



Potential roles of histone deacetylases in diabetic wound healing

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Abstract

Diabetic foot ulcer is the most prevalent and serious lower-limb complication among individuals with diabetes, and it significantly contributes to the incidence of non-traumatic amputations. The repeated failure of diabetic wounds to heal can result in diabetic foot ulcers, inflicting considerable physical suffering and imposing substantial economic burdens on both patients and global healthcare systems because of the complexity and high costs of treatment. The mechanisms underlying the impaired healing of diabetic wounds are intricate and incompletely understood. Histone deacetylases (HDACs) are critical epigenetic regulators that catalyze the removal of acetyl or acyl groups from lysine residues in proteins, thereby modulating various biological processes, including transcription, apoptosis, and metabolism. Nevertheless, the precise roles of HDACs in diabetic wound healing remain largely unexplored. Thus, the current review describes the pivotal roles of HDACs in diabetic wound healing, focusing on their regulation of inflammatory responses, vascular dysfunction, and epithelial renewal, which are critical events in wound healing. Furthermore, we discuss the therapeutic potential of HDAC inhibitors and propose future directions for clinical application.

Key Words: Histone deacetylases; Diabetic wound healing; Inflammation; Angiogenesis; Histone deacetylases inhibitors

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Core Tip: Repeated failure of diabetic wounds to heal is a critical global health issue that significantly contributes to the incidence of non-traumatic amputations. However, the mechanisms underlying the impaired healing of diabetic wounds are intricate and incompletely elucidated. In this review, we analyze the pivotal roles of histone deacetylases in the critical events in diabetic wound healing.

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INTRODUCTION

Epidemiology and pathophysiology of diabetic foot ulcer

Diabetic foot ulcer (DFU) is the most common and serious lower-limb complication in individuals with diabetes and a major cause of non-traumatic amputations[1]. The global prevalence of diabetes remains grim, with 9.3% (463 million people) of the population affected in 2019, and projections suggesting an increase to 10.2% (578 million people) in 2030 and 10.9% (700 million people) by 2045[2,3]. DFUs occur in 19%-34% of patients with diabetes, and they generally lead to varying degrees of amputation. Each year, approximately 1.6 million individuals globally undergo amputation, 33% of which are major amputations[4]. Furthermore, the mortality rate within 5 years following diabetes-related amputations exceeds 70%[1]. Multiple factors lead to persistent non-healing of diabetic wounds, which ultimately results in the formation of DFUs[5], including impaired leukocyte function[6], reduced growth factor secretion[7,8], impaired macrophage function[9], reduced collagen deposition, epidermal barrier dysfunction, reduced granulation tissue formation[8], impaired keratinocyte and fibroblast migration and proliferation, reduced epidermal nerve counts[10], inflammatory cell accumulation, imbalance of extracellular matrix (ECM) component accumulation and ECM remodeling[11], and impaired vascular function and angiogenesis[8,12].

Persistent hyperglycemia and prolonged elevation of free fatty acid levels in patients with diabetes can trigger the excessive release of inflammatory molecules, impair leukocyte and macrophage function, and disrupt immune responses, resulting in a chronic inflammatory state that prevents the transition of wounds to the proliferative phase of healing[6,13,14]. Additionally, patients with diabetes exhibit a higher incidence of macrovascular and peripheral artery diseases, like stenosis or occlusion of aortoiliac artery, femoral artery, popliteal artery, infrapopliteal artery and foot artery, than individuals without diabetes, and microcirculatory insufficiency potentially occurs early in the disease course. Pathological changes, including capillary shrinkage, basement membrane thickening, and arterial hyalinization (a pathological change in which homogeneous and transparent hyaline material deposition result in arterial wall thickening and decreased elasticity), are common in diabetes[8,15]. Long-term hyperglycemia can also lead to peripheral neuropathy, resulting in nerve and vascular damage in multiple body areas. Endothelial cells lose their integrity, making them prone to detachment and apoptosis, which ultimately impairs vascular function and neovascularization[16,17]. Insufficient angiogenesis exacerbates tissue ischemia and hypoxia and limits the support necessary for collagen synthesis, which is required for mature granulation tissue and subsequent re-epithelialization[18]. During the tissue formation phase of wound repair, keratinocyte proliferation and migration, as well as fibroblast proliferation and differentiation, are crucial for restoring epithelial barrier function[19]. However, this process is significantly impaired in diabetes due to defects in keratinocyte migration and proliferation, abnormal gap junctions, reduced fibroblast proliferation, impaired cell migration, and decreased growth factor expression[20,21]. The combined effects of these impairments reduce the overall healing capacity in patients with diabetes, making even minor skin injuries prone to developing into chronic wounds, such as DFUs[22]. The complex mechanisms underlying impaired diabetic wound healing present a significant challenge to effective treatment.

Epigenetic regulation in diabetic wound healing

In recent decades, substantial efforts have been dedicated to exploring potential strategies to promote diabetic wound healing, with increasing attention devoted to the effects of epigenetic modifications[23-25]. Diabetes-induced epigenetic dysregulation, such as methylation, phosphorylation, ubiquitination, and acetylation, significantly contributes to delayed wound healing in patients with diabetes. Targeted regulation of specific epigenetic modifications can alter the healing process and improve outcomes[26]. For example, decreased expression of the N6-methyladenosine (m6A) reader *YTHDC1* was detected both *in vitro* in hyperglycemia-treated epidermal cells and *in vivo* in diabetic wounds, and the decrease in m6A level caused by *YTHDC1* downregulation significantly delayed skin wound healing[23]. Phosphorylation inhibition of myeloid differentiation primary response protein (*MYD88*) by purpurulide C improved diabetic wound healing[27]. Ubiquitination of vascular endothelial growth factor receptor 2 (*VEGFR2*) induced by pro-protein convertase subtilisin/kexin type 9 significantly delayed healing in diabetic skin wound[28]. Inhibition of hypoxia-inducible factor-1 α (*HIF-1 α*) ubiquitination promoted cell proliferation and migration, thus promoting wound angiogenesis and diabetic wound healing[29].

As important epigenetic regulators, histone deacetylases (HDACs) remove acetyl or acyl groups from lysine residues of proteins to regulate various biological processes, including transcription, cell death, and metabolism[26,30-32]. Crosstalk exists between different epigenetic regulators. For example, HDAC inhibition triggered the elevation of m6A RNA modification in ocular melanoma as well as altered DNA and histone methylation in mouse models of Huntington's disease[33,34]. In neurons, HDAC2 phosphorylation at Y222 contributes to maintaining HDAC2 protein expression. In parathyroid hormone signaling, protein kinase A promotes HDAC4 nuclear export by phosphorylating HDAC4 at S740 [35]. HDAC/H3K27ac-mediated transcription of nicotinamide adenine dinucleotide: Ubiquinone oxidoreductase subunit A3 suppresses apoptosis, eliminates reactive oxygen species (ROS), improves mitochondrial function and oxidative phosphorylation, protecting human nucleus pulposus cells against high glucose-induced injuries[36]. In addition, the E3 ubiquitin ligase parkin interacts with acetylase acetyl-CoA acetyltransferase 1 and deacetylase HDAC2. Therefore, inhibiting HDAC activity mediates parkin acetylation and activates mitophagy, inhibiting cervical cancer cell proliferation[37]. As the regulation of methylation, phosphorylation and ubiquitination play important roles in diabetic wound healing, the above results suggest potential roles of HDACs in diabetic wound healing. HDACs can target angiogenic markers such as vascular endothelial growth factor (VEGF) and HIF-1 α , and their targeted regulation might play a critical role in angiogenesis. Additionally, HDACs are involved in the polarization of macrophages from M1 to M2, a key event in wound healing. Furthermore, HDACs are associated with insulin release, thus contributing to glucose homeostasis and playing roles in the development of diabetes mellitus and its complications[38-40]. However, the roles of HDACs in diabetic wound healing are incompletely understood. This review summarizes the current research on HDAC functions in diabetic wound healing, discusses potential HDAC targets, and explores their therapeutic potential, thereby offering new insights for addressing impaired diabetic wound healing.

HDACs

HDACs are highly evolutionarily conserved[36]. Eighteen HDACs have been identified, and they are divided into four classes based on sequence and functional homology. Class I HDACs, namely HDAC1, HDAC2, HDAC3, and HDAC8, share homology in the catalytic pocket with the yeast enzyme reduced potassium dependency 3. Primarily localized in the nucleus, class I HDACs regulate cell cycle, apoptosis, development, metabolism, and disease processes through chromatin modification and transcriptional regulation[41-43]. Class II HDACs have six members: HDAC4, HDAC5, HDAC6, HDAC7, HDAC9 and HDAC10. Among them, HDAC4, HDAC5, HDAC7, and HDAC9 are further grouped into class IIa, whereas HDAC6 and HDAC10 are categorized into class IIb. All of class II HDACs are similar to the yeast protein HDA1. By deacetylating histone and non-histone substrates, class II HDACs play important roles in tissue development, transcriptional repression, and cytoplasmic functions[42,43]. Class III HDACs, which are also known as sirtuins (SIRT), consist of seven members: SIRT1-7. They are nicotinamide adenine dinucleotide-dependent and have various tissue specificities and subcellular localization, where they play critical roles in aging, metabolism, genome stability, and inflammation[41,44]. Meanwhile, the only class IV HDAC is HDAC11, which can localize to both the nucleus and cytoplasm[38,41,42]. In addition to deacetylase activity, HDAC11 has defatty-acylase activity, indicating its broad physiological functions and pleiotropic regulatory roles in immunity, metabolism, cancer, and nervous system function[45]. The structure, cellular localization, tissue distribution, and biological functions of the four HDAC classes and their involvement in various disease are presented in [Figure 1](#).

THE ROLES OF HDACs IN DIABETIC WOUND HEALING

Characteristics of diabetic wound healing

Impaired wound healing is a common and severe complication of diabetes, characterized by a complex pathophysiology involving dysregulated inflammatory responses, impaired angiogenesis, and abnormal epithelial regeneration.

Inflammation in diabetic wounds

Chronic inflammation is a central feature of delayed healing in diabetic wounds, with mechanisms involving disruption in both the innate and adaptive immune systems. Hyperglycemia promotes the accumulation of advanced glycation end-products (AGEs), which activate the receptor of AGE (RAGE) signaling pathway, leading to the persistent release of nuclear factor kappa-B (NF- κ B)-dependent pro-inflammatory factors, such as interleukin (IL)-6, tumor necrosis factor- α (TNF- α), and IL-1 β [8]. Clinical studies demonstrated that IL-1 β levels in wound exudates from patients with DFUs are 2-3-fold higher than those in individuals without diabetes, and this increase is negatively correlated with healing time [46]. Furthermore, neutrophil chemotaxis and phagocytic function are impaired in the diabetic state, and apoptosis is delayed, resulting in excessive production of ROS and proteases [e.g., matrix metalloproteinase (MMP)-8], further damaging the ECM and inhibiting re-epithelialization[47]. Abnormal macrophage polarization is another key factor in diabetic wound healing. In normal healing, the dynamic transition of macrophages from pro-inflammatory (M1) to anti-inflammatory/repair (M2) phenotype is crucial for resolving inflammation. However, in diabetic wounds, hyperglycemia and oxidative stress inhibit M2 polarization by suppressing the peroxisome proliferators-activated receptor- γ and signal transducer and activator of transcription (STAT) 6 signaling pathways[48]. Animal studies revealed that M1 marker expression [inducible nitric oxide synthase, cluster of differentiation (CD) 86] increased in mice with diabetes, whereas M2 marker expression [arginase-1 (Arg-1), CD206] decreased. This imbalance in the M1/M2 ratio is directly associated

				Localization	Tissue distribution	Biological function	Related diseases
CLASS I (Zn ²⁺ dependent)	HDAC1		482aa	Nucleus	Ubiquitous	Synergistically regulate cell cycle arrest, apoptosis	Tumor, neurodevelopment, cardiac development, lipogenesis
	HDAC2		488aa	Nucleus	Ubiquitous		
	HDAC3		428aa	Nucleus	Ubiquitous	Inflammation, metabolism, reproduction	Atherosclerosis, liver diseases, congenital heart diseases, tumor
	HDAC8		377aa	Nucleus	Ubiquitous	Development, DNA damage, metabolism	Pulmonary arterial hypertension, tumor, genetic diseases
CLASS IIa (Zn ²⁺ dependent)	HDAC4		1084aa	Nucleus/cytoplasm	Heart, skeletal muscle, brain	Androgenesis, inflammation	Prostate cancer, viral infection
	HDAC5		1122aa	Nucleus/cytoplasm	Heart, skeletal muscle, brain	Cell proliferation, cell apoptosis, inflammation	Tumor, autoimmune Disease
	HDAC7		952aa	Nucleus/cytoplasm/mitochondria	Heart, skeletal muscle, pancreas, placenta	Neuroprotection, osteoblast differentiation	Osteoporosis
	HDAC9		1011aa	Nucleus/cytoplasm	Heart, skeletal muscle	Lipogenesis	Hyperlipidemia
CLASS IIb (Zn ²⁺ dependent)	HDAC6		1215aa	cytoplasm	Testis, heart, liver kidney, placenta	Inflammation	Tumor
	HDAC10		669aa	cytoplasm	Liver kidney, spleen	Polyamine deacetylase, type I interferon signalling, inflammation	Viral infections, tumor
CLASS IV (Zn ²⁺ dependent)	HDAC11		347aa	Nucleus/cytoplasm	Brain, heart, skeletal muscle, kidney	Type I interferon signalling	Viral infections, multiple sclerosis, cancer
CLASS III (NAD ⁺ dependent)	SIRT1		747aa	Nucleus/cytoplasm	Ubiquitous	Ketogenesis	Pseudo aldosteronism, primary hypertension
	SIRT4		314aa	Mitochondria	Muscle, pancreas	Tumor cell proliferation, insulin secretion	Tumor, diabete
	SIRT5		310aa	Mitochondria	Ubiquitous	Metabolism, cell proliferation, ketogenesis	Tumor
	SIRT6		355aa	Nucleus	Ubiquitous	Inflammation, DNA damage, cell apoptosis	Tumor, heart failure

HDAC catalytic domain
 Nucleus localization signal
 Serine binding motif
 MEF2-binding motif
 Nucleus export signal
 Serine-glutamate tetradecapeptide
 Zinc-binding domain
 UB P-type
 Leucine-rich domain
 SIRT catalytic domain
 Zinc-binding domain
 Proline-rich region

Figure 1 The structure, cellular localization, tissue distribution, biological functions, and related diseases of the four classes of histone deacetylases. Class I, class II and class IV histone deacetylases (HDACs) are zinc ion-dependent, whereas class III HDACs are nicotinamide adenine dinucleotide-dependent. Class I HDACs are primarily distributed in the nucleus, and they are related to the pathogenesis of tumors, genetic diseases, and metabolic diseases. The Class IV HDAC is distributed in both the nucleus and cytoplasm, and it participates in the development of infectious diseases, nervous system diseases and tumors. Class II and class III HDACs are distributed in the nucleus, cytoplasm, and mitochondria, and they are involved in the pathogenesis of tumors, infectious diseases, metabolic diseases, and cardiovascular diseases. HDAC: Histone deacetylase; Zn²⁺: Zinc ion; SIRT: Sirtuin; NAD: Nicotinamide adenine dinucleotide; MEF2: Myocyte enhancer factor 2; UB P: Ubiquitin-specific proteases.

with increased wound area[49]. Additionally, macrophages in patients with diabetes exhibit impaired efferocytosis, leading to the accumulation of necrotic tissue and chronic inflammation[50]. Recent research demonstrated that neutrophil extracellular traps (NETs) are excessively formed in diabetic wounds, directly damaging endothelial cells and keratinocytes by releasing histones and antimicrobial proteins (such as myeloperoxidase)[50]. Wong *et al*[51] confirmed that NET levels are elevated in diabetic wounds in mice, and DNase I treatment significantly reduced tissue damage and accelerated healing. Moreover, diabetes-related hyperlipidemia activates the Toll-like receptor 4 signaling pathway, enhancing NETosis and perpetuating a vicious cycle[52].

Angiogenesis in diabetic wound

Angiogenesis is also impaired in diabetic wounds, and this impairment involves endothelial dysfunction, growth factor signaling inhibition, and abnormal perivascular matrix. Hyperglycemia reduces HIF-1 α stability, resulting in decreased VEGF and platelet-derived growth factor (PDGF) expression[16]. In mice with diabetes, the half-life of HIF-1 α in wounds decreased by 50%, and VEGF messenger RNA levels decreased by 60%[53]. Additionally, AGEs activate nicotinamide adenine dinucleotide phosphate oxidase by binding to RAGE, thereby increasing ROS production and leading to the uncoupling of endothelial nitric oxide synthase and a decrease in nitric oxide (NO) bioavailability[53]. Diabetes-specific microvascular lesions exacerbate ischemia. Histopathological analysis revealed that capillary basement membranes are thickened in patients with DFUs, and the expression of endothelial junction proteins (such as vascular endothelial-cadherin) is reduced, increasing vascular permeability and plasma leakage[54]. Furthermore, pericyte dropout is common in both diabetic retinopathy and wound vasculature degradation. Studies suggest that hyperglycemia induces pericyte apoptosis *via* activation of the protein kinase C- β signaling pathway, compromising vascular stability[55]. Recent studies also highlighted the role of non-coding RNAs in angiogenesis regulation. For instance, miR-200b is upregulated in diabetic wounds, and it inhibits endothelial cell migration by targeting GATA2 and VEGFR2[56]. Conversely, miR-126-3p is downregulated in diabetes, resulting in impaired angiopoietin-1 signaling[57].

Epidermal regeneration in diabetic wound

Abnormalities in epidermal regeneration, primarily impaired keratinocyte function and diminished stem cell repair capacity, also occur in diabetic wounds. Integrin $\alpha 5\beta 1$, a core receptor for keratinocyte adhesion to the ECM, is activated by the phosphorylation of focal adhesion kinase (FAK) at phospho-FAK (Tyr397). Research has demonstrated that integrin $\alpha 5\beta 1$ expression is downregulated in keratinocytes from patients with diabetes, leading to decreased FAK phosphorylation, causing weakened cell-matrix adhesion and significantly slower cell migration[58]. *In vitro* scratch assays confirmed that under high glucose conditions (25 mmol/L glucose), keratinocyte migration is significantly slowed compared with that in the normal glucose group (5.5 mmol/L), and directional migration was impaired[59]. This phenomenon is closely linked to hyperglycemia-induced oxidative stress. Specifically, ROS activate the p38 mitogen-activated protein kinase pathway, thereby inhibiting the activity of small G proteins (*Rac1/Cdc42*) and disrupting cytoskeletal rearrangement. The basement membrane serves as a scaffold for keratinocyte migration, and its integrity depends on stable expression of laminin-332 and type IV collagen. In diabetes, abnormal basement membrane components represent another key factor limiting epidermal regeneration. Prior studies illustrated that laminin-332 and type IV collagen expression is reduced in diabetic wounds, whereas MMP-9 activity is increased, leading to a loose basement membrane structure that hinders directional keratinocyte migration[58,60]. Additionally, the repair capacity of epidermal stem cells (EpSCs) and mesenchymal stem cells (MSCs) is significantly diminished in diabetes. EpSCs, located in the basal layer of the epidermis, rely on Wnt/ β -catenin signaling for self-renewal. Hyperglycemia activates glycogen synthase kinase-3 β , thereby promoting β -catenin phosphorylation and degradation, and repressing EpSC proliferation [61]. Flow cytometry revealed reduced Ki-67 positivity in EpSCs from mice with diabetes compared with control mice. MSC paracrine function is also suppressed in diabetes. In prior research, diabetic bone marrow MSCs exhibited a 60% reduction in the secretion of stromal cell-derived factor-1 α and VEGF, impairing their homing ability[62]. Mechanistically, hyperglycemia excessively activates the mechanistic target of rapamycin complex 1 signaling pathway, inducing autophagic flux blockage in MSCs and promoting a senescence-associated secretory phenotype[63]. The characteristics of wound healing in diabetes are presented in Figure 2.

HDACs and inflammation

The transformation of macrophages from the M1 phenotype to the M2 phenotype is critical for wound healing, as this polarization promotes the non-inflammatory clearance of neutrophils, expression of anti-inflammatory mediators, and production of growth factors, such as IL-10, transforming growth factor (TGF) $\beta 1$, VEGF, and insulin-like growth factor 1, which promote wound healing[64,65]. Mullican *et al*[66] reported that HDAC3 deletion in macrophages leads to increased inflammatory gene expression, demonstrating the role of HDAC3 in restraining the M1-to-M2 polarization of macrophages. In addition, HDAC3 can deacetylate NF- κ B subunits, thereby enhancing the DNA binding ability of NF- κ B, promoting the expression of pro-inflammatory factors such as TNF- α and IL-6. Inhibition of HDAC3 reduced inflammatory responses[67].

In RAW 264.7 and human THP-1-derived macrophages, HDAC9 knockout increased M2 marker expression, demonstrating the negative regulation of HDAC9 in M2 macrophage polarization. On the contrary, HDAC4 increased Arg-1 expression and activated STAT6 signaling in mouse dendritic cells, indicating its positive regulatory effect on M2 polarization[24,68]. It has been reported that HDAC6 promotes inflammasome assembly by deacetylating nucleotide-binding oligomerization domain-like receptor thermal protein domain associated protein 3 (NLRP3) protein, leading to IL-1 β release[69]. The inhibition of HDAC activity enhanced the immunosuppressive function of regulatory T cells and reduced autoimmune inflammation in HDAC9 knockout mice[70].

SIRT6 also play pivotal roles in inflammation regulation. SIRT1 promotes M2-type anti-inflammatory macrophage differentiation by enhancing adenosine 5'-monophosphate-activated protein kinase (AMPK) signaling and inhibiting the mammalian target of rapamycin (mTOR) pathway. SIRT1 also activates peroxisome proliferator-activated receptor- γ coactivator (PGC)-1 α , improves mitochondrial biosynthesis, reduces ROS accumulation, and thus inhibits NLRP3 inflammasome activation[71-73]. SIRT2 reduced inflammation in gout models by deacetylating NLRP3, inhibiting NLRP3 oligomerization and suppressing IL-1 β maturation[74,75]. By deacetylating *SOD2* and *IDH2*, SIRT3 enhanced antioxidant defenses and reduced ROS-induced activation of NLRP3 inflammasome, thereby protecting against sepsis and atherosclerosis[76,77]. In addition, SIRT3 can inhibit macrophage polarization to the pro-inflammatory M1 type, and miR-421 delivery to macrophages inhibits SIRT3, thus increasing M1-type macrophage polarization[78]. SIRT6 has been shown to inhibit TNF- α and IL-8 expression and delay aging-related inflammation by directly binding to the promoters of NF- κ B target genes and deacetylating histone H3 Lysine 9[79].

As the only class IV HDAC[80], HDAC11 primarily regulates metabolic inflammation by controlling IL-10 released by antigen-presenting cells. It plays an important role in regulating macrophage phenotype in several diseases. HDAC11 inhibition can increase IL-10 expression in macrophages and polarize them to the M2 type, whereas HDAC11 overexpression can reduce IL-10 expression[39]. Inhibition of HDAC11 promoted the anti-inflammatory properties of macrophages[40,81]. HDAC11-deficient macrophage infiltration can also promote the regeneration of skeletal muscle by producing high levels of IL-10[82]. In hepatocellular carcinoma (HCC), HDAC11 inhibitors increased arachidonic acid metabolism, thereby inhibiting its effect on M1 macrophage polarization[83]. In addition, in mice infected with fungi, HDAC11 deficiency led to a significant reduction in serum levels of the pro-inflammatory cytokines IL-1 β and IL-6, thereby affecting the anti-fungal ability of macrophages[84]. Furthermore, HDAC11 deficiency can improve insulin sensitivity in mice by triggering *UCP2* and *PGC-1 α* gene expression[85]. HDAC11 deficiency increases *UCP1* expression and activity and enhances the level of adiponectin, which regulates glucose levels and fatty acid oxidation through adiponectin-adiponectin-AMPK pathway activation. In mice fed a high-fat diet, HDAC11 deletion significantly reduced blood insulin levels, stabilized blood glucose, and greatly reduced blood glucose levels after insulin stimulation, thereby

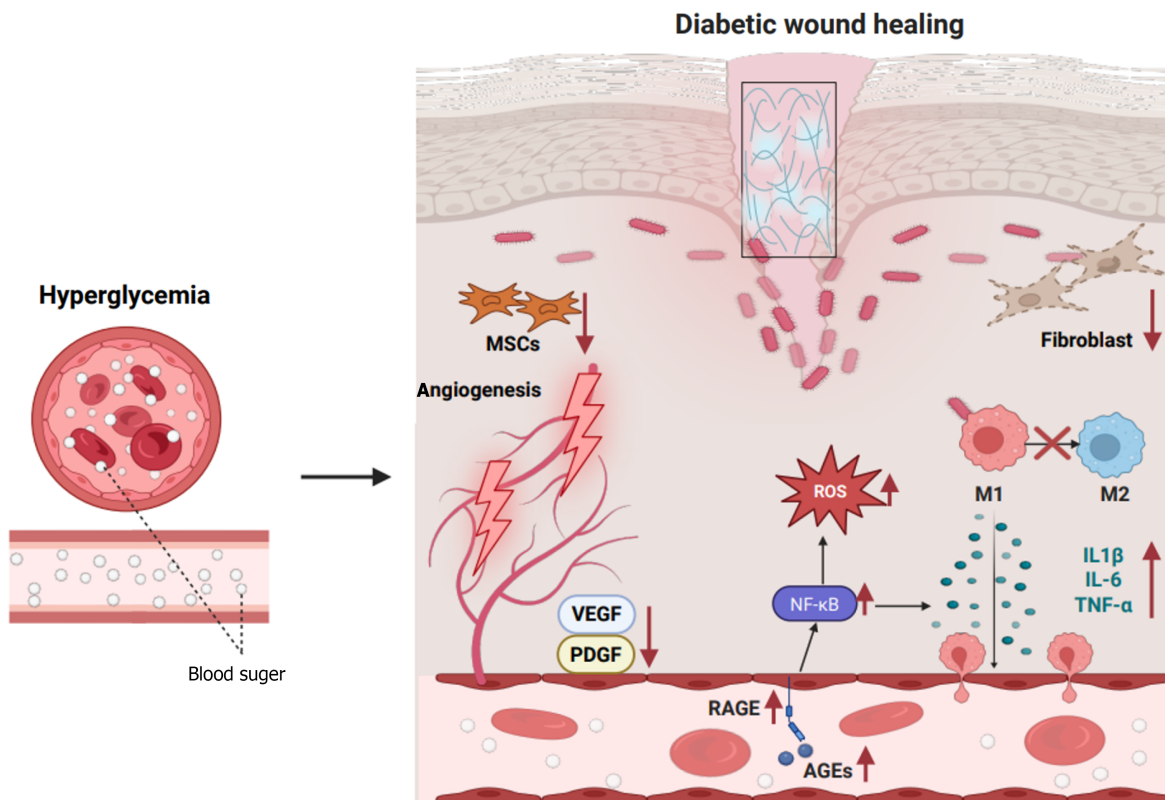


Figure 2 Characteristics of wound healing in diabetes. In diabetic wounds, persistent hyperglycemia leads to the chaotic release of cytokines and abnormal activation of pathways that play critical roles in wound healing, such as receptor of the advanced glycation end-products, nuclear factor kappa-B, and vascular endothelial growth factor signaling pathway. Thus, chronic inflammation and dysfunction of macrophages, fibroblasts, and mesenchymal stem cells leads to abnormal epithelial regeneration and impaired angiogenesis and extracellular matrix formation, contributing to non-healing wounds and ulcer formation. MSCs: Mesenchymal stem cells; VEGF: Vascular endothelial growth factor; PDGF: Platelet-derived growth factor; RAGE: Receptor of the advanced glycation end-products; AGEs: Advanced glycation end-products; ROS: Reactive oxygen species; IL: Interleukin; TNF- α : Tumor necrosis factor- α ; NF- κ B: Nuclear factor kappa-B.

enhancing glucose tolerance and ameliorating diabetes[86,87]. Moreover, in a mouse model of diabetic heart failure induced by fructose damage, loss of HDAC11 resulted in significantly reduced apoptosis, dyslipidemia, inflammation, and oxidative stress[88].

The exact mechanism of HDACs in regulating diabetic wound inflammation is still unclear. However, the studies reported above have suggested its great potential in diabetic wound healing. To clarify these effects, alterations of HDAC expression in critical cells (such as macrophages, vascular endothelial cells and epithelial cells) treated with high glucose and in animal models of diabetes warrant further exploration. The impact of HDAC regulation on inflammatory factor expression, signaling pathways, and wound healing outcomes, such as the rate and quality of healing, remains to be explored. Notably, studies incorporating clinical samples and data, such as analyses of skin tissue or blood from patients with DFU, would make the results more convincing.

The stages of wound healing are distinct but overlapping. Prolonged inflammation in the wound contributes to impaired angiogenesis and re-epithelialization. Macrophages regulate the behavior of endothelial cells, fibroblasts and epithelial cells. Consequently, macrophage depletion by pharmacological agents may reduce angiogenesis and cause abnormal ECM deposition in the wound bed, leading to impaired keratinocyte migration, proliferation, and gap junctions [89]. Chronic inflammation also impairs M2 macrophage polarization, resulting in reduced release of growth factors such as VEGF, PDGF, members of the epidermal growth factor family (including EGF, heparin binding-EGF, and TGF- α), and fibroblast growth factors (particularly FGF2 and keratinocyte growth factor). This deficiency hinders neovascularization and disrupts epithelial tongue migration. Injury causes neutrophil recruitment to the wound site. In chronic wounds, the production of neutrophil-derived proteolytic enzymes is abnormally increased, resulting in decreased growth factors and receptor expression, impairing the angiogenesis processes and blood flow[90]. Thus, the regulation of HDACs in inflammation may directly or indirectly influence angiogenesis and epithelial renewal.

HDACs and angiogenesis

Neovascularization is a key event in wound healing. Several studies suggested that HDACs play important roles in angiogenesis by regulating acetylation in both histone and non-histone proteins. The function of HDACs in angiogenesis is subtype-specific and disease context-dependent, meaning that they can either promote or inhibit vessel regeneration [91,92]. By deacetylating histones, HDAC1 and HDAC3 can inhibit the expression of anti-angiogenic genes, such as thrombospondin-1, and promote endothelial cell proliferation and migration[93]. Under hypoxia, HDAC7 is recruited to the VEGF promoter region by HIF-1 α to enhance VEGF expression and promote angiogenesis, whereas HDAC4 enhances

VEGF expression by deacetylating HIF-1 α and enhancing its stability[94,95]. HDAC6 was reported to deacetylate α -tubulin, causing changes in cytoskeletal dynamics and enhancing endothelial cell migration[96]. Besides, HDAC9 upregulation was involved in AGE-induced angiogenesis[92]. Silencing of HDAC9 inhibited VEGF-A expression in diabetic retinopathy, which is important for angiogenesis[97]. HDAC5 plays an antiangiogenic role in vascular homeostasis. Deletion of HDAC5 increased the expression of FGF2 and angiogenic guidance factor Slit2, thereby promoting endothelial cell migration, sprouting, and tube formation[98].

Deletion of SIRT1 downregulated angiogenic genes and reduced angiogenic sprouting, and SIRT1 abolished anti-angiogenic effects by deacetylating the anti-angiogenic factor forkhead transcription factor O1[99]. SIRT1 also promoted cardiac angiogenesis in rats with type 2 diabetes by deacetylating HIF-1 α and inhibiting its degradation[100]. It has been reported that SIRT2 activity is reduced in aged aortas. SIRT2 deficiency has been shown to increase mitochondrial oxidative stress, aggravate aging-induced arterial stiffness, and accelerate vascular aging, suggesting its therapeutic value in vascular rejuvenation[101]. Concerning angiogenesis inhibition, HDAC9 contributes to oxygen-glucose deprivation-induced endothelial cell dysfunction and exacerbates endothelial injury in cerebral ischemia/reperfusion injury[102]. In pericytes, HDAC7 impaired vascular maturation by deacetylating PDGF receptor- β , thereby inhibiting its phosphorylation and downstream signaling[103]. HDAC11 inhibited VEGFR2 transcription by binding to its promoter region, thus reducing endothelial cell response to VEGF, resulting in impaired angiogenesis[45]. HDAC11 expression was increased in the aortas of mice fed a high-fat diet, and it promoted endothelial cell pyroptosis, contributing to atherosclerosis development[104]. Meanwhile, HDAC11 was upregulated in different grades of DFUs, with its expression being highest in patients with grade 3 DFUs, suggesting its important role in diabetic wound healing.

Studies reported that HDAC2 activity was increased in aortic endothelial cells of diabetic patients, and HDAC2 overexpression increased hyperglycemia-induced vascular injury and abolished the vasculo-protective effect of adiponectin [105]. The HDAC1 inhibitor 1,3-Diphenylurea exhibited wound healing effects in human immortalized keratinocyte (HaCaT) cells, promoted HaCaT cell migration and increased LL-37 and VEGF expression in both HaCaT cells and primary keratinocytes from patients with DFU, and promoted angiogenesis in a mouse aortic ring model[106]. However, the exact characteristics of HDACs in diabetic wound angiogenesis are not yet clear. Further investigations are needed to elucidate the role of HDACs in regulating vascular endothelial cell function, as well as angiogenic and anti-angiogenic factors, in both *in vitro* and *in vivo* diabetic wound models.

HDACs and epithelial regeneration

Dysregulation of HDAC activity results in skin cell dysfunction. HDAC1 deletion leads to abnormal epidermal thickness with hyperkeratosis, hair follicle dystrophy, alopecia, claw dystrophy, and abnormal pigmentation in mice during skin morphogenesis and homeostasis. Double deletion of HDAC1 and HDAC2 was associated with more severe symptoms [107]. Regarding skin regeneration, HDAC1 and HDAC2 are abundantly expressed in the migrating epithelial tongue. According to prior research, hair follicle stem cell (HFSC) activation is also related to histone H4 acetylation. Global H4 deacetylation occurs after the initial injury and contributes to increased HFSC activity, thus promoting proliferation and migration to the wound edge to promote healing[108,109].

Qin *et al*[110] reported that HDAC6 reversed impaired fibroblast function in aged mice, thereby promoting fibroblast migration and differentiation and accelerating wound healing in aged mice. Interestingly, in diabetic wounds, HDAC6 inhibition induced collagen deposition, angiogenesis, and fibrotic factor expression in the late phase of healing, consequently promoting wound healing in diabetic mice[111].

The importance of SIRT1 in keratinocyte migration and differentiation during wound healing has been reported. Following SIRT1 knockdown in epithelial cells, p53 deacetylation and autophagy-related protein expression were reduced, and FGF21-induced autophagy was inhibited during wound healing. As a result, the pro-healing effect of FGF21 was abolished[112]. Meanwhile, SIRT1 activation promoted the self-renewal and differentiation of type 2 alveolar epithelial cells in patients with idiopathic pulmonary fibrosis and aged mice[113]. Yang *et al*[114] reported that SIRT3 protected retinal pigment epithelial cells from high glucose-induced injury by activating the AMPK/mTOR/ULK1 signaling pathway. SIRT3 overexpression activated the forkhead box protein O3/PTEN-induced putative kinase protein 1/parkin pathway, promoting diabetic corneal epithelial wound healing by stimulating mitophagy[115]. It has been reported that SIRT6 is responsible for maintaining epithelial integrity and corneal transparency, and SIRT6 deficiency led to Notch signaling pathway dysfunction and delayed healing after corneal epithelial injury[116].

In age-related macular degeneration, HDAC11 overexpression partially contributed to reduced chromatin accessibility, leading to retinal pigment epithelial cell dysfunction and disease onset[117]. HDAC11 also participates in intestinal epithelial barrier dysfunction. An interaction with the vitamin D receptor prevented HDAC11 from binding the promoters of zona occluden-1, claudin-5 and occludin, thereby maintaining epithelial barrier integrity[118]. Furthermore, HDAC11 upregulation was observed in renal tubular epithelial cells in different animal models of renal fibrosis, and HDAC11 inhibition inhibited the pro-fibrogenic response and ameliorated renal fibrosis development[119].

It is still not clear how HDACs affect epithelial cell function and biological behavior under high glucose and in diabetic wound skin. Local injection of small interfering RNA or clustered regularly interspaced short palindromic repeats-associated protein 9 technology for local selective knockout in the skin or lentiviral transfection for local overexpression could be alternative research methods for further study[120].

POTENTIAL REGULATION OF SIGNALING PATHWAYS IN DIABETIC WOUND HEALING BY HDACS

Wnt/ β -catenin signaling pathway

The wound healing process involves numerous signaling pathways, and the dysregulation of any of these pathways affects wound healing. Evidence suggests that Wnt/ β -catenin pathway activation promotes skin tissue repair by regulating cell proliferation, hair regeneration, EpSC function, and angiogenesis, and is one of the main ways to regulate wound healing, improve wound angiogenesis and epithelial remodeling[121-123]. Dysregulation of the Wnt/ β -catenin signaling pathway led to impaired diabetic wound healing, whereas Wnt/ β -catenin signaling activation significantly promoted diabetic skin wound healing[124]. During diabetic wound healing, the size of the ulcer is closely related to β -catenin protein expression[125]. Multiple studies have reported the regulation of HDACs in Wnt/ β -catenin signaling. HDAC1 inhibition caused Wnt/ β -catenin pathway activation by upregulating *TCF4*, *LEF1*, and β -catenin, thereby enhancing chimeric antigen receptor T cell function[126]. Inhibiting HDAC activity with trichostatin A (TSA) increased the expression of the transcription factor *TCF* and activated Wnt/ β -catenin signaling in HepG2 cells[127]. HDAC6 contributed to Wnt signaling activation by increasing Wnt5a expression and promoted cervical cancer progression[128]. HDAC6 activation stimulated c-Myc expression, the downstream proto-oncogene of the Wnt/ β -catenin signaling pathway, and promoted tumor growth[129]. HDAC6 deacetylase activity enhanced β -catenin stability, thereby activating the targets of β -catenin signaling. HDAC6 downregulation resulted in increased β -catenin acetylation and degradation, thereby inhibiting Wnt/ β -catenin signaling pathway activation and significantly suppressing TGF- β 1-induced epithelial-mesenchymal transition (EMT) and metastasis[130]. In HCC cells, SIRT7 promoted *FZD7* expression, contributing to β -catenin stability and activation to promote HCC cell migration. Knockdown of SIRT7 decreased β -catenin stability, nuclear localization, and activation[131]. In an inflammatory bowel disease model, SIRT2 inhibited Wnt/ β -catenin signaling activation[132]. Meanwhile, butyrate treatment suppressed HDAC11 expression and activated Wnt/ β -catenin signaling in vascular smooth muscle cells[133].

Notch signaling pathway

Notch signaling is activated by the interaction of membrane-bound Notch receptors (Notch-1-4) on adjacent cells with their ligands (Jagged-1-2 and Delta-like-1/3/4)[134]. Notch signaling participates in wound healing by actively regulating angiogenesis, cell migration, and inflammation[135]. However, Notch signaling is over-activated in diabetic skin, leading to impaired diabetic wound healing[120]. HDACs regulate Notch signaling in various manners. In peripheral neuropathies, recruitment of HDAC1/2-nucleosome remodeling and deacetylase (2-NuRD) complexes inhibited the Notch/*Hey2* signaling axis[136]. In pulmonary endothelial cells, HDAC6 inhibition repressed the binding of the Notch intracellular cytoplasmic domain and its transcriptional co-regulator *SNW1*, thereby inhibiting Notch transcriptional responses[137]. In human crypt-derived intestinal organoids, short-chain fatty acids inhibited HDAC activity and enhanced Notch signaling, resulting in activation of the Notch target gene *Hes1* and the promotion of enterocyte differentiation[138]. In non-small cell lung cancer cells, inhibition of SIRT6 suppressed the Notch signaling pathway and impaired cell proliferation and differentiation[139]. Additionally, high-fat ketogenic diet-induced inhibition of HDACs reinforced Notch signaling, activated *LGR5*⁺ intestinal stem cell (ISC) self-renewal, and increased ISC function and post-injury regeneration[140].

TGF- β /suppressor of mother against decapentaplegic signaling pathway

Activation of the TGF- β /suppressor of mother against decapentaplegic (Smad) signaling pathway plays important role in wound healing, as it promotes keratinocyte proliferation and migration and participates in the maturation of granulation tissue. The pathway is activated by TGF- β ligand binding to the TGF- β receptor I/II (TBR I/II), which leads to Smad protein phosphorylation, initiating their nuclear translocation and target gene activation. However, TGF- β /Smad signaling is inhibited in diabetic wounds, resulting in delayed wound healing[141,142]. The regulation of HDACs in the TGF- β /Smad signaling pathway suggests its potential role in diabetic wound healing. Inhibition of HDAC6 impaired TGF- β -induced EMT through Smad3 inactivation in A549 cells, resulting in α -tubulin acetylation and impairing mesenchymal stress fiber formation. Inhibiting HDAC10 activity also decreased TGF- β 1-induced type 1 collagen expression[143]. In human mammary fibroblasts, high-dose glutamine supplementation significantly inhibited class I HDAC activity, thereby inactivating TGF- β -Smad2/3 signaling. This is important for maintaining the myofibroblast state [144]. In fibrotic buccal mucosal fibroblasts (fBMFs), HDAC8 knockdown significantly reduced TGF- β secretion and the expression of *SNAIL* and phospho-Smad, thereby inhibiting collagen gel contraction and decreasing wound healing in fBMFs[145]. By recruiting HDAC4 and HDAC5, the oncoprotein *Ski*, inhibited TGF- β /Smad3 signaling, thereby accelerating chondrocyte differentiation[146]. In 2.5-micrometer particulate matter (PM2.5)-induced lung injury mouse models, HDAC3 knockout reduced TGF- β and Smad2/3 protein expression. Consistently, HDAC3 deficiency inhibited TGF- β /Smad2/3 signaling pathway activation and ameliorated PM2.5-induced inflammation response in lung epithelial cells[147].

HIF-1 α /VEGF signaling pathway

Dysregulation of HIF-1 α /VEGF signaling delayed diabetic wound healing due to impaired angiogenesis in response to hypoxia and a failure to upregulate VEGF[148]. By inhibiting HDAC1 activity, curcumin and sodium butyrate suppressed phospho-protein kinase B/phospho-phosphatidylinositol 3-kinase/HIF-1 α /VEGF axis, thereby attenuating airway inflammation of asthma[149]. HDAC5 overexpression enhanced HIF-1 α stabilization and nuclear translocation, whereas HDAC5 knockdown impaired hypoxia-induced HIF-1 α accumulation[150]. In nucleus pulposus cells, HDAC inhibition by TSA decreased HIF-1 α expression in a dose-dependent fashion. Selective inhibition of HDAC6 also reduced

Table 1 Histone deacetylase inhibitors approved by the Food and Drug Administration for clinical use[163-172]

Inhibitor	Target	Application	Ref.
Vorinostat (SAHA)	Broad-spectrum, mainly targets HDAC1, HDAC2, HDAC3, and HDAC6	Relapsed or refractory cutaneous T-cell lymphoma, multiple myeloma	Kim <i>et al</i> [163]; Olsen <i>et al</i> [164]; Sborov <i>et al</i> [165]
Romidepsin (FK228)	Selectively targets HDAC1 and HDAC2	Relapsed or refractory cutaneous T cell lymphoma and peripheral T cell lymphoma, multiple myeloma	Piekarczyk <i>et al</i> [166]; Harrison <i>et al</i> [167]
Belinostat (PXD101)	Broad-spectrum, targets HDAC1-9	Relapsed or refractory peripheral T cell lymphoma	O'Connor <i>et al</i> [168]
Panobinostat (LBH589)	Broad-spectrum, targets HDAC1-11	Relapsed or relapsed and refractory multiple myeloma	San-Miguel <i>et al</i> [169]
Givinostat (DUVYZAT™)	Pan-HDAC inhibitor	Duchenne muscular dystrophy	Lamb[170]
Chidamide	Class I HDAC inhibitor	Relapsed or refractory extranodal natural killer T-cell lymphoma, relapsed or refractory peripheral T cell lymphoma	Shi <i>et al</i> [171]; Gao <i>et al</i> [172]

HDAC: Histone deacetylase.

HIF-1 α -mediated transcription by deacetylating heat-shock protein 90[151]. The inhibition of HDAC activity by TSA might target tumor angiogenesis by inhibiting HIF-1 α and VEGF expression. The HDAC inhibitor Diallyl trisulfide inhibited HIF-1 α transcriptional activity and hypoxia-induced hematogenous metastasis in MDA-MB-231 cells in a dose-dependent manner[152]. The potential HDAC-associated signaling pathways in diabetic wound healing are presented in Figure 3.

HDAC INHIBITORS AS THERAPEUTIC POTENTIAL CANDIDATES FOR DIABETIC WOUND HEALING REGULATION

Many studies have reported the application of HDAC inhibitors in the treatment of different diseases, and some inhibitors have been approved by the Food and Drug Administration for clinical use (Table 1). Although there are no clinical studies directly testing wound healing, a series of preclinical animal studies demonstrated the great potential of HDAC inhibitors in regulating wound healing.

The regulation of specific HDACs can have completely opposite effects on skin wound healing, either ameliorating or delaying healing, and even the same HDAC inhibitor can have differential effects. For example, sodium valproate prevented tail regeneration in amphibians but reduced apoptosis in mice[108].

By increasing histone H3 and H4 acetylation, vorinostat decreased collagen deposits at the site of sclerotomy and reduced F-actin and α -smooth muscle actin expression in eye tissue, thereby preventing excessive wound healing and scar formation in a rabbit model of glaucoma filtration surgery[153]. Furthermore, in the treatment of triple-negative breast cancer, vorinostat decreased the deleterious effect of paclitaxel on wound healing[154]. Givinostat was reported to ameliorate glycemic control and restore insulin secretion in diabetic mice that underwent bone marrow transplantation, thereby achieving complete remission of diabetes, suggesting its pivotal role in diabetes and diabetic complications[155]. Treatment with givinostat and vorinostat increased TGF- β 1 and IL-8 secretion, thereby improving epithelial wound healing in a mouse model of dextran sodium sulfate-stressed inflammatory bowel disease[156].

It has been reported that the class I HDAC selective inhibitor entinostat, promoted the healing process in mouse skin excisional wounds. However, this effect was abolished by sirtinol, a class III HDAC inhibitor that delayed skin repair by inhibiting SIRT activity, which enhanced cell motility, stimulated keratinocyte proliferation and promoted skin regeneration *via* endothelial NO synthase phosphorylation and NO production[157].

Topical treatment of TSA, a representative HDAC inhibitor, increased macrophage plasticity in wound beds and achieved better reconstitution in both epithelial and dermal layers in acute wounds compared with control[31]. TSA-pretreated bone marrow MSC-derived exosomes contributed to the polarization of M1 macrophages to M2 macrophages and promoted the migration and angiogenesis of human umbilical vein endothelial cells and formation of collagen *in vivo*, thereby further promoting wound healing[158]. Additionally, inhibition of HDAC activity by TSA may change bone marrow myeloid progenitor cell behavior and promote the expansion of the Ly6C^{low} subset, which produces a variety of pro-healing mediators, consequently promoting tissue regeneration and wound healing[31]. TSA can also enhance skin repair by promoting keratinocyte proliferation[159]. TSA treatment can also promote cell proliferation and collagen deposition and expand stem cell populations in digital amputation wounds in mice and frogs[108].

In chronic wounds in human, endoplasmic reticulum stress impairs keratinocyte and fibroblast migration, resulting in prolonged wound healing, the HDAC inhibitor 4-phenylbutyrate significantly rescued keratinocyte migration from elderly leg amputation donors and improved re-epithelialization in an *ex vivo* human skin wound healing model, suggesting its promising use for wound healing[160].

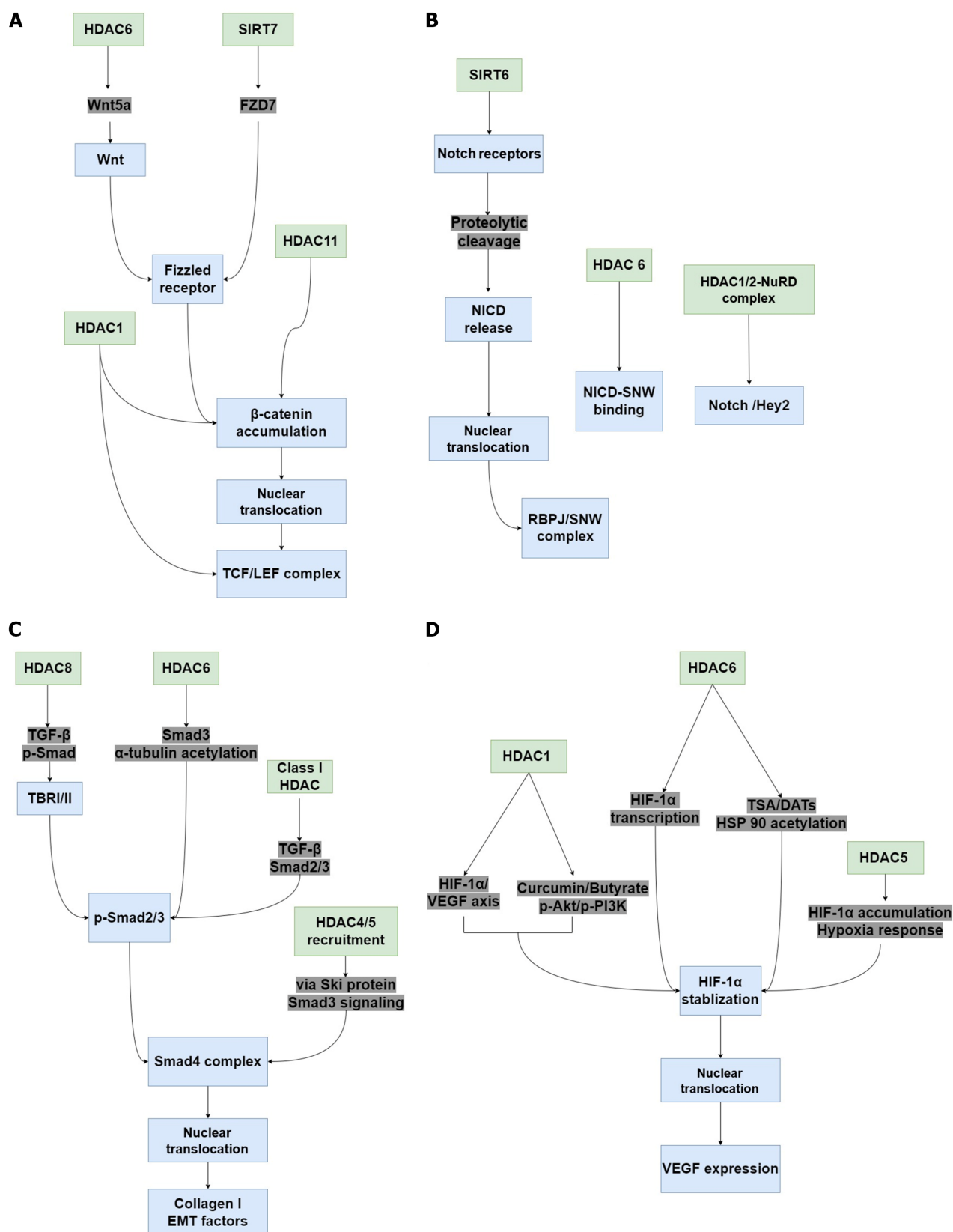


Figure 3 The potential signaling pathways associated with histone deacetylases in diabetic wound healing. When histone deacetylase (HDAC) activity is altered in tissue, many pathways with critical roles in wound healing, such as Wnt/ β -catenin, Notch, transforming growth factor (TGF)- β /suppressor of mother against decapentaplegic (Smad), and hypoxia-inducible factor-1 α (HIF-1 α)/vascular endothelial growth factor (VEGF) signaling are regulated. A: Inhibiting HDAC1 upregulates *TCF* and *LEF* expression, promotes the accumulation and nuclear translocation of β -catenin, and activates the Wnt/ β -catenin pathway. HDAC6 increases *Wnt5a* expression and activates the Wnt signaling pathway. Sirtuin (SIRT) 7 promotes *FZD7* expression, contributing to β -catenin stability and activation, thereby activating the Wnt/ β -catenin pathway. HDAC11 suppression also promotes β -catenin stability and activates Wnt/ β -catenin signaling in vascular smooth muscle cells; B: Silencing SIRT6 Leads to dysregulation of the *RBPJ/SNW* complex and inhibits Notch signaling. HDAC6 inhibition represses the binding of Notch

intracellular cytoplasmic domain and SNW domain containing 1, thereby inhibiting Notch transcriptional responses. Recruitment of HDAC1/2-nucleosome remodeling and deacetylase also inhibits the Notch/*Hey2* signaling axis; C: Inhibition of HDAC6 and HDAC8 inactivates Smad3, resulting in α -tubulin acetylation and impairing TGF- β -induced epithelial-mesenchymal transition (EMT). Class I HDAC inhibition inactivates the TGF- β -Smad2/3 signaling axis and decreases type 1 collagen expression induced by TGF- β 1. The oncoprotein Sloan-kettering institute recruits HDAC4 and HDAC5, thereby inhibiting TGF- β /Smad3 signaling, leading to the decrease of EMT factors; D: Curcumin and sodium butyrate-induced HDAC1 inhibition suppresses the phospho-protein kinase B/phospho-phosphatidylinositol 3-kinase/HIF-1 α /VEGF axis, whereas HDAC1 inhibition by 1,3-diphenylurea induces VEGF expression via HIF-1 α , thereby increasing the migration and wound healing effects. HDAC5 overexpression enhances HIF-1 α stabilization and nuclear translocation in response to hypoxia. Selective HDAC6 inhibition reduces HIF-1-mediated transcription by deacetylating heat-shock protein 90. HDAC: Histone deacetylase; SIRT: Sirtuin; NICD: Notch intracellular cytoplasmic domain; 2-NuRD: 2-nucleosome remodeling and deacetylase; TGF: Transforming growth factor; p-Smad: Phospho-suppressor of mother against decapentaplegic; TBR: Transforming growth factor- β receptor; Ski: Sloan-kettering institute; EMT: Epithelial-mesenchymal transition; VEGF: Vascular endothelial growth factor; HIF-1 α : Hypoxia-inducible factor-1 α ; p-Akt: Phospho-protein kinase B; p-PI3K: Phospho-phosphatidylinositol 3-kinase; TSA: Trichostatin A; DATs: Diallyl trisulfide; HSP90: Heat-shock protein 90.

Although the critical roles of HDAC inhibitors in wound healing are emerging, there are still very few direct studies of HDAC inhibitors in diabetic wound healing models. To reveal the roles that they play in healing in a diabetic setting, explorations of the effects of HDAC inhibitors on diabetic skin coloboma wound healing are necessary, as it would allow for the mechanistic exploration of various key cells involved in healing, including epithelial cells, vascular endothelial cells, macrophages and fibroblasts. After verifying its efficacy and safety in animal models, a small-sample clinical study can be conducted to evaluate the safety and efficacy of HDAC inhibitors in patients with DFU. For example, a single-center, randomized, double-blind, placebo-controlled phase I/II exploratory clinical trial in which topical application of the HDAC inhibitor TSA or HDAC11 selective inhibitor FT895 in DFU patients are considered the treatment group. However, many studies are needed to achieve this goal.

In addition to the known HDAC inhibitors, efforts to identify new HDAC inhibitors are ongoing. In recent years, artificial intelligence (AI) technology has significantly accelerated the drug discovery process by integrating multi-source data and algorithm optimization. Generative adversarial networks and variational autoencoders can generate entirely new molecular structures with HDAC inhibition potential. AI models can rapidly predict the inhibitory activity and selectivity of new compounds by analyzing the structure-activity relationship of known HDAC inhibitors. For example, deep learning-based frameworks can identify key pharmacophore features and optimize the binding affinity of candidate molecules. AI can simultaneously optimize the properties of compounds, including absorption, metabolism, and toxicity, through multi-task models to reduce the risk of later research and development failure. AI-generated molecules exhibited comparable activity to known inhibitors *in vitro*, along with superior drug-like properties[161,162]. Thus, the application of AI in HDAC inhibitor development will also be a hot topic for future research.

CONCLUSION

HDACs play pivotal regulatory roles in the healing processes, including inflammation resolution, vascular repair and neovascularization, and tissue regeneration. Yet now, studies about the exact mechanism of HDACs and its inhibitors in regulating diabetic wound healing are still rare. Both animal and clinical studies are lacking. This review synthesized current knowledge on HDACs in diabetic wound healing and provided a roadmap for the translation of epigenetic insights in diabetic wound into clinical breakthroughs. To elucidate the roles of HDACs in diabetic wound healing, both molecular mechanism studies in cells and animal models and human tissue specimens and clinical efficacy studies are essential. Although HDAC inhibitors have tremendous potential as candidate drugs for effective treatment of diabetic wounds, there is a lack of adequate animal studies to evaluate the optimal drug delivery method, and clinical efficacy and safety. Further research is needed to clarify the specific roles of different HDAC isoforms, develop tissue-specific delivery systems, and promote individualized therapeutic strategies based on HDAC regulation.

FOOTNOTES

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