Cell migration in diabetic wound healing: Molecular mechanisms and therapeutic strategies (Review)

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Received April 6, 2025; Accepted May 21, 2025

DOI: 10.3892/ijmm.2025.5567

Abstract. Diabetic wounds are among the most prevalent forms of chronic wound and are a prominent clinical challenge in contemporary healthcare. Impaired cell migration represents one of the key mechanisms underlying the difficulty in diabetic wound healing, involving multiple cell types including neutrophils, macrophages, keratinocytes, endothelial cells and fibroblasts. Under the influence of pathological factors, including hyperglycemia, chronic inflammation, oxidative stress and an abnormal microenvironment, the cell migration becomes impaired, leading to delayed wound healing. Key signaling pathways including Rho GTPase, PI3K/Akt, TGF-β/Smad and Wnt/β-catenin are involved in the regulation of cell migration. Non-coding RNAs exert a pivotal influence on diabetic wound healing by modulating these signaling pathways or their downstream targets. Notably, stem cells and their exosomes, growth factor therapy, drug-loaded dressings and traditional Chinese medicine can modulate cell migration via non-coding RNAs and associated signaling pathways, thereby establishing a therapeutic regulatory axis. This review systematically consolidates advances in this field, providing novel insight into the mechanisms of cell migration in diabetic wounds and facilitating the development of innovative therapeutic strategies.

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Key words: diabetic wound, cell migration, signaling pathway, non-coding RNA, mechanism, therapy

Contents

1. Introduction

Diabetic wounds are a prevalent and severe complication of diabetes mellitus, characterized by impaired healing, increased infection risk and failure to achieve complete closure (1,2). Among reported cases of diabetes mellitus, ~25% are at risk of developing diabetic wounds (3). Diabetes disrupts wound healing, potentially leading to chronic foot ulcers, lower extremity amputation and increased mortality (4,5). Moreover, the high treatment costs of diabetic wounds place an economic burden on healthcare systems (6). The global prevalence of diabetes was estimated at 529 million cases in 2021, with projections indicating a potential surge to 1.31 billion by 2050 (7). With the increasing prevalence of diabetes, the incidence of diabetic wounds is expected to rise, posing a challenge to public health systems.

The difficulty in diabetic wound healing primarily arises from a multifactorial combination of neuropathy, vasculopathy and infection, which collectively exacerbate the complexity and challenges of wound management (8). At the cellular level, a key factor influencing wound healing is the efficient and rapid migration of cells to the wound center (9). This involves multiple cell types, including neutrophils, macrophages, keratinocytes, fibroblasts and endothelial cells (ECs) (10-14). The diabetic microenvironment impairs the migratory capacity of cells via multiple mechanisms, thereby contributing to delayed

wound healing (15,16). Consequently, understanding of cell migration regulatory mechanisms is key to formulate novel therapeutic interventions for diabetic wounds.

The present study aimed to summarize cell migration dysfunction in diabetic wounds and the mechanisms underlying cell migration impairment induced by hyperglycemia, chronic inflammation, oxidative stress and an abnormal microenvironment. Based on key signaling pathways, non-coding RNAs (ncRNAs) and their associated molecular networks that regulate cell migration in diabetic wounds, the present study further explores innovative therapeutic strategies to enhance cell migration, as well as therapeutic challenges and future research directions, offering innovative perspectives to advance diabetic wound clinical management.

2. Cell migration

Cell migration is a synchronized and dynamic phenomenon that generally commences with the polarization of cells (Fig. 1) (17). Cell polarization occurs when migrating cells detect chemotactic signals such as chemokines, growth factors or extracellular matrix (ECM) cues. This process involves coordinated activity of key molecular players, including Rho GTPases, integrins, phosphoinositide 3-kinase (PI3K), microtubules and vesicular transport systems, to establish front-rear polarity and generate distinct functional patterns between the leading and trailing edges (18). Actin polymerization at the leading edge drives membrane protrusion, forming pseudopodial structures such as lamellipodia and filopodia, facilitating cell extension. The extended pseudopodia adhere to the ECM through adhesion molecules such as integrins, forming focal adhesions that mechanically link the cytoskeleton to the extracellular environment (19). Through myosin-mediated contractile forces, the cell body is propelled forward, driving translocation. Disassembly of adhesion complexes at the trailing edge permits tail detachment from the substrate, finalizing the de-adhesion process (20). The coordinated actions of the anterior and posterior regions complete one cycle of migration.

3. Cell migration in normal wound healing

Cell migration is a critical and continuous process in wound healing, integral to every phase of repair. Various cell types facilitate tissue regeneration, notably the migration of neutrophils, macrophages, keratinocytes, vascular ECs and fibroblasts. Through precise migration and functional modulation, these cells contribute to pathogen clearance, angiogenesis promotion, ECM secretion and epidermal barrier reconstruction. Their migration is regulated by signaling molecules and microenvironmental factors to ensure efficient repair (21,22). Investigating these migration mechanisms not only enhances understanding of the physiological principles governing wound healing but also offers a solid theoretical framework for potential therapeutic strategies for managing chronic wounds and impaired repair.

Neutrophil migration. Neutrophils are the initial immune responders during wound healing, rapidly mobilizing to injury sites via intricate migratory mechanisms (Fig. 2A). Neutrophils detect 'find-me' signals, including damage-associated molecular patterns (DAMPs), hydrogen peroxide, lipid mediators and chemokines, via surface receptors such as G protein-coupled receptors (GPCRs), integrins, Fc receptors and pattern recognition receptors. These signals, released from injured tissues, drive neutrophil directed migration to the site of damage and trigger inflammatory responses (23,24). The migration process is coordinated by ~30 distinct neutrophil receptors and multiple signaling pathways. Neutrophils recognize fMet-Leu-Phe (fMLP) released by damaged cells and bacteria through specific formyl peptide receptors (25). Mast cells augment vascular permeability and facilitate neutrophil infiltration via the release of histamine, chemokines and inflammatory mediators. Macrophages identify DAMPs or pathogen-associated molecular patterns, leading to their activation and guidance of neutrophils to the site of injury (26). Local cells and neutrophils release chemokines, including C-C motif ligand 3 (CCL3) and C-X-C motif ligands 1/2 (CXCL1/2). These chemokines interact with their receptors (CCR1, CXCR1, and CXCR2) to guide neutrophil migration (21). Furthermore, neutrophils produce leukotriene B4, which binds leukotriene B4 receptor 1 to drive neutrophil recruitment from distant tissue (27). During migration, neutrophils utilize adhesion molecules (such as CD11b) and downstream signaling pathways (such as Src and Rho GTPases) to drive actin remodeling and membrane extension, enabling transendothelial migration and deep tissue infiltration through ECM degradation (23,28). At the wound site, neutrophils perform essential antimicrobial functions through various mechanisms, including the secretion of toxic granules, production of reactive oxygen species, phagocytosis of invading pathogens and the formation of neutrophil extracellular traps (29,30). Additionally, they secrete proteases to remodel the ECM, recruit immune cells and facilitate tissue repair. While these functions are essential for combating infections, they can also lead to bystander effects, causing tissue damage, particularly in chronic inflammatory conditions (31,32). Upon completion of their task, neutrophils are cleared by macrophages or re-enter the vasculature via reverse migration, thereby contributing to the resolution of inflammation (33). Excessive neutrophil retention or migration defects may sustain inflammatory responses and hinder healing processes, contributing to chronic wound pathogenesis (34). The CXCL12-CXCR4 axis serves a pivotal role in neutrophil retention at inflammatory sites. Inhibition of this pathway may enhance inflammation resolution by inducing neutrophil reverse migration (35).

Monocyte/macrophage migration. Following tissue injury, a coordinated chemokine cascade drives monocyte and macrophage trafficking to the wound site (Fig. 2B). Damaged cells release calcium waves that activate NADPH oxidase, producing hydrogen peroxide, which, together with calcium, serves as an early signal to mobilize immune cells to the injury site (36-38). Additionally, DAMPs such as high-mobility group box 1 and ATP, along with inflammatory cytokines such as IL-1 and IL-33, activate resident macrophages, prompting the release of pro-inflammatory factors that establish a localized inflammatory environment (39). During the initial injury phase, monocytes expressing CCR2 migrate in response to CCL2 signaling. These monocytes simultaneously

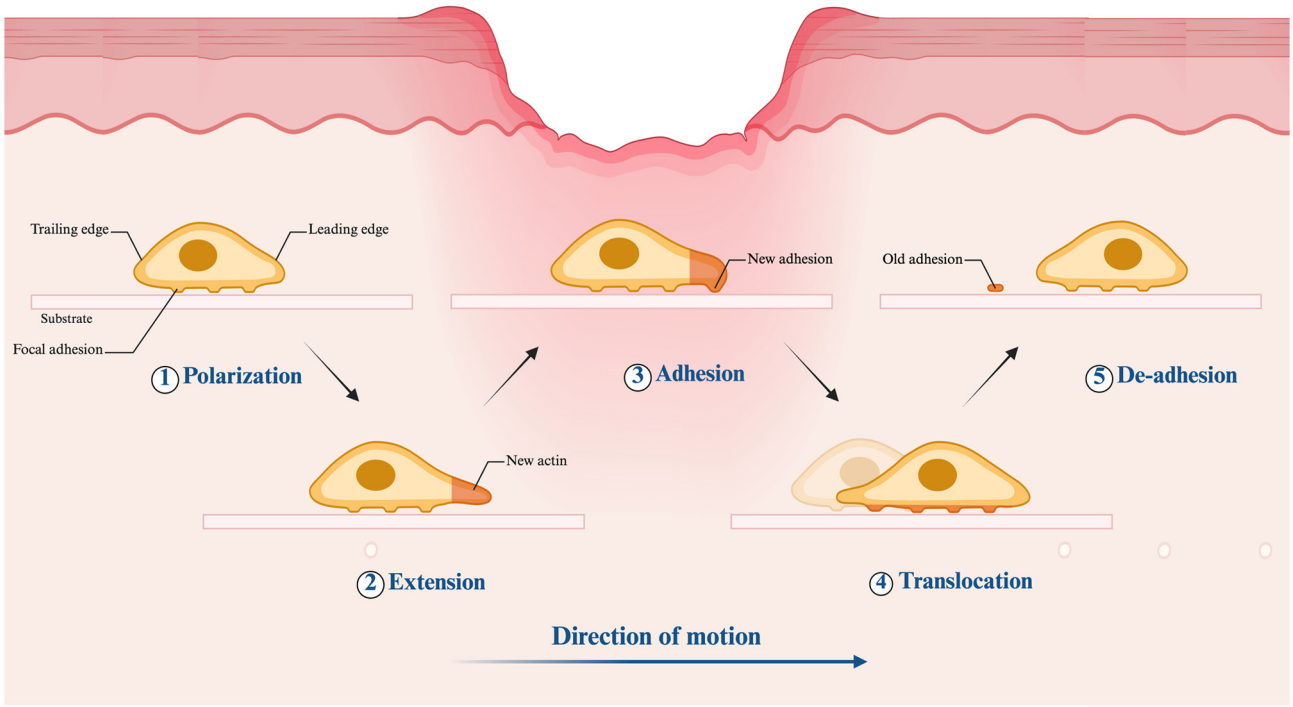

Figure 1. Key stages of cell migration. Polarization involves establishment of front-rear polarity. This is followed by extension of pseudopodial structures at the leading edge and anchorage of pseudopodia to the extracellular matrix via adhesion complexes. Cell body contraction generates traction forces for forward movement. Dissociation of adhesion structures at the trailing edge completes the migration cycle. Created with BioRender.com.

express and respond to CCL7, promoting the recruitment of myeloid cells (monocytes and macrophages) to the injury site (21). Furthermore, the degranulation of platelets and mast cells releases chemokines such as stromal cell-derived factor 1/CXCL12, while hypoxia-inducible factors (HIFs) amplify chemotactic signals, promoting the recruitment of monocytes (23). The clotting mechanism initiated by blood vessel damage further liberates compounds such as unbound heme, exacerbating the inflammatory reaction and drawing monocytes to the site of injury (40). Upon reaching the wound site, monocytes develop into macrophages and serve essential roles throughout the healing process. Initially, M1-polarized macrophages dominate, displaying potent antimicrobial and inflammatory properties (41). As healing progresses, macrophages transition to the M2 phenotype, facilitating inflammation resolution and angiogenesis while orchestrating collagen deposition and ECM remodeling to promote tissue regeneration and functional recovery (42,43).

Keratinocyte migration. Keratinocyte movement is key for successful wound closure, facilitating re-epithelialization and barrier function recovery (Fig. 2C). Following tissue injury, edge-located keratinocytes respond to inflammatory mediators (IL-1, TNF-α) by adopting a flattened morphology, cellular elongation and forming membrane protrusions such as lamellipodia and filopodia (22). These changes are driven by cytoskeletal reorganization, which provides the structural support and mechanical force required for migration. Fibroblasts promote keratinocyte proliferation, migration and differentiation by secreting growth factors such as keratinocyte and hepatocyte growth factors, thereby driving the re-epithelialization of wounds (44). During motility, keratinocytes engage with the ECM via integrin receptors such as αvβ5 and α5β1 while releasing MMPs to remodel temporary matrix proteins (fibrin, fibronectin), thereby promoting cellular migration (45-48). Dynamic regulation of cell-cell and cell-ECM connections, along with increased gap junction communication, ensures coordinated and efficient migration (49). Keratinocytes employ multiple mechanisms for migration, including the 'leapfrog' and 'sliding' models and suprabasal cell dedifferentiation in collaboration with basal cells (22). The leapfrog mechanism proposes that suprabasal cells roll over the leading edge basal cells, undergo dedifferentiation, and subsequently form new migratory leaders within the cohesive epidermal tongue (50). In the sliding mechanism, keratinocytes from the basal layer move forward as a cohesive block at the leading edge, while the overlying cluster of superficial cells is passively dragged along (51). Suprabasal cell dedifferentiation refers to the reversal of differentiation in committed suprabasal keratinocytes, which regain migratory and proliferative capacity to directly contribute to epidermal regeneration. During migration, keratinocytes proliferate and differentiate to form new epithelium, reestablishing the skin barrier. They also regulate local inflammation, promote ECM remodeling and coordinate the activity of neighboring cells through autocrine and paracrine signaling (52). Additionally, keratinocytes adapt their migratory behavior and functional characteristics to the dynamic wound microenvironment, providing key flexibility and support for effective wound repair.

EC migration. New blood vessel formation (angiogenesis) peaks in the proliferative stage of repair, delivering oxygen and nutrients critical for tissue regeneration and functional restoration (53). EC movement is key for vascular restructuring

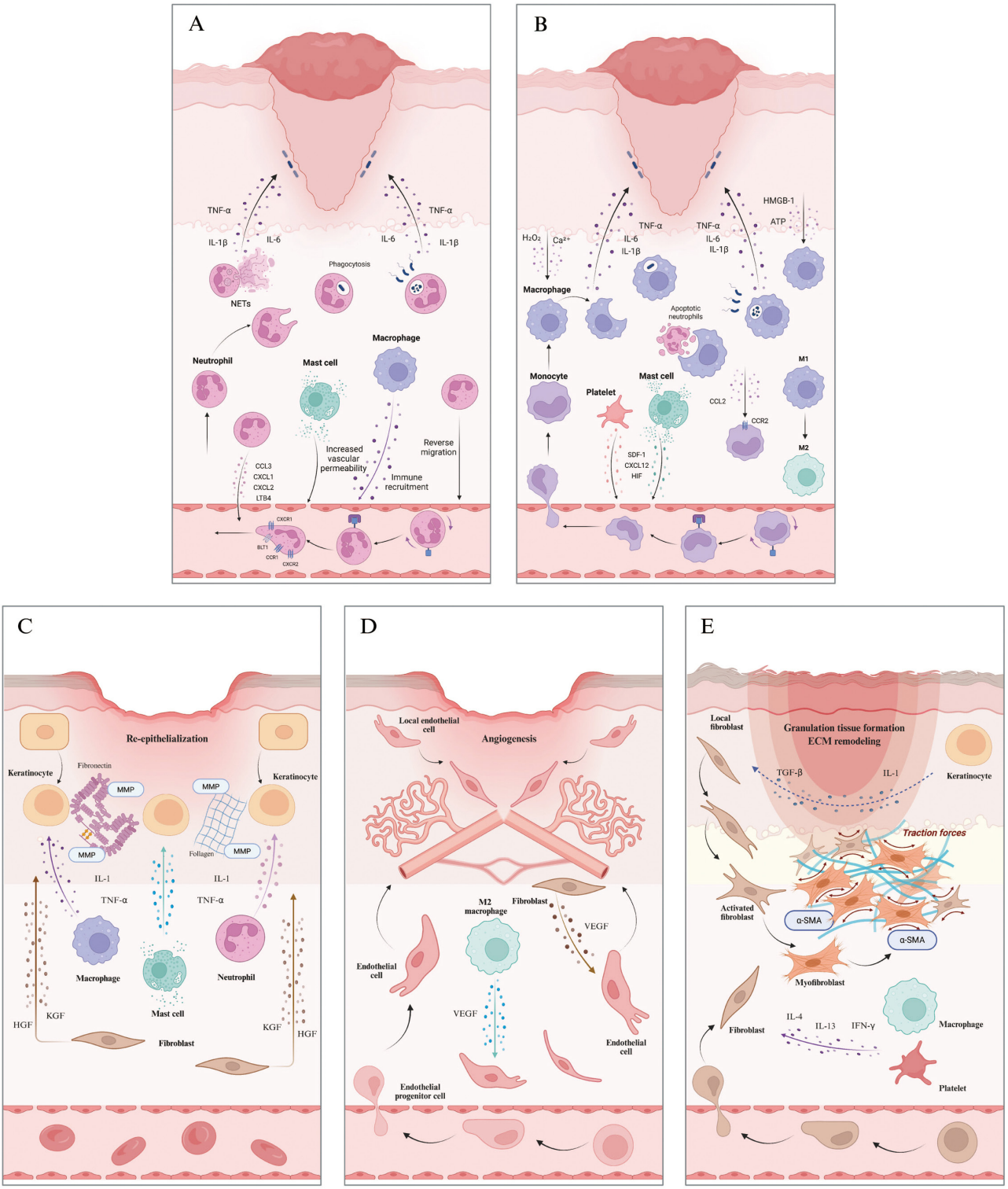

Figure 2. Cell migration and function during normal wound healing. (A) Neutrophil migration in wound healing. Neutrophils are regulated by immune signals from macrophages and mast cells, as well as positive autocrine feedback, leading to migration to the wound site to initiate the inflammatory response. After fulfilling their role, neutrophils are phagocytosed by macrophages or re-enter circulation through reverse migration. (B) Monocyte/macrophage recruitment and polarization. Platelets, mast cells and endogenous chemokines recruit monocytes to the wound site, where they differentiate into M1 macrophages, mediating pro-inflammatory and phagocytic responses. Upon inflammation resolution, these macrophages shift to the M2 phenotype, promoting tissue repair and regeneration. (C) Keratinocyte migration and epithelialization. Inflammatory mediators released by macrophages, neutrophils and mast cells, along with growth factors secreted by fibroblasts, facilitate the migration of keratinocytes towards the wound site. MMPs facilitate ECM removal, thereby creating pathways that promote cell migration and re-epithelialization. (D) Endothelial cell migration-driven angiogenesis. Vascular endothelial cells, influenced by growth factors such as VEGF secreted by macrophages and fibroblasts, migrate both locally and systemically toward the wound site, thereby facilitating angiogenesis. (E) Fibroblast migration and tissue remodeling. Keratinocytes, macrophages and platelets secrete cytokines and growth factors that recruit fibroblasts to the wound site. These fibroblasts synthesize collagen to generate granulation tissue, differentiate into myofibroblasts to induce wound contraction and drive scar maturation through ECM remodeling. Created with BioRender.com. ECM, extracellular matrix; NET, neutrophil extracellular trap; CCL, C-C motif ligand; CXCL, C-X-C motif ligand; LTB, leukotriene B; CXCR, CXC chemokine receptor; BLT, leukotriene B4 receptor; CCR, CC chemokine receptor; HMGB, high-mobility group box; SDF, stromal cell-derived factor; HIF, hypoxia-inducible factor; KGF, keratinocyte growth factor; HGF, hepatocyte growth factor; SMA, smooth muscle actin.

and necessary for new blood vessel formation, primarily mediated by chemotactic, haptotactic and mechanotactic cues (Fig. 2D) (54). Chemotaxis in angiogenesis involves the directional migration of ECs along chemical gradients of attractants such as VEGF and basic fibroblast growth factor. This migration is initiated when VEGF binds to VEGF receptor (R)-2, activating downstream effectors such as PI3K/Akt and Rho GTPases to remodel the cytoskeleton. VEGFR-2 serves as the primary regulator of this process (55). Through paracrine signaling, VEGF is secreted by repair-associated macrophages, keratinocytes and fibroblasts, driving EC expansion and motility to enhance blood vessel formation (56,57). Haptotaxis refers to the directional movement of ECs during angiogenesis, driven by the interaction of integrins (such as αvβ3 and αvβ5) with ECM components along a ligand gradient (58). Integrin activation triggers downstream signaling pathways, including Ras-related C3 botulinum toxin substrate (Rac) and cell division cycle 42 (Cdc42), which regulate cytoskeletal remodeling and mechanical force generation to propel cell movement (59). Additionally, integrins synergize with growth factor signaling pathways to enhance migratory efficiency. Mechanotaxis is the process by which ECs undergo directed migration in response to mechanical forces, such as shear stress, mediated by integrin activation and cytoskeletal remodeling (60).

Fibroblast migration. As key mediators of tissue regeneration, fibroblasts generate and remodel ECM proteins, including collagen, elastin, fibronectin and laminin, to support structural integrity (61). Chemokines and cytokines secreted by platelets and inflammatory cells guide fibroblasts to the injury site during early wound healing (62,63). Keratinocytes support this process by releasing IL-1 and transforming growth factor (TGF)-β, which enhance fibroblast migration and activation (Fig. 2E) (44). Fibroblasts recruited to the wound site synthesize and secrete ECM components, such as collagen, promoting granulation tissue formation. Under mechanical tension and cytokine stimulation (TGF-β), these fibroblasts differentiate into myofibroblasts. This transition is marked by α-smooth muscle actin expression, which forms stress fibers that generate contractile forces to draw the wound edges together, aiding in closure (64). Additionally, a small population of bone marrow-derived circulating fibroblasts migrates to the wound bed in response to cytokines such as IL-4, IL-13 and IFN-γ and differentiates into myofibroblasts (65); however, their contribution to skin wound healing is relatively minor (66). Persistent fibroblast overproliferation and hyperactivation drive excessive ECM deposition, primarily collagen, promoting hypertrophic scar or keloid formation (67,68). In the final remodeling phase, fibroblasts deposit type I collagen to replace type III collagen, reinforcing the ECM and forming a mature, mechanically stable scar. This process may persist for months to years (69).

In wound healing, although different cell types exhibit distinct migration characteristics, their movement is regulated by signaling molecules such as chemokines and cytokines, as well as microenvironmental factors including hypoxia, mechanical forces and ECM composition (21,23,44,56). These cells sense external cues via surface receptors, facilitate migration through cytoskeletal reorganization and dynamic adhesion molecule interactions and maintain coordinated motility via cell-cell and cell-matrix communications (23,28). Collectively, these mechanisms establish an efficient and orderly repair network that drives the wound healing process.

4. Mechanisms of cellular migration impairment in diabetic wound healing

Diabetic patients exhibit impairment in cell migration function during wound repair (70,71). This impairment may be linked to the interplay of multiple factors, including hyperglycemia, chronic inflammatory responses, oxidative stress and an aberrant wound microenvironment. These factors influence cell migration via complex biological pathways, ultimately leading to the obstruction of wound healing and potentially resulting in prolonged refractory states (Fig. 3).

Effects of high glucose on cell migration. High glucose may impair cell migration by promoting the formation of unstable protrusions, decreasing adhesion maturation, altering RhoA activity to disrupt migration regulation and enhancing glucose uptake and metabolism to activate the mTOR pathway (72). These mechanisms are implicated in various cell types such as neutrophils, macrophages, keratinocytes and endothelial cells. Chronic elevation of blood glucose levels results in the buildup of advanced glycation end products (AGEs) within tissue. AGE-modified proteins disrupt chemotactic signaling, impairing the migration of neutrophils to wound sites (73). Under chronic hyperglycemia, monocyte motility is compromised, resulting in inadequate macrophage infiltration, decreased phagocytic capacity and dysregulated polarization from M1 to M2 phenotypes (74). Inadequate migration of neutrophils and macrophages to the wound site increases the risk of wound infection (75). Additionally, high glucose upregulates STING expression and activates the interferon regulatory factor 3 and NF-κB signaling pathway, thereby inhibiting EC migration and delaying the healing of diabetic wounds (70). Under physiological conditions, keratinocyte proliferation and migration are key for re-epithelialization during cutaneous wound repair. Phosphorylated focal adhesion kinase (p125FAK) is a key regulator of keratinocyte migration. However, hyperglycemia attenuates p125FAK phosphorylation, compromising keratinocyte migration in diabetic wound healing. (76). High glucose also inhibits the PI3K signaling pathway, impairing the function of ClC-2 chloride channels and suppressing the migratory capacity of keratinocytes. Conversely, hyperglycemia-induced upregulation of keratin 17 activates c-MYB/PI3K/AKT signaling, promoting excessive keratinocyte proliferation and migration. This dysregulation contributes to hyperkeratosis and impairs wound healing (77). Thus, high glucose conditions exert a dual effect, both inhibiting and promoting cell migration through distinct mechanisms, leading to delayed diabetic wound healing.

Effects of chronic inflammation on cell migration. Chronic inflammation is a key pathological mechanism underlying diabetic wound healing disorder, exerting its effects on cell migration and delaying the wound repair process through a variety of mechanisms (78-80). Hyperglycemia impedes macrophage polarization from the M1 to M2 phenotype, leading to persistent secretion of pro-inflammatory mediators including

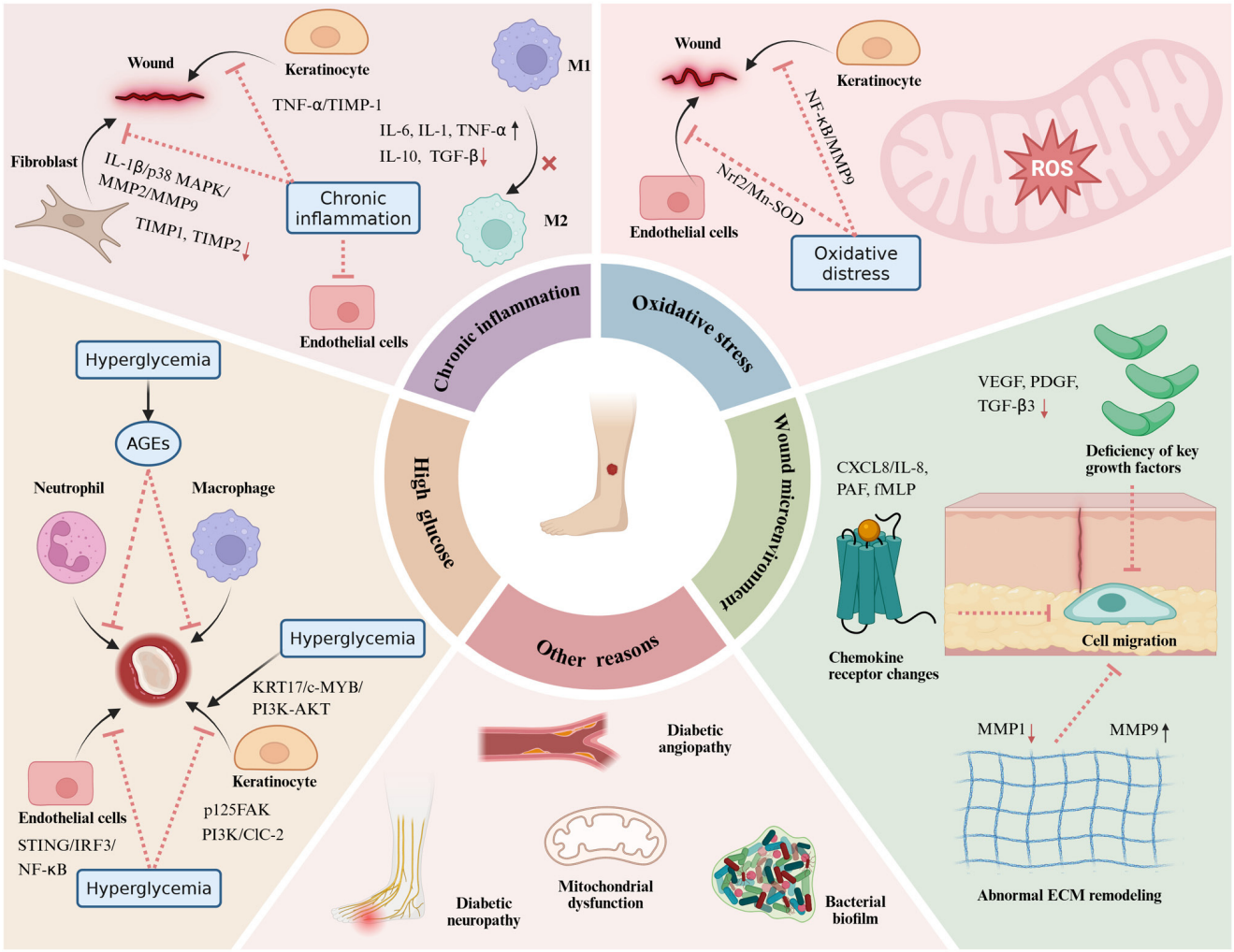

Figure 3. Mechanisms of cellular migration impairment in diabetic wound healing. High glucose, chronic inflammation, oxidative stress and abnormal wound microenvironment contribute to delayed wound healing in diabetes. Created with BioRender.com. TIMP, tissue inhibitor of metalloproteinases; ROS, reactive oxygen species; PDGF, platelet-derived growth factor; CXCL, C-X-C motif ligand; PAF, ; fMLP, fMet-Leu-Phe; ECM, extracellular matrix; AGE, advanced glycation end-products; KRT, keratin; c-MYB, v-myb avian myeloblastosis viral oncogene homolog; p125FAK, focal adhesion kinase; IRF, interferon regulatory factor.

IL-6, IL-1 and TNF-α, alongside decreased production of anti-inflammatory factors such as IL-10 and TGF-β (57,80). This persistent pro-inflammatory microenvironment markedly impairs the motility of keratinocytes, fibroblasts and vascular ECs, extending the inflammatory phase and impairing wound repair (81-83). Overproduction of TNF-α from M1-polarized macrophages elevates tissue inhibitor of metalloproteinases-1 (TIMP-1) expression in keratinocytes, suppressing motility and ultimately impairing diabetic wound repair (71). IL-1β is a key contributor to maintaining a pro-inflammatory state. It activates the p38 MAPK pathway to upregulate MMP2 and MMP9 expression while downregulating TIMP1 and TIMP2, thereby altering the levels of ECM remodeling proteins. This suppresses proliferation and motility of dermal fibroblasts, thereby delaying wound repair in diabetic individuals (84).

Effects of oxidative stress on cell migration. Oxidative stress reflects a disrupted equilibrium where oxidation predominates over antioxidant defenses. Tissue in diabetic hyperglycemic wound microenvironments exhibits heightened vulnerability to this oxidative imbalance (85). Reactive oxygen species (ROS) serve a dual role in wound healing: Moderate levels promote tissue repair, while excess accumulation impairs wound closure and delays regenerative processes (86). High concentrations of ROS inhibit cell migration by oxidizing related proteins such as actin and myosin II, disrupting the structure and function of the cytoskeleton and impairing cell contractility (87). High glucose exacerbates oxidative stress, resulting in excessive Rac1 activation. This overactivation promotes the formation of unstable protrusions, disrupts cell polarity and impairs adhesion maturation, collectively decreasing cell migration speed and directionality, ultimately contributing to defective wound healing (72). A study has shown that hyperglycemia exacerbates oxidative stress, impairing the migratory and proliferative capacity of keratinocytes, thereby impairing wound repair in diabetic conditions (88). Moreover, oxidative stress decreases nuclear Nrf2 levels and manganese-superoxide dismutase (Mn-SOD) expression, thereby weakening the cellular antioxidant defense system, exacerbating ROS accumulation, impairing EC proliferation and migration and ultimately delaying tissue regeneration (89). MMP9 impedes diabetic wound repair (90,91). In human keratinocytes, ROS

activate NF-κB, upregulating MMP-9 and suppressing keratinocyte migration, thereby delaying wound closure (92,93).

Effects of wound microenvironment on cell migration. Alterations in the wound microenvironment, such as deficiencies in key growth factors, changes in chemokine receptors and abnormal ECM remodeling, disrupt cell migration and impede wound healing. Diminished growth factor secretion in diabetic wounds disrupts cellular migration. During early wound repair, platelet-derived growth factor (PDGF) recruits fibroblasts, neutrophils and monocytes to the injury site (94). However, in diabetic wounds, PDGF and its receptor expression are downregulated, compromising cell migration and delaying wound closure (95). Similarly, hyperglycemia suppresses VEGF secretion by macrophages, fibroblasts and keratinocytes, impairing EC and keratinocyte migration, thereby hindering vascularization and re-epithelialization and delaying wound healing (94,96). TGF-β3 has been shown to facilitate the migration of fibroblasts and keratinocytes; considering the marked downregulation of TGF-β3 in diabetic wounds, restoring its activity locally may represent a viable approach to improving wound regeneration in diabetic patients (97). The alteration of chemokine receptors is also a key factor in impaired cell migration in diabetic wounds. Compared with healthy individuals, neutrophils from diabetic patients exhibit a substantial decrease in chemotaxis towards the chemokines CXCL8/IL-8, platelet-activating factor and fMLP (98). This attenuated chemotactic response may hinder cellular migration to the wound site, disrupting healing progression. Moreover, in chronic diabetic wounds, an imbalance in the regulation of MMPs disrupts ECM remodeling, impairing cell migration and delaying tissue repair (99,100). Normal function of MMP1 in keratinocytes is key for their migration on type I collagen (101). Hyperglycemia may impair keratinocyte migration via inhibition of the p-Stat-1 pathway and α2β1 integrin-dependent MMP1 activation, contributing to delayed diabetic wound healing (102). Hyperglycemia upregulates FOXO1, increasing MMP-9 while decreasing TGF-β1, thereby disrupting ECM homeostasis, impairing keratinocyte migration and delaying diabetic wound healing (100,103,104).

Other effects on cell migration. Complications of diabetes, including vasculopathy and neuropathy, are key pathological factors that impair wound healing by affecting cellular migration. Vascular disease in diabetic patients contributes to the delayed migration of white blood cells to injury sites (105). Diabetic neuropathy may disrupt keratinocyte and immune cell migration by altering neuropeptide release (substance P and calcitonin gene-related peptide), thereby impairing wound healing (106,107). Bacterial biofilms are highly structured, surface-associated microbial aggregates encased in a self-secreted extracellular polymeric substance, which provides mechanical stability and protects against environmental stresses (108). Diabetic wounds exhibit heightened susceptibility to infection and biofilm formation due to hyperglycemia-induced immunosuppression. The presence of these bacteria and their associated biofilms hinders cellular migration and disrupts the normal wound healing process (18,109). In diabetic wounds, aberrant mechanical signals may contribute to impaired cell migration function. Beyond its structural scaffolding role, the ECM also serves as a platform for initiating and integrating mechanotransduction signals. Under diabetic conditions, fibroblasts secrete a thicker and less porous ECM, hindering the migration of normal fibroblasts. Diabetic fibroblasts exhibit increased cellular stiffness yet generate markedly reduced traction and contractile forces within collagen matrices (110). These pathological changes may impair cell migration, disrupting wound contraction and delaying healing. Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) are the central effectors of the Hippo pathway and serve as the primary nuclear sensors for a variety of extracellular and intrinsic mechanical signals (111,112). Downregulation of Agrin (a key component of the ECM) in diabetic wounds may decrease MMP12 expression by inhibiting the nuclear localization of YAP/TAZ and its positive feedback regulation in keratinocytes (113). This weakens the cell ability to respond to mechanical stress, impairs their migration efficiency and ultimately delays wound healing. Mitochondria serve a crucial role in cell migration by providing ATP and maintaining calcium homeostasis (114). Mitochondrial dysfunction in diabetic wounds may be a key factor impairing cell migration. Sirtuin 3 (SIRT3), a key mitochondrial deacetylase, regulates energy metabolism and oxidative stress (115,116). SIRT3 deficiency in diabetic wounds disrupts mitochondrial structure and function, leading to oxidative stress, necroptosis, impaired migration of skin fibroblasts and delayed wound healing (117).

The impaired wound healing in diabetes arises from multifaceted interactions of various factors that compromise cellular migratory function. Research has predominantly focused on conventional mechanisms including metabolic dysregulation, oxidative stress, inflammatory responses and microenvironmental alterations (70,79,88,95). However, knowledge remains limited regarding regulatory pathways such as neural modulation, mechanical signals, mitochondrial dynamics, epigenetic modification and microbial community regulation (106,113,117). Future investigations should broaden the research scope to elucidate the precise roles of these factors in cellular migration, thereby providing theoretical foundations for developing targeted therapeutic strategies for diabetic wounds.

5. Key signaling pathways regulating cell migration to promote wound healing

During wound healing, cell migration is controlled by multiple signaling cascades, including Rho GTPase, PI3K/Akt, TGF-β/Smad and Wnt/β-catenin pathways (118-121). These signaling axes regulate key migratory processes such as cytoskeletal dynamics, cell polarization and force generation through distinct molecular mechanisms (122-125).

Rho GTPase signaling pathway. Rho GTPases serve as master regulators of cell migration, controlling cytoskeletal dynamics to facilitate directional cell movement (Fig. 4) (122). Rho GTPases are a distinct subclass within the Ras superfamily, serving as molecular switches that cycle between their biologically active GTP-bound conformation and inactive GDP-bound state. The Rho GTPase regulatory cycle is orchestrated by

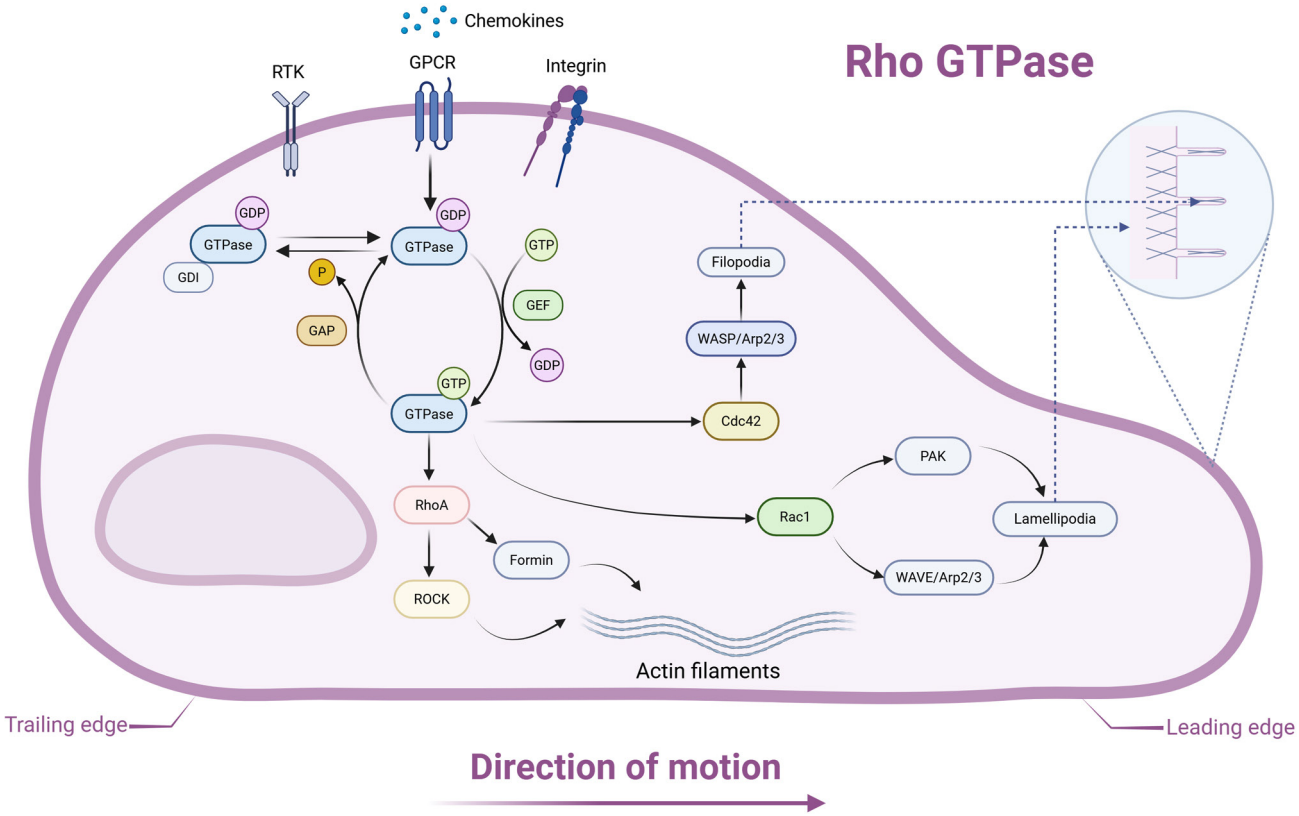

Figure 4. Rho GTPase signaling pathway in cell migration. Rho GTPases regulate cell migration via effector molecules: RhoA mediates cell contraction, Rac1 drives lamellipodia extension and Cdc42 promotes filopodia formation. Created with BioRender.com. RTK, receptor tyrosine kinase; GPCR, G protein-coupled receptor; GDI, GDP dissociation inhibitor; GAP, GTPase-activating protein; GEF, guanine nucleotide exchange factor; ROCK, Rho-associated coiled-coil forming protein kinase; WASP, Wiskott-Aldrich syndrome protein; Arp, actin-related protein; Rac, Ras-related C3 botulinum toxin substrate; PAK, p21-activated kinase.

three protein families: Guanine nucleotide exchange factors, which promote GDP-to-GTP exchange to activate Rho GTPases; GTPase-activating proteins, which enhance GTP hydrolysis, inducing inactivation, and GDP dissociation inhibitors, which stabilize the inactive GDP-bound form and sequester Rho GTPases from membranes, thus maintaining quiescence (126).

Recent investigations into cell migration have largely centered on three key Rho GTPases: RhoA, Rac1 and Cdc42 (127-129). RhoA exhibits activity at both the leading and trailing edges of migrating cells, where it orchestrates actomyosin contractility via Rho-associated coiled-coil forming protein kinase (ROCK) and modulates actin polymerization via formin family nucleators (130). Rac1 initiates cytoskeletal remodeling by sequential activation of downstream effectors, first stimulating PAK kinase and the Wiskott-Aldrich syndrome protein (WASP) family verprolin-homologous protein (WAVE) regulatory complex. This signaling cascade induces WAVE-mediated direct activation of the actin-related protein (Arp) 2/3 complex, resulting in the nucleation of highly branched actin filament networks that mechanically drive lamellipodial membrane extension (122). Cdc42 orchestrates a distinct morphological response by specifically activating WASP family proteins, which serve as molecular scaffolds to facilitate precise Arp2/3 complex assembly and generation of parallel actin bundles, thereby promoting filopodial protrusion.

PI3K/Akt signaling pathway. The PI3K/Akt pathway is a central regulator of fundamental cellular functions, such as proliferative signaling, migratory behavior and immune modulation (Fig. 5) (131). Initiation of this pathway occurs through upstream membrane-associated receptors, such as receptor tyrosine kinases, integrins, antigen/cytokine receptors and GPCRs, which trigger PI3K activation (132). Following stimulation, PI3K mediates the phosphorylation of phosphatidylinositol-4,5-bisphosphate, generating the second messenger phosphatidylinositol-3,4,5-trisphosphate (PIP3). This lipid product recruits Akt to the membrane via interaction with its pleckstrin homology domain, enabling dual phosphorylation (Thr308/Ser473) and consequent functional activation (133). Once activated, Akt phosphorylates multiple downstream substrates in both the cytoplasm and nucleus, thereby modulating cellular motility.

Previous studies have suggested that the PI3K/Akt axis may contribute to wound repair by modulating the migratory dynamics of target cells (134,135). Through modulation of cytoskeletal component equilibrium, this pathway drives cell migration. Specifically, the PI3K/Akt-mediated signaling cascade activates Rho family small GTPases, including Rac1 and Cdc42, as well as actin-polymerization-promoting factors such as WASP/WAVE-Arp2/3 complexes (136). These components enhance actin nucleation and branched assembly at the advancing front, fostering lamellipodia growth and other protrusions that support cell motility. Secondly, the

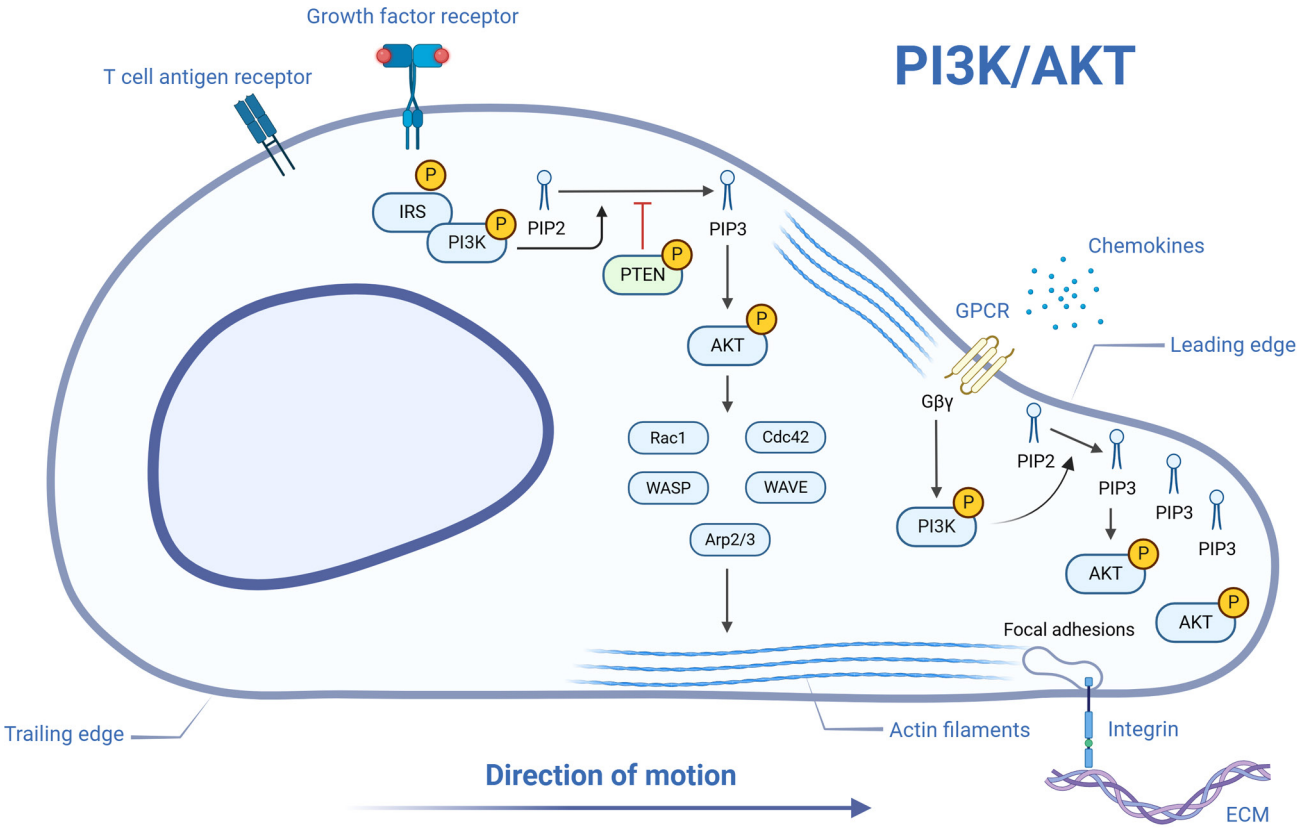

Figure 5. PI3K/Akt signaling pathway in cell migration. PI3K/Akt promotes cell migration via Rac1/Cdc42-mediated actin polymerization, integrin adhesion turnover and PIP3-dependent polarization. Created with BioRender.com. Rac, Ras-related C3 botulinum toxin substrate; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; IRS, insulin receptor substrate; WASP, Wiskott-Aldrich syndrome protein; WAVE, WASP family verprolin-homologous protein; Arp, actin-related protein; GPCR, G protein-coupled receptor; ECM, extracellular matrix.

PI3K/Akt pathway modulates migratory capacity by regulating the dynamics of cell adhesion. Akt kinase activity enhances the formation and turnover of integrin-mediated focal adhesions, thereby allowing migrating cells to maintain traction at the leading edge while efficiently releasing adhesions at the rear (137). This mechanism ensures continuous and coordinated cell movement. Furthermore, this pathway exerts a key influence on chemotactic cell migration. When chemokines bind to GPCRs, the Gβγ subunit rapidly activates PI3K, particularly the PI3Kγ isoform, leading to increased PIP3 accumulation at the cell membrane leading edge. Subsequently, PIP3 recruits and activates Akt at the cell front, locally eliciting downstream pro-migratory effects and guiding the cell toward areas with higher chemokine concentrations (138).

TGF-β/Smad signaling pathway. The TGF-β superfamily signaling cascade regulates a wide range of cell processes, including proliferation, migration and ECM synthesis and reorganization (139). Central to this pathway is the TGF-β/Smad axis, which involves TGF-β ligands, cognate receptors (TGFβRI and TGFβRII) and downstream Smad mediators (Fig. 6). Upon ligand binding, TGFβRII interacts with TGF-β to assemble a heteromeric receptor complex, facilitating the recruitment and phosphorylation of TGFβRI (140). Activated TGFβRI exhibits kinase function, specifically phosphorylating Smad2 and Smad3. These phosphorylated Smads dimerize with Smad4, forming a transcriptionally active oligomeric complex that translocates into the nucleus to modulate target gene expression (141).

The TGF-β/Smad signaling pathway activates ROCK through the stimulation of RhoA (142). ROCK facilitates cell migration by modulating actin cytoskeletal rearrangement and myosin contractility. TGF-β signaling promotes keratinocyte migration and facilitates wound healing through the transcriptional regulation of key ECM-associated molecules. This includes the upregulation of integrin subunits (α5, αv and β5) as well as specific MMPs, particularly MMP3 and MMP9 (143,144). The TGF-β/Smad pathway serves as a key regulator of epithelial-mesenchymal transition (EMT) by downregulating E-cadherin and tight junction proteins, including occludin, claudins and zona occludens-1 (145). Simultaneously, elevated expression of mesenchymal markers, including N-cadherin and vimentin, reinforces cell motility, promoting the advancement of EMT.

Wnt/β-catenin signaling pathway. The Wnt/β-catenin signaling pathway, an evolutionarily conserved regulatory mechanism, governs a spectrum of biological functions including cellular proliferation, differentiation, apoptotic regulation and migratory behavior (Fig. 7) (146). In the absence of Wnt signaling , cytosolic β-catenin undergoes sequential phosphorylation mediated by the multiprotein degradation complex, comprising adenomatous polyposis coli, axin, casein kinase 1 and glycogen synthase kinase-3β, leading to its proteasomal degradation and thus ensuring minimal intracellular

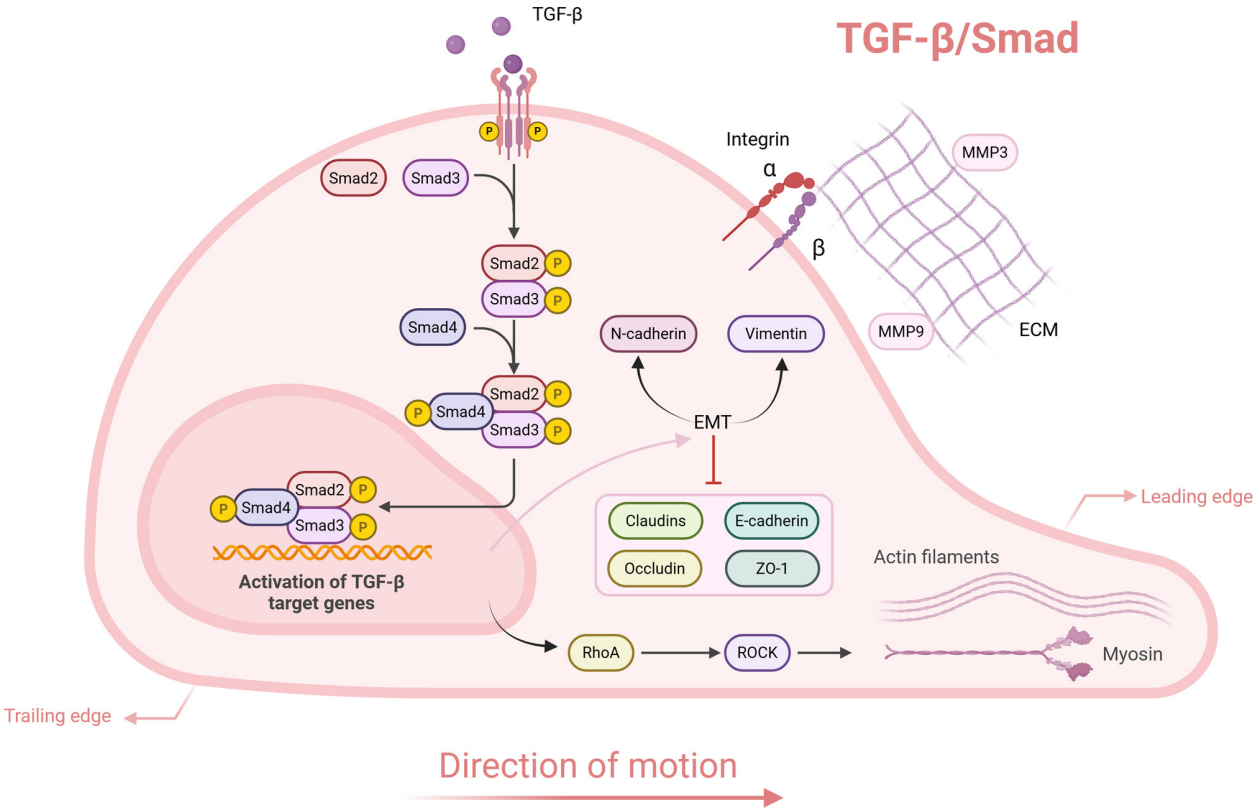

Figure 6. TGF-β/Smad signaling pathway in cell migration. TGF-β/Smad synergizes cytoskeletal dynamics (RhoA/ROCK), ECM degradation (MMPs) and EMT to drive cell migration. Created with BioRender.com. ROCK, Rho-associated coiled-coil forming protein kinase; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; ZO, Zonula occludens.

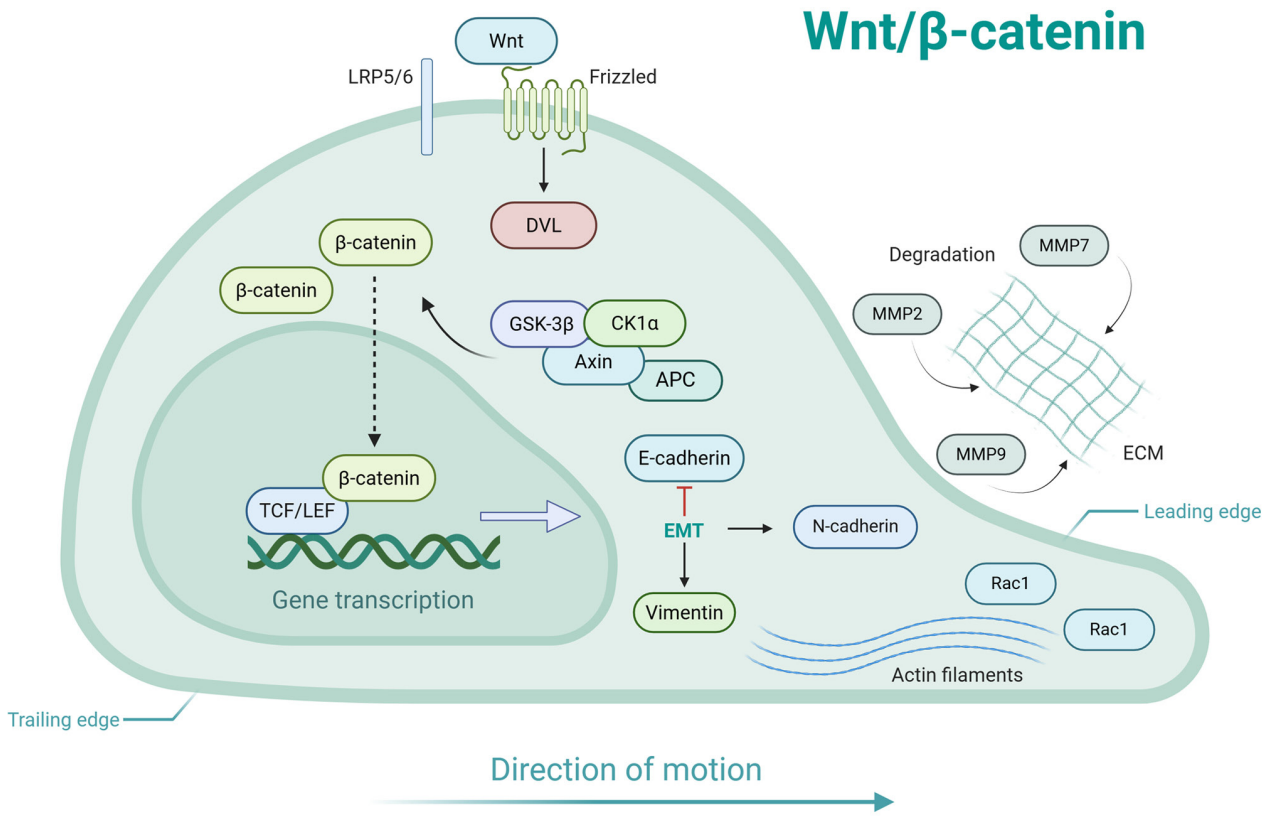

Figure 7. Wnt/β-catenin signaling pathway in cell migration. Wnt/β-catenin orchestrates migration via cytoskeletal dynamics (Rac1), EMT and ECM degradation (MMPs). Created with BioRender.com. EMT, epithelial-mesenchymal transition; Rac, Ras-related C3 botulinum toxin substrate; ECM, extracellular matrix; LRP, low-density lipoprotein receptor-related protein; DVL, Dishevelled; TCF, T-cell Factor; LEF, lymphoid enhancer factor; GSK, glycogen synthase kinase; CK, casein kinase; APC, Adenomatous polyposis coli.

Table I. Signaling pathways regulating migration of distinct cell types during diabetic wound healing.

First author/s, year	Wound type	Signaling pathway	Type of cell	(Refs.)
Johan *et al*, 2024	Diabetic	Rho GTPase (ROCK)	Fibroblast	(118)
Wang et al, 2022	Diabetic foot ulcer	Rho GTPase (ROCK1)	Fibroblast, endothelial cell	(158)
Yu *et al*, 2020	Diabetic	Rho GTPase (Rac1, ROCK)	Fibroblast	(159)
Li *et al*, 2025	Diabetic	PI3K/Akt	Fibroblast	(119)
Huang *et al*, 2025	Diabetic	PI3K/Akt	Keratinocyte, endothelial cell	(160)
Xu *et al*, 2024	Diabetic	PI3K/Akt	Endothelial cell	(161)
Gao *et al*, 2022	Diabetic	TGF-β/Smad	Keratinocyte	(120)
Peng *et al*, 2019	Diabetic	TGF-β1/Smad	Fibroblast	(162)
Oyebode and Houreld, 2022	Diabetic	TGF-β1/Smad	Fibroblast	(163)
Dong *et al*, 2025	Diabetic	Wnt/β-catenin	Fibroblast	(121)
Wang *et al*, 2024	Diabetic	Wnt/β-catenin	Fibroblast	(164)
Liu *et al*, 2023	Diabetic	Wnt/β-catenin	Endothelial cell	(165)
Lv *et al*, 2020	Diabetic cutaneous	Wnt/β-catenin	Keratinocyte	(166)

ROCK, Rho-associated coiled-coil forming protein kinase; Rac, Ras-related C3 botulinum toxin substrate.

concentrations (147). Activation occurs upon binding of Wnt ligands (Wnt3a) to the Frizzled receptor family and its coreceptor low-density lipoprotein receptor-related protein 5/6, which disrupts the destabilization complex (148). This stabilization allows β-catenin to accumulate in the cytoplasm, undergo nuclear translocation and form complexes with T cell factor/lymphoid enhancer factor transcription factors, driving transcription of downstream target genes (149).

Wnt signaling induces localized activation of Rho family GTPases, including Rac1, at the leading edge of migrating cells. This stimulates actin polymerization, which is essential for driving forward cell motility (150). Wnt signaling promotes EMT through the suppression of E-cadherin and concurrent upregulation of mesenchymal markers such as vimentin and N-cadherin. This shift disrupts intercellular adhesion and augments the migratory potential of cells. In addition, Wnt/β-catenin signaling can upregulate the expression of MMPs, including MMP2, MMP7 and MMP9, thereby promoting the degradation of the ECM and facilitating cell migration (151,152). Activation of Wnt downstream targets serves a crucial role in cell migration, which significantly enhances wound healing processes. For example, Wnt1-inducible signaling pathway protein 1 stimulates proliferation and directional movement of dermal fibroblasts (153), while epidermal growth factor receptor (EGFR) activation is essential for keratinocyte recruitment to wound sites (154). Additionally, VEGF promotes mitogenic activity and chemotactic migration of ECs during neovascularization (155).

Crosstalk between signaling pathways may regulate cell migration during wound healing. Hypoxic conditioned medium from human amniotic fluid-derived mesenchymal stem cells (MSCs) promotes fibroblast migration and accelerates wound healing by modulating the TGF-β/SMAD2 and PI3K/Akt signaling pathways (156). Toraldo *et al* (157) demonstrated that topical androgen antagonism accelerates keratinocyte migration and promotes skin wound healing by inhibiting β-catenin nuclear translocation and its crosstalk with TGF-β signaling in keratinocytes. Furthermore, the Rho GTPase signaling pathway may serve as a common downstream node for other pathways to regulate cell migration (136,142,150). The types of cell migration regulated by different pathways exhibit distinct characteristics (Table I) (118-121,158-166).

6. ncRNAs of cell migration in diabetic wounds

ncRNAs represent a diverse class of RNA transcripts that lack protein-coding potential yet serve key roles in modulating gene expression and orchestrating cell processes (167). Among these transcripts, distinct subcategories, including long ncRNAs (lncRNAs), microRNAs (miRNAs or miRs) and circular RNAs (circRNAs), have been identified and functionally characterized (168). Emerging evidence underscores the significance of ncRNAs in controlling migratory behaviors of cells and their impact on diabetic wound repair (Table II) (169-171). Given their regulatory versatility, targeting ncRNAs may offer novel therapeutic avenues for improving wound outcomes in diabetic patients.

lncRNAs. lncRNAs are ncRNAs >200 nucleotides in length (172). These molecules serve as master regulators in key biological activities, spanning cellular proliferation, lineage specification, embryogenesis, programmed cell death and metastatic dissemination. lncRNAs frequently function via the competitive endogenous RNA (ceRNA) network, where they sequester miRNAs to modulate the abundance of miRNA target transcripts (173). Hong *et al* (174) demonstrated that decreased lncRNA XIST expression in diabetic wounds elevates miR-126-3p levels, which subsequently suppresses

Table II. ncRNAs regulating cell migration in diabetic wounds.

First author/s, year	ncRNA	Exosome	Target	Type of cell	Effect on cell migration	(Refs.)
Hong *et al*, 2024	lncRNA XIST	N/A	miR-126-3p/EGFR	Keratinocyte	Promotion	(174)
Chen *et al*, 2023	lncRNA SNHG16	N/A	miR-31-5p	Human dermal fibroblast	Inhibition	(169)
He *et al*, 2022	lncRNA CASC2	N/A	miR-155/HIF-1α	Fibroblast	Promotion	(175)
Li *et al*, 2021	lncRNA H19	N/A	miR-29b, FBN1	Fibroblast	Promotion	(176)
Hu *et al*, 2020	lnc-URIDS	N/A	Plod1	Fibroblast	Inhibition	(177)
Li *et al*, 2020	lncRNA H19	MSC-exos	miR-152-3p, PTEN	Fibroblast	Promotion	(179)
Han *et al*, 2022	lncRNA KLF3-AS1	BMSCs-exo	miR-383, VEGFA	HUVEC	Promotion	(180)
Fu *et al*, 2022	LINC01435	Keratinocyte-exos	YY1, HDAC8	HUVEC	Inhibition	(181)
Peng *et al*, 2024	miR-155	N/A	HIF-1α, SOX2, EGFR/MEK/ERK	Keratinocyte	Inhibition	(170)
Tsai *et al*, 2024	miR-3138	N/A	PALM2-AKAP2, SNX30, ZNF365	Keratinocyte	Promotion	(184)
Tsai *et al*, 2024	miR-3679-5p	N/A	DMXL1, PPP2R2A, TTC39C	Keratinocyte	Inhibition	(184)
Zhao *et al*, 2023	miR-204-3p	N/A	KLF6	Keratinocyte	Promotion	(185)
Zhang *et al*, 2022	miR-146a	N/A	AKAP12	Keratinocyte	Promotion	(186)
Li *et al*, 2023	miR-182-5p	EPC-exos	PPARG	Keratinocyte	Promotion	(188)
Lv, *et al* 2020	miR-21-5p	hASC-exos	Wnt/β-catenin	Keratinocyte	Promotion	(166)
Wang *et al*, 2018	miR-129, miR-335	N/A	Sp1, MMP9	Keratinocyte	Promotion	(187)
Song *et al*, 2025	miR-204-5p	ADSC-exos	TGF-β1/Smad	Fibroblast	Promotion	(275)
Zheng *et al*, 2024	miR-132-3p	Insig1-exos	MMP9, PDGF, VEGF	Dermal fibroblast	Promotion	(195)
Wang *et al*, 2024	miR-145-5p	N/A	PDGFD	Human foreskin fibroblast	Inhibition	(192)
Wang *et al*, 2023	miR-185-5p	N/A	IL-6, TNF-α, ICAM-1	Human skin fibroblast	Promotion	(189)
Wu *et al*, 2023	miR-16-5p	N/A	SP5	Rat fibroblast	Promotion	(190)
Zhao *et al*, 2022	miR-103	N/A	RCAN1	Dermal fibroblast	Inhibition	(193)
Zhang *et al*, 2020	miR-27-3p	N/A	NOVA1	Fibroblast	Inhibition	(194)
Wu *et al*, 2020	miR-21-3p	N/A	SPRY1	Fibroblast	Promotion	(191)
Wang *et al*, 2022	miR-199a-5p	N/A	VEGFA, ROCK1	Human, foreskin fibroblast HUVEC	Inhibition	(158)
Zuo *et al*, 2024	miR-488-3p	N/A	MeCP2, CYP1B1, Wnt4/β-catenin	HUVEC	Promotion	(196)
Qiu *et al*, 2024	miR-221-3p	BMSC-exos	FOXP1/SPRY1	HUVEC	Promotion	(198)
Guo *et al*, 2024	miR-125b	ADSC-exos	CD34, Ki-67, VEGF, TGFβ1	HUVEC	Promotion	(200)
Che *et al*, 2024	miR-146a-5p	ADSC-exos	JAZF1	HUVEC	Promotion	(201)
Zhou *et al*, 2024	miR-146a-5p	BMSC-exos	TRAF6	HUVEC	Promotion	(199)
Huang *et al*, 2023	miR-204-3p	N/A	HIPK2	HUVEC	Promotion	(197)

Table II. Continued.

First author/s, year	ncRNA	Exosome	Target	Type of cell	Effect on cell migration	(Refs.)
Ge *et al*, 2023	miR-132	ADSC-exos	NF-κB	HUVEC	Promotion	(202)
Yan *et al*, 2022	miR-31-5p	Milk-exos	HIF1AN	HUVEC	Promotion	(205)
Huang *et al*, 2024	circCDK13	sEVs	IGF2BP3, CD44, c-MYC	Human dermal fibroblast, human epidermal keratinocyte	Promotion	(213)
Tian *et al*, 2023	circ_072697	N/A	miR-3150a-3p/ KDM2A, MAPK	Keratinocyte	Inhibition	(171)
Fu *et al*, 2023	circ_0080968	N/A	miR-326, miR-766-3p	Keratinocyte	Inhibition	(209)
Han *et al*, 2021	circ_PRKDC	N/A	miR-31/FBN1	Keratinocyte	Inhibition	(210)
Wang *et al*, 2020	hsa_circ_ 0084443	N/A	PI3K, EGFR and ERK pathways	Keratinocyte	Inhibition	(211)
Wang *et al*, 2024	circMYO9B	MSCs-exos	hnRNPU/CBL/ KDM1A/VEGFA	HUVEC	Promotion	(285)
Liang *et al*, 2022	mmu_circ_ 0001052	ADSCs-exos	FGF4/p38MAPK pathway	HUVEC	Promotion	(212)

FBN1, fibrillin 1; YY1, yin yang 1; HDAC8, histone deacetylase 8; Plod1, procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1; SOX2, sex determining region Y-box 2; PALM2-AKAP2, paralemmin 2-A kinase anchoring protein 2; SNX30, sorting nexin family member 30; ZNF365, zinc finger protein 365; DMXL1, Dmx-like 1; PPP2R2A, protein phosphatase 2; TTC39C, tetratricopeptide repeat domain 39C; KLF6, Kruppel-like factor 6; AKAP12, A-kinase-anchoring protein 12; PPARG, peroxisome proliferator activated receptor γ; Sp1, specificity protein-1; ICAM-1, intercellular adhesion molecule 1; SP5, transacting transcription factor 5; RCAN1, regulator of calcineurin; NOVA1, neuro-oncological ventral antigen 1; SPRY1, protein sprout homolog 1; ROCK1, Rho-associated kinase 1; MeCP2, methyl-CpG-binding protein 2; CYP1B1, cytochrome P450 1B1; FOXP1, forkhead box P1; JAZF1, juxtaposed with another zinc finger 1; TRAF6, tumor necrosis factor receptor-associated factor 6; HIPK2, homeodomain-interacting protein kinase 2; HIF1AN, hypoxia-inducible factor 1 subunit α inhibitor. IGF2BP3, insulin-like growth factor 2 mRNA binding protein 3; KDM2A, lysine demethylase 2 A; N/A, no information available; miR, microRNA; lnc, long non-coding; circ, circular.

EGFR (174). This inhibition impairs keratinocyte proliferation and migration in high-glucose environments, contributing to delayed wound healing. These observations indicate that XIST could serve as a promising therapeutic target to enhance keratinocyte motility during wound repair. lncRNAs CASC2 and H19 accelerate fibroblast migration in diabetic wounds through miRNA modulation, ultimately altering the expression of downstream effector genes (175,176). By contrast, lncRNA SNHG16 and lnc-URIDS have been found to inhibit fibroblast migration and impair wound healing (169,177). Exosomes represent a distinct subclass of extracellular vesicles that serve a pivotal role in cell-to-cell signaling by transporting bioactive cargo, including proteins, lipids and nucleic acids. lncRNAs, which are expressed at low levels in cells, tend to be enriched in exosome secretion (178). lncRNA H19 encapsulated in MSC-derived exosomes alleviates fibroblast apoptosis and inflammatory responses by attenuating miR-152-3p-dependent suppression of PTEN, enhancing fibroblast proliferation and motility to accelerate diabetic wound repair (179). Exosomal lncRNA KLF3-AS1 secreted by bone marrow MSCs (BMSCs) enhances EC proliferation, migration and angiogenic tube formation via the miR-383/VEGFA axis, where KLF3-AS1 competitively sponges miR-383 to decrease its suppression of VEGFA, ultimately accelerating diabetic cutaneous wound regeneration (180). Fu *et al* revealed that keratinocyte-derived exosomal LINC01435 inhibits the migration of human umbilical vein ECs (HUVECs) via the Yin Yang 1 (YY1)/histone deacetylase 8 (HDAC8) pathway, thereby suppressing angiogenesis and hindering diabetic wound healing (181).

miRNAs. miRNAs, a class of evolutionarily conserved small ncRNAs averaging 21-25 nucleotides in length (182), serve as critical mediators of post-transcriptional regulation, exerting their effects through either mRNA destabilization or translational suppression upon target binding (183). Certain miRNAs, including miR-3138, miR-204-3p, miR-146a, miR-129, and miR-335, promote keratinocyte migration through regulation of downstream targets or key signaling pathways, thereby accelerating wound healing in diabetic models (184-187). By contrast, elevated expression of miR-155 and miR-3679-5p suppresses keratinocyte migratory capacity, contributing to impaired re-epithelialization and protracted wound closure in

diabetic conditions (170,184). Exosomes derived from endothelial progenitor cells deliver miR-182-5p, which downregulates PPARG expression, enhances keratinocyte proliferation and migration under hyperglycemic conditions, decreases apoptotic activity and ultimately facilitates diabetic wound repair (188). In addition, loading miR-21-5p into human adipose stem cell-derived exosomes facilitates keratinocyte proliferation and migration by activating the Wnt/β-catenin signaling pathway. This improves diabetic wound repair by concurrently stimulating re-epithelialization, optimizing collagen deposition and organization, boosting neovascularization and fostering functional vascular network maturation (166).

In a high-glucose environment, miR-185-5p, miR-16-5p, and miR-21-3p enhance the migratory capacity of fibroblasts (189-191). By contrast, miR-145-5p, miR-103, miR-27-3p, and miR-199a-5p exert a pronounced inhibitory effect on fibroblast migration in diabetic wounds (192-194,158). Recent research demonstrates that exosomes derived from insulin-induced gene 1 (Insig1)-overexpressing BMSCs (Insig1-exos), which are highly enriched with miR-132-3p, markedly enhance dermal fibroblast migration, proliferation and angiogenic activity under hyperglycemic conditions (195). Mechanistically, Insig1-exos modulate key wound repair mediators, including MMP9, PDGF and VEGF, thereby improving diabetic wound closure in murine models. These results underscore the key contribution of miR-132-3p in facilitating cellular motility and tissue regeneration.

Recent studies have demonstrated that miR-488-3p, miR-199a-5p and miR-204-3p facilitate diabetic wound repair by enhancing EC migration under hyperglycemia (158,196,197). Moreover, BMSCs release miR-221-3p and miR-146a-5p, while exosomes from adipose-derived SCs (ADSCs) deliver miR-125b, miR-146a-5p and miR-132, all of which collaboratively enhance EC migration, proliferation and angiogenic functions. These effects contribute to accelerated wound healing in diabetic models, underscoring their therapeutic promise (198-202). Milk-derived exosomes, obtained from both bovine colostrum and mature milk, present benefits such as excellent safety profiles, cost-effectiveness and high production yields (203). These natural vesicles exhibit remarkable drug-loading capacity and robust biological functionality across both *in vitro* and *in vivo* systems, highlighting their potential for pharmaceutical delivery and immunomodulatory applications (204). Notably, Yan *et al* (205) revealed that milk exosome-encapsulated miR-31-5p exhibits enhanced stability and cellular internalization (compared with free miR-31-5p mimics), stimulates EC proliferation, migration and neovascularization through hypoxia-inducible factor 1 subunit α inhibitor suppression and ultimately promotes diabetic wound repair.

circRNAs. circRNAs are a unique class of ncRNA molecules distinguished by their covalently closed-loop conformation, which confers resistance to exonuclease-mediated degradation (206). circRNAs function as 'sponges' to inhibit specific miRNAs, preventing their binding to target mRNAs, thereby serving as endogenous miRNA regulators (inhibitors) (207). Moreover, circRNAs modulate post-transcriptional gene expression and transcriptional processes through interactions with transcription factors and RNA-binding proteins (208). circ_072697, circ_0080968, circ_PRKDC and hsa_circ_0084443 exert inhibitory effects on keratinocyte migration and impair diabetic wound healing by suppressing miRNAs or directly modulating target gene expression (171,209-211). ADSC-derived exosomes carrying mmu_circ_0001052 downregulate miR-106a-5p, which elevates fibroblast growth factor 4 (FGF4) levels, triggers the FGF4/p38MAPK signaling cascade and stimulates HUVEC proliferation, migration and angiogenic activity in high-glucose environments, collectively improving diabetic wound healing (212). Huang *et al* (213) reported that engineered small extracellular vesicles (sEVs) with circCDK13 overexpression bind insulin-like growth factor 2 mRNA-binding protein 3, stabilizing CD44 and c-MYC transcripts to enhance keratinocyte and fibroblast motility and division, thus accelerating wound closure in diabetic mouse models.

ncRNAs modulate cell migration via signaling pathways or downstream targets, presenting a promising intervention strategy for diabetic wounds. Both lncRNAs and circRNAs serve as ceRNAs, sequestering specific miRNAs to prevent their suppressive effects on target mRNAs, thereby indirectly regulating gene expression (171,174). By contrast, miRNAs directly bind to mRNAs to induce degradation or translational inhibition, forming an integrated miRNA-mRNA-functional protein regulatory network (170,186). Future studies should delineate the dynamic ncRNA-mediated regulatory networks in diabetic wound healing to develop precision-based therapeutic approaches for clinical translation.

7. Regulation of cell migration for the treatment of diabetic wounds

SCs and derived exosomes. SCs are undifferentiated cells characterized by their capacity for self-renewal and pluripotency, allowing differentiation into specialized lineages (214). Additionally, they secrete bioactive factors, modulate inflammatory responses, stimulate angiogenesis and enhance tissue remodeling, highlighting their therapeutic potential in regenerative medicine and tissue repair (Table III) (215). Their low immunogenicity and diverse sources enhance clinical potential. A recent investigation revealed that perinatal tissue-derived MSCs potentiate keratinocyte and EC proliferation and migration via PI3K/Akt pathway activation, culminating in accelerated healing of diabetic wounds (160). Furthermore, SCs can serve as carriers for drugs or bioactive molecules, facilitating sustained release while protecting them from degradation. Administration of genetically modified umbilical cord MSCs expressing angiopoietin-1 improves wound vascularization in diabetic murine models by stimulating EC migration and tubulogenesis, leading to faster healing kinetics (216).

The application of SCs is limited by several factors, including a low survival rate, difficulty in controlling differentiation direction and the potential for immune rejection (217). By contrast, SC-derived exosomes, characterized by strong targeting ability, well-defined mechanisms of action and high safety profiles, offer a more precise and controllable cell-free therapeutic strategy for tissue repair. Beyond ncRNA-mediated regulation, SC-derived exosomes also promote cell migration and improve diabetic wound repair by targeting key signaling pathways. For example, ADSC-exos enhance EC migration

Table III. SCs and exos regulating cell migration in diabetic wounds.

First author/s, year	Type of SC	Exos	Target	Type of cell migration	(Refs.)
Huang *et al*, 2025	MSCs derived from perinatal tissue	N/A	PI3K/Akt	Keratinocyte, HUVEC	(160)
Deng *et al*, 2024	MSCs derived from human umbilical cords	N/A	ANG1	HUVEC	(216)
He *et al*, 2024	ADSC	ADSC-exos	TRIM32/STING	HUVEC	(218)
Liu *et al*, 2023	GMSC	GMSC-exos	Wnt/β-catenin	HUVEC	(165)

TRIM32, tripartite motif-containing 32; STING, stimulator of interferon genes; N/A, no information available; MSC, mesenchymal stem cell; exo, exosome; ADSC, adipose-derived stem cell; GMSC, gingival mesenchymal stem cell; ANG, angiopoietin; HUVEC, human umbilical vein endothelial cell.

and angiogenesis via the Tripartite motif-containing protein 32 (TRIM32)/STING axis, expediting wound closure in diabetic models (218). Liu *et al* (165) reported that exosomes isolated from gingival MSCs stimulate EC proliferation, migration and tube formation by activating the Wnt/β-catenin cascade, offering a potential therapeutic strategy for diabetic wound management.

SC therapy has demonstrated substantial therapeutic potential in diabetic wound repair; however, limitations persist (215). The precise mechanistic pathways governing its efficacy remain incompletely characterized, underscoring the need for further exploration of its molecular and cellular regulatory networks. Safety concerns need to be addressed by defining optimal dosages and administration routes to minimize potential adverse effects. Additionally, the complex processes involved in SC collection and pretreatment require simplification to enhance clinical feasibility and efficiency. The preparation and quality control of exosomes require the establishment of a unified standard (219). Additionally, due to the low molecular concentration of natural exosomes and their limited repair capabilities, exploring pretreatment methods, genetically engineered exosomes and the integration of exosomes with biomaterials may represent promising directions for development (220).

Growth factor therapy. Growth factor therapy for diabetic wound healing is based on its ability to coordinate key cellular responses and molecular pathways governing tissue regeneration. Key growth factors, including PDGF, VEGF, EGF, FGF and TGF, demonstrate potent pro-healing effects by stimulating cell migration and other regenerative processes that collectively accelerate wound repair (221). FGF-21 markedly improves EC proliferation, migration and angiogenic tube formation under hyperglycemic conditions, accelerating diabetic wound repair and underscoring its potential as a therapeutic agent for diabetic wounds (222). Tang et *al* (223) reported that PDGF-loaded nanocapsules with sustained release properties efficiently regulate fibroblast migration, proliferation and neovascularization, contributing to enhanced wound repair in diabetic models. Jeong *et al* (224) found that EGF encapsulated within gelatin-alginate coacervates enhances keratinocyte migration *in vitro* and accelerates wound closure in diabetic mice.

Growth factor therapy exhibits potential for promoting tissue regeneration; however, its clinical translation is hindered by rapid degradation, poor diffusion efficiency and insufficient local retention (221). Future studies should prioritize design of advanced biocompatible biomaterials with tunable degradation kinetics, alongside optimization of nanoscale delivery platforms to enable spatiotemporal control of drug release, targeted accumulation at wound sites and improved pharmacokinetic profile, which are key for expanding therapeutic utility in clinical settings.

Drug-loaded dressings

Hydrogel-based drug therapy. Hydrogels are three-dimensional polymeric networks distinguished by high hydration capacity and structural integrity, formed via cross-linked polymer chains. Owing to their biocompatibility, low immunogenicity and ability to retain moisture, hydrogels have gained prominence as an ideal biomaterial for diabetic wound management (Table IV) (225,226). These materials are capable of absorbing excess wound exudate, sustaining a moist microenvironment and preventing anaerobic bacterial proliferation through enhanced oxygen diffusion, facilitating cellular migration, tissue repair mechanisms and an accelerated healing trajectory (227,228). Recent studies have demonstrated that drug-loaded hydrogel dressings accelerate diabetic wound closure by facilitating cell motility and tissue remodeling (229,230). Notably, PDGF and cytokines stimulate ECM production, neovascularization and directed cellular movement, contributing to enhanced tissue repair (231). Xu *et al* (232) demonstrated that platelet-rich plasma-loaded multifunctional hydrogels exhibit dual therapeutic effects, suppressing excessive inflammation while shifting macrophage differentiation in favor of the regenerative M2 subset. This phenotypical modulation enhances migratory activity in both fibroblasts and vascular ECs, contributing to accelerated wound repair. This approach presents a clinically viable therapeutic paradigm for enhancing diabetic wound repair mechanisms. In addition, the incorporation of engineered sEVs into hydrogels prolongs their residence within the wound microenvironment, establishing them as optimal vehicles for bioactive molecule delivery. Wei *et al* (233) revealed that miR-17-5p-modified sEVs encapsulated in gelatin methacryloyl hydrogels enhance ECM remodeling via PTEN/p21

Table IV. Modulation of cell migration by drug-loaded dressings for diabetic wound healing.

First author/s, year	Dressing type	Name	Components	Type of cell migration	(Refs.)
Bei *et al*, 2024	Hydrogel	PAN/Ag-PLG hydrogel	Gallic acid; functionalized polylysine; Ag-PLG, oxidized HA, cross-linked polyacrylic acid grafted with N-hydrosuccinimide ester	HUVEC	(229)
Li *et al*, 2022	Hydrogel	HA-DA/MXene@ PDA hydrogel	HA-DA; PDA; Ti_3C_2 MXene nanosheets	HUVEC	(230)
Xu *et al*, 2023	Hydrogel	PRP loaded multifunctional hydrogel	PRP; DA-grafted alginate; 6-aminobenzo[c][1,2] oxaborol-1(3H)-ol-conjugated HA	Fibroblast, HUVEC	(232)
Liu *et al*, 2022	Hydrogel	B-G hydrogel	Methacryloyl-substituted B; G	Fibroblast	(286)
Wu *et al*, 2022	Hydrogel	Injectable conductive and angiogenic hydrogel	Quaternized chitosan; polyaniline; four-armed aldehyde-terminated polyethylene glycol; deferoxamine	HUVEC	(287)
Wei *et al*, 2024	Hydrogel	GelMA hydrogel loaded with $sEVs^{17\text{-}OE}$	$sEVs^{17\text{-}OE}$; GelMA	Fibroblast, HUVEC	(233)
Wu *et al*, 2024	Aerogel	TDNP functionalized aerogel	TDNPs	Fibroblast	(242)
John *et al*, 2023	Aerogel	Nanofiber aerogels with precision macrochannels and LL-37-mimic peptides	Poly(glycolide-co-lactide) (90:10 glycolide: lactide); gelatin; poly-p-dioxanone; LL-37-mimic peptide W379	Keratinocyte, fibroblast	(245)
Yin *et al*, 2021	Microneedle patch	MN-MOF-GO-Ag	Mg-MOF; poly(γ-glutamic acid) hydrogel; gallic acid; GO-Ag; Mg^{2+}	HUVEC	(248)
Wang *et al*, 2023	Microneedle patch	MN-MgH_2	MgH_2; poly(lactic-co-glycolic acid)	Fibroblast, HUVEC	(249)
Liu *et al*, 2023	Microneedle patch	Double-layer drug-loaded microneedles (DMN@TH/rh-EGF)	TH; rh-EGF; HA; carboxymethyl chitosan; gelatin	HUVEC	(288)

PAN, polyacrylic acid grafted with N-hydrosuccinimide ester; PLG, polylysine-gallic acid; HUVEC, human umbilical vein endothelial cell; HA, hyaluronic acid; DA, dopamine; PDA, polydopamine; MXene, two-dimensional transition metal carbides, carbonitrides, and nitrides; PRP, platelet rich plasma; G, gelatin; B, Bletilla Striata polysaccharide; GelMA, Gelatin methacryloyl; $sEVs^{17\text{-}OE}$, miR-17-5p-engineered small extracellular vesicles; miR, microRNA; TDNP, Turmeric-derived nanoparticle; LL-37, human cathelicidin antimicrobial peptide; MN, microneedle; MOF, magnesium organic framework; GO, graphene oxide; DMN@TH, double-layer microneedle loaded with tetracycline hydrochloride; rh-EGF, recombinant human epidermal growth factor.

pathway modulation, thus stimulating both EC and fibroblast motility. Such a therapeutic strategy markedly improves the healing kinetics of diabetic wounds.

Hydrogels face limitations in their application. Due to their time-dependent viscoelastic properties, long-term structural degradation and stress relaxation under load may occur, which can impair cell adhesion, migration and proliferation (234). Additionally, insufficient mechanical strength, challenges in controlling degradation rate and narrow functionality further restrict their practical use. Future integration of artificial intelligence-based screening with advanced 3D bioprinting platforms may simultaneously optimize the biomechanical performance, biofunctional characteristics and therapeutic applicability of next-generation hydrogels (235,236). Combined with personalized customization, these advancements may provide more efficient and precise solutions for wound healing.

Aerogel-based drug therapy. Aerogels are ultra-lightweight nanoporous materials formed by removing the liquid from gel pores to create interconnected porous structures (237). They exhibit rapid absorption of exudate while maintaining a moist wound environment and facilitating efficient gas exchange (238). Compared with conventional hydrogels and

standard wound dressings, aerogels demonstrate superior structural characteristics, including ultralow density, minimal thermal conductivity, interconnected macroporosity and an extensive surface-to-volume ratio, which position them as promising alternatives for advanced wound management (Table IV) (239). Emerging evidence highlights the therapeutic potential of aerogel-based drug delivery systems in accelerating cell migration during wound regeneration (240,241). Wu *et al* (242) developed a turmeric nanoparticle-embedded aerogel dressing that demonstrates controlled drug release kinetics and potent anti-inflammatory and antioxidant activity, alongside enhanced fibroblast migration and proliferation. This formulation exhibited remarkable effectiveness in treating diabetic ulcers. Furthermore, LL-37, a cathelicidin-derived host defense peptide, serves key biological functions beyond its antimicrobial effects, including the modulation of keratinocyte and fibroblast activity to facilitate cutaneous wound closure (243,244). John *et al* (245) developed a nanofiber aerogel scaffold engineered with tailored macrochannels and LL-37 biomimetic peptides for diabetic wound therapy. The results demonstrated notable stimulation of both keratinocyte and fibroblast migratory activity and mitotic expansion, alongside marked enhancement in neovascularization and epidermal regeneration.

The application of aerogel requires further enhancement. Its intrinsic porous structure results in inadequate mechanical properties, low mechanical strength and susceptibility to fragmentation (238). Moreover, the intricate preparation process and high production costs hinder large-scale manufacturing and clinical adoption (242). In future, it may be feasible to enhance mechanical strength and flexibility through composite material design (by integrating with polymers), while simultaneously optimizing manufacturing processes, reducing expenses and developing more environmentally friendly and sustainable preparation methodologies.

Drug therapy based on microneedle patches. Microneedles are miniature, spine-like structures made from biocompatible materials, typically measuring from tens to hundreds of microns in size. Microneedle technology facilitates the penetration of the stratum corneum, enabling drug delivery, substance extraction or physical therapy targeting deep skin tissue (Table IV) (246). The microneedle patch integrates microneedle technology with a patch format, using tiny needle-like structures distributed on a substrate for transdermal drug delivery. Given their high exudate absorption capacity, robust bioadhesive performance and sustained drug release kinetics, microneedle patches have emerged as a promising therapeutic modality for chronic wound management (247). Yin *et al* (248) engineered a microneedle system incorporating magnesium-based organic frameworks, enabling efficient transdermal drug transport in diabetic wounds. This platform significantly augments EC migratory activity, stimulates neovascularization and accelerates tissue repair processes. Wang *et al* (249) developed a biodegradable poly (lactic-co-glycolic acid) microneedle patch loaded with magnesium hydride. This platform effectively scavenges ROS, induces a shift toward pro-regenerative M2 macrophage phenotypes and stimulates the proliferation and motility of fibroblasts and ECs, enhancing the healing trajectory of diabetic wounds.

Microneedle technology encounters several challenges, including limited drug-loading capacity, high production cost and insufficient stability in complex wound environments (246,250). Future advancements are required, such as optimizing materials and structures for the design of novel microneedles, assessing drug stability and enhancing biocompatibility and safety profiles. Additionally, the combination of micromachining and 3D printing techniques may streamline the manufacturing process and decrease production expenses (250).

Traditional chinese medicine (TCM) treatment. Phytochemicals derived from medicinal plants demonstrate multifunctional bioactive properties, including the stimulation of cellular proliferation and migratory capacity, potent antimicrobial effects and the induction of neovascularization, all of which contribute to enhanced tissue regeneration (Table V) (251,252). Recent research has shown that topical administration of *Crocus sativus L*. (saffron) petal extract markedly accelerates diabetic wound repair by elevating Collagen type I alpha 1 and VEGF levels, stimulating fibroblast and EC motility and enhancing overall re-epithelialization in mice (253). Ginsenoside Rg1 (Rg1), a principal active component derived from *Panax ginseng*, exerts pro-angiogenic effects by stimulating the proliferation and migration of ECs, thereby facilitating wound repair in diabetic wounds. Mechanistically, Rg1 downregulates miR-48-3p, elevates Sirt1 expression and triggers the PI3K/AKT/endothelial nitric oxide synthase) cascade, collectively enhancing vascular regeneration (254). Similarly, paeoniflorin, a key monoterpene glycoside isolated from *Paeoniae alba radix*, was demonstrated by Sun *et al* to attenuate oxidative damage while promoting keratinocyte proliferation and motility (255). These reparative effects are achieved via Nrf2 pathway activation coupled with increased VEGF and TGF-β1 production, expediting diabetic wound closure in rats.

Chinese herbal formulas have potential in facilitating cell migration in diabetic wound healing (256,257). Danggui Sini decoction (DSD), a TCM formulation, exhibits multi-target pharmacological actions such as vasodilatory, anti-inflammatory and antioxidant activity (258). Mechanistic study has revealed that DSD facilitates diabetic wound repair by augmenting fibroblast proliferation and migratory capacity, mediated via regulation of the AGE/RAGE (Receptor for advanced glycation end-products)/TGF-β/Smad2/3 signaling axis in diabetic foot ulcer rats (256). Moist exposed burn ointment, a herbal oil-based preparation, is utilized for burn management and chronic refractory wound care due to its clinical effectiveness (259). When applied to diabetic wounds, as demonstrated by Gong *et al* (257), this formulation accelerates tissue regeneration by stimulating keratinocyte migration, promoting granulation tissue development and collagen reorganization and enhancing re-epithelialization.

While TCM demonstrates therapeutic promise in enhancing diabetic wound repair, several challenges remain to be resolved, including poorly characterized molecular mechanisms, intricate multi-component formulations and restricted administration options. Overcoming these limitations requires systematic research strategies to elucidate fundamental mechanisms, optimize bioactive compound extraction protocols,

Table V. Regulation of cell migration in diabetic wound healing by traditional Chinese medicine.

First author/s, year	Drug category	Name	Target	Type of cell migration	(Refs.)
Soheilifar *et al*, 2024	Natural product	Saffron (*Crocus Sativus L.)* petal extract	COL1A1, VEGF	Fibroblast, HUVEC	(253)
Xiong *et al*, 2024	Natural product	Astragaloside IV	PIK3R2, VEGF/ PI3K/AKT	HUVEC	(289)
Lei *et al*, 2022	Natural product	*Panax notoginseng* saponins	GSK-3β/β-catenin/ VEGF	HUVEC	(290)
Huang *et al*, 2021	Natural product	Ginsenoside Rg1	miR-489-3p/Sirt1, PI3K/AKT/eNOS	HUVEC	(254)
Sun *et al*, 2020	Natural product	Paeoniflorin	Nrf2, VEGF, TGF-β1	Keratinocyte	(255)
Lu *et al*, 2021	Herbal formula	Quyu Shengji formula	PGT	Human dermal microvascular endothelial cell	(291)
Zhang *et al*, 2024	Herbal formula	Dang-Gui-Si-Ni decoction	AGE/RAGE/TGF-β/ Smad2/3	Fibroblast	(256)
Gong *et al*, 2022	Herbal formula	Moist exposed burn ointment	N/A	Keratinocyte	(257)
Liu *et al*, 2023	Herbal formula	Pien-tze-huang	Nrf2/ARE	HUVEC	(292)

COL1A1, collagen type I α1; PIK3R2, phosphoinositol-3 kinase regulatory subunit 2; GSK-3β, glycogen synthase kinase-3β; PGT, prostaglandin transporter; ARE, antioxidant response element; N/A, no information available; HUVEC, human umbilical vein endothelial cell; miR, microRNA; Sirt, Sirtuin; eNOS, endothelial nitric oxide synthase; RAGE, receptor for advanced glycation end-products.

develop novel delivery systems and validate therapeutic effects through multicenter clinical studies.

Additional treatment options. Diabetic foot ulcers are frequently attributed to inadequate blood supply to the lower limb vessels, leading to localized hypoxia in the wound and consequently impairing the healing process. Hyperbaric oxygen therapy (HBOT) serves as an adjunctive therapy that elevates oxygen concentrations in arterial blood and tissues (260). This therapeutic intervention involves the administration of 100% oxygen in a pressurized chamber, elevating environmental pressure to 2-3 atmospheres absolute (261). Under hyperbaric conditions, tissue hypoxia is alleviated, improving oxygenation for key metabolic processes, cellular proliferation and wound repair. HBOT stimulates fibroblast and EC activity via HIF-1α pathway activation, which enhances vascularization and accelerates healing of diabetic wounds (262).

Negative pressure wound therapy (NPWT) is a non-surgical therapeutic approach utilizing an airtight dressing system to achieve localized sub-atmospheric pressure at the wound bed, facilitating enhanced tissue perfusion and wound closure. This therapy effectively removes wound exudate and necrotic tissue, decreases tissue edema, promotes the growth of granulation tissue and angiogenesis, thereby providing optimal conditions for wound healing (263,264). Huang *et al* (265) revealed that NPWT promotes human dermal fibroblast proliferation and migration via miR-155 downregulation in diabetic wound granulation tissue, concurrently augmenting FGF7 expression to accelerate wound repair (265). Liu *et al* (266) demonstrated that NPWT stimulates keratinocyte proliferation and migration by suppressing hsa-miR-203, which elevates p63 protein levels in both peripheral blood and wound edge tissue, contributing to enhanced diabetic wound healing.

Photobiomodulation (PBM), commonly known as low-intensity laser therapy, is a non-interventional treatment approach that employs low-power optical radiation, typically delivered via lasers or light-emitting diodes (267). PBM enhances wound closure and tissue regeneration, with optimal therapeutic outcomes depend on precise selection of wavelength and fluence parameters (268,269). PBM at 830 nm (5 J/cm^2 fluence) significantly boosts fibroblast viability, migration and proliferative capacity via activation of the TGF-β1/Smad pathway, leading to accelerated healing of diabetic wounds (163). Cai *et al* (270) examined dual-wavelength (red/blue) phototherapy in diabetic rats, observing substantial decreases in inflammatory markers and ROS accumulation alongside enhanced EC activity. This combined approach promotes NO synthesis and markedly improves wound closure rates.

Filgrastim, a recombinant human granulocyte colony-stimulating factor analog, promotes both neutrophil progenitor differentiation and functional maturation (271). Additionally, this cytokine directs neutrophil trafficking toward inflammatory and infectious foci, amplifying localized immune defenses via targeted cellular recruitment. A retrospective analysis of patients with infectious diabetic wounds demonstrated that those treated with filgrastim exhibited significantly faster recovery times (272). This indicates the

potential therapeutic value of filgrastim in enhancing infection control and promoting wound healing via increased neutrophil production and migration, bolstered immune response and accelerated tissue repair.

There are limitations in the application of the aforementioned therapies. The high cost of treatment and reliance on specialized equipment restrict the widespread adoption of HBOT. Future research should focus on optimizing treatment parameters, decreasing cost and investigating combination therapies. NPWT may induce pain and skin damage, with limited efficacy for infected wounds. Advances in dressing materials and refined control of negative pressure are required to minimize adverse reactions (273). PBM lacks standardized therapeutic parameters, such as wavelength and fluence, and its efficacy varies between individuals (268,269). Large-scale clinical trials are necessary to establish optimal parameters and indications. Filgrastim may lead to overactivation of neutrophils, potentially causing increased inflammation and other adverse reactions (274). Future studies should aim to optimize dosing regimens and develop novel drugs to enhance therapeutic outcomes.

8. Conclusion

The present review summarizes cell migration dynamics in diabetic wounds, with a focus on cellular mechanisms, signaling cascades, ncRNA-mediated regulation and their translational implications for targeted therapies. Emerging therapies, such as SCs, exosomes, drug-loaded dressings and TCM, enhance cell migration via ncRNA-mediated signaling (160,275). This establishes regulatory axes of drug/therapy-ncRNA-signaling pathway/downstream target-cell migration (166,254). These breakthroughs substantially enhance understanding of diabetic wound pathological mechanisms while establishing a framework for targeted therapeutic development.

Although the mechanisms underlying abnormal cell migration in diabetic wounds and targeted therapeutic approaches have seen advancements, notable gaps remain. The majority of studies emphasize the regulation of individual cell types or specific signaling pathways, with limited exploration of cellular interactions and signaling crosstalk (160,165,166,275). Research on the regulation of cell migration primarily focuses on ncRNAs, whereas other epigenetic modifications, such as DNA methylation and histone modification, warrant further investigation (170,177,192,211). Most studies rely on *in vitro* experiments or animal models, which differ from the complex pathological environment of the human body, limiting their clinical translation and necessitating further validation (170,253). Despite their growing use, SC/exosome and growth factor therapy, advanced drug-loaded dressings and TCM intervention lack comprehensive clinical trial data to confirm their long-term safety and therapeutic efficacy. Furthermore, given the high heterogeneity of patients, there is a lack of research on personalized treatment approaches in existing studies, which restricts broader clinical application (276-278).

Future research should explore crosstalk between immune cells, fibroblasts, keratinocytes and ECs in diabetic wounds, focusing on key pathways. The application of organoids or 3D-printed tissue models may facilitate the development of more accurate models that closely mimic the human pathological environment (279,280). It is essential to refine the preparation and delivery technologies for SCs and exosomes, enhance the manufacturing processes of drug-loaded dressings and design intelligent dressing delivery systems to improve the precision and control of therapeutic interventions (281-283). The integration of topical TCM agents with advanced wound dressings may enhance therapeutic efficacy, presenting a potential strategy for diabetic wound management. Large-scale, multi-center clinical trials are required to validate the efficacy of existing treatments. Integrating multi-omics techniques with artificial intelligence-based analysis to explore personalized treatment strategies will aid in achieving precise intervention tailored to individual patient characteristics (284). Ultimately, it is essential to enhance multi-disciplinary collaboration between basic research and clinical practice, thereby facilitating the translation of research findings into practical applications and providing more efficient and safer solutions for the treatment of diabetic wounds.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Construction Project of the TCM Institute of Sore and Ulcer, Tianjin University of Traditional Chinese Medicine (grant no. 202206), the Construction Project of the Institute of Traditional Chinese Medicine and Integrated Chinese and Western Medicine under the Tianjin Municipal Health Commission (grant no. 202455) and the Research Planning Projects of the Tianjin Municipal Education Commission (grant no. 2024ZD014).

Availability of data and materials

Not applicable.

Authors' contributions

JLS designed the study, wrote the manuscript and constructed figures. TZ and CW performed the literature review and created figures. XS, JCS and ZZ revised the manuscript. JCS and ZZ supervised the study and acquired funding. Data authentication is not applicable. All authors have read and approved the final manuscript.

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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