Promote inflammation	(149,150)
Peng, 2022	miR-146a	M2↑	TLR4/NF-κB	Improve wound healing	(151)
Zhou, 2023	miR-146a-5p	M1↓ M2↑	TRAF6	Improve inflammation, promote proliferation, migration and angiogenesis of HUVECs	(174)
Hao, 2021	miR-145a-5p	M2↑	-	Promote inflammatory regression and tissue remodeling	(152)
Yang, 2023	miR-203a-3p	M2↑	SOCS3/JAK2/STA T3	Improve inflammation, promote collagen deposition and angiogenesis in granulation tissue	(176)
Liechty, 2020	miR-21	M1↑	pTEN, ROS	Promote inflammation	(153)
Xia, 2023	miR-222-3p	M2↑	Bim	Improve inflammation	(161)
Shi, 2022	circ-Snhg11	M2↑	miR-144-3p, HIF-1α	Promote angiogenesis and inhibit endothelial cell damage induced by hyperglycemia	(190)

lnc, long non-coding; mi, micro; circ, circular; MALAT1, metastasis-associated lung adenocarcinoma transcript 1.

wounds. The expression of MOF in macrophages is regulated by TNF-α. Inhibition of TNF-α has been shown to reduce the level of MOF in macrophages and suppress the inflammatory response at the wound site, thereby facilitating diabetic wound repair. Targeting MOF with TNF-α has the potential to reverse the pro-inflammatory macrophage phenotype in diabetic wounds, thereby representing a promising avenue for chronic diabetic wound treatment (130). Histone deacetylase 3 (HDAC3) has been shown to trigger the inflammatory response and suppress the anti-inflammatory phenotype in macrophages (131-133). HDAC3 expression is upregulated in both human and mouse diabetic wounds, when compared with corresponding levels in normal wounds (134-136). BG45 is a selective HDAC3 inhibitor that has been proven to effectively reverse the macrophage phenotype, reduce the expression of pro-inflammatory factors secreted by M1 macrophages and increase the levels of anti-inflammatory pro-healing factors secreted by M2 macrophages. Furthermore, BG45 treatment also decreases the number of neutrophils and macrophages that infiltrate the diabetic wounds. Overall, BG45 facilitates wound healing by enhancing the M2 phenotype (Arg-1, CD206 macrophages) and promoting the expression of wound-healing markers such as CD31, VEGF and colligation-1A, while inhibiting the expression of IL-1β. It was hypothesized that HDAC3 delays wound healing by inhibiting the phenotypic switch from M1 to M2, thus negatively regulating angiogenesis and increasing the infiltration of both neutrophils and macrophages. Therefore, the development of corresponding regulators of histone modifications has significant potential for advancing diabetic wound healing (136). Regulation of the macrophage phenotype in diabetic wounds and the promotion or delay of wound healing can be achieved through histone modifications such as methylation, demethylation, acetylation and deacetylation. Therefore, the development of corresponding regulators of histone modifications holds significant potential for advancing diabetic wound healing.

ncRNAs. ncRNAs have emerged as potential novel biomarkers. These molecules are transcribed from the genome, do not encode proteins and are involved in regulating the expression levels of certain genes that are crucial for orderly cell differentiation and development (137,138). These RNAs have markedly enhanced our understanding of gene expression regulatory networks and offer novel targets and foundations for disease diagnosis, treatment and prevention. In recent years, advancements in high-throughput sequencing technology and bioinformatics have revealed the functions and mechanisms of ncRNAs. Among these, the primary components consist of long non-coding RNAs (lncRNAs), miRNAs and circular RNAs (circRNAs). Accumulating evidence indicates that ncRNAs play an instrumental role in influencing the phenotypes of macrophages and offer a potential avenue for therapies targeting diabetic wounds (Table III).

lncRNAs. lncRNAs are an important part of gene regulatory networks that can affect gene expression in various ways,

including chromatin remodeling, transcriptional regulation and post-transcriptional regulation. It was previously hypothesized that lncRNAs were simply byproducts of transcription (139). It has since become evident that they perform various regulatory functions related to chromatin, cytoplasmic mRNA, membraneless nucleosomes and signaling pathways (140). These RNA molecules regulate various physiological processes such as immunity, inflammation, proliferation, cell differentiation and cell survival (141). They have emerged as critical regulators of gene expression in a number of human diseases (142). lncRNAs influence the inflammatory response by regulating macrophage polarization, making them significant factors in diabetic wound healing. Hu *et al* (143) discovered a significant increase in the expression of the GAS5 LncRNA in diabetic wounds and human diabetic skin. Further investigations revealed that the overexpression of GAS5 leads to a considerable rise in the expression levels of mRNA markers related to the M1 macrophage phenotype, including inducible nitric oxide synthase (iNOS), TNFα and IL-1β. Conversely, there was no effect on the expression levels of M2 macrophage marker RNAs such as Arg1 and Mrc1. Finally, it was observed that GAS5 knockout boosted diabetic wound healing. This indicates that GAS5 affects wound healing by stimulating the activation of M1 pro-inflammatory macrophages, potentially by inducing the expression of STAT1 (143). Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is a lncRNA that functions as a transcriptional regulator of numerous genes, including those involved in cancer metastasis, cell migration and cell cycle regulation. MALAT1 functions as a competitive RNA by binding diverse miRNAs to execute biological processes. For instance, it upregulates MFGE8 expression by competitively binding to miR-1914-3p, thereby inhibiting TGFB1 and SMAD3, promoting M2 macrophage polarization, enhancing macrophage phagocytosis and reducing apoptosis, thus promoting diabetic wound healing (144).

Although there is limited research on the role of lncRNAs in diabetic wounds, their ability to induce the polarization of pro-inflammatory M1 macrophages and regulate the polarization of pro-healing M2 macrophages suggests that targeting lncRNAs to modulate macrophage phenotypes holds promise for treating diabetic wounds. However, the precise mechanisms of action of lncRNAs remain unclear, warranting further exploration through additional studies.

miRNAs. The miRNA class of ncRNAs is involved in a variety of physiological and pathological processes, including metabolism, proliferation, apoptosis, differentiation and development. They also act as potent gene regulators of a wide range of cellular activities (145,146). Increasing attention is being paid to the role of miRNAs in terms of regulating macrophage plasticity and polarization (147). For example, it has been shown that miR-155 expression significantly influences the polarization of M1 macrophages (148). One group observed miR-155 overexpression in the skin of diabetic mice (149). Local inhibition of miR-155 decreases wound infiltration by T cells and macrophages, leading to improved tissue inflammation and accelerated healing of diabetic wounds (150). However, the precise mediating pathways behind this phenomenon merit further investigation. The expression of miR-146a has been found to be reduced in the macrophages of patients with diabetes. TLR4 is a target gene that is negatively regulated by miR-146. Peng *et al* (151) discovered that overexpressing miR-146a leads to the polarization of M2 macrophages by suppression of the TLR4/NF-κB axis, resulting in improved wound healing of diabetic ulcers. Overexpression of miR-145a-5p inhibits M1 macrophage polarization while promoting M2 polarization in RAW 264.7 macrophages and M2 macrophages promote inflammatory regression and tissue remodeling by releasing growth and anti-inflammatory cytokines, suggesting that this may be an essential mechanism for their therapeutic effect on diabetic wound repair (152). Hyperglycemia induces the expression of miRNA-21, downregulating phosphatase and tensin homolog. This indirectly induces the production of NOX2 and ROS, thereby promoting the polarization of M1 macrophages and the inflammatory response. This may represent another important mechanism for treating refractory non-healing diabetic wounds (153).

Previous studies have indicated that negatively charged miRNAs encounter challenges in terms of penetrating cell membranes and are susceptible to degradation and elimination in the wound microenvironment (154,155). Exosomes are extracellular vesicles found in various bodily fluids that facilitate the transfer of biomolecules and represent key players in intercellular communication. The membrane structure of exosomes protects miRNAs from degradation by enzymes and other chemicals, allowing for stable loading into exosomes and their subsequent transport to target cells for expression (156). Most exosomes carry miRNAs and their combination presents promising prospects for translational medicine (157-159). Previous studies have shown that exosomes isolated from relatively lean donor adipose tissues promote the polarization of macrophages toward the M2 phenotype (160). Xia *et al* (161) found that exosomes extracted from the adipose tissue of a relatively lean donor hindered the expression of the Bim protein, by activating miR-222-3p. This activation induced macrophages to convert to the M2 phenotype, ultimately resulting in reduced inflammation and improved wound healing (161). Epidermal stem cells (EpiSCs) play a critical role in skin wound repair, where they are readily available (162,163). Previous studies have established the potential of EpiSCs to heal wounds associated with diabetes (164,165). JAK2 and STAT3 signaling has been shown to be a key factor regulating the polarization of macrophages into the M2 type. Cytokine signal transduction inhibitor 3 (SOCS3) inhibits JAK kinase activity, thereby blocking the JAK2/STAT3 pathway and serving as a primary negative regulator of its signaling. Enrichment of miR-203a-3p in exosomes originating from EpiSCs SOCS3 expression in macrophages. This activation triggers the JAK2/STAT3 signaling pathway and induces the polarization of M2 macrophages, releasing anti-inflammatory factors and promoting collagen deposition as well as angiogenesis within granulation tissue. As a result, wound healing in diabetes is accelerated (166). The application of mesenchymal stromal cells (MSCs) to skin wounds has shown promise because of their ease of collection and low risk of immune rejection (167-169). MSCs promote skin cell migration, blood vessel development, re-epithelialization of wounds and granulation tissue generation, all of which ultimately accelerate healing (170). The biological properties of MSCs, which facilitate the transition from the inflammatory to proliferative

phases, are crucial for treating wounds with high levels of inflammation that hinder the healing process. Ti *et al* (171) discovered that MiR-let-7b in exosomes derived from MSCs pre-treated with LPS encourage macrophage M2 polarization by suppressing the TLR4/NF-κB/STAT3/AKT signaling pathway, thereby reducing inflammation and promoting diabetic skin wound healing. Bone MSCs (BMSCs) play a major role in tissue repair, particularly in terms of accelerating wound healing (172,173). By suppressing the expression of TRAF6, BMSC-derived exosomes carrying miR-146a-5p stimulate the polarization of M2 macrophages and reduce the polarization of M1 macrophages, leading to the proliferation, migration and angiogenesis of endothelial cells. This results in improved healing of recalcitrant diabetic wounds (174). Overall, miRNA-carrying exosomes have shown significant potential for the treatment of chronic diabetic wounds.

miR-29ab1 has also been shown to play a crucial role in diabetes-associated inflammation and the transformation of macrophage phenotypes (175). Compared with healthy subjects, individuals with diabetes experience a rise in ectopic miR-29ab1, alongside an increase in M1 polarization and elevated levels of IL-1β and TNF-α in skin wounds. After using a Chinese traditional medicine hydrogel containing chitosan and puerarin to treat diabetic wounds, Zeng *et al* (176) observed that inhibiting ectopic miR-29ab1 expression leads to a reduction in IL-1β and TNF-α levels and inhibits the polarization of M1 macrophages within diabetic wounds. This improves the inflammatory response and promotes healing. Overall, miRNAs participate in several diabetic wound-healing processes by regulating M1 vs. M2 polarization, particularly during inflammation and are emerging as promising therapeutic targets for managing diabetes (152,153,174).

Research on miRNAs has reached a mature state, with significant achievements having been demonstrated in the treatment of diabetic wounds. By targeting specific genes, miRNAs can precisely modulate macrophage polarization, offering the potential to enhance the healing environment within diabetic wounds. Furthermore, miRNAs possess certain advantages such as multi-targeting and long-lasting effects that facilitate their broad application (177,178). At the same time, the intricate regulatory network between miRNAs and genes poses a significant challenge to research and applications. Moreover, miRNAs can inadvertently regulate unexpected targets, potentially causing adverse reactions (179). Exosomes, which serve as efficient carriers for intercellular communication, can facilitate the targeted delivery of miRNAs to improve the bioavailability of therapeutic molecules (180). However, there are still challenges associated with exosomes, including their limited capacity and the complexities of separation and purification, that warrant further research before they can be resolved (181).

CircRNAs. CircRNAs are a cohort of biologically active ncRNAs that exist in a closed-loop form (182). Most circRNAs contain multiple miRNA-binding sites and function as miRNA sponges within cells. Some have also been identified as competitive endogenous RNAs (ceRNAs). These ceRNAs compete for miRNA-binding sites, leading to reduced miRNA activity and consequent effects on gene expression and protein synthesis (183-185). Increasing evidence has linked circRNAs to the mechanisms underlying various diseases, including diabetic ulcers (186,187). The expression of circRNA Snhg11 decreases significantly under hyperglycemic conditions. Compared with healthy controls, patients with diabetes have been shown to have increased expression of miR-144-3p, which is the downstream target of circRNA Snhg11 (188). Exosomes derived from adipose stem cells (ADSCs) can enhance fibroblast migration and proliferation, as well as collagen synthesis, to accelerate skin wound healing (189). The high expression of circRNA Snhg11 in exosomes derived from hypoxic-preconditioned ADSCs acts as a sponge for miR-144-3p, thereby augmenting HIF-1α expression, facilitating angiogenesis and M2 macrophage polarization, suppressing hyperglycemia-induced endothelial cell damage and expediting diabetic wound healing (190).

Overall, circRNAs represent potential targets for treating diabetic foot ulcers and have a range of potential applications. However, relatively few studies have been conducted on these molecules to date. Further studies are therefore warranted to explore their regulatory mechanisms.

6. Interaction of epigenetic modifications regulating macrophage polarization in diabetic wounds

In the diabetic environment, various epigenetic modifications, including DNA methylation, histone modification and regulation of ncRNAs, may interact in complex ways to modulate macrophage polarization by influencing the expression of specific genes, thereby either promoting or delaying wound healing. A number of studies have shown that ncRNAs can regulate the expression and activity of DNMT through various mechanisms (191,192). For instance, certain miRNAs can directly target DNMT mRNA, inhibit its translation, or facilitate its degradation to reduce its expression. This reduction may result in the hypomethylation of specific gene promoter regions and impact gene expression and cellular function. Davis *et al* (114) discovered that, in diabetic wounds, TGF-β1 can stimulate miR-29b expression within local macrophages to inhibit DNMT3B-mediated hypermethylation of the Cox-2 promoter, thereby enhancing the production of Cox-2/PGE2 and leading to a sustained pro-inflammatory phenotype and impaired macrophage function that impacts wound healing. A wide range of diverse inter-regulatory relationships exist among ncRNAs. Specifically, lncRNAs and circRNAs have been the focus of extensive research into the regulatory mechanisms that involve miRNAs. lncRNAs can function as molecular sponges for miRNAs, inhibiting their activity, or they can bind with miRNAs to form RNA-induced silencing complexes that participate in gene expression regulation. Closed-loop circRNAs can act as ceRNAs for miRNAs, thereby preventing miRNAs from inhibiting target genes. These reciprocal regulations play pivotal roles in biological processes and their aberrant control is intricately linked to disease progression. MALAT1 competitively binds to miR-1914-3p, while circRNA Snhg11 functions as a sponge for miR-144-3p (144,190). Both of these interactions have the potential to modulate the macrophage phenotype by regulating the expression of target genes, thereby playing a crucial role in diabetic wound healing.

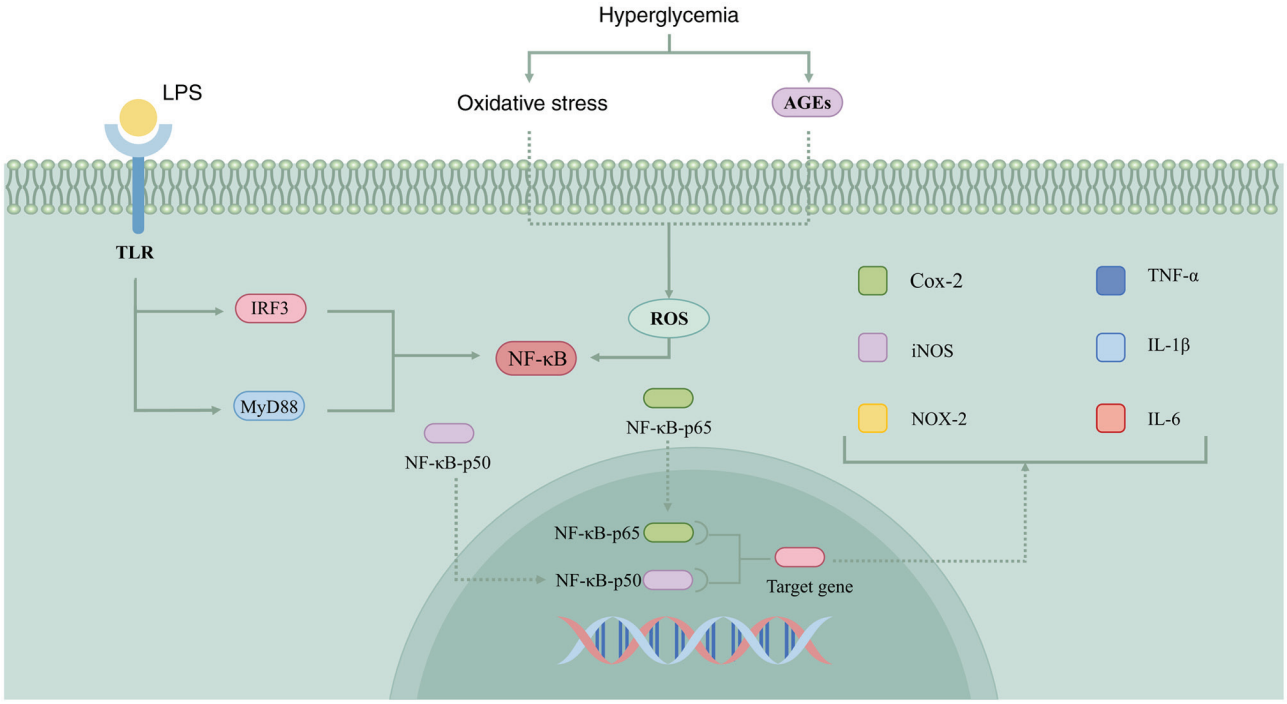

Figure 3. The NF-κB signaling pathway in macrophage polarization. LPS, lipopolysaccharide; AGEs, advanced glycation end products; TLR, Toll-like receptor; IRF3, interferon regulatory factor 3; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor kappa B; ROS, reactive oxygen species; Cox-2, cyclooxygenase-2; TNF, tumor necrosis factor; iNOS, inducible nitric oxide synthase; IL, interleukin; NOX-2, NADPH oxidase 2.

7. Key signaling pathways regulating macrophage polarization

Under the influence of different microenvironments, epigenetics can activate or suppress various signaling pathways, to modulate the differentiation of macrophages into distinct phenotypes. Consequently, the signaling pathway serves as a mediator to some extent. These signaling pathways interact to form an intricate network that collectively regulates macrophage polarization. A thorough exploration of the signaling pathways associated with macrophage polarization is advantageous for enhancing our understanding of the function and biological activity of macrophages and for identifying new targets and strategies for disease treatment.

NF-κB signaling pathway. The NF-κB signaling pathway is a canonical pathway that governs macrophage polarization (Fig. 3). NF-κB has been implicated in the pathogenesis of numerous immune and inflammatory diseases, where it binds to specific gene sequences to initiate gene expression processes, thereby facilitating the production and release of a range of pro-inflammatory mediators (193). TLR serves as a crucial sentinel within the immune system, detecting pathogen invasion and exhibiting expression on a variety of immune and non-immune cell surfaces. It specifically recognizes substances released by invading bacteria and viruses (for example, LPS, mannose, teichoic acid and peptidoglycans) and regulates inflammation and other innate immune responses. TLRs on macrophage surfaces bind to LPS and activate the classical NF-κB pathway through either the MyD88-dependent or the interferon regulatory factor 3 pathway (194). The NF-κB-p65 and NF-κB-p50 proteins are activated and translocated to the nucleus, where they bind to target genes that lead to the release of inflammatory cytokines such as TNF-α, IL-1β, IL-6, COX-2, iNOS and NOX-2 (195). They also play a role in regulating the polarization of macrophages toward the M1 type (196).

Excessive ROS can activate intracellular metabolic pathways such as NF-κB. Hyperglycemic environments may induce excessive oxidative stress in wounds, disrupting the balance between oxidative and antioxidant activities. This can result in the overproduction of ROS and hinder the healing process in diabetic wounds (197,198). Furthermore, the production of pro-oxidant advanced glycation end products (AGEs) in patients with diabetes also stimulates the accumulation of excessive ROS, leading to the activation of the nuclear transcription factor NF-κB (199). Elevated AGE levels can also induce heightened inflammation by modulating macrophage M1 polarization, impeding the transition of diabetic wounds from the inflammatory to the proliferative stage and delaying wound healing (200).

JAK/STAT signaling pathway. The JAK/STAT pathway is primarily responsible for facilitating the signal transduction of cytokine receptors and plays a vital role in a number of biological processes, including cellular growth and proliferation, inflammatory responses, immune regulation and the modulation of neural function (201). In addition, it serves as a significant signaling pathway for macrophage polarization (Fig. 4). The presence of cytokines, growth factors and chemokines in diabetic wounds can trigger activation of the JAK-STAT pathway. JAK refers to a family of tyrosine kinases comprising four types: JAK1, JAK2, JAK3 and TYK2. The STAT protein family comprises seven major members: STAT1,

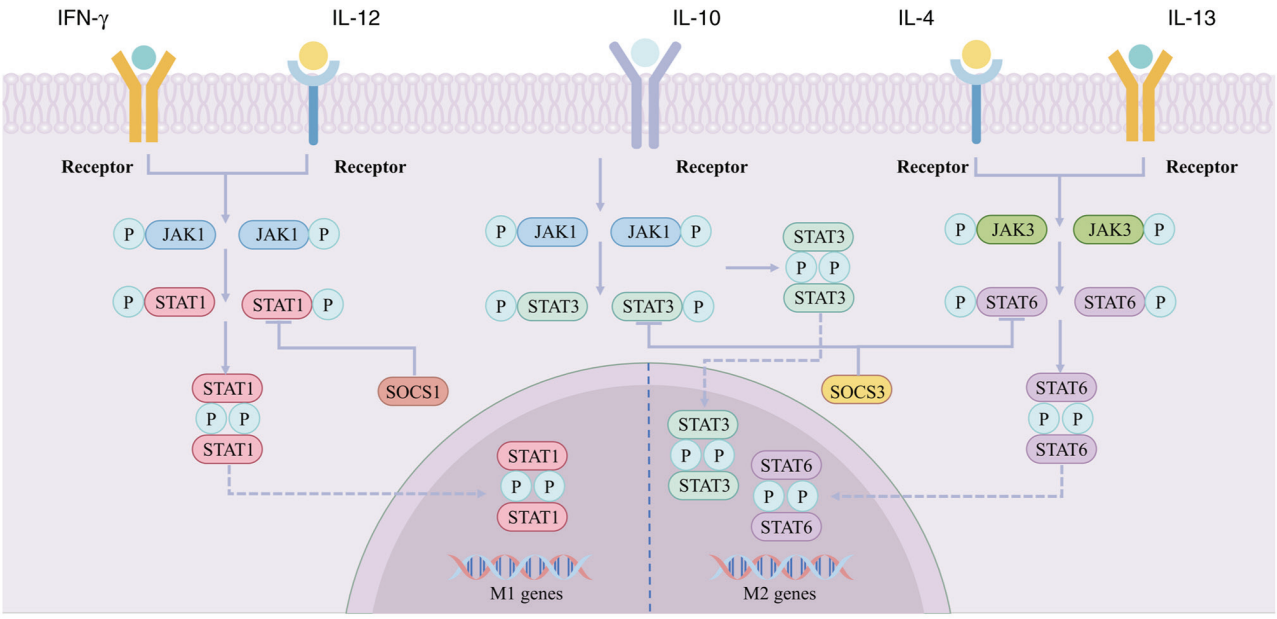

Figure 4. The JAK/STAT signaling pathway in macrophage polarization. IFN, interferon; IL, interleukin.

STAT2, STAT3, STAT4, STAT5a, STAT5b and STAT6. These proteins are activated by various cytokines and exhibit diverse biological effects. Among these, STAT1, STAT3 and STAT6 are the primary members of the STAT family that regulate macrophage polarization and the inflammatory response. Specifically, IFN-γ and IL-12 bind to their respective receptors, leading to the activation of JAK and subsequent phosphorylation of STAT1. This process results in the polarization of M1-type macrophages, which in turn leads to the production of a multitude of pro-inflammatory factors that initiate and amplify the inflammatory response of the body against pathogen invasion (202). IL-4 and IL-13 both stimulate the M2 polarization of macrophages via the JAK3/STAT6 pathway, whereas IL-10 promotes the M2 polarization of macrophages through the JAK1/STAT3 pathway (203,204).

SOCS1 and SOCS3 are rapidly upregulated following activation by IFN-γ or LPS (205). SOCS1 is a direct target of STAT1 and serves as a negative feedback regulator of the JAK1-STAT1 pathway (206). Increased phosphorylation of JAK1-STAT1 suppresses the expression of SOCS1, promoting the M1-type polarization of macrophages. Conversely, elevated SOCS1 expression inhibits JAK1-STAT1 pathway phosphorylation, leading to the inhibition of macrophage M1 polarization (207). SOCS3 can negatively modulate the expression of STAT3 and STAT6, preventing the excessive activation of M2-type macrophages (166,208). Therefore, SOCS proteins represent potential targets for modulating JAK/STAT signaling in disease states. Studies have shown that exosomal miR-203a-3p derived from EpiSCs induces M2 macrophage polarization by regulating the SOCS3/JAK2/STAT3 axis and facilitating diabetic wound healing (166). Targeting the JAK/STAT signaling pathway to intervene in macrophage polarization thus represents a promising therapeutic approach for treating diabetic wounds.

Notch signaling pathway. The Notch signaling pathway is a highly conserved mechanism that exerts a significant influence on the development of various biological organs and tissues, regulating processes such as cell differentiation, tissue homeostasis maintenance, immune function and neurodevelopment (209). The Notch receptor, a type I transmembrane protein comprising Notch1, 2, 3 and 4, is located on the plasma membrane in its inactive state. Its ligands are members of the DSL protein family, encompassing Jagged (JAG) 1, JAG2, delta-like (DLL)1, DLL3 and DLL4. The Notch signaling pathway is a classical signaling pathway involved in macrophage polarization. When JAG1 binds to a Notch receptor (1-4), it leads to cleavage of the receptor, resulting in the translocation of the Notch intracellular domain (NICD) to the nucleus. Once there, the NICD forms complexes with the DNA-binding protein Suppressor of Hairless, Lag-1 and the coactivator master-mind-like family, leading to the transcriptional activation of downstream target genes such as Hes1, 2 and 5. This process promotes M1 macrophage polarization and induces the expression of related genes.

Activation of the Notch signaling pathway via the TLR signaling cascade can also modulate the polarization of mononuclear macrophages toward the pro-inflammatory M1 phenotype. The expression of Notch1 is upregulated by LPS through MyD88-dependent or-independent pathways, leading to the activation of the downstream genes Hes1 and Deltex (124). Activation of the Notch signaling pathway can upregulate IL-6 and iNOS secretion, downregulate IL-10 production and induce macrophage polarization toward M1. Furthermore, the Notch signaling pathway can enhance inflammatory responses through synergistic interactions with the NF-κB signaling pathway. In one study, Notch1 receptor expression was found to be significantly increased in M1 macrophages. The reversal of Notch1 receptor inhibition was shown to induce a shift from the M1 macrophage phenotype to the M2 one, thereby initiating an anti-inflammatory response (210). Given the pivotal role of the Notch pathway in modulating the phenotypes of wound macrophages and the inflammatory response *in vivo* (Fig. 5), it is evident that targeting Notch signaling pathway

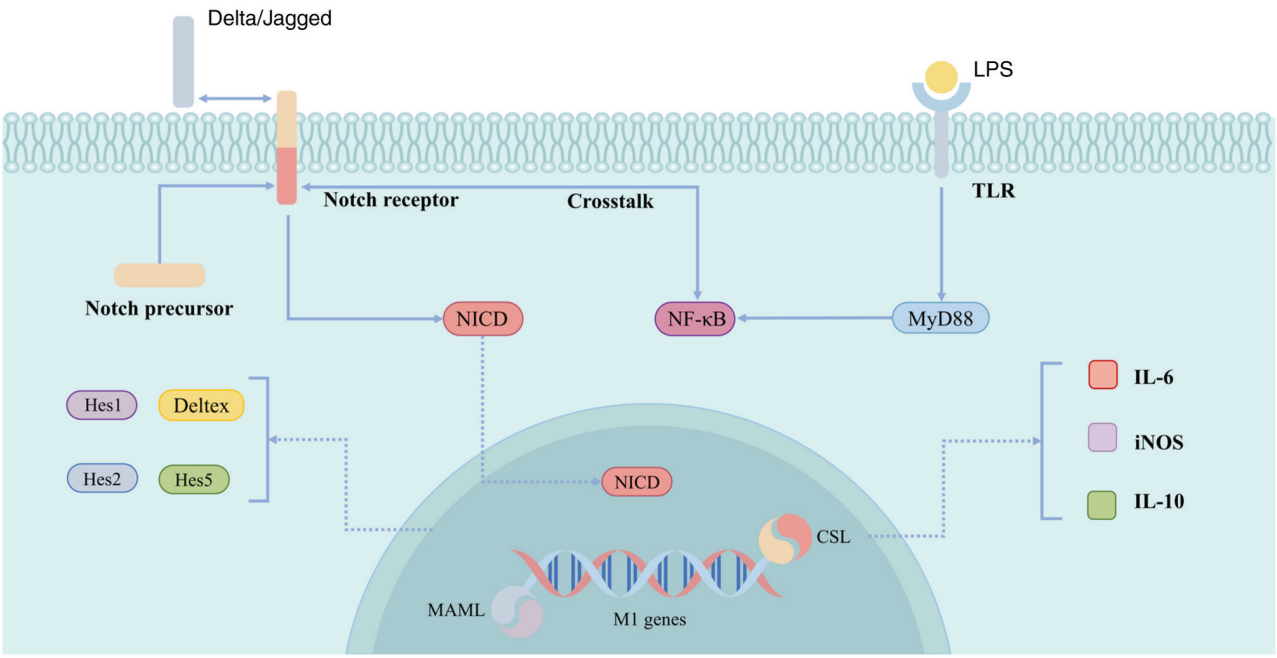

Figure 5. The Notch signaling pathway in macrophage polarization. LPS, lipopolysaccharide; TLR, Toll-like receptor; NICD, Notch intracellular domain; NF-κB, nuclear factor kappa B; MyD88, myeloid differentiation primary response 88; iNOS, inducible nitric oxide synthase; IL, interleukin; CSL, Suppressor of Hairless, Lag-1; MAML, mastermind-like protein.

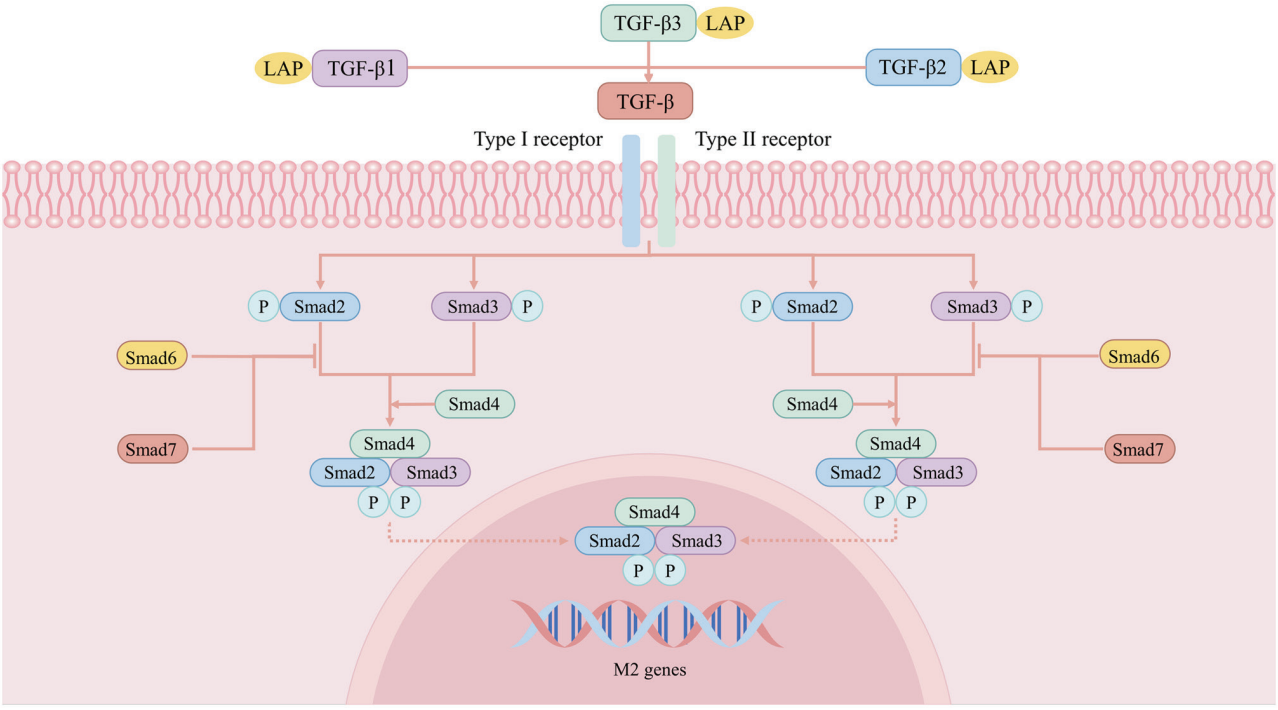

Figure 6. The TGF-β/SMAD signaling pathway in macrophage polarization. LAP, latency-associated peptide.

regulation represents a crucial direction for the treatment of diabetic foot ulcers.

TGF-β/SMAD signaling pathway. The TGF-β/Smad signaling pathway can be involved in the regulation of cell growth and differentiation, regulation of the ECM, immune regulation, wound healing, organ fibrosis and other processes. The regulation of the TGF-β/Smad pathway in macrophage polarization has received increasing attention in recent years (Fig. 6). There are three isomers of TGF-β: TGF-β1, TGF-β2 and TGF-β3. Smad proteins (Smad1-9) play crucial roles as downstream signaling molecules in the TGF-β pathway. TGF-β initially interacts with the type II receptor and subsequently forms a receptor complex by binding to the type I receptor, leading to phosphorylation and activation of the type I receptor domain. Activated type I receptors initiate intracellular signal

transduction by phosphorylating the C-terminus of specific receptor-regulated SMADs (R-SMADs) (211,212). Under the action of SMAD4, one common Smad forms heteropolymers with two R-Smads (SMAD2 and/or SMAD3), which then translocate to the nucleus and initiate the transcription of target genes (213). These SMADs also induce the transcription of inhibitory SMADs (SMAD6 and SMAD7), thereby initiating negative feedback loops that suppress signaling. Research has consistently demonstrated a correlation between M2 macrophage polarization and increased TGF-β pathway activation. For instance, growth differentiation factor 3 from the TGF-β superfamily has been shown to inhibit M1 polarization and facilitate M2 polarization through the promotion of Smad2 and Smad3 phosphorylation (214). The TGF-β/Smad signaling pathway can also facilitate the activation of the PI3K pathway to induce the polarization of M2 macrophages. Therefore, promoting diabetic wound healing by modulating the TGF-β/Smad signaling pathway to activate M2 polarization in macrophages may also represent a promising therapeutic direction.

8. Conclusion and perspectives

The present review provides an overview of the current epigenetic regulation of macrophage polarization in diabetic wounds. From the perspective of macrophages, the challenge of diabetic wound healing primarily stems from the excessive activation of M1 macrophages and hindered transition from the M1 state to the M2 one (76,81,215). Various epigenetic modifications, including DNA methylation, histone modification and ncRNA modification, can modulate the functional behavior of macrophages within the diabetic wound microenvironment by regulating gene expression, thereby affecting wound healing. Targeting epigenetic modifications to modulate macrophage phenotype and function has recently emerged as a promising therapeutic strategy for diabetic wound healing.

However, current research on the matter would benefit greatly from further exploration and refinement. Despite the powerful regulatory ability of epigenetics on gene expression, this field is still in its early stages, particularly with regard to lncRNAs and circRNAs, which have received comparatively little attention. The precise mechanisms behind this form of regulation warrant further investigation. While existing studies have primarily focused on individual epigenetic modifications or regulatory pathways, these modifications actually form a complex network of interactions *in vivo* that complicate the regulatory process and present challenges in terms of clinical applications. Furthermore, considering that current research has been limited to animal and cell models, it is imperative to conduct additional clinical studies to facilitate the translation of basic research into clinical applications (113,149).

Currently, research on macrophages in diabetic wounds primarily focuses on the inflammatory response. Notably, epigenetic factors may also influence additional mechanisms of diabetic wound healing through macrophage polarization, including angiogenesis, re-epithelialization and ECM remodeling. However, there is still a scarcity of studies addressing these dimensions to provide a comprehensive overview; therefore, future investigations are expected to explore this process in greater depth. The healing of diabetic wounds represents a complex process involving multiple cell types, cytokines and signaling pathways. The epigenetic regulation of macrophage polarization represents just one aspect of the process. Its synergistic relationships with other relevant factors such as glycemic control, neurovascular function and overall immune system regulation remain unclear. Future research should emphasize the comprehensive analysis of epigenetic regulatory networks, foster interdisciplinary collaboration, develop more precise and effective treatment methods and actively promote clinical applications to provide practical treatment options for patients with diabetic wounds, while improving their quality of life and prognoses.

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Authors' contributions

The manuscript was written by JS. Images were obtained by YW and YC. The manuscript was edited and revised by XS and ZZ, respectively. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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