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HDAC4: an emerging target in diabetes mellitus and diabetic complications

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Abstract

Diabetes mellitus (DM) is a metabolic disease with complex pathogenic mechanisms. Histone deacetylase 4 (HDAC4) is a member of an important family of epigenetic modifications. An increasing amount of research indicates that HDAC4 may control DM by modulating the epigenetic and post-translational expression of numerous transcription factors and taking part in different signaling cascades. In this review, HDAC4 was reported to control the differentiation, growth, and function of pancreatic β-cells. Furthermore, HDAC4 regulates glucose metabolism by targeting GLUT4 and FOXO1 and further modulates insulin signaling pathways through cytoplasmic-nuclear shuttling. Moreover, HDAC4 has also been implicated in the regulation of diabetic nephropathy, diabetic cardiomyopathy, diabetes osteoporosis, diabetic wounds, and diabetic encephalopathy. Therefore, HDAC4 is consider to be a viable therapeutic target for the treatment of DM and its complications. HDAC inhibitors and other targeted inhibitions of HDAC4 provide us with new ideas for developing novel intervention strategies. This article reviews the role of HDAC4 in diabetes mellitus and its complications.

Keywords Histone deacetylase 4, Diabetes mellitus, Epigenetic modifications, Signaling, HDAC4 inhibitors, Diabetic complications, MiRNA

Introduction

Diabetes mellitus (DM) constitutes a chronic metabolic disorder. The International Diabetes Federation reports that approximately 537 million adults globally had diabetes in 2021, with the number projected to increase to 643 million by the year 2030 [1]. Type 1 diabetes (T1DM) is insulin-dependent and is caused by the destruction of pancreatic β cells, resulting in a complete lack of insulin. Type 2 diabetes (T2DM) arises from a combination of insulin resistance, which triggers compensatory hyperinsulinemia, and the progressive loss of pancreatic β-cell function, resulting in impaired insulin production [2], accounting for over 90% of diabetes cases globally. Due to this increase, there is an emerging need to investigate the complications associated with diabetes. To understand the associated physiological alterations, research on gene-level modulations is necessary. In view of the potential threats of diabetes and its complications, it is urgent to establish an early prevention and intervention system and carry out precise treatment.

Gene regulation plays a crucial role in the occurrence, development and treatment of diabetes. Abnormalities in gene regulation can cause insufficient insulin secretion or defect in its function, leading to diabetes. Elucidating whether DM and its complications share common pathophysiological pathways and molecular targets remains a critical research priority, with the development of

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targeted therapeutic strategies for these pathways constituting a major focus of contemporary biomedical investigation. Histone acetylation modification mainly involves histone acetyltransferases (HAT) and histone deacetylases (HDACs). HDACs are responsible for the deacetylation of histone lysine residues, which tightly wraps the chromatin structure to inhibit transcription [3]. Among them, HDACs regulate not only histone deacetylation but also the activity of non-histone proteins [4], including the glucose transporter 4 (GLUT4) [5], the transcription factor forkhead box protein O1 (FOXO1) [6], and the myocyte enhancer factor 2 (MEF2) [7]. HDACs can regulate pancreatic endocrine cell fate, β-cell function, insulin signaling, glucose metabolism, cell injury, inflammation, oxidative stress and apoptosis, which are critical for developing diabetes-related vascular dysfunction [8]. This makes HDAC as an emerging target being studied and hence HDAC inhibitors to be developed as a treatment option of DM [8, 9].

Eighteen HDACs have been identified in humans, categorized into four classes (I–IV) based on sequence homology and cofactor dependence (Fig. 1A). Class I (HDAC1, 2, 3, 8), Class IIa (HDAC4, 5, 7, 9), Class IIb (HDAC6, 10), and Class IV(HDAC11) are Zn^{2+}-dependent, while Class III (SIRT 1–7) are NAD^{+}-dependent. Unlike other classes, Class IIa HDACs possess conserved serine (Ser) residues in their N-terminal domains that undergo signal-dependent phosphorylation, enabling nucleocytoplasmic shuttling to regulate transcriptional activity. Class IIa HDACs are critical to the development of DM and its complications [10]. In a mouse model of T2DM, Class IIa HDACs can control glucose homeostasis and stimulate the transcription of genes involved in gluconeogenesis [11]. The loss of Class IIa HDACs, particularly through short hairpin RNA (shRNA) treatment, can improve glucose tolerance and reduce fasting blood glucose in mouse models of T2DM [11]. As a member of this class, HDAC4 is widely expressed in multiple tissues, including the liver, brain, heart, and skeletal muscle, where it regulates gene transcription, glucose metabolism, senescence, autophagy, apoptosis, inflammation, and cellular stress responses [12]. HDAC4 can shuttle between nucleoplasms through its serine residue site modification transformation [13]. Figure 1B shows

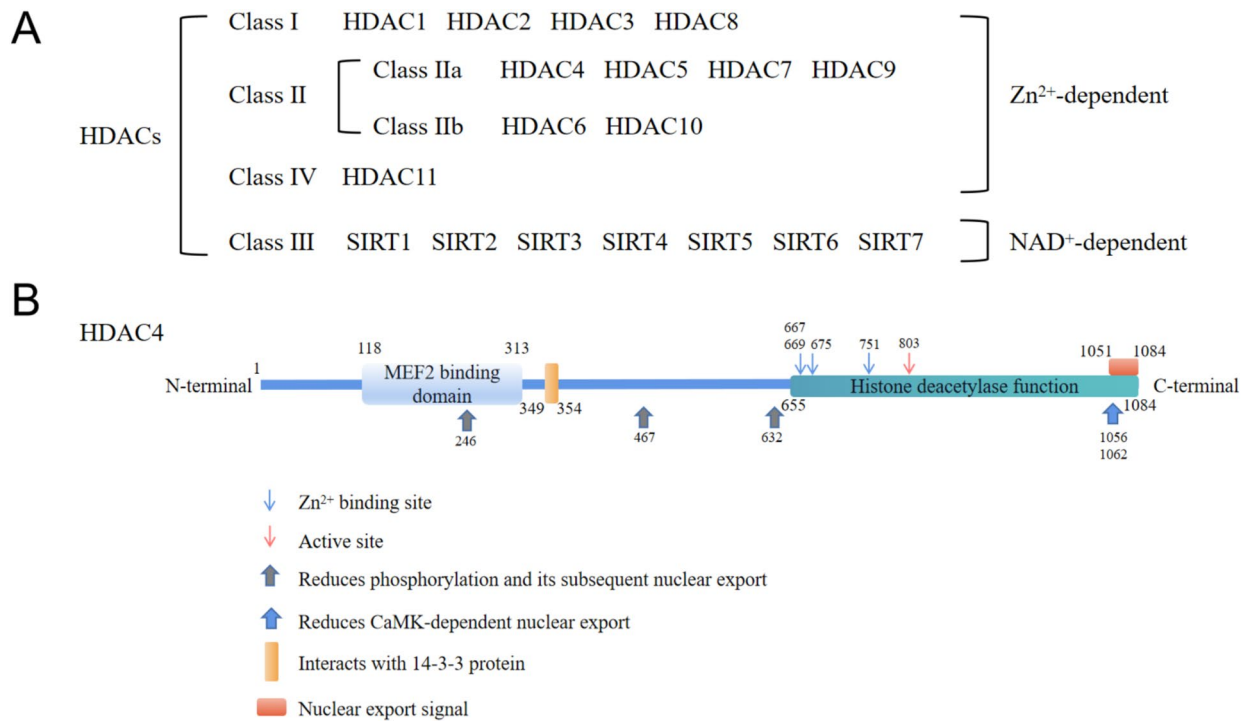

Fig. 1 Classification of HDACs and the protein structure of HDAC4. **A** HDACs are categorized into four classes (I–IV) based on sequence homology and cofactor requirements. Class I (HDAC1, 2, 3, 8), Class IIa (HDAC4, 5, 7, 9), Class IIb (HDAC6, 10), and Class IV (HDAC11) utilize Zn^{2+} for catalytic activity, while Class III (SIRT1–7) are NAD^{+}-dependent. **B** Protein structure of HDAC4. These numbers refer to the sites or amino acid locations located on either side of the domain [97]. N-terminal MEF2-binding domain (residues 118–313): Mediates interaction with the transcription factor MEF2. Catalytic core (residues 657–1084): Contains $Zn2^{+}$-coordinating residues (667, 669, 675, 751) and the deacetylase active site (803), essential for enzymatic function. C-terminal regulatory region (residues 1051–1084): Includes a phosphorylation-responsive nuclear export signal that drives cytoplasmic translocation, including CaMK-dependent nuclear export sites (residues 1056–1062)

the protein structure of HDAC4. HDAC4 contains critical structural motifs: (i) an N-terminal MEF2 binding domain (residues 118–313), which directly interacts with the transcription factor MEF2 to repress hypertrophic gene programs; (ii) Zn^{2+}-binding sites (residues 667, 669, 675, 751) and an active site (residue 803) essential for its deacetylase activity; and (iii) a nuclear export signal (residues 1051–1084) that facilitates cytoplasmic translocation upon phosphorylation. HDAC4 functions as a transcriptional regulator that modulates the expression of energy-related genes, including glucose-6-phosphatase (G6PC) and phosphoenolpyruvate carboxykinase (Pck1) [11]. Due to its dynamic nucleocytoplasmic shuttling and its role in regulating genes involved in glucose metabolism, insulin signaling, and pancreatic endocrine cell function, HDAC4 has emerged as a promising therapeutic target. This review addresses the gap by focusing on HDAC4 and its emerging therapeutic potential in DM. This review provides new insights into the pathogenesis of HDAC4 in DM and its complications and summarizes recent advances in targeting HDAC4 for treating DM.

HDAC4 regulates the differentiation, development and function of pancreatic endocrine cell

The endocrine cells in the pancreatic islets include α, β, δ, and pancreatic polypeptide cells, which produce glucagon, insulin, somatostatin, and pancreatic polypeptides, respectively. HDAC4 is specifically expressed in β-cells and δ-cells, as well as regulates their development and differentiation. Mice with HDAC4 loss-of-function exhibit an increased number of δ-cells. HDAC4 overexpression leads to a reduced pool of β- and δ-cells, suggesting its role in suppressing the β/δ-cell lineage. Lentivirus-mediated overexpression of HDAC4 in E13.5 (Embryonic day 13.5) rat embryos significantly downregulated key β-cell development genes, including NeuroD1, Pdx1, MafA, Nkx2.2, Znt8, and Ia1. Lenoir et al. proposed that HDAC4 inhibition, which is a Class IIa HDAC inhibitor MC1568, promotes β/δ-cell expansion, and thus offers a novel approach to diabetes treatment [14].

In mammals, β-cells make up about 70% of pancreatic islet cells [15] and are critical for maintaining glucose homeostasis by secreting insulin. Recent studies on HDAC4's role in β-cell function have yielded conflicting results. One study found a decrease in β-cell area and insulin content in the pancreas of mice with osteoblast-specific knockout of HDAC4, which impaired insulin secretion [16]. However, the specific impact of osteoblast-derived HDAC4 on pancreatic function remains unexplored, with some suggesting osteocalcin-dependent regulation. McCann et al. reported that HDAC4 did not affect insulin production under normal or hyperglycemic conditions [17]. Other reports, however, suggest that HDAC4 acts negatively on β-cell function. Inhibition of HDAC4 has been shown to enhance insulin production in β-cells [14, 18]. Furthermore, three HDAC4 missense mutations, including p.His227 Arg (histidine to arginine at residue 227), p.Asp234 Asn (aspartate to asparagine at residue 234), and p.Glu374Lys (glutamate to lysine at residue 374), have been associated with impaired insulin secretion. These mutations are located in the N-terminal region of HDAC4, which contains critical phosphorylation sites and proteolytic cleavage motifs. Although these mutants do not alter endogenous HDAC4 protein expression levels or intrinsic deacetylase activity, mouse MIN6 β-cells transfected with plasmids encoding the mutant forms of HDAC4 exhibited enhanced nuclear export of HDAC4. Transfection of the above three HDAC4 mutant plasmids in SJ β-cells resulted in downregulation of the β cell-specific transcription factors FoxO1, Pdx1, Neurod1 and Gck, thereby reducing the function of β-cells. Further experiments revealed that FoxO1 is a target of HDAC4-mediated deacetylation in MIN6 β-cells. These diabetes-associated mutations prevent FoxO1 deacetylation and nuclear export, disrupting β-cell function [19]. In conclusion, while the effect of HDAC4 overexpression on β-cell function remains inconclusive, mutations or defects in HDAC4 have been shown to negatively impact β-cell activity. Given the contrasting findings in the literature, further investigation into the specific mutation sites and defects in HDAC4 is essential to better understand its role in β-cell function, beyond merely examining its expression levels.

HDAC4 regulates insulin signaling pathway and glucose metabolism

Insulin plays a unique role in regulating glucose homeostasis. Insulin resistance refers to the decreased sensitivity to the action of insulin in the target organs of insulin action, primarily the liver, muscle and adipose tissue. Impaired insulin secretion and insulin resistance are currently considered to be key defects in T2DM [20]. Summarizing recent studies, HDAC4 targeting GLUT4 and FOXO1 play an important role in insulin signaling pathway and glucose metabolism.

HDAC4 targets GLUT4

A hallmark of insulin resistance is impaired GLUT4 membrane translocation, which leads to reduced glucose uptake [21, 22], making GLUT4 regulation a key focus in T2DM research. HDAC4 has been identified as a repressor of GLUT4 expression through targeted transcriptional inhibition [23]. Insulin lowers blood glucose levels by promoting hepatic glucose uptake and glycogen synthesis while inhibiting gluconeogenesis and glycogenolysis. In skeletal muscle and adipose tissue,

insulin enhances glucose uptake via phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway activation. Akt further mediates the glucose transport regulation, inhibiting lipid synthesis, and modulating overall metabolism [21, 24]. Figure 2 illustrates the complete pathway of insulin activation of the PI3K/Akt pathway in the liver. Under physiological conditions, Akt phosphorylation induced by insulin promotes GLUT4 translocation to the cell membrane, thereby facilitating glucose uptake [25]. Lin et al. demonstrated that microRNA (miR)-155 downregulation in T2DM patients and diabetic mice impairs pancreatic islet function, driving hyperglycemia, glucose intolerance, and systemic insulin resistance. Normally, miR-155 suppresses HDAC4 expression and thus miR-155 deficiency results in HDAC4 upregulation, which inhibits Akt phosphorylation, ultimately blocking GLUT4 membrane translocation and glucose uptake [5].

Skeletal muscle GLUT4 knockout induces insulin resistance and glucose intolerance [26]. HDAC4 regulates skeletal muscle glucose uptake via GLUT4 expression control (Fig. 3A). Exercise upregulates GLUT4 mRNA via HDAC4/5 nuclear export [27]. Besides, AMP-activated protein kinase α2 (AMPKα2)-mediated HDAC4 phosphorylation (Ser246/Ser632) enhances MEF2A-driven GLUT4 transcription [13]. These mechanisms collectively improve insulin sensitivity, glucose utilization, and muscle metabolic function in both healthy and clinical populations [28]. HDAC4 contributes to skeletal muscle insulin resistance by suppressing GLUT4 expression. Enhanced interaction between the transcriptional repressor MEF2D and HDAC1/HDAC4 in skeletal muscle inhibits GLUT4 transcription, impairing glucose uptake and promoting insulin resistance and T2DM pathogenesis [29]. Conversely, HDAC inhibition (tauroursodeoxycholic acid (TUDCA)) restores GLUT4 transcription,

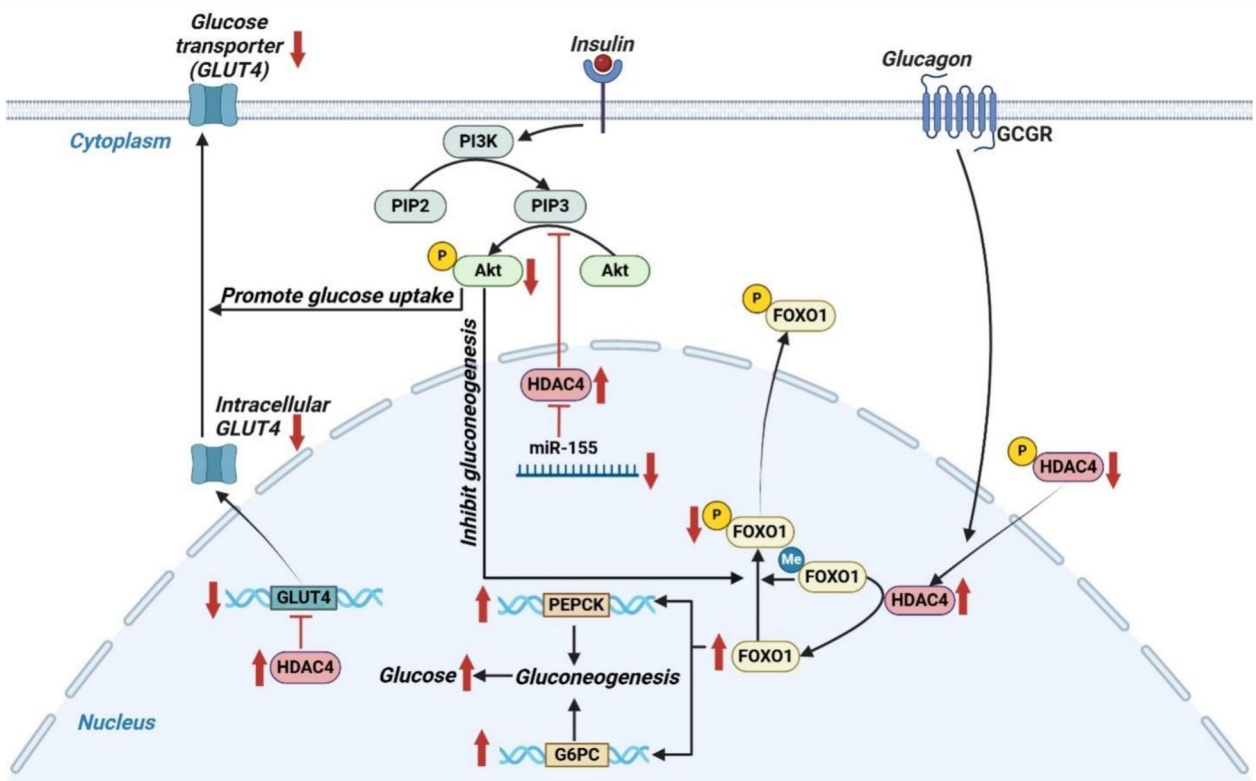

Fig. 2 HDAC4-mediated regulation of insulin signaling and glucose metabolism in the liver. Insulin-PI3K/Akt pathway activation: Insulin binding triggers PI3K activation, generating PIP3, which recruits and activates Akt. Phosphorylated Akt promotes GLUT4 translocation to the plasma membrane, enhancing hepatic glucose uptake and suppressing gluconeogenesis. HDAC4 represses GLUT4 transcription and blocks Akt phosphorylation, impairing glucose transport. miR-155 deficiency exacerbates insulin resistance by elevating HDAC4 levels. FOXO1 regulation in gluconeogenesis: Akt-mediated phosphorylation of FOXO1 induces its nuclear export, downregulating gluconeogenic enzymes (G6PC, PEPCK). Under fasting or insulin-resistant conditions, dephosphorylated HDAC4 accumulates in the nucleus, deacetylating FOXO1 to activate gluconeogenic gene transcription. Reduced Akt phosphorylation (e.g., in palmitic acid-treated cells) correlates with nuclear HDAC4 retention, driving hyperglycemia via FOXO1-mediated glucose production. PI3K, phosphatidylinositol 3 kinase; PIP2, phosphatidylinositol diphosphate; PIP3, phosphatidylinositol triphosphate; Akt, protein kinase B; GLUT4, glucose transporter protein 4; FOXO1, forkhead framing protein O1; PEPCK, phosphoenolpyruvate carboxykinase; G6PC, glucose-6-phosphatase; miR-155, microRNA-155; HDAC4, histone deacetylase 4

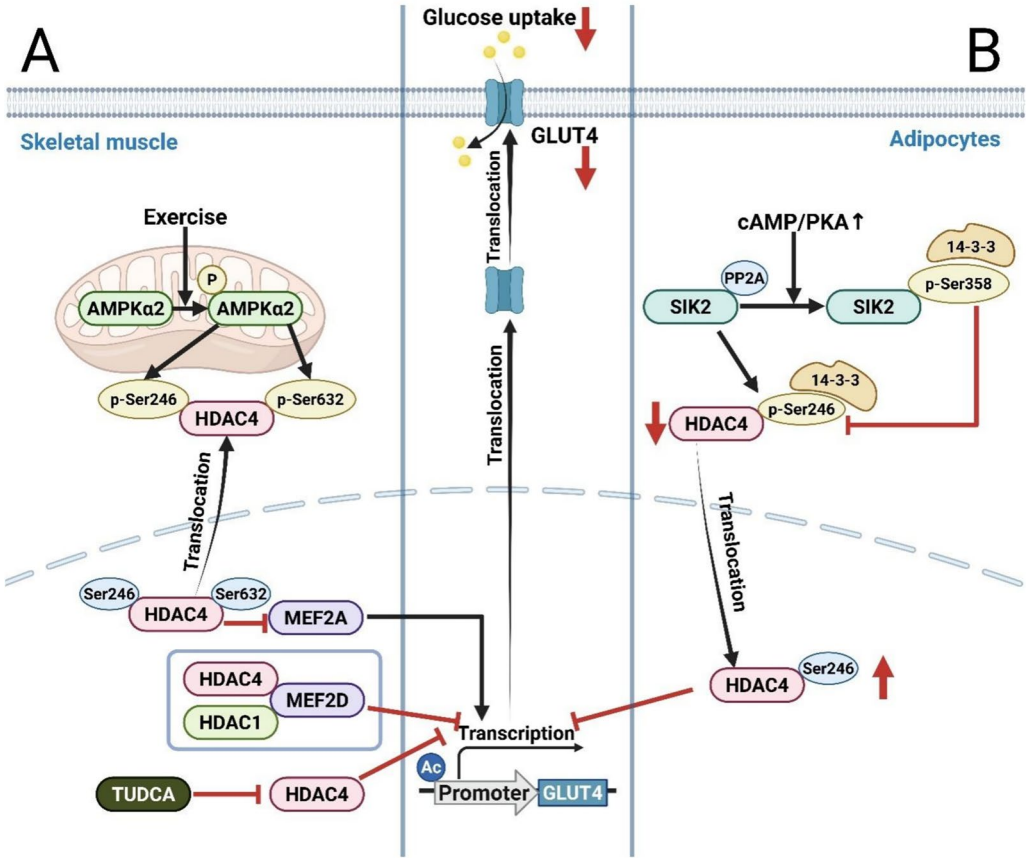

Fig. 3 HDAC4 regulates GLUT4 expression in skeletal muscle cells and adipocytes. **A** HDAC4-mediated regulation of GLUT4 in skeletal muscle. Exercise-induced AMPKα2 activation: Physical activity stimulates AMPKα2, which phosphorylates HDAC4 at Ser246 and Ser632, promoting its cytoplasmic translocation. This relieves HDAC4-mediated repression of MEF2A, enhancing GLUT4 transcription and glucose uptake. HDAC4/MEF2D repression complex: In insulin-resistant states, nuclear HDAC4 interacts with HDAC1 and MEF2D to suppress GLUT4 expression, impairing glucose transport and exacerbating insulin resistance. Therapeutic intervention: HDAC inhibitors (e.g., TUDCA) disrupt this repressive complex, restoring GLUT4 transcription and insulin sensitivity. **B** Adipose tissue regulation of HDAC4-GLUT4 axis via the cAMP-PKA-SIK2 pathway. Activation of cAMP-PKA phosphorylates SIK2 at Ser358, enabling 14–3-3 protein binding and inhibiting SIK2's ability to phosphorylate HDAC4. This leads to HDAC4 dephosphorylation, nuclear translocation, and GLUT4 suppression. PP2A stabilizes SIK2 activity, maintaining HDAC4 phosphorylation and cytoplasmic localization, thereby perpetuating GLUT4 repression and insulin resistance

thereby boosting insulin sensitivity [30]. Nuclear HDAC4 thus drives insulin resistance via GLUT4 epigenetic silencing, and thus positioning HDAC4-targeted therapies as potential interventions.

Wild-type (WT) human HDAC4 overexpression in 3 T3-L1 adipocytes suppresses GLUT4 promoter activity [31]. As illustrated in Fig. 3B, the upstream mechanism by which HDAC4 binds to the GLUT4 promoter and represses its transcription has also been investigated. Salt-induced protein kinase 2 (SIK2) is widely expressed in human and mouse adipose tissue, and primarily regulates glucose and lipid metabolism by phosphorylating downstream factors [32]. Obese models show elevated SIK2 expression/activity [33, 34], inversely correlating with human insulin resistance/obesity severity [35]. Adipocyte cyclic adenosine monophosphate (cAMP)–protein kinase A (PKA) signaling phosphorylates SIK2 Ser358 and enables 14-3-3 binding to inhibit SIK2 substrate phosphorylation, thereby reducing HDAC4 Ser246 phosphorylation. Dephosphorylated HDAC4 translocates to the nucleus, repressing GLUT4 transcription and impairing glucose uptake. Conversely, PP2A binding sustains SIK2 activity, enhancing HDAC4/GLUT4 phosphorylation [36]. Collectively, nuclear dephosphorylated HDAC4 suppresses GLUT4, with upstream regulation via the cAMP–PKA–SIK2–HDAC4 axis.

HDAC4 targets FOXO1

FOXO1, a critical pancreatic β-cell regulator, undergoes Akt-driven phosphorylation and triggers its nuclear

export to diminish transcriptional activity [37]. The insulin–PI3K–Akt pathway suppresses hepatic gluconeogenesis via Akt-mediated FOXO1 inhibition, downregulating key enzymes phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) [38, 39]. This activity blocks non-carbohydrate precursors (e.g., lactate and glycerol) into glucose, thereby decreasing hepatic glucose output. FOXO1 acetylation synergizes with phosphorylation to inhibit its transcriptional function [6, 40]. Under fasting conditions, glucagon promotes nuclear translocation of dephosphorylated HDAC4. The nuclear translocation of dephosphorylated HDAC4 enhances hepatic gluconeogenesis by deacetylating FOXO1 (a master regulator of glucose homeostasis) to activate transcription of G6PC and other gluconeogenic genes [6] (Fig. 2). This phosphorylation-dependent nuclear shuttling of HDAC4 is mechanistically linked to insulin resistance. In palmitic acid (PA)-treated HepG2 cells, reduced Akt phosphorylation correlates with elevated gluconeogenic markers (G6PC, PEPCK, FOXO1) and hyperglycemia, concurrent with decreased cytoplasmic phosphorylated HDAC4 and increased nuclear dephosphorylated HDAC4 [41]. Notably, HDAC4/5/7 knockdown in diabetic mice reverses this phenotype, restoring hepatic glycogen storage, glucose tolerance, and insulin sensitivity [6, 42]. This result underscores HDAC4's dual role as both a driver of gluconeogenesis and a therapeutic target.

Nuclear dephosphorylated HDAC4 was found to promote FOXO1-driven gluconeogenesis and exacerbates PI3K/AKT pathway dysfunction. Although preclinical studies provide mechanistic insights into HDAC4's role in insulin resistance, in which nuclear dephosphorylated HDAC4 promotes FOXO1-driven gluconeogenesis and exacerbates PI3K/Akt pathway dysfunction, the translational relevance of these findings requires cautious interpretation. HepG2 cells lack the metabolic complexity of human hepatocytes, and rodent models exhibit species-specific differences in HDAC4 regulation (e.g., compensatory HDAC5/7 activity) compared to humans. Critically, clinical evidence linking HDAC4 modifications to hepatic insulin resistance in diabetic patients remains scarce. HDAC4 knockdown was found to reverse metabolic dysfunction in diabetic mice. However, the lack of data on the correlation between the phosphorylation status of HDAC4 and gluconeogenic markers in clinical diabetic liver biopsy limits the extrapolation of treatment. The clinical validation of patient-derived hepatocyte models and the pathophysiological effects of HDAC4 should be considered for inclusion in the study. In addition, the safety and efficacy of HDAC4-targeted therapy in the management of human diabetes should also be evaluated.

Role of HDAC4 in diabetes complications

The epidemic of DM and its complications poses a significant threat to global health, with the majority of people with DM having at least one complication [43]. HDAC4 plays an important role in diabetic nephropathy and diabetic cardiomyopathy and is emerging in diabetes osteoporosis, diabetic encephalopathy, and diabetic wounds. Nevertheless, there are still very few relevant reports. HDAC4 modulators, HDAC inhibitors, and gene therapies represent widening therapeutic strategies to be evaluated for the management of diabetic complications.

HDAC4 regulates podocyte death in diabetic nephropathy

Diabetic nephropathy (DN) accounts for 30% to 40% of diabetic patients and is one of the most common causes of end-stage renal disease [44, 45]. Wang et al. initially investigated the expression patterns of several HDACs in DN and discovered that glomerular capillaries as the primary sites of HDAC4 expression [46]. Podocytes are involved in the regulation of glomerular filtration and the preservation of the glomerular filtration barrier [47]. Different forms of podocyte death, such as apoptosis and autophagy, are key pathological features of diabetic nephropathy progression [48].

Autophagy, a lysosomal degradation pathway, is essential in renal physiology to remove protein aggregates and damaged organelles to maintain intracellular homeostasis [49]. Podocytes exhibit high levels of autophagy in a physiological state [50]. Podocyte-specific autophagy-deficient mice due to a defect in the Atg5 gene experienced podocyte loss and increased proteinuria, suggesting that podocytes maintain cellular homeostasis through autophagy. Evidence showed that autophagy levels decrease in renal cells and tissues in DN [51]. On the contrary, both ex vivo and in vivo experiments have confirmed that autophagy attenuated high glucose-induced glomerular injury and podocyte damage [52]. HDAC4 is one of the critical components linking autophagy-related signaling pathways and podocyte injury in DN. High glucose (HG) and podocyte damage factors induced up-regulation of HDAC4 and down-regulation of autophagy-related proteins in podocytes. Silencing the expression of the HDAC4 gene at the podocyte level and rat kidney level could restore the expression of autophagy-related proteins and improve podocyte function. HDAC4 promotes signal transducerand activator of transcription 1 (STAT1) nuclear translocation and activation by deacetylating STAT1 [46]. STAT1 may be a key molecule linking HDAC4 to podocyte autophagy regulation, but the specific mechanism has not been elucidated.

The calcium/calmodulated neural phosphatase (CaN) signaling pathway plays a crucial role in podocyte

apoptosis [53]. In podocytes cultured with high glucose, the silencing and overexpression of HDAC4 led to a significant decrease and increase, respectively, in Ca^{2+}-CaN expression [54]. In podocytes with HDAC4 overexpression, the expression of pro-apoptotic Bax protein was increased, whereas the expression of anti-apoptotic B cell lymphoma/leukemia 2 gene (Bcl-2) protein was decreased, resulting in apoptosis of podocytes. The pharmacological inhibitor of CaN, FK506, effectively rescued the apoptosis induced by the overexpression of HDAC4 in podocytes [54]. However, the exact mechanism by which HDAC4 specifically regulates the expression of apoptosis-related genes is still unknown.

As a non-coding single-stranded RNA with a length of 18–25 nucleotides, microRNA (miRNA) regulates hyperglycemia-induced homeostatic disturbances in renal tissues. Circular RNA (circRNA) regulates gene expression by acting as a chelator of RNA-binding proteins, a sponge for miRNAs, or a regulator of nuclear transcription [55]. The expression of multiple miRNAs decreased in diabetes mellitus and its complications and play a role in diabetic nephropathy (Table 1). MiR-29a and miR-29b play a protective role against podocyte function. In a diabetic mouse model, hyperglycemia decreases miR-29a levels and enhances HDAC4 effects that contribute to deacetylation and degradation of nephrin, a key podocyte protein, as well as renal dysfunction. Conversely, miR-29a overexpression protected renal function in diabetic mice by inhibiting HDAC4. HDAC4 inhibits miR-29a expression. In vitro experiments showed that HDAC4 knockout enhanced histone H3 lysine 9 acetylation (H3K9Ac) at the proximal promoter of miR-29a and increased miR-29a transcription [56]. Therefore, in a state of high glucose, the imbalance between miR-29a and HDAC4 forms a vicious cycle and aggravates diabetic nephropathy. MiR-29b, which is highly homologous to miR-29a, was found to target the 3'untranslated Region (UTR) of HDAC4 [57]. MiR-29b can inhibit transforming growth factor-β (TGF-β1) directly or through downregulation of HDAC4, thereby slowing down podocyte renal fibrosis. Renal tubules may play a key regulatory role in the progression of DN, with hyperglycemia inducing apoptosis of renal tubular epithelial cells in DN [58]. In high glucose-induced proximal tubular epithelial cells [human kidney-2 (HK-2) cells], the expression of miR-483-5p was decreased. Furthermore, the overexpression of miR-483-5p significantly inhibited apoptosis and injury of HK-2 cells. This protective effect may be attributed to the direct targeting inhibition of HDAC4 by miR-483-5p [59]. In the serum of DN patients and HG-induced HK-2 cells, the expression of circ_0003928 and HDAC4 was significantly up-regulated, while the expression of miR-506-3p was down-regulated. Circ_0003928 acted as a sponge for miR-506-3p, and HDAC4 was identified as a target gene of miR-506-3p. Circ_0003928 promoted oxidative stress and apoptosis in HK-2 cells by upregulating HDAC4 in a high-glucose state [60]. Inhibition of circ_0003928/miR-506-3p/HDAC4 axis may be an effective way to treat DN. Therefore, miR-483-5p and miR-506-3p are protective against tubular epithelial cell injury in DN. However, how HDAC4 impairs tubular function has not been studied.

HDAC4 regulates diabetes osteoporosis

Diabetes Osteoporosis (DOP) is characterized by osteopenia and deterioration of bone microstructure. Studies have recently confirmed that because HDACs govern osteoclast development and activity, they may be useful therapeutic targets for the treatment of osteoporosis [61]. Currently, the vital role of stem cells–extracellular vehicles (EVs) in curative replacement therapy for osteoporosis has been demonstrated [62]. Recent studies have found that HDAC4 plays a negative role in DOP. Urine-derived stem cells-EVs (USCs-EVs) were able to transfer miR-26a-5p into osteogenic precursor cells, leading to the inhibition of HDAC4 expression, enhanced osteoclast activity, and suppressed osteoblasts activity [63]. Inhibition of HDAC4 activated the hypoxia inducible factor-α (HIF-α)/vascular endothelial growth factor A (VEGFA) pathway. This provides a new approach and a new

Table 1 miRNAs interact with HDAC4 in diabetic complications

MicroRNA	Expression in HG/Diabetes	Diabetic complications	Relationship with HDAC4	References
miR-29a	Downregulated	Diabetic nephropathy	miR-29a inhibits HDAC4 HDAC4 inhibits miR-29a transcription by deacetylating H3 K9 Ac on the proximal promoter of miR-29a	[56]
miR-29b	Downregulated	Diabetic nephropathy	miR-29b targets HDAC4 3'UTR and inhibits HDAC4 expression	[57]
miR-483-5p	Down-regulated	Diabetic nephropathy	miR-483-5p targets HDAC4	[59]
Cir_0003928/ miR-506-3p	Upregulated/down-regulated	Diabetic nephropathy	miR-506-3p targets HDAC4 and inhibits HDAC4	[60]
miR-26a-5p	Unknown	Diabetes Osteoporosis	miR-26a-5p inhibits HDAC4	[63]

target for improving DOP, and further clinical studies are needed to verify its efficacy.

MiR-26a-5p also plays an important role in DOP (Table 1). The aforementioned miRNAs target HDAC4, leading to its downregulation and inhibition of its associated pathological effects in diabetic complications. However, it is still unknown whether there are commonalities in the regulation of HDAC4 by various miRNAs and the specific mechanism of HDAC4 regulation of diabetic complications.

HDAC4 regulates diabetic cardiomyopathy

Diabetic cardiomyopathy (DCM) is a prevalent and severe complication of DM characterized by myocardial hypertrophy, impaired cardiac function, microcirculatory disturbances, cardiomyocyte apoptosis, and interstitial fibrosis. It represents a significant cause of heart failure [64], which causes a substantial social and economic burden globally. HDAC4 emerges as an essential component mediating diabetic cardiovascular disease, exhibiting both detrimental and protective roles depending on its post-translational modifications, subcellular localization, and interaction partners (Fig. 4). Thus, we clarify this duality through mechanistic insights and therapeutic implications below.

HDAC4 and cardiac hypertrophy

Heart hypertrophy is a significant pathophysiological characteristic of DCM [65]. Cardiac hypertrophy is initially an adaptation to high glucose metabolism but may progress to a stage of maladaptation, leading to ventricular dilatation and even heart failure. Animal models of diabetes-induced cardiac hypertrophy exhibit an increased ratio of heart weight to body weight, enlarged

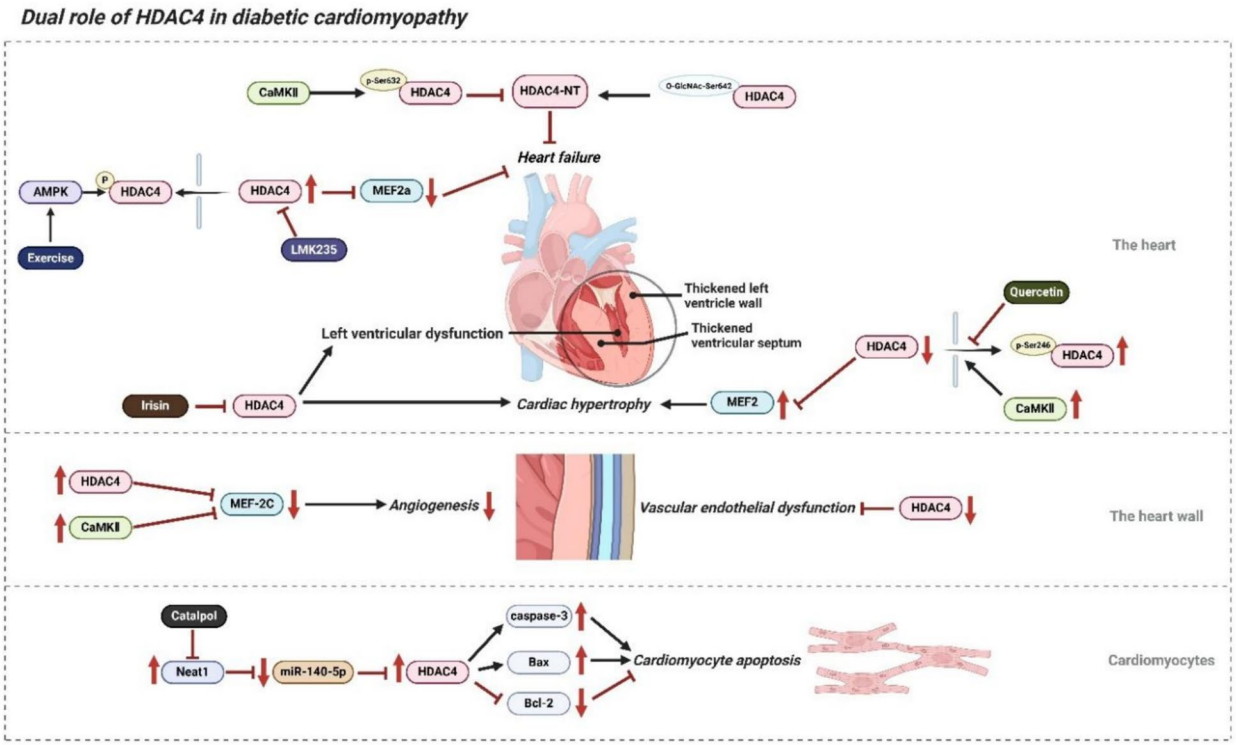

Fig. 4 HDAC4 has a dual effect on diabetic cardiomyopathy. The cardioprotective N-terminal fragment of HDAC4 counteracts diabetic cardiac dysfunction. Pathological CaMKII-mediated phosphorylation at Ser632 suppresses fragment generation, exacerbating heart failure, while O-GlcNAc glycosylation at Ser642 promotes its production. Exercise activates AMPK to phosphorylate HDAC4, promoting nuclear export and alleviating MEF2a repression, thereby enhancing cardiac function in heart failure models. LMK235 mimics these benefits by suppressing HDAC4 expression. Irisin ameliorates diabetic mice's left ventricular dysfunction and myocardial hypertrophy by suppressing elevated HDAC4 expression, preserving cardiac function. CaMKII phosphorylates HDAC4 at Ser246, triggering cytoplasmic translocation and relieving MEF2 repression, which drives pathological remodeling and heart failure. Quercetin inhibits HDAC4 phosphorylation, restoring nuclear retention and MEF2 suppression to mitigate cardiac dysfunction. In diabetic rat hearts, HDAC4/CaMKII upregulation and MEF-2C downregulation inhibit angiogenesis, exacerbating vascular insufficiency and myocardial hypoxia. Restoring diminished HDAC4 activity in diabetic mouse aortas ameliorates vascular endothelial dysfunction. Catalpol disrupts the Neat1/miR-140-5p/HDAC4 axis, mitigating high glucose-induced cardiomyocyte apoptosis and providing cardioprotection. CaMKII, calmodulin-dependent protein kinase II; HDAC4, histone deacetylase 4; Ser, serine; O-GlcNAc, oxygen–glucosamine; MEF2, myocyte-specific enhancer factor 2; AMPK, adenosine monophosphate-activated protein kinase; Neat1, one kind of lncRNA

cardiomyocytes, and upregulated expression of hypertrophic genes [66]. HDAC4 exhibits a unique dual role in this process, functioning as either a driver of pathology or a protective agent depending on its phosphorylation status and subcellular localization. Leptin (Lep), an adipose-derived hormone critical for energy and appetite regulation, is linked to metabolic disorders (e.g., obesity, insulin resistance, and hepatic steatosis) when Lep and Lep receptor (Lepr) mutations. In diabetic Zucker Diabetic Fatty (ZDF) rats with a missense mutation (fa) in the Lepr [67], hyperglycemia-induced intracellular calcium overload activates calcium/calmodulin-dependent protein kinase II (CaMKII), which phosphorylates HDAC4 at Ser246, promoting its translocation from the nucleus to the cytoplasm. This relieves HDAC4-mediated repression of the pro-hypertrophic transcription factor MEF2. Sustained MEF2 activation drives maladaptive remodeling through increased collagen synthesis, fibrosis, and cardiomyocyte apoptosis, ultimately leading to diastolic dysfunction and heart failure [68]. Notably, aberrant HDAC4 overexpression correlates with reduced p38 phosphorylation in leptin receptor-mutant ($Lepr^{db}$) mice, exacerbating insulin resistance and myocardial hypertrophy and highlighting its pathological role [69].

Conversely, HDAC4's protective functions emerge under therapeutic interventions. For instance, the natural compound quercetin inhibits CaMKII-mediated HDAC4 phosphorylation, restoring its nuclear retention and reinstating transcriptional repression of MEF2 [7]. Irisin is a newly discovered polypeptide critical for regulating metabolism, thermogenesis, and oxidative stress reduction. Irisin suppresses HDAC4 expression, improving metabolic flexibility and attenuating hypertrophy [69]. This duality stems from HDAC4's phosphorylation-dependent nucleocytoplasmic shuttling. Cytoplasmic phosphorylated HDAC4 drives pathological remodeling via MEF2 activation, while nuclear dephosphorylated HDAC4 exerts protection by repressing MEF2. Future research should focus on precision modulation of HDAC4's post-translational states. For example, developing inhibitors that selectively target CaMKII–HDAC4 interactions to block pathological phosphorylation or combining natural compounds (e.g., quercetin and irisin) to synergistically restore epigenetic balance.

HDAC4 and vascular injury

Diabetic myocardial hypertrophy causes reduced contractility accompanied by impaired angiogenesis [70]. Vascular damage, in turn, exacerbates myocardial hypertrophy and contractile dysfunction. In the heart of diabetic rats, hyperglycemia and metabolic stress upregulate HDAC4 and CaMKII, downregulating the pro-angiogenic transcription factor MEF-2C [72]. MEF-2C is critical for endothelial cell function and neovascularization [71]. Its suppression by HDAC4/CaMKII disrupts angiogenic processes, aggravating vascular insufficiency and myocardial hypoxia. This imbalance in the CaMKII/HDAC4/MEF-2C axis promotes microvascular rarefaction, further impairing cardiac perfusion and accelerating maladaptive remodeling [72].

Paradoxically, HDAC4 activity is diminished in the aortas of diabetic mice, and restoring its activity ameliorates vascular endothelial dysfunction [73]. This suggests a tissue-specific protective role of HDAC4 in large vessels, where it may stabilize endothelial homeostasis through mechanisms distinct from its cardiac actions. The divergent roles of HDAC4 in the microvasculature and large arteries underscore the necessity for precision therapeutic strategies. These strategies must selectively target HDAC4 in pathological compartments (e.g., cardiac microvasculature) to inhibit its detrimental effects, preserving or enhancing its protective functions in other compartments (e.g., aortic endothelium).

HDAC4 and cardiomyocyte apoptosis

High glucose-induced cardiomyocyte apoptosis is one of the major causes of the development of DCM [74]. In mouse cardiomyocytes treated with high glucose, HDAC4 levels were upregulated due to the repression of miR-140-5p transcription by nuclear-enriched transcriptosome 1 (Neat1), leading to the de-repression of HDAC4. Aberrant expression of the Neat1/miR-140-5p/HDAC4 axis in the high glucose state caused an imbalance of apoptosis-related proteins to promote cardiomyocyte apoptosis. HDAC4 silencing or miR-140-5p overexpression prevented Neat1-induced cardiomyocyte death. Catalpol inhibited apoptosis via the Neat1/miR-140-5p/HDAC4 axis and had cardioprotective benefits against DCM [75].

HDAC4 and heart failure

In the end stage of DCM, heart failure is a common outcome. Exercise has been shown to reduce mortality and hospitalization rates, alleviating symptoms in patients with heart failure [76]. Mechanistic studies indicate that exercise improves cardiac function and glucose metabolism through modulation of the HDAC4/MEF2 axis in heart failure models [77]. Specifically, exercise activates AMPK, leading to phosphorylation and nuclear export of HDAC4. This process decreases the deacetylation of histone H3K9 at the promoter of glucose transporter 1 (GLUT1), relieves MEF2a inhibition, and increases GLUT1 expression. Similarly, treatment with LMK235, a selective HDAC4/5 inhibitor [78], led to improved cardiac

function and glucose uptake in heart failure mice [77]. This result suggests that inhibition of HDAC4 may be beneficial in certain pathological contexts.

However, recent studies suggest that HDAC4 plays a more complex and context-dependent role in diabetic cardiac pathology. While HDAC4 inhibition appears beneficial under some conditions, other evidence suggests that HDAC4 may exert protective effects depending on its post-translational modifications. Kronlage et al. reported that the cardioprotective N-terminal protein hydrolysis fragment of HDAC4 was enhanced in vivo and in vitro in diabetic patients and in high-glucose models. Moreover, complete knockout of HDAC4 in diabetic mice resulted in heart failure, whereas WT mice were protected. Mechanistically, O-GlcNAc glycosylation at Ser642 of HDAC4 counters pathological phosphorylation by CaMKII and promotes the formation of the cardioprotective N-terminal fragment. In contrast, phosphorylation at Ser632 appears to contribute to cardiac dysfunction [79].

These findings underscore the dual nature of HDAC4's role in diabetic heart failure, where its effects. Either protective or detrimental of HDAC4 are determined by specific post-translational modifications. Thus, while HDAC4 inhibition may offer therapeutic benefit in some contexts, indiscriminate targeting could disrupt its protective functions. Notably, no cardiac side effects of HDAC4-selective inhibitors have been explicitly reported so far. Nevertheless, future studies should prioritize detailed evaluation of cardiac safety. Future studies also should aim to develop precision therapies that selectively inhibit pathological HDAC4 activity while preserving its beneficial roles. Further mechanistic and translational research is needed to clarify the context-dependent impact of HDAC4 modifications in diabetic cardiomyopathy.

HDAC4 regulates diabetic encephalopathy

Diabetic encephalopathy (DE) has a direct impact on the cognitive function of patients [80]. Hippocampal neuronal apoptosis [81] and oxidative stress [82] are closely related to DE. HDAC4 expression is elevated in the hippocampus of diabetic rats and in hyperglucose-treated HT-22 cells, an immortalized cell line derived from mouse hippocampal neurons. Activation of the c-Jun N-terminal kinase (JNK) signaling pathway is considered a key cause of apoptosis. Elevated HDAC4 is key to increased apoptosis in hippocampal neurons and is associated with HDAC4 activation of the JNK pathway [83]. However, it is still unclear how HDAC4 regulates the JNK pathway.

HDAC4 regulates diabetic wounds

Diabetic wounds, especially diabetic foot ulcers, exhibit a chronic inflammatory response and limited efficacy of standard treatments, impeding normal wound healing and increasing the susceptibility to wound infection. Many reviews have emphasized the significance of chronic inflammation and the involvement of the inflammatory vesicle NOD-like receptor thermal protein domain associated protein 3 (NLRP3) in hindering diabetic wound healing [84]. Pyroptosis is a form of cell death triggered by the formation of gasdermin pores in the plasma membrane [85]. The expression levels of HDAC4 and factors related to the NLRP3-mediated cellular pyroptosis pathway were significantly elevated in high glucose-stimulated macrophages. Whereas, after treatment with the non-selective HDAC inhibitor trichostatin A (TSA), the expression of HDAC4 and NLRP3, among others, was down-regulated. In addition, a microneedle-mediated TSA-loaded patch has been invented, which has the characteristics of low invasiveness and long-lasting effect, and has been shown to promote wound healing in diabetic rats [86]. Although this preclinical proof-of-concept highlights the therapeutic potential of localized HDAC inhibition, further validation in higher-order models and human trials is essential to assess clinical applicability. This innovative drug-delivery system, combining TSA with advanced carrier materials, represents a promising experimental strategy for addressing chronic diabetic wounds.

HDAC4: a potential therapeutic target for diabetes mellitus

Currently, the mainstay of diabetes treatment is still the application of insulin and hypoglycemic drugs [87]. Epigenetic mechanisms in the pathogenesis of diabetes are gradually revealed, and the involvement of HDACs in the etiology of diabetes has made them a new target for treating both types of DM [88]. HDAC inhibitors are expected to be novel drugs for the prevention and treatment of diabetes, to ameliorate and delay the onset of diabetic complications, and the loading of HDAC inhibitors with the proper way of action on the site of the disease is also a new direction of research. Notably, in recent years, the application of biological materials loaded with small interfering RNA (siRNA) targeting knockdown of HDAC4 for treating diabetic nephropathy has also been validated at the animal level [89, 90].

Progress of pan-HDAC inhibitors in diabetes treatment

The HDAC inhibitors that have been demonstrated to suppress HDAC4 activity and exert therapeutic effects in diabetes include TSA, sodium valproate, and sodium

Table 2 Pan-HDAC inhibitors that inhibit HDAC4 in diabetes mellitus

HDACi	HDAC class selectivity	Experimental models	Target	Role of HDACi	References
TSA	Class I, II, IV and SIRT6	Isolated pancreatic islets from SD rats	HDAC4, HDAC7	Improved islet function and viability in vitro Controlled hyperglycemia in islet transplantation	[98]
		STZ-induced diabetes model in SD rats	HDAC4	Improved diabetic wound healing	[86]
NaB	Class I and IIa	STZ-induced diabetic ICR mice	HDAC4	Improved angiogenesis Attenuated cardiac hypertrophy Inhibited interstitial fibrosis	[99]
		High-fat diet feeding-induced T2DM CD-1 mice	HDAC4	Activated the MKK3/p38/PRAK pathway Prevented cardiac dysfunction and metabolic disorders	[100]
VAP	Class I and IIa	STZ-induced diabetes model in SD rats	HDAC4, HDAC5, HDAC7	Ameliorated diabetic renal damage and fibrosis	[101]
		SD rats	HDAC4, HDAC5	Promoted autophagy Inactivated NF-kB/iNOS signaling Ameliorate podocyte and kidney injury	[102]

butyrate. They mainly play a role in DM treatment by protecting pancreatic β-cells and improving diabetic kidney and heart (Table 2).

IIa HDAC-selective inhibitors

The exploration of subtype-selective HDAC inhibitors has emerged as a prominent research focus in recent years. Consequently, an increasing number of high-efficiency, low-toxicity HDAC inhibitors are applied to treat the disease. Currently, known Class IIa HDAC-selective inhibitors include LMK-235, TMP269 and TMP195, MC1568, and MC1575, but at this stage, research on these inhibitors is mainly focused on the treatment of cancer, and there are very few studies on the use of these inhibitors in DM.

TMP269 may promote the in vitro differentiation of Wharton's jelly mesenchymal stem cells (WJMSCs) into insulin-secreting cells. This provides new ideas for alternative therapeutic approaches for T1DM [91]. TMP269 and TMP195 inhibit HDAC4 and acetyl histone H3 elevation, exerting nephroprotective by ameliorating apoptosis and inflammation in acute kidney injury [92, 93]. An attempt can be made to investigate whether TMP269 and TMP195 are also protective in diabetic nephropathy.

MC1568 is a selective Class IIa HDAC inhibitor that promotes pancreatic progenitor cell differentiation and protects β-cell survival. Treatment of pancreatic explants with MC1568 promotes the development of neurogenin 3 (NGN3)-positive endocrine progenitor cells and enhances the expression of pairing box gene 4 (Pax4), which is essential for β/δ cell differentiation, thereby promoting lineage differentiation and expansion of β/δ cells [14]. It is suggested that MC1568 may be a potential tool for obtaining stem cell-derived β-cells. Notably, MC1568 protected mouse β-cells from mitochondrial dysfunction and apoptosis by inhibiting HDAC7 [94]. Thus, MC1568 promotes islet endocrine cell differentiation and protects the function of β-cells, a potential diabetes therapeutic drug. Furthermore, MC1568 reduces kidney fibrosis by preventing HDAC4 and other pro-fibrotic molecules from being expressed [95]. MC1568 may prevent diabetic nephropathy as well.

HDAC4-specific inhibitors—Tasquinimod

The only HDAC4-specific inhibitor currently in development is tasquinimod. Tasquinimod inhibits tumor angiogenesis, binds to the Zn^{2+} structural domain of HDAC4, and inhibits HDAC4 signaling through a variant of HDAC4. Tasquinimod is also an S100A9 inhibitor. Tasquinimod has been studied in patients with solid tumors, including a phase III randomized trial in patients with metastatic prostate cancer that demonstrated excellent tolerability. A clinical phase Ib/IIa study of tasquinimod in relapsed or refractory multiple myeloma is underway.

In high glucose-cultured human retinal endothelial cells, a 24-h tasquinimod treatment inhibited proliferation, migration, and lumen formation, thereby suppressing key mechanisms underlying diabetic retinopathy progression [96]. However, tasquinimod mainly inhibits S100A9 to exert antidiabetic retinopathy effects, and the study did not evaluate the level of HDAC4 pre- and post-tasquinimod administration. Consequently, more research is required to ascertain whether tasquinimod has a therapeutic or preventive impact on diabetes.

Other HDAC4-mediated therapeutic options in diabetes

Since HDAC4 mainly plays a role in inhibiting gene transcription by dephosphorylating into the nucleus. Some compounds modulate HDAC4 phosphorylation to control gene transcription. Resveratrol reduces hepatic HDAC4 phosphorylation, decreases HDAC4 entry into the nucleus, and inhibits gluconeogenesis in insulin-resistant states [41]. Que reduced HDAC4 Ser246 phosphorylation and attenuated the transcription of the hypertrophy gene MEF2, thereby inhibiting cardiac hypertrophy in diabetic rats. On the contrary, exercise promoted phosphorylation of HDAC4 Ser246 and Ser632 sites, enhanced skeletal muscle GLUT4 transcription, and regulated skeletal muscle metabolism [13]. Not surprisingly, phosphorylation of HDAC4 Ser246 and Ser632 sites, especially the Ser246 site, may influence the nucleoplasmic translocation of HDAC4. Phosphorylation of the HDAC4 Ser site by specific drugs may promote the expression of beneficial genes; dephosphorylation of HDAC4 can inhibit the expression of disease-related genes.

Irisin protected myocardial function and insulin resistance in Lepr^{db} mice by reducing HDAC4 [69]. Moderate-intensity endurance training (ET) effectively controlled glucose homeostasis, down-regulated HDAC4, and promoted the expression of angiogenesis-related genes in diabetic rats [72]. Radix polygoni multiflori can inhibit HDAC4, JNK signaling pathway in the hippocampus to reduce apoptosis of hippocampal neurons in vivo and protect against the development of diabetic encephalopathy [83]. These are three ways to inhibit HDAC4 and thus protect diabetic cardioencephalic function, but whether they also act by regulating HDAC4 phosphorylation is not clear.

HuangqiGuizhiWuwu Decoction (HGWWD), a classic Chinese herbal formula, has been widely used in diabetes treatment for many years. Recently, HGWWD was found to have a protective effect on vascular endothelial function in diabetic mice by activating HDAC4 [73]. This provides a scientific basis for applying HGWWD to regulate HDAC4 in diabetes and vascular diseases.

Conclusion and future perspectives

This article reviews the regulation of differentiation, development and function of pancreatic endocrine cells by HDAC4. Besides, HDAC4 plays a key regulatory role in insulin signal transduction and glucose metabolism through phosphorylation-dependent nuclear cytoplasmic shuttle and epigenetic regulation of key metabolic genes, such as FOXO1 and GLUT4. This article also reviews comprehensively synthesizes the multifaceted role of HDAC4 in DM and its complications, including diabetic nephropathy, diabetes osteoporosis, diabetic cardiomyopathy, diabetic encephalopathy and diabetic wounds. Preclinical studies highlight its dual functionality: HDAC4 acts as both a driver of pathology and a protective mediator. Emerging therapeutic strategies, including pan-HDAC inhibitors and class IIa-selective agents. They demonstrate potential in preclinical models by restoring β-cell function, improving insulin sensitivity, and mitigating diabetic nephropathy or cardiomyopathy. However, the clinical translation of these findings remains limited by incomplete mechanistic insights into HDAC4's context-dependent roles and species-specific regulatory differences. Collectively, while HDAC4 represents a compelling therapeutic target, its complex interplay in metabolic and cellular pathways necessitates further exploration to unlock its full therapeutic potential.

Future research should prioritize validating HDAC4's pathophysiological roles in human-relevant systems, such as patient-derived organoids and clinical cohorts. Deciphering tissue-specific regulatory mechanisms through spatial multi-omics and phosphorylation-state mapping should also be considered for inclusion in future research. Therapeutic innovation must focus on developing precision modulators (e.g., Ser632/Ser642-targeted inhibitors and nanoparticle-delivered siRNA) to selectively disrupt HDAC4's detrimental functions while preserving its protective roles. Integrating AI-driven structural biology and single-cell transcriptomics will accelerate mechanistic insights into HDAC4's context-dependent interactions. Whereas, rigorous safety assessments in advanced models (e.g., non-human primates) and pharmacogenomic studies targeting HDAC4 variants will pave the way for personalized therapies. Cross-disciplinary collaboration among epigenetics, bioengineering, and clinical research is essential to translate these discoveries into transformative strategies for diabetes management.

Abbreviations

AMPK	AMP-activated protein kinase
Akt	Protein kinase B
Bax	Bcl-2-associated X protein
Bcl-2	B-cell lymphoma/leukemia 2 gene
cAMP	Cyclic adenosine monophosphate
CaMKII	Calcium/calmodulin-dependent protein kinase II
CaN	Calcium/calmodulated neural phosphatase
circRNA	Circular RNA
DCM	Diabetic cardiomyopathy
DE	Diabetic encephalopathy
DM	Diabetes mellitus
DN	Diabetic nephropathy
DNA	Deoxyribonucleic acid
DOP	Diabetes Osteoporosis
DTsiANp-cRGD	CRGD Targeted Dendrimer-Templated Albumin siRNA Nanoplex
ET	Endurance training
EVs	Extracellular vehicles
FOXO1	Forkhead box protein O1
GLUT1	Glucose transporter 1
GLUT4	Glucose transporter 4

G6Pase	Glucose-6-phosphatase
G6PC	Glucose-6-phosphatase, catalytic
HAT	Histone acetyltransferases
HDAC	Histone deacetylase
HDAC4	Histone deacetylase 4
HG	High glucose
HGWWD	HuangqiGuizhiWuwu Decoction
HIF-α	Hypoxia inducible factor-α
HK2	Human kidney-2
iNOS	Inducible Isoform of Nitric Oxide Synthase
JNK	C-Jun N-terminal kinase
$Lepr^{db}$	Leptin receptor spontaneous mutant
MEF2	Myocyte enhancer factor 2
miR	MicroRNA
MKK3	Mitogen-activated protein kinase kinase kinase 3
ncRNA	Non-coding RNA
NaB	Sodium butyrate
Neat1	Nuclear-enriched transcriptosome 1
NF-kB	Nuclear factor-κ-gene binding
NGN3	Neurogenin 3
NLRP3	NOD-like receptor thermal protein domain associated protein 3
PA	Palmitic acid
Pax4	Pairing box gene 4
PEPCK/Pck1	Phosphoenolpyruvate carboxykinase
PIP2	Phosphatidylinositol bisphosphate
PIP3	Phosphatidylinositol trisphosphate
PI3K	Phosphatidylinositol 3-kinase
PKA	Protein kinase A
PRAK	P38 regulated/activated protein kinase
Que	Quercetin
Ser	Serine
SIK2	Salt-induced protein kinase 2
shRNA	Short hairpin RNA
siRNA	Small interfering RNA
SIRT6	Sirtuin (silent mating type information regulation 2 homolog) 6 (S. cerevisiae)
STAT1	Signal transducerand activator of transcription 1
TGF-β	Transforming growth factor-β
TSA	Trichostatin A
T1DM	Type 1 diabetes
T2DM	Type 2 diabetes
TUDCA	Tauroursodeoxycholic acid
USCs-EVs	Urine-derived stem cells-EVs
UTR	Untranslated Region
VEGFA	Vascular endothelial growth factor A
VPA	Valproic acid
WJMSCs	Wharton's jelly mesenchymal stem cells
WT	Wild type
ZDF	Zucker diabetic fatty

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Author contributions
YQL drafted and revised the manuscript. YTL revised the manuscript. YJ, CYK, and WWL illustrated figures and collected the related references. YLW, YL, XYK and JQ illustrated tables and collected the related references. AXZ and CLB conceived the project and edited the manuscript. All authors read and approved the final manuscript.

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Declarations

Ethics and consent to participate
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