Epigenetic regulation in a high-sugar environment (Review)

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Abstract. The prevalence of diabetes and its complications has become a major global health challenge, with its pathological process closely linked to the phenomenon of 'metabolic memory' induced by persistent hyperglycemia. Epigenetic regulation is recognized as the core molecular mechanism underpinning this process. The present review systematically elucidated how the hyperglycemic microenvironment profoundly regulates cellular functions and drives the onset and progression of diabetes and its vascular complications by reprogramming three major epigenetic pathways: DNA methylation, histone modifications and non-coding RNA expression. The present review elaborated in detail how high glucose induces alterations in the DNA methylation status of specific genes (such as PDX1 and CXCR4) within key target cells including pancreatic β-cells, hepatocytes, muscle cells and adipocytes; how it modulates multiple histone modifications, including emerging histone lactylation (such as H3K18la), thereby directly activating pathogenic gene transcription; and how it disrupts non-coding) RNA networks (such as long non-coding RNA MALAT1 and microRNA 21) to mediate inflammation, oxidative stress and fibrosis by interfering with signaling pathways such as PI3K/Akt and TGF-β. Furthermore, the present review specifically emphasized the cellular and tissue specificity of high-glucose-induced epigenetic regulation, thereby elucidating its unique mode of action in specific complications such as diabetic nephropathy and cardiovascular disease. Finally, the present review considered the substantial potential of targeting key epigenetic enzymes (such as DNA methyltransferases, histone deacetylases) or using epigenetic markers as biomarkers and novel therapeutic strategies. This provides a conceptual framework and directions for ultimately 'eradicating' metabolic memory and achieving precise prevention and treatment of diabetes and its complications.

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Abbreviations: CXCR4, C-X-C motif chemokine receptor 4; ChREBP, carbohydrate response element binding protein; DKD, diabetic kidney disease; *LEP*, leptin gene; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; *Meg3*, maternally expressed gene 3; p/CAF, p300/CBP-associated factor; *RELA*, RELA proto-oncogene; TET1, the transcriptional regulatory protein tet-methylcytosine dioxygenase 1; USF1, upstream stimulating factor 1

Key words: hyperglycemia, epigenetics, DNA methylation, histone modifications, non-coding RNA, diabetic complications

Contents

1. Introduction

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (1). Clinically, diabetes mellitus is primarily categorized into Type 1 diabetes (T1DM, accounting for 5-10%) and Type 2 diabetes (T2DM, accounting for 90-95%). T1DM is chiefly caused by absolute insulin deficiency resulting from autoimmune-mediated destruction of pancreatic islet β-cells; whereas T2DM is characterized by insulin resistance accompanied by relative insufficiency in insulin secretion. Diabetes has become an epidemic disease (2), with China's prevalence projected to rise to 592 million by 2035 (3). Chronic hyperglycemia also disrupts insulin secretion and/or function and is associated with long-term damage and dysfunction in various tissues and organs (eyes, kidneys, nerves, heart and blood vessels) as well as cancer (4). The management of diabetes and its complications remains a significant challenge, particularly

diabetic kidney disease (DKD). Existing biomarkers as therapeutic targets only partially mitigate DKD progression and provide rough predictions of disease advancement. When diabetes coexists with cardiovascular disease (CVD), mortality nearly doubles (5). Even after restoring normal blood glucose and metabolic balance, the effects of hyperglycemia on diabetes and its complications do not immediately reverse; a phenomenon termed 'metabolic memory' (6-8). Metabolic memory primarily manifests as epigenetic alterations in target cells under diabetic conditions (9). Since epigenetic modifications are often reversible, this offers therapeutic opportunities to improve cellular dysfunction and mitigate or 'erase' metabolic memory (10).

Epigenetics refers to the study of heritable phenotypic changes that do not involve alterations in DNA sequences (11-13). Research in epigenetics has shown a rapid growth trend (14). DNA methylation, histone modifications and non-coding RNA regulation are three major research directions in epigenetics (15). Epigenetic research not only provides new perspectives for understanding gene expression regulation but also offers novel approaches for disease prevention and treatment (16). For instance, by modulating epigenetic modifications, novel therapeutic strategies can be developed to combat environmentally induced diseases such as CVD, diabetes and cancer. Furthermore, epigenetic markers serve as diagnostic biomarkers for diseases, underpinning personalized treatment and precision medicine (17).

Emerging epigenetic tools can be used for the prevention, diagnosis and treatment of diabetes and its complications (18). Therefore, investigating epigenetic variations under high-sugar environments and their regulatory roles in diabetes progression holds significant potential for clinical applications in diabetes diagnosis and therapy (19). The present review primarily introduced the epigenetic regulatory mechanisms of high-sugar microenvironments across different cell types and disease models, offering novel insights for treating diabetes and its complications through epigenetic modulation. The present review uniquely integrates findings across pancreatic, hepatic, vascular and renal systems to provide a holistic view of the epigenetic landscape reshaped by hyperglycemia.

2. Epigenetic regulatory mechanisms of high glucose on cells

High glucose and cellular DNA methylation. DNA methylation is one of the most common epigenetic modifications (20), primarily occurring on cytosine residues. Specifically, methylation typically occurs within CpG dinucleotides (21). The addition of a methyl group leads to gene expression suppression, as methylated DNA often binds to transcription factors, preventing RNA polymerase binding and thereby inhibiting gene transcription (22). DNA methylation is frequently associated with gene silencing (23). For instance, in tumor cells, tumor suppressor genes may lose expression due to hypermethylation (24,25). Concurrently, DNA methylation influences genomic stability, participating in processes such as genomic imprinting and X chromosome inactivation (26). A high-sugar environment, particularly prolonged exposure to elevated glucose levels, induces significant alterations in DNA methylation within pancreatic β-cells (27), potentially disrupting insulin secretion and metabolic function. DNA methylation is primarily catalyzed by DNA methyltransferases (DNMTs) (28,29), involving the transfer of methyl groups onto cytosine residues in DNA. Methylation levels and patterns are influenced by multiple factors, including dietary habits, environmental factors and genetic background (30). A high-sugar diet affects DNA methylation levels by influencing one-carbon metabolism pathways, increasing the availability of methyl donors such as S-adenosylmethionine (31). However, excessive methyl donors may also lead to methylation suppression, highlighting the complexity of high-sugar environments (32). Research indicates that glucose excess induces increased methylation density in specific genes, thereby suppressing their expression (27). For example, Vigorelli *et al* (33) found that methylation levels in the promoter region of the C-X-C motif chemokine receptor 4 (*CXCR4*) gene in human CD34+ stem cells markedly increased under high-sugar conditions, affecting cellular proliferation and migration capabilities. Furthermore, high glucose also affects the methylation status of genes associated with insulin signaling pathways, lipid metabolism and inflammatory responses, potentially contributing to the development of diseases such as metabolic syndrome, obesity and T2DM (34). Table I describes some genes undergoing DNA methylation changes influenced by high glucose (34-44).

Histone modifications. Histones are proteins around which DNA is wound, forming the fundamental units of chromatin (45,46). Modifications of histones include methylation, acetylation, phosphorylation, ubiquitylation, ADP-ribosylation, SUMOylation and other novel modifications, which can directly influence chromatin structure (47). Different histone modification states are closely associated with gene activity levels (48). For example, acetylation is typically linked to transcriptional activation (49), while methylation can lead to transcriptional repression (50).

Histone modifications in high-sugar environments. In high-sugar environments, the most common histone modification type includes histone acetylation. Histone acetylation occurs when acetyltransferases (such as CBP and p300) add acetyl groups to histone lysine residues. This modification leads to chromatin relaxation, making DNA more accessible to transcription factors and other regulatory proteins, thereby promoting gene transcription (51). Biernacka *et al* (52) discovered that high-glucose-treated LNCaP cells (a human prostate cancer cell line) exhibited markedly increased histone H3 acetylation associated with the *insulin-like growth factor binding protein 2 gen*e, leading to chemotherapy resistance in prostate cancer (PCa). High glucose also induces histone H3 methylation (53). Histone methylation refers to the addition of methyl groups to lysine or arginine residues on histone proteins. Depending on methylation levels, histone methylation can either promote or suppress gene transcription. For example, tri-methylation of lysine 4 on histone H3 catalyzed by histone methyltransferases (H3K4me3) is typically associated with gene activation, whereas H3K27me3 is often linked to gene silencing (54,55). Ishikawa *et al* (56) discovered that in type 2 diabetes mellitus (T2DM), increased expression and decreased methylation of the *cyclin-dependent kinase inhibitor 1A* and *phosphodiesterase 7B* in T2DM exhibit

Table I. Genes affected by high sugar exposure in terms of DNA methylation.

Authors, year	Cell type	Species	Gene	Effect	Consequence	(Refs.)
Gill *et al*, 1994	Hepatocytes	Female mice	*Sult1e1*	DNA methylation	Impaired angiogenesis	(35)
Jain *et al*, 2011	Vascular endothelial cells	Homo sapiens	*IL-8*	DNA methylation	Endothelial dysfunction	(36)
Hamad *et al*, 2021	INS-1	Rat	*Hmox1*	DNA methylation	Oxidative stress diabetic	(37)
Chen *et al*, 2020	Human retinal venules	Human and Porcine	*Endothelin-1*	DNA methylation	Diabetic retinopathy	(38)
Jurado-Aguilar *et al*, 2024	Hepatocytes	Wild-type and Gdf15-/- mice	*SMAD3*	DNA methylation	Vascular remodeling	(39)
Tewari *et al*, 2012	Retinal endothelial cells	Streptozotocin-diabetic rats	*Polg1*	DNA methylation	Transcriptional repression	(40)
Park *et al*, 2008	Pancreatic beta cells	Rats	*PDX1*	DNA methylation	Insulin resistance	(41)
Ding *et al*, 2012	Pancreatic islet cells	GDM(F1-GDM) mice	*Igf2/H19*	DNA methylation	Impaired glucose tolerance	(42)
Zhang *et al*, 2019	HRECs	Diabetic mice	*NF-kB*	DNA methylation	Inflammation	(43)
Gunes *et al*, 2023	LX-2	Homo sapiens	*IL-6*	DNA methylation	Fibrosis	(44)

Sult1e1, estrogen sulfotransferase 1E1; *IL*, interleukin; *Hmox1*, heme oxygenase 1; *polg1*, polymerase γ1; *PDX1*, pancreatic and duodenal homeobox 1; *Igf2*, insulin-like growth factor 2; *H19*, imprinted maternally expressed transcript; *NF-kB*, nuclear factor-κB; INS-1, insulinoma cell line-1; HRECs, human retinal endothelial cells; LX-2, human hepatic stellate cell line-LX-2.

increased expression and reduced methylation. This combination impairs glucose-stimulated insulin release by inhibiting β-cell proliferation, promoting apoptosis and disrupting cAMP signaling pathways (56). In a study of *Drosophila* oocytes, Sun *et al* (57) found that under high-sugar conditions, histone H3 methylation levels (such as, H3K9 and H3K27) increase, suppressing *cyclin D1* gene expression and disrupting cell cycle progression, thereby impairing early embryonic development.

High sugar and lactylation. Lactylation is a newly discovered post-translational modification of proteins. It uses lactate, the end product of glycolysis, as a substrate to covalently attach a lactyl group to lysine residues on both histone and non-histone proteins (58). In high-glucose microenvironments, cellular metabolic pathways undergo significant alterations that directly influence lactylation levels, targets and functions, thereby driving disease progression in conditions including cancer and diabetic complications (59).

The high-glucose microenvironment drives cellular metabolic reprogramming via the Warburg Effect, causing cells to preferentially metabolize glucose through efficient glycolysis even under oxygen-sufficient conditions. This process leads to a substantial increase in intracellular lactate production. Research confirms that high-glucose conditions specifically upregulate L-lactic acid levels, while D-lactic acid remains unaffected. This indicates that hyperglycemia primarily rewrites the cellular modification profile through the L-lactic acid pathway (60).

In a high-sugar environment, lactylated histone modifications do not simply increase overall but exhibit site-specific enrichment and functional reprogramming. The hyperglycemic microenvironment induces elevated levels at specific histone lactylation sites, with H3K18la and H3K9la being the most characteristic sites (61). For instance, in diabetic retinopathy models, hyperglycemia/hypoxia triggers explosive increases in H3K9la and H3K18la in retinal endothelial cells, thereby activating transcription programs of pro-angiogenic genes. Evidence also shows that, Alanyl-tRNA synthetase 1 acts as a lactyltransferase to modulate H3K18, thereby regulating elongase-5 transcription and mediating ferroptosis in individuals with DKD (62).

Abnormally expressed histone modifying enzymes in high-glucose environments. Research indicates that elevated glucose levels induce abnormal expression of certain histone modification enzymes (63). Altered activity of these enzymes directly modifies histone modification states, thereby affecting gene transcriptional activity (64). For example, Sánchez-Ceinos *et al* (65) found that the histone lysine N-methyltransferase (enhancer of Zeste 2 polycomb repressive complex 2 subunit) increases under high glucose conditions in both human aortic endothelial cells (HAECs) exposed to high glucose *in vitro* and those isolated from individuals with diabetes (D-HAECs). This leads to elevated H3K27me3 levels and the oxidative stress driven by H3K27me3 enhances nuclear

Table II. High-sugar-induced histone modifications in selected genes.

Authors, year	Cell type	Species	Target gene	Histone modification	Regulation	Consequence	(Refs.)
Sánchez-Ceinos *et al*, 2024	D-HAEC	Human	*EZH2*	Histone methylation	↑	Endothelial oxidative stress	(65)
Malmgren *et al*, 2013	Pancreatic β-cell	Human	*UTX and JMJD3*	Histone demethylation	↓	Endothelial oxidative stress	(74)
Liao *et al*, 2022	HepG2, L02 and A673 cells	Mice	*GCN5*	Histone acetylation	↑	Glucose uptake inhibition	(75)
Lee *et al*, 2018	293 cells	Sprague-Dawley rats	*HDACs*	Histone deacetylation	↑	Reduced transcriptional activity	(76)
Horitani *et al*, 2021	EPCs	Mice	*H3K27me3*	Histone demethylation	↑	Atherosclerosis	(77)
Qiu *et al*, 2020	Pancreatic β cells	Mice	*IL-17A*	Histone acetylation	↑	Inflammation	(78)

↑, upregulation; ↓, downregulation; D-HAEC, diabetic human aortic endothelial cells; HepG2, L02 and A673 cells, human hepatocellular carcinoma G2, human normal liver L02 cells and A673 rhabdomyosarcoma cell line; 293 cells, 293 cells; EPCs, endothelial progenitor cells; *EZH2*, enhancer of zeste 2 polycomb repressive complex 2 subunit; *UTX* and *JMJD3*, KDM6A and KDM6B; *GCN5*, general control non-derepressible 5; *HDAC*, histone deacetylase; *H3K27me3*, Tri-methylation of lysine 27 on histone H3; *IL-17A*, interleukin-17A.

factor κB p65 (NF-κB p65) activity, ultimately causing endothelial dysfunction (65). Furthermore, Miao *et al* (66) found that high-glucose-treated monocytes exhibited increased transcriptional activity of histone acetyltransferases CBP (CREB-binding protein) and p/CAF (p300/CBP-associated factor), leading to elevated levels of HH3 (histone H3) acetylation at TNF-α and COX-2 promoters in monocytes in human blood monocytes from type 1 and type 2 diabetic. This alteration promotes the expression of metabolism- and inflammation-related genes such as NF-κB (66).

High-glucose-induced histone modifications and gene expression regulation. Changes in histone modifications induced by high-sugar environments directly influence gene expression. For example, Sun *et al* (67) found P/CAF acetylated lysine residues 328 and lysine 450, in liver cells from mice treated with high glucose, leading to proteasomal degradation and increased blood glucose and hepatic glucose output. Yamazaki *et al* (68) also found that H3K9 acetylation (H3K9ac) is elevated in the promoter region of the high glycated hemoglobin group in blood lymphocytes and monocytes from type 1 diabetes mellitus patients, according to the report on histone modification status. H3K9ac also influences NF-κB expression, with studies indicating that increased H3K9ac correlates with inflammation-induced progression of DKD (69). A high-sugar environment not only affects individual gene expression but also, as research shows, a high-sugar diet can alter the epigenetic state of pregnant women, leading to genomic changes in their offspring (70). For example, leptin gene *(LEP)* is a gene regulating energy balance. Allard *et al* (71) demonstrated through a Mendelian randomization study that maternal hyperglycemia reduces *LEP* DNA methylation levels in offspring and correlates with elevated umbilical cord blood leptin levels. This suggests that *in utero*-induced epigenetic regulation may contribute to increased obesity rates later in life (71-73). Table II describes the histone modifications induced by high sugar in certain genes (65,74-78).

Effects of high-glucose environment on non-coding RNA expression and consequences. Non-coding RNAs refer to RNA molecules that do not encode proteins, including long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) (79). They play crucial roles in regulating gene expression. Non-coding RNAs possess several important functions, including: i) Transcription regulation: Non-coding RNAs influence gene transcription levels by modulating the activity of transcription factors (80); ii) Splicing functions: Certain lncRNAs can influence mRNA splicing processes, thereby altering the final protein product type (81); iii) Stabilizing mRNA molecules: Non-coding RNAs can bind to mRNA, affecting its stability and degradation rate; iv) Regulating translation: By binding to translation-related factors, ncRNAs can modulate mRNA translation efficiency.

Research indicates that under high-glucose/diabetes conditions, the expression of certain non-coding RNAs undergoes significant alterations (82). These changes may be mediated through the following mechanisms: i) Modulating transcription factor activity: High glucose levels induce alterations in the activity of specific transcription factors, which in turn regulate the expression of particular lncRNAs. For instance, Zhang *et al* (83) observed that in genetically diabetic C57BKS mouse cells, signal transducer and activator of transcription 1 phosphorylation markedly upregulates metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) expression and downregulates miR-205 expression through the JAK-STAT

Table III. Effects of high glucose on non-coding RNA expression.

Authors, year	Cell or disease	Species	Non coding RNA (lncRNA or microRNA)	Regulation (↑or↓)	Consequence	(Refs.)
Pradas-Juni *et al*, 2020	DIO	Mice	lincIRS2	↓	Insulin resistance	(88)
Cui *et al*, 2018	Hepatocytes	Mice	GM10768	↑	Gluconeogenesis	(89)
Li *et al*, 2024	Keratinocytes	Human	miR181A2HG	↑	Anti-angiogenesis	(90)
Zhao *et al*, 2020	Microglia	SD female rats	lncRNA-Gm4419	↓	Apoptosis	(91)
Liu *et al*, 2021	HUVECs	Human	PVT1	↑	Oxidative stress	(92)
He *et al*, 2020	Adipose-derived stem cell	Human	MALAT1	↑	Podocyte injury	(93)
Heydari *et al*, 2023	Type 2 diabetes	Human	TUG1	↓	Regulation of mitochondrial function	(94)

↑, upregulation; ↓, downregulation; DIO, obesity; HUVECs, human umbilical vein endothelial cells; lincIRS2, a long intergenic non-coding RNA that regulates insulin receptor substrate 2; PVT1, plasmacytoma variant translocation 1; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; TUG1, taurine up-regulated gene 1.

signaling pathway, disrupting epithelial-mesenchymal transition (EMT) and impairing wound healing in patients with diabetes. ii) Epigenetic modifications: A high-sugar environment may also indirectly regulate non-coding RNA expression by affecting DNA methylation and histone modifications. For example, in a study on gestational diabetes mellitus (GDM), Li *et al* (84) found that the *NADPH oxidase 5* gene exhibited higher methylation levels in the peripheral blood of GDM pregnant women, indirectly leading to the lncRNA *RPL13P5* forming a co-expression network with the *TSC complex subunit 2* gene through the PI3K/AKT signaling pathway, thereby inhibiting pancreatic islet β-cell growth and reducing insulin secretion under both hypoglycemic and hyperglycemic conditions.

In high-glucose environments, specific non-coding RNAs have been identified as closely associated with insulin signaling and glucose/lipid metabolism. For instance, maternally expressed gene 3 (*Meg3*), an lncRNA located on human chromosome 14q32, is upregulated under hyperglycemic conditions. It induces ferroptosis by activating the p53 pathway (85). Abnormal Meg3 expression may be closely linked to diabetes development. In diabetic mice, the lncRNA H19 exhibits reduced expression levels in hepatocytes. It enhances hepatic gluconeogenesis and glucose output by regulating the MAPK, PI3K/Akt and mTOR signaling pathways (86). Wu *et al* (87) further discovered that in high-glucose-induced mouse hepatocytes, downregulated miR-206 impairs lipogenesis and promotes insulin signaling by regulating the PTPN1-INSR/IRS and PTPN1-PP2A-SP1-Srebp1c pathways. Table III describes the effects of high glucose on the expression of selected ncRNAs (88-94).

3. Differences in the epigenetic regulation of high glucose on different cell types

A high-sugar environment influences gene expression in different cell types through multiple epigenetic mechanisms, specifically manifested in alterations such as DNA methylation, histone modifications and non-coding RNAs. These changes may lead to abnormal cellular functions, thereby affecting organismal health.

Epigenetic regulation of pancreatic islet cells by high glucose. In pancreatic islet cells from patients with T2DM, epigenetic variations cause β-cell dysfunction, manifesting as reduced insulin secretion and insulin resistance (95). Research indicates the existence of functionally distinct β-cell subtypes within islets, which may possess different epigenetic backgrounds and regulatory specificities, playing a crucial role in insulin secretion and blood glucose regulation (96).

In pancreatic islet cells, high glucose regulates epigenetic variation through the following mechanisms: i) Enhancing transcriptional activity: For example, Bevacqua *et al* (97) discovered in an adult pancreatic islet study that exposure to high glucose concentrations activates the histone methyltransferase SET domain containing 7, histone lysine methyltransferase in pancreatic β cells. This enzyme catalyzes the H3K4me1 in the PDX-1 gene promoter region. This epigenetic modification leads to chromatin relaxation, facilitating PDX-1 binding to the promoter and enhancing its transcriptional activity. This binding further induced methylation modifications on the PDX-1 protein itself (such as K91 site methylation), forming a positive feedback loop that impaired glucose-stimulated insulin secretion (GSIS) (97). ii) Regulation of signaling pathways: Hyperglycemia can influence the epigenetic characteristics of pancreatic islet cells through multiple signaling pathways. For example, hyperglycemia regulates mitochondrial autophagy via the PI3K/Akt/mTOR pathway, thereby impairing pancreatic β-cell function. Under fluctuating hyperglycemic conditions, elevated DNMT activity causes hypomethylation in the *miR-99* gene promoter region (CpG island demethylation), releasing transcriptional repression of miR-99. Elevated miR-99 suppresses

the PI3K/Akt/mTOR pathway in pancreatic β-cells, leading to increased mitochondrial autophagy and consequently inhibiting β-cell proliferation and insulin secretion (98).

Epigenetic regulation of hepatocytes by high glucose. A high-glucose environment may regulate hepatocyte function by influencing epigenetic mechanisms. For example, elevated glucose concentrations promote O-GlcNAc glycosylation modification at serine and threonine residues of the transcriptional regulatory protein tet-methylcytosine dioxygenase 1 (TET1), thereby activating TET1 protein function. TET1 catalyzes the conversion of 5-methylcytosine to 5-hydroxymethylcytosine, initiating DNA demethylation processes that promote inflammatory responses and oxidative stress in hepatocytes (99,100). High glucose also affects hepatocyte function by inducing epigenetic variations that alter cellular signaling pathways. Wang *et al* (101) discovered that SIRT1 (NAD-dependent histone deacetylase) is downregulated in HG-treated hepatocytes. This deficiency leads to suppressed mTORC2 activity and Akt dephosphorylation, resulting in upregulation of gluconeogenic genes (*glucose-6-phosphatase, catalytic subunit, phosphoenolpyruvate carboxykinase 1*) and insulin resistance in mice (102).

High concentrations of glucose can activate multiple transcription factors in liver cells, which play crucial roles in glucose and lipid metabolism. For example, Yun *et al* (103) found that elevated glucose levels activate NF-κB in human monocytic (THP-1) cells, a key inflammatory transcription factor. Activation of NF-κB induces the expression of miR-146 and miR-155. miR-146 contributes to insulin resistance by regulating gene expression in the insulin signaling pathway, while miR-155 promotes fatty liver development by modulating suppressor of cytokine signaling 1 (SOCS1) expression (103). Multiple transcription factors also interact with each other under high glucose conditions. The glucose-responsive transcription factor carbohydrate response element binding protein (ChREBP) is a key regulator of hepatic lipogenesis. Together with upstream stimulating factor 1 (USF1), it activates the transcription of lipogenic genes, thereby regulating lipid synthesis in the liver (102). When glucose levels rise, ChREBP is activated by acetylation at the K672 site by p300 (an acetyltransferase). It then synergizes with USF1 to influence the conversion of fatty acids into triglycerides for storage via the PI3K/AKT pathway, thereby enhancing lipid synthesis in hepatocytes (103). This interaction holds significant importance in both glucose and lipid metabolism. Liver X receptor alpha (LXRα) in THP-1 is another key transcription factor that positively regulates GLUT4 expression. Under high-glucose conditions, LXRα expression is upregulated. It interacts with JMJD1C (an H3K9 histone demethylase), leading to H3K9 demethylation and subsequent promotion of GLUT4 expression, thereby enhancing hepatic lipogenesis (103).

High glucose-induced DNA methylation in hepatocytes is another common epigenetic phenomenon. Studies indicate that high glucose affects the methylation status of certain genes in hepatocytes, potentially leading to disorders in glucose and lipid metabolism. For example, Krause *et al* (104) demonstrated that in T2DM, sterol regulatory element-binding protein 1c (SREBP-1c, a key transcription factor that binds to the SRE sterol regulatory element within the promoters of lipogenic genes to enhance their transcription) exhibits hypomethylation at CpG sites, impairing its transcription. This enhances IRS-2 expression and induces excessive lipidsynthesis via the PI3K/Akt pathway, closely associated with hepatic steatosis (104,105).

Epigenetic regulation of muscle and adipose cells by high glucose. Epigenetic alterations induced by high glucose concentrations in human cells markedly affect metabolic functions in muscle and fat cells. These epigenetic changes not only influence gene expression but are also closely associated with the development of T2DM and obesity.

In a high-glucose environment, the metabolic function of muscle cells is markedly impaired. Research indicates that high glucose levels induce insulin resistance, thereby reducing glucose uptake in muscle and adipose tissue while promoting hepatic glucose release. Friedrichsen *et al* discovered that in the muscles of patients with T2DM, genes associated with mitochondrial function, such as *ubiquinone oxidoreductase subunit B6* and *cytochrome c oxidase subunit 7A1* exhibit elevated DNA methylation levels, impairing NADH oxidation. This subsequently blocks the PI3K/Akt pathway, leading to insulin resistance in muscle cells (106). The acetylation or deacetylation status of histones in muscle cells is also affected by high glucose. Research indicates that increased histone acetylation correlates with enhanced muscle cell metabolic activity, whereas high glucose environments activate deacetylases, thereby suppressing muscle cell metabolism and reducing glucose utilization efficiency (107). High glucose also modulates muscle cell signaling pathways, inducing epigenetic alterations. For instance, activation of the mTOR pathway typically drives cell growth by promoting anabolic processes and inhibiting catabolism. Saha *et al* (108) discovered that under high glucose conditions, mTORC1 phosphorylates the T505 site of the JMJD1C protein and inhibits LC3-II activity. LC3-II is a hallmark protein for autophagosome formation; its suppressed activity reduces cellular autophagy levels, leading to abnormal proliferation of muscle cells. Since JMJD1C is established as a histone demethylase, its phosphorylation specifically enhances H3K9me2 demethylation in muscle cells, particularly in promoter regions of muscle differentiation-related genes (such as *MyoD*). This epigenetic modification promotes the upregulation of myogenic transcription factors such as *MyoD*, ultimately accelerating muscle cell differentiation and enhancing glucose metabolism capacity (108).

Adipocytes play a crucial role in energy storage and metabolic regulation. Under high glucose concentrations, the epigenetic regulation of adipocytes also exhibits significant alterations. In a high-glucose environment, adipocytes promote lipogenesis by modifying epigenetic modifications. For instance, Stegemann and Buchner (109) discovered that methylation occurs in the promoter region of the peroxisome proliferator-activated receptor gamma (*PPARγ*) gene under high-sugar conditions, thereby promoting lipogenesis (109-112). High glucose also disrupts insulin signaling pathways in adipocytes, a disruption often associated with epigenetic alterations. For example, miR-150 regulates lipogenesis in bovine preadipocytes via the mTOR signaling pathway (111). A high-glucose environment can also induce inflammatory responses within adipocytes through epigenetic

mechanisms. For instance, Zhao *et al* (91) found that Gm4419 (a long non-coding RNA) regulates mesangial cell inflammatory factor expression via the NF-κB signaling pathway under high-glucose conditions, thereby promoting chronic low-grade inflammation and damaging adipose tissue, a process closely linked to obesity and metabolic syndrome (113,114).

4. Epigenetic regulation of different diseases by high glucose

Hyperglycemia, a clinically prevalent metabolic abnormality, can trigger multiple diseases including diabetes, DKD, diabetic CVD and diabetic retinopathy. Under identical high-sugar conditions, the cellular behavioral changes induced in different diseases vary, exhibiting diverse molecular mechanisms and epigenetic alterations.

Epigenetic regulatory mechanisms in diabetes. The present review focused on the direct epigenetic effects of hyperglycemia, it is crucial to acknowledge the inherent complexity of diabetes as a metabolic disorder. Epigenetic alterations observed in clinical and preclinical studies are likely attributable to the synergistic effects of the diabetic environment, encompassing hyperglycemia, insulin resistance, dyslipidaemia and elevated levels of advanced glycation end products. The epigenetic modifications observed in patients with diabetes or animal models are therefore the result of a concerted action of these multiple factors. Although *in vitro* studies using high-glucose treatment can isolate the effects of hyperglycemia, translating these findings to the *in vivo* context requires caution. Future mechanistic studies should aim to dissect the individual and synergistic contributions of each metabolic abnormality to the overall epigenetic landscape.

Abnormal glucose metabolism is a hallmark feature of diabetes patients. The effects of a high-sugar environment on the epigenetics of diabetes patients include abnormal DNA methylation (see *High glucose and cellular DNA methylation*), disruption of histone modification homeostasis (see *Histone modifications in high-sugar environments*) and disordered non-coding RNA regulatory networks (see *Effects of high-glucose environment on non-coding RNA expression and consequences*). The effect of hyperglycemic symptoms on pancreatic function in patients with diabetes (see *Epigenetic regulation of pancreatic islet cells by high glucose*) primarily involves the regulation of transcription factors and signaling pathways. These aspects will not be elaborated upon further here. It is particularly worth noting that epigenetic alterations are often closely associated with nutritional metabolism (115-117). Jiang *et al* (118) first revealed that hypermethylation of the CpG island in the promoter region of hepatic glycogen synthase kinase β (*GSK-β*) suppresses transcription of this gene. By activating the downstream PI3K-Akt pathway, this leads to reduced hepatic glycogen synthesis capacity and elevated fasting blood glucose levels. This epigenetic regulatory mechanism has been demonstrated to be markedly associated with the development of T2DM. In subsequent studies, the team further discovered in a high-fat diet-induced obese mouse model that liver *GSK-β* promoter methylation levels in the experimental group were 2.3 times higher than in the control group, accompanied by a 68% decrease in GSK-β mRNA expression. This abnormal methylation positively correlated with the insulin resistance index, suggesting that nutritional metabolic stress can exacerbate diabetes progression through epigenetic reprogramming (117,118).

Epigenetic regulation of CVD by high sugar. In modern societies, dietary shifts have led to markedly increased sugar intake. This high-sugar diet not only affects metabolism but also induces CVD through epigenetic alterations (119). Research indicates that hyperglycemia is a major CVD risk factor (120-122). Hyperglycemia not only directly causes vascular damage but also accelerates CVD progression through multiple pathways. For instance, persistent hyperglycemia leads to atherosclerosis, increased inflammatory responses and impaired vascular endothelial function: All key pathological features of CVD (123).

A high-sugar environment can induce a series of gene expression changes through epigenetic regulation, thereby affecting cardiovascular system function. Under hyperglycemic conditions, the expression levels of genes encoding NF-κB subunits (such as *RELA* and *NFKB1*) and the *SOD2* gene increase in cardiomyocytes. This may be associated with the demethylation of specific CpG islands in the promoter regions of these genes. This epigenetic regulation may lead to enhanced NF-κB-mediated inflammatory responses and oxidative stress imbalance, subsequently triggering cardiomyocyte dysfunction and promoting atherosclerosis progression (122,123). Hao *et al* (124) observed increased H3K4me3 levels in the Smad3 gene promoter region during their study of cardiomyocytes from patients with diabetes. Smad3, a key regulator of myocardial fibrosis, undergoes methylation that leads to either overexpression or silencing of SOD2, inducing cardiovascular dysfunction. Hyperglycemia also affects the expression of non-coding RNAs (such as miRNAs), playing crucial roles in CVD pathogenesis (125). Specific miRNAs influence cardiomyocyte proliferation, apoptosis and inflammatory responses by regulating target gene expression. Studies indicate that miR-1 expression is suppressed in cardiomyocytes under high-sugar conditions, while its appropriate expression can prevent diabetic-induced cellular oxidative damage (126). Furthermore, altered expression of miR-21 and miR-208 is implicated in high-sugar-induced cardiac hypertrophy and dysfunction (127). High-sugar-induced epigenetic changes also elevate inflammatory cytokine expression in endothelial cells, thereby promoting atherosclerosis formation. Overexpression of inflammatory factors damages vascular endothelium, further exacerbating CVD risk (128). A high-sugar environment also induces epigenetic alterations in vascular smooth muscle cells (VSMCs), such as abnormal methylation of the *tet methylcytosine dioxygenase 2* gene, which drives phenotypic shifts in VSMCs. This promotes cell proliferation and migration, leading to vascular narrowing and dysfunction (129).

Epigenetic regulation of kidney disease by high sugar. DKD is one of the common complications in patients with diabetes, primarily manifested as declining renal function that may ultimately lead to renal failure (130). Increasing evidence indicates that epigenetic regulation plays a crucial role in the onset and progression of DKD (131). In DKD, abnormal DNA

methylation patterns have been found to be closely associated with functional impairment of renal cells (115,132). For instance, Chen *et al* (133) discovered markedly upregulated methylation of Annexin A2 (*ANXA2*) in patients with DKD, leading to disruption of podocyte cytoskeletal structures, increased renal cell apoptosis and detachment and subsequent impairment of the glomerular filtration barrier, resulting in reduced renal function (133). Studies indicate that in diabetic kidney tissue, DNMTs mediate hypermethylation of COL1A2, which activates TGF-β1, IL-6, TNF-α and IL-1β, exacerbating renal inflammation and fibrosis. This disrupts extracellular matrix (ECM) structure and releases damage-associated molecular patterns, such as fragmented collagen peptides, thereby perpetuating the inflammatory response (134,135). Methylation may also impair transcription factor binding capacity. Certain transcription factors require binding to unmethylated DNA to function and this binding may be inhibited in DKD. As noted by Bechtel *et al* (136), hypermethylation of RASAL1 in patients with DKD promotes Ras gene activation in fibroblasts, preventing its activation of GAP and consequently accelerating renal fibrosis. Certain genes promoting cell proliferation and fibrosis may exhibit hyperacetylation in diabetic kidneys, thereby driving pathological processes (137-139). For instance, Lazar *et al* (140) found that activation of the histone acetyltransferase p300/CBP in diabetic mouse kidneys enhanced ROS production and promoted renal inflammation. Briest *et al* (141) also revealed that under high-glucose conditions, KDM6A, acting as a histone demethylase, reduces H3K27me3 levels and accelerates glomerular inflammation progression.

Certain miRNAs and lncRNAs are up- or downregulated in patients with DKD, affecting the expression of genes associated with kidney injury (142). For example, miR-21 has been demonstrated to be upregulated in DKD. miR-21 suppresses PTEN expression by directly binding to its 3'-UTR region. PTEN serves as a negative regulator of the PI3K/Akt/mTOR signaling pathway; its downregulation leads to enhanced Akt phosphorylation, activating the downstream mTOR pathway. The activated Akt/mTOR pathway further stimulates TGF-β1 secretion, inducing EMT in renal tubular epithelial cells and promoting ECM deposition (such as type I collagen, fibronectin), thereby facilitating tubular cell proliferation and fibrosis (143-145). As noted by Sur *et al* (146), in high-glucose-treated renal cells, hypermethylation of the miRNA-29b promoter region and enhanced DNMT3B activity elevate promoter methylation levels of anti-fibrotic genes (such as *TIMP3*, *MMP9*), silencing their expression. This epigenetic dysregulation exacerbates glomerular fibrosis in patients with DKD. lncRNAs also play a crucial role in DKD progression. For instance, Dieter *et al* (147) discovered that PVT1 expression increases in high-glucose-induced human glomerular mesangial cells, accompanied by significant elevations in levels of major ECM fibronectin and type IV collagen α1, as well as TGF-β1 and plasminogen activator inhibitor-1 (PAI-1), thereby inducing renal inflammatory responses and glomerular mesangial cell apoptosis.

Fig. 1 summarizes the correlations between various epigenetic variations (primarily DNA methylation, histone modification and non-coding RNA expression) and different tissue/organ damage and diseases under high-sugar/diabetic/hyperglycemic conditions (148).

5. Epigenetically regulated therapeutics for high-sugar-induced diseases

The reversibility of epigenetic marks transforms them from mere diagnostic indicators into promising therapeutic targets in modern medicine. Their role is particularly significant in various metabolic diseases such as diabetes, cancer and CVD (149-153). Since epigenetic markers reflect cellular states under specific environmental conditions, they are considered potential disease diagnostic indicators (154,155). Epigenetic markers can be used for early screening of various diseases, providing earlier warning signals than traditional methods. For instance, methylation of MALAT1 is commonly observed in patients with diabetes, enabling its clinical application for early diagnosis (156). Epigenetic markers also facilitate disease progression monitoring and treatment response assessment. By periodically analyzing patients' epigenetic profiles, clinicians can improve the evaluation of disease progression and adjust treatment strategies as needed (157). Epigenetic characteristics further support prognostic evaluation, as certain markers directly correlate with disease outcomes. For example, in patients with diabetes, elevated *GLP-1R* methylation risk correlates with increased complication risk, providing a basis for personalized treatment (158). Regarding epigenetic regulation-based therapies for diabetes and related diseases, Liu *et al* (134) detailed therapeutic approaches for DKD. The present study primarily supplemented how epigenetics can be used to treat diabetes and its associated CVD.

Epigenetic changes are reversible, thus offering new possibilities for diabetes treatment. Researchers are exploring strategies to reverse diabetes and its complications through epigenetic therapies. This includes utilizing small-molecule drugs or gene editing technologies to modulate epigenetic marks, thereby restoring normal gene expression patterns (159,160). Such modulation can be achieved through several key mechanisms, including: i) DNA methylation regulation: Hyperglycemia can cause abnormal methylation in key genes, such as those involved in insulin signaling pathways (such as the *PIK3R1* promoter region), affecting insulin secretion and sensitivity (161). For instance, inhibiting DNMTs can reverse abnormal methylation in certain genes, restore β-cell function and improve insulin resistance. 5-Aza-cytidine (5-AzaC), a chemical inhibitor, suppresses DNMT activity (162). Filip *et al* (163) shows that treating diabetic mouse models with 5-AzaC restores expression of key insulin secretion genes (such as *Ins1 and Ins2*), thereby improving β-cell function and lowering blood glucose levels. ii) Histone modification intervention: Reduced histone acetylation correlates with insulin resistance. Histone deacetylase inhibitors (HDACi), such as sodium valproate, increase histone acetylation, promote *GLUT4* gene expression and improve glucose metabolism (164). iii) Non-coding RNA regulation: miRNAs (such as miR-29, miR-375) exhibit abnormal expression in diabetes, targeting insulin secretion and inflammatory responses. Modulating their levels via antisense oligonucleotides or miRNA mimics improves pancreatic function and reduces β-cell apoptosis. For example, miR-34a is a known miRNA associated with β-cell apoptosis. Research from Wang *et al* (165) indicates that using miR-34a inhibitors (such as antisense oligonucleotides) effectively reduces miR-34a

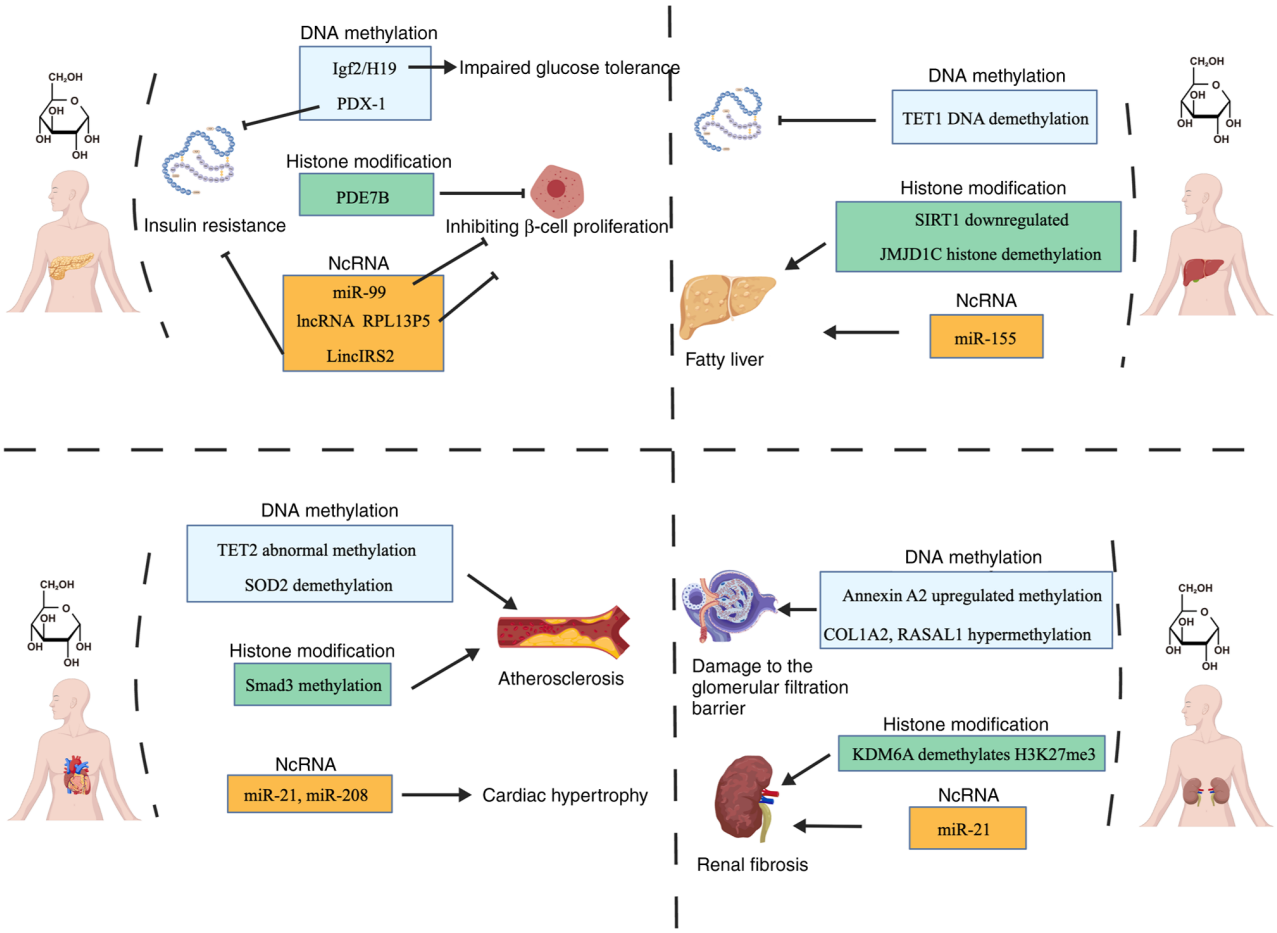

Figure 1. Correlations between distinct epigenetic variations and tissue/organ damage and disease under conditions of high sugar intake, diabetes and hyperglycemia. Igf2, insulin-like growth factor 2; *H19*, imprinted maternally expressed transcript; *PDX1*, pancreatic and duodenal homeobox 1; *PDE7B*, phosphodiesterase 7B; lincIRS2, a long intergenic non-coding RNA that regulates insulin receptor substrate 2; TET, ten-eleven translocation methylcytosine dioxygenase; SIRT1, sirtuin 1; JMJD1C, jumonji domain-containing protein 1C; SOD2, superoxide dismutase 2; Smad3, mothers against decapentaplegic homolog 3; COL1A2, collagen type I alpha 2 chain; RASAL1, ras protein activator like 1; KDM6A, lysine demethylase 6A.

expression. This suppression increases insulin secretion in β-cells and reduces cell apoptosis, thereby improving β-cell survival and function (165).

Epigenetic interventions offer a novel perspective for CVD therapy and their potential is exemplified by the following approaches: i) Regulation of vascular inflammation and metabolic memory: Hyperglycemia-induced 'metabolic memory' leads to persistent vascular inflammation through epigenetic mechanisms (such as sustained DNA methylation or histone modifications). Inhibiting DNMTs or HDACs can reduce inflammatory responses in vascular endothelial cells and delay atherosclerosis progression. ii) Myocardial fibrosis and cardiac remodeling: In diabetic cardiomyopathy, abnormal methylation or histone modifications of pro-fibrotic genes such as TGF-β drive myocardial fibrosis. Epigenetic drugs (such as HDACi) suppress fibrosis-related gene expression, improving cardiac function. Vorinostat, an FDA-approved HDAC inhibitor, has been shown to suppress expression of type I and III collagen genes (such as *COL1A1* and *COL3A1*) and improve cardiovascular function by modulating fibrosis-related signaling pathways (such as the TGF-β pathway) (166). iii) Endothelial function repair: non-coding RNAs (such as lncRNA MALAT1) play regulatory roles in endothelial cell injury. Studies indicate that inhibiting MALAT1 expression enhances survival capacity in human microvascular endothelial cells and reduces apoptosis induced by hyperglycemia or oxidative stress. Research indicates that MALAT1 regulates the expression of miR-199a-5p target genes, phosphatase and vesicle-associated genes (such as *RAP1A and RAP1B*), by competing for binding. Targeting MALAT1 increases miR-199a-5p expression, thereby promoting endothelial functional recovery and reducing inflammation and thrombosis (167). Table IV illustrates the progress of drugs targeting epigenetic regulation for treating diseases induced by hyperglycemia (161,162,164-167).

6. Perspective

The epigenetic regulatory mechanisms triggered by high-sugar environments (including hyperglycemia, or high glucose treatment) are increasingly becoming a research focus to elucidate the pathogenesis of diabetes and its complications (such as cardiovascular disease, nephropathy and neuropathy). In clinic, hyperglycemia not only alters cellular metabolic states but also induces persistent changes in cellular function by affecting multiple epigenetic modifications, including DNA methylation, histone modifications and non-coding RNA expression. Hyperglycemia-induced epigenetic variations trigger functional alterations across multiple organs and

Table IV. Therapeutic progress.

Authors, year	Epigenetic Target	Therapeutic strategy	Research status	Clinical application prospects	(Refs.)
A, DNA methylation					
Chen *et al*, 2020	DNMTs	DNMT inhibitors (such as 5-Aza-cytidine)	Animal models of diabetes:diabetes mice	Potential for reversing metabolic memory	(162)
Asano *et al*, 2007	PIK3R1 promoter	Targeted demethylation	*In vitro* studies; endothelial cells	Restoring insulin signaling	(161)
B, Histone modifications					
Özel *et al*, 2021	HDACs	HDAC inhibitors (such as Vorinostat, Sodium Valproate)	Some have already in Animal models; some have in clinical trials	Improving insulin sensitivity, reducing fibrosis	(166)
Thakur *et al*, 2024	HATs (p300/CBP)	HAT inhibitors	Preclinical studies in diabetic nephropathy	Attenuating renal inflammation and fibrosis	(164)
C, Non-coding RNAs					
Wang *et al*, 2022	miR-34a	Antisense oligonucleotides (inhibitors)	*In vitro* and animal models: in liver tissues of db/db mice	Protecting β-cells from apoptosis	(165)
Samidurai *et al*, 2023	lncRNA MALAT1	siRNA, ASO-mediated knockdown	*In vitro* cell and animal models of vascular dysfunction	Improving endothelial function	(167)
Wang *et al*, 2022	Circulating miRNAs (such as miR-21)	As diagnostic/prognostic biomarkers	Clinical association studies	Non-invasive monitoring of DKD progression (requires standardization)	(165)

DNMT, DNA methyltransferase; PIK3R1, phosphoinositide-3-kinase regulatory subunit 1; HDAC, histone deacetylase; HAT, histone acetyltransferase.

precipitate diverse diseases. The present review highlighted only well-researched cellular, organ and disease models; numerous other disease models, such as diabetic retinopathy and diabetic foot, due to the scarcity of research materials, remain incompletely elucidated.

Despite the abundance of existing research on epigenetic alterations in high-sugar environments and diabetes (including its complications), numerous uncharted territories warrant further exploration. It is therefore recommend to strengthen research in the following three areas: i) Mechanistic studies: Deepening our understanding of the specific roles played by different epigenetic mechanisms in diabetes pathogenesis. For instance, analyzing the epigenetic characteristics of vascular cells in patients with diabetes via high-throughput sequencing techniques. ii) Intervention strategy research: Investigating how various environmental factors (such as diet and exercise) influence epigenetic alterations. iii) Epigenetics and metabolic disease association studies: Further exploring the links between epigenetic modifications and other metabolic disorders to uncover broader biological mechanisms.

Regarding the application of epigenetics tools for disease diagnosis and treatment, the following areas warrant greater emphasis: i) Therapeutic strategies targeting epigenetic modifications: Developing drugs and tools (such as CRISPR/Cas9-based modification tools) that target specific epigenetic markers to restore normal cellular function; ii) Application of personalized medicine: Analyzing patients' epigenetic profiles to formulate tailored treatment plans, which holds promise for enhancing therapeutic outcomes; Changes in epigenetic markers under hyperglycemic conditions carry significant implications for disease diagnosis and monitoring. As research progresses, these markers may emerge as a new generation of diagnostic indicators, providing clinicians with more sensitive and specific detection methods, ultimately improving patient treatment outcomes and quality of life.

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DY and WW contributed to the conception and design of the article. HZ drafted the manuscript. XL and YL revised the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

References

1. Harreiter J and Roden M: Diabetes mellitus-Definition, classification, diagnosis, screening and prevention (Update 2019). Wien Klin Wochenschr 131 (Suppl 1): S6-S15, 2019 (In German).
2. Menke A, Casagrande S, Geiss L and Cowie CC: Prevalence of and trends in diabetes among adults in the United States, 1988-2012. JAMA 314: 1021-1029, 2015.
3. Forouhi NG and Wareham NJ: Epidemiology of diabetes. Medicine (Abingdon) 42: 698-702, 2014.
4. Association AD: Diagnosis and classification of diabetes mellitus. Diabetes Care 36 (Suppl 1): S67-S74, 2013.
5. Schmidt AM: Diabetes Mellitus and Cardiovascular Disease. Arteriosclerosis, Thrombosis, and Vascular Biology, 2019.
6. Berezin A: Metabolic memory phenomenon in diabetes mellitus: Achieving and perspectives. Diabetes Metab Syndr 10 (Suppl 1): S176-S183, 2016.
7. Vasishta S, Umakanth S, Adiga P and Joshi MB: Extrinsic and intrinsic factors influencing metabolic memory in type 2 diabetes. Vascul Pharmacol 142: 106933, 2022.
8. Kato M and Natarajan R: Epigenetics and epigenomics in diabetic kidney disease and metabolic memory. Nat Rev Nephrol 15: 327-345, 2019.
9. Intine RV and Sarras MP Jr: Metabolic memory and chronic diabetes complications: Potential role for epigenetic mechanisms. Curr Diab Rep 12: 551-559, 2012.
10. Cavalli G and Heard E: Advances in epigenetics link genetics to the environment and disease. Nature 571: 489-499, 2019.
11. Peixoto P, Cartron PF, Serandour AA and Hervouet E: From 1957 to nowadays: A brief history of epigenetics. Int J Mol Sci 21: 7571, 2020.
12. Sapienza C and Issa JP: Diet, nutrition, and cancer epigenetics. Annu Rev Nutr 36: 665-681, 2016.
13. Gayon J: From Mendel to epigenetics: History of genetics. C R Biol 339: 225-230, 2016.
14. Grunau C, Le Luyer J, Laporte M and Joly D: The epigenetics dilemma. Genes (Basel) 11: 23, 2019.
15. Zhang L, Lu Q and Chang C: Epigenetics in health and disease. Adv Exp Med Biol 1253: 3-55, 2020.
16. Kaliman P: Epigenetics and meditation. Curr Opin Psychol 28: 76-80, 2019.
17. Villanueva L, Álvarez-Errico D and Esteller M: The contribution of epigenetics to cancer immunotherapy. Trends Immunol 41: 676-691, 2020.
18. Recillas-Targa F: Cancer epigenetics: An overview. Arch Med Res 53: 732-740, 2022.
19. Dawson MA and Kouzarides T: Cancer epigenetics: From mechanism to therapy. Cell 150: 12-27, 2012.
20. Huang W, Li H, Yu Q, Xiao W and Wang DO: LncRNA-mediated DNA methylation: An emerging mechanism in cancer and beyond. J Exp Clin Cancer Res 41: 100, 2022.
21. Bird A, Taggart M, Frommer M, Miller OJ and Macleod D: A fraction of the mouse genome that is derived from islands of nonmethylated, CpG-rich DNA. Cell 40: 91-99, 1985.
22. Meng H, Cao Y, Qin J, Song X, Zhang Q, Shi Y and Cao L: DNA methylation, its mediators and genome integrity. Int J Biolo Sci 11: 604-617, 2015.
23. Takai D and Jones PA: Comprehensive analysis of CpG islands in human chromosomes 21 and 22. Proc Natl Acad Sci USA 99: 3740-3745, 2002.
24. Zhao SG, Chen WS, Li H, Foye A, Zhang M, Sjöström M, Aggarwal R, Playdle D, Liao A, Alumkal JJ, *et al*: DNA methylation landscapes in advanced prostate cancer. Nat Genet 52: 778-789, 2020.
25. Sina AAI, Carrascosa LG, Liang Z, Grewal YS, Wardiana A, Shiddiky MJA, Gardiner RA, Samaratunga H, Gandhi MK, Scott RJ, *et al*: Epigenetically reprogrammed methylation landscape drives the DNA self-assembly and serves as a universal cancer biomarker. Nat Commun 9: 4915, 2018.
26. Riggs AD: X chromosome inactivation, differentiation, and DNA methylation revisited, with a tribute to Susumu Ohno. Cytogenet Genome Res 99: 17-24, 2002.
27. Chen ACH, Huang W, Fong SW, Chan C, Lee KC, Yeung WSB and Lee YL: Hyperglycemia altered DNA methylation status and impaired pancreatic differentiation from embryonic stem cells. Int J Mol Sci 22: 10729, 2021.
28. Ginno PA, Gaidatzis D, Feldmann A, Hoerner L, Imanci D, Burger L, Zilbermann F, Peters AHFM, Edenhofer F, Smallwood SA, *et al*: A genome-scale map of DNA methylation turnover identifies site-specific dependencies of DNMT and TET activity. Nat Commun 11: 2680, 2020.
29. Charlton J, Jung EJ, Mattei AL, Bailly N, Liao J, Martin EJ, Giesselmann P, Brändl B, Stamenova EK, Müller FJ, *et al*: TETs compete with DNMT3 activity in pluripotent cells at thousands of methylated somatic enhancers. Nat Genet 52: 819-827, 2020.
30. Law PP and Holland ML: DNA methylation at the crossroads of gene and environment interactions. Essays Biochem 63: 717-726, 2019.
31. Łoboś P and Regulska-Ilow B: Link between methyl nutrients and the DNA methylation process in the course of selected diseases in adults. Rocz Panstw Zakl Hig 72: 123-136, 2021.
32. Qu Y, Dang S and Hou P: Gene methylation in gastric cancer. Clin Chim Acta 424: 53-65, 2013.
33. Vigorelli V, Resta J, Bianchessi V, Lauri A, Bassetti B, Agrifoglio M, Pesce M, Polvani G, Bonalumi G, Cavallotti L, *et al*: Abnormal DNA methylation induced by hyperglycemia reduces CXCR 4 gene expression in CD 34+ stem cells. J Am Heart Assoc 8: e010012, 2019.
34. de Mello VDF, Pulkkinen L, Lalli M, Kolehmainen M, Pihlajamäki J and Uusitupa M: DNA methylation in obesity and type 2 diabetes. Ann Med 46: 103-113, 2014.
35. Gill AM, Leiter EH, Powell JG, Chapman HD and Yen TT: Dexamethasone-induced hyperglycemia in obese Avy/a (viable yellow) female mice entails preferential induction of a hepatic estrogen sulfotransferase. Diabetes 43: 999-1004, 1994.
36. Jain M, LoGerfo FW, Guthrie P and Pradhan L: Effect of hyperglycemia and neuropeptides on interleukin-8 expression and angiogenesis in dermal microvascular endothelial cells. J Vasc Surg 53: 1654-1660.e2, 2011.
37. Hamad M, Mohammed AK, Hachim MY, Mukhopadhy D, Khalique A, Laham A, Dhaiban S, Bajbouj K and Taneera J: Heme Oxygenase-1 (HMOX-1) and inhibitor of differentiation proteins (ID1, ID3) are key response mechanisms against iron-overload in pancreatic β-cells. Mol Cell Endocrinol 538: 111462, 2021.
38. Chen YL, Rosa RH, Kuo L and Hein TW: Hyperglycemia augments Endothelin-1-Induced constriction of human retinal venules. Transl Vis Sci Technol 9: 1, 2020.
39. Jurado-Aguilar J, Barroso E, Bernard M, Zhang M, Peyman M, Rada P, Valverde ÁM, Wahli W, Palomer X and Vázquez-Carrera M: GDF15 activates AMPK and inhibits gluconeogenesis and fibrosis in the liver by attenuating the TGF-β1/SMAD3 pathway. Metabolism 152: 155772, 2024.

40. Tewari S, Zhong Q, Santos JM and Kowluru RA: Mitochondria DNA replication and DNA methylation in the metabolic memory associated with continued progression of diabetic retinopathy. Invest Ophthalmol Vis Sci 53: 4881-4888, 2012.
41. Park JH, Stoffers DA, Nicholls RD and Simmons RA: Development of type 2 diabetes following intrauterine growth retardation in rats is associated with progressive epigenetic silencing of Pdx1. J Clin Invest 118: 2316-2324, 2008.
42. Ding GL, Wang FF, Shu J, Tian S, Jiang Y, Zhang D, Wang N, Luo Q, Zhang Y, Jin F, *et al*: Transgenerational glucose intolerance with Igf2/H19 epigenetic alterations in mouse islet induced by intrauterine hyperglycemia. Diabetes 61: 1133-1142, 2012.
43. Zhang T, Ouyang H, Mei X, Lu B, Yu Z, Chen K, Wang Z and Ji L: Erianin alleviates diabetic retinopathy by reducing retinal inflammation initiated by microglial cells via inhibiting hyperglycemia-mediated ERK1/2-NF-κB signaling pathway. FASEB J 33: 11776-11790, 2019.
44. Gunes A, Schmitt C, Bilodeau L, Huet C, Belblidia A, Baldwin C, Giard JM, Biertho L, Lafortune A, Couture CY, *et al*: IL-6 Trans-signaling is increased in diabetes, impacted by glucolipotoxicity, and associated with liver stiffness and fibrosis in fatty liver disease. Diabetes 72: 1820-1834, 2023.
45. Millán-Zambrano G, Burton A, Bannister AJ and Schneider R: Histone post-translational modifications-cause and consequence of genome function. Nat Rev Genet 23: 563-580, 2022.
46. Zhou LQ and Dean J: Reprogramming the genome to totipotency in mouse embryos. Trends Cell Biol 25: 82-91, 2015.
47. Lawrence M, Daujat S and Schneider R: Lateral thinking: How histone modifications regulate gene expression. Trends Genet 32: 42-56, 2016.
48. Zhang Y, Sun Z, Jia J, Du T, Zhang N, Tang Y, Fang Y and Fang D: Overview of histone modification. Adv Exp Med Biol 1283: 1-16, 2021.
49. Shen Y, Wei W and Zhou DX: Histone acetylation enzymes coordinate metabolism and gene expression. Trends Plant Sci 20: 614-621, 2015.
50. Gong F and Miller KM: Histone methylation and the DNA damage response. Mutat Res Rev Mutat Res 780: 37-47, 2019.
51. He W, Li Q and Li X: Acetyl-CoA regulates lipid metabolism and histone acetylation modification in cancer. Biochim Biophys Acta Rev Cancer 1878: 188837, 2023.
52. Biernacka KM, Uzoh CC, Zeng L, Persad RA, Bahl A, Gillatt D, Perks CM and Holly JM: Hyperglycaemia-induced chemoresistance of prostate cancer cells due to IGFBP2. Endocr Relat Cancer 20: 741-751, 2013.
53. Hong H, Li YM, Meng XM, Deng T and Zhu BM: Histone methylation and diabetic cardiomyopathy. Sheng Li Xue Bao 74: 461-468, 2022 (In Chinese).
54. Brasacchio D, Okabe J, Tikellis C, Balcerczyk A, George P, Baker EK, Calkin AC, Brownlee M, Cooper ME and El-Osta A: Hyperglycemia induces a dynamic cooperativity of histone methylase and demethylase enzymes associated with gene-activating epigenetic marks that coexist on the lysine tail. Diabetes 58: 1229-1236, 2009.
55. Yuan Y, Zhu C, Wang Y, Sun J, Feng J, Ma Z, Li P, Peng W, Yin C, Xu G, *et al*: α-Ketoglutaric acid ameliorates hyperglycemia in diabetes by inhibiting hepatic gluconeogenesis via serpinale signaling. Sci Adv 8: eabn2879, 2022.
56. Ishikawa K, Tsunekawa S, Ikeniwa M, Izumoto T, Iida A, Ogata H, Uenishi E, Seino Y, Ozaki N, Sugimura Y, *et al*: Long-term pancreatic beta cell exposure to high levels of glucose but not palmitate induces DNA methylation within the insulin gene promoter and represses transcriptional activity. PLoS One 10: e0115350, 2015.
57. Sun Y, Ma X and Su Y: Research progress on methylation of histones H3K9 and H3K27 in early-stage embryos. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 37: 1296-1300, 2020 (In Chinese).
58. Zhang D, Tang Z, Huang H, Zhou G, Cui C, Weng Y, Liu W, Kim S, Lee S, Perez-Neut M, *et al*: Metabolic regulation of gene expression by histone lactylation. Nature 574: 575-580, 2019.
59. Zheng B, Pan Y, Qian F, Liu D, Ye D, Yu B, Zhong S, Zheng W, Wang X, Zhou B, *et al*: High sugar induced RCC2 lactylation drives breast cancer tumorigenicity through upregulating MAD2L1. Adv Sci (Weinh) 12: e2415530, 2025.
60. Ren H, Tang Y and Zhang D: The emerging role of protein L-lactylation in metabolic regulation and cell signaling. Nat Metab 7: 647-664, 2025.
61. Raychaudhuri D, Singh P, Chakraborty B, Hennessey M, Tannir AJ, Byregowda S, Natarajan SM, Trujillo-Ocampo A, Im JS and Goswami S: Histone lactylation drives CD8+ T cell metabolism and function. Nat Immunol 25: 2140-2151, 2024.
62. Hong J, Xu H, Yu L, Yu Z, Chen X, Meng Z, Zhu J, Li J and Zhu M: AARS1-mediated lactylation of H3K18 and STAT1 promotes ferroptosis in diabetic nephropathy. Cell Death Differ: Sep 23.2025 doi: 10.1038/s41418-025-01587-4 (Epub ahead of print).
63. Gao L, Yu W, Song P and Li Q: Non-histone Methylation of SET7/9 and its Biological Functions. Recent Pat Anticancer Drug Discov 17: 231-243, 2022.
64. Pradhan S, Chin HG, Estève PO and Jacobsen SE: SET7/9 mediated methylation of non-histone proteins in mammalian cells. Epigenetics 4: 383-387, 2009.
65. Sánchez-Ceinos J, Hussain S, Khan AW, Zhang L, Almahmeed W, Pernow J and Cosentino F: Repressive H3K27me3 drives hyperglycemia-induced oxidative and inflammatory transcriptional programs in human endothelium. Cardiovasc Diabetol 23: 122, 2024.
66. Miao F, Gonzalo IG, Lanting L and Natarajan R: In vivo chromatin remodeling events leading to inflammatory gene transcription under diabetic conditions. J Biol Chem 279: 18091-18097, 2004.
67. Sun C, Wang M, Liu X, Luo L, Li K, Zhang S, Wang Y, Yang Y, Ding F and Gu X: PCAF improves glucose homeostasis by suppressing the gluconeogenic activity of PGC-1α. Cell Rep 9: 2250-2262, 2014.
68. Yamazaki T, Mimura I, Tanaka T and Nangaku M: Treatment of diabetic kidney disease: Current and future. Diabetes Metab J 45: 11-26, 2021.
69. Singh R, Chandel S, Dey D, Ghosh A, Roy S, Ravichandiran V and Ghosh D: Epigenetic modification and therapeutic targets of diabetes mellitus. Biosci Rep 40: BSR20202160, 2020.
70. Dalfrà MG, Burlina S, Del Vescovo GG and Lapolla A: Genetics and epigenetics: New insight on gestational diabetes mellitus. Front Endocrinol (Lausanne) 11: 602477, 2020.
71. Allard C, Desgagné V, Patenaude J, Lacroix M, Guillemette L, Battista MC, Doyon M, Ménard J, Ardilouze JL, Perron P, *et al*: Mendelian randomization supports causality between maternal hyperglycemia and epigenetic regulation of leptin gene in newborns. Epigenetics 10: 342-351, 2015.
72. Ling C and Rönn T: Epigenetics in human obesity and type 2 diabetes. Cell Metab 29: 1028-1044, 2019.
73. Chen B, Du YR, Zhu H, Sun ML, Wang C, Cheng Y, Pang H, Ding G, Gao J, Tan Y, *et al*: Maternal inheritance of glucose intolerance via oocyte TET3 insufficiency. Nature 605: 761-766, 2022.
74. Malmgren S, Spégel P, Danielsson AP, Nagorny CL, Andersson LE, Nitert MD, Ridderstråle M, Mulder H and Ling C: Coordinate changes in histone modifications, mRNA levels, and metabolite profiles in clonal INS-1 832/13 β-cells accompany functional adaptations to lipotoxicity. J Biol Chem 288: 11973-11987, 2013.
75. Liao W, Xu N, Zhang H, Liao W, Wang Y, Wang S, Zhang S, Jiang Y, Xie W and Zhang Y: Persistent high glucose induced EPB41L4A-AS1 inhibits glucose uptake via GCN5 mediating crotonylation and acetylation of histones and non-histones. Clin Transl Med 12: e699, 2022.
76. Lee HA, Kang SH, Kim M, Lee E, Cho HM, Moon EK and Kim I: Histone deacetylase inhibition ameliorates hypertension and hyperglycemia in a model of Cushing's syndrome. Am J Physiol Endocrinol Metab 314: E39-E52, 2018.
77. Horitani K, Iwasaki M, Kishimoto H, Wada K, Nakano M, Park H, Adachi Y, Motooka D, Okuzaki D and Shiojima I: Repetitive spikes of glucose and lipid induce senescence-like phenotypes of bone marrow stem cells through H3K27me3 demethylase-mediated epigenetic regulation. Am J Physiol Heart Circ Physiol 321: H920-H932, 2021.
78. Qiu AW, Cao X, Zhang WW and Liu QH: IL-17A is involved in diabetic inflammatory pathogenesis by its receptor IL-17RA. Exp Biol Med (Maywood) 246: 57-65, 2021.
79. Zogg H, Singh R and Ro S: Current Advances in RNA Therapeutics for Human Diseases. Int J Mol Sci 23: 2736, 2022.
80. Hombach S and Kretz M: Non-coding RNAs: Classification, biology and functioning. Adv Exp Med Biol 937: 3-17, 2016.
81. Mattick JS and Makunin IV: Non-coding RNA. Hum Mol Genet 15: R17-R29, 2006.
82. Dong Y, Wan G, Peng G, Yan P, Qian C and Li F: Long non-coding RNA XIST regulates hyperglycemia-associated apoptosis and migration in human retinal pigment epithelial cells. Biomed Pharmacother 125: 109959, 2020.
83. Zhang L, Hung GCC, Meng S, Evans R and Xu J: LncRNA MALAT1 Regulates Hyperglycemia Induced EMT in Keratinocyte via miR-205. Noncoding RNA 9: 14, 2023.

84. Li J, Du B, Geng X and Zhou L: lncRNA SNHG17 is downregulated in gestational diabetes mellitus (GDM) and has predictive values. Diabetes Metab Syndr Obes 14: 831-838, 2021.
85. Chen C, Huang Y, Xia P, Zhang F, Li L, Wang E, Guo Q and Ye Z: Long noncoding RNA Meg3 mediates ferroptosis induced by oxygen and glucose deprivation combined with hyperglycemia in rat brain microvascular endothelial cells, through modulating the p53/GPX4 axis. Eur J Histochem 65: 3224, 2021.
86. Goyal N, Tiwary S, Kesharwani D and Datta M: Long non-coding RNA H19 inhibition promotes hyperglycemia in mice by upregulating hepatic FoxO1 levels and promoting gluconeogenesis. J Mol Med (Berl) 97: 115-126, 2019.
87. Wu H, Zhang T, Pan F, Steer CJ, Li Z, Chen X and Song G: MicroRNA-206 prevents hepatosteatosis and hyperglycemia by facilitating insulin signaling and impairing lipogenesis. J Hepatology 66: 816-824, 2017.
88. Pradas-Juni M, Hansmeier NR, Link JC, Schmidt E, Larsen BD, Klemm P, Meola N, Topel H, Loureiro R, Dhaouadi I, *et al*: A MAFG-lncRNA axis links systemic nutrient abundance to hepatic glucose metabolism. Nat Commun 11: 644, 2020.
89. Cui X, Tan J, Shi Y, Sun C, Li Y, Ji C, Wu J, Zhang Z, Chen S, Guo X and Liu C: The long non-coding RNA Gm10768 activates hepatic gluconeogenesis by sequestering microRNA-214 in mice. J Biol Chem 293: 4097-4109, 2018.
90. Li M, Niu M, Fan X, Chen F, Cao H, Liu Q, Gan S, Yue P and Gao J: LncRNA MIR181A2HG inhibits keratinocytes proliferation through miR-223-3p/SOX6 axis. Aging (Albany NY) 16: 9846-9858, 2024.
91. Zhao G, Hailati J, Ma X, Bao Z, Bakeyi M and Liu Z: LncRNA Gm4419 regulates myocardial Ischemia/Reperfusion injury through targeting the miR-682/TRAF3 axis. J Cardiovasc Pharmacol 76: 305-312, 2020.
92. Liu B, Gu Y, Luo JH, Fan YS and Feng ZY: Effects of inhibiting the expression of lncRNA PVT1 on the proliferation, apoptosis and oxidative stress of vascular endothelial cells induced by hyperglycemia. Zhongguo Ying Yong Sheng Li Xue Za Zhi 37: 561-565, 2021 (In Chinese).
93. He L, Zhu C, Jia J, Hao XY, Yu XY, Liu XY and Shu MG: ADSC-Exos containing MALAT1 promotes wound healing by targeting miR-124 through activating Wnt/β-catenin pathway. Biosci Rep 40: BSR20192549, 2020.
94. Heydari N, Sharifi R, Nourbakhsh M, Golpour P and Nourbakhsh M: Long non-coding RNAs TUG1 and MEG3 in patients with type 2 diabetes and their association with endoplasmic reticulum stress markers. J Endocrinol Invest 46: 1441-1448, 2023.
95. Golson ML and Kaestner KH: Epigenetics in formation, function, and failure of the endocrine pancreas. Mol Metab 6: 1066-1076, 2017.
96. Dror E, Fagnocchi L, Wegert V, Apostle S, Grimaldi B, Gruber T, Panzeri I, Heyne S, Höffler KD, Kreiner V, *et al*: Epigenetic dosage identifies two major and functionally distinct β cell subtypes. Cell Metabolism 35: 821-836.7, 2023.
97. Bevacqua RJ, Zhao W, Merheb E, Kim SH, Marson A, Gloyn AL and Kim SK: Multiplexed CRISPR gene editing in primary human islet cells with Cas9 ribonucleoprotein. bioRxiv: Sep 17, 2023 doi: 10.1101/2023.09.16.558090.
98. Brown MR and Matveyenko AV: It's what and when you eat: An overview of transcriptional and epigenetic responses to dietary perturbations in pancreatic islets. Front Endocrinol (Lausanne) 13: 842603, 2022.
99. Klimontov VV, Saik OV and Korbut AI: Glucose variability: How does it work? Int J Mol Sci 22: 7783, 2021.
100. Ayodeji SA, Bao B, Teslow EA, Polin LA, Dyson G, Bollig-Fischer A and Fehl C: Hyperglycemia and O-GlcNAc transferase activity drive a cancer stem cell pathway in triple-negative breast cancer. Cancer Cell Int 23: 102, 2023.
101. Wang RH, Kim HS, Xiao C, Xu X, Gavrilova O and Deng CX: Hepatic Sirt1 deficiency in mice impairs mTorc2/Akt signaling and results in hyperglycemia, oxidative damage, and insulin resistance. J Clin Invest 121: 4477-4490, 2011.
102. Xue W, Huang J, Chen H, Zhang Y, Zhu X, Li J, Zhang W, Yuan Y, Wang Y, Zheng L and Huang K: Histone methyltransferase G9a modulates hepatic insulin signaling via regulating HMGA1. Biochim Biophys Acta Mol Basis Dis 1864: 338-346, 2018.
103. Yun JM, Jialal I and Devaraj S: Epigenetic regulation of high glucose-induced proinflammatory cytokine production in monocytes by curcumin. J Nutr Biochem 22: 450-458, 2011.
104. Krause C, Geißler C, Tackenberg H, El Gammal AT, Wolter S, Spranger J, Mann O, Lehnert H and Kirchner H: Multi-layered epigenetic regulation of IRS2 expression in the liver of obese individuals with type 2 diabetes. Diabetologia 63: 2182-2193, 2020.
105. Benichou E, Seffou B, Topçu S, Renoult O, Lenoir V, Planchais J, Bonner C, Postic C, Prip-Buus C, Pecqueur C, *et al*: The transcription factor ChREBP Orchestrates liver carcinogenesis by coordinating the PI3K/AKT signaling and cancer metabolism. Nat Commun 15: 1879, 2024.
106. Friedrichsen M, Ribel-Madsen R, Mortensen B, Hansen CN, Alibegovic AC, Højbjerre L, Sonne MP, Wojtaszewski JF, Stallknecht B, Dela F and Vaag A: Muscle inflammatory signaling in response to 9 days of physical inactivity in young men with low compared with normal birth weight. Eur J Endocrinol 167: 829-838, 2012.
107. Yucel N, Wang YX, Mai T, Porpiglia E, Lund PJ, Markov G, Garcia BA, Bendall SC, Angelo M and Blau HM: Glucose metabolism drives histone acetylation landscape transitions that dictate muscle stem cell function. Cell Rep 27: 3939-3955.e6, 2019.
108. Saha S, Fang X, Green CD and Das A: mTORC1 and SGLT2 Inhibitors-A therapeutic perspective for diabetic cardiomyopathy. Int J Mol Sci 24: 15078, 2023.
109. Stegemann R and Buchner DA: Transgenerational inheritance of metabolic disease. Semin Cell Dev Biol 43: 131-140, 2015.
110. Lee HH, An SM, Ye BJ, Lee JH, Yoo EJ, Jeong GW, Kang HJ, Alfadda AA, Lim SW, Park J *et al*: TonEBP/NFAT5 promotes obesity and insulin resistance by epigenetic suppression of white adipose tissue beiging. Nat Commun 10: 3536, 2019.
111. Hansen NS, Strasko KS, Hjort L, Kelstrup L, Houshmand-Øregaard A, Schrölkamp M, Schultz HS, Scheele C, Pedersen BK, Ling C, *et al*: Fetal hyperglycemia changes human preadipocyte function in adult life. J Clin Endocrinol Metab 102: 1141-1150, 2017.
112. Houde AA, Hivert MF and Bouchard L: Fetal epigenetic programming of adipokines. Adipocyte 2: 41-46, 2013.
113. Ishida T, Morisawa S, Iizuka M, Fujita H, Jobu K, Morita Y and Miyamura M: Juzentaihoto extract suppresses adipocyte hypertrophy and improves hyperglycemia in KKAy mice. Pharmazie 75: 191-194, 2020.
114. Villarroya F, Cereijo R, Gavaldà-Navarro A, Villarroya J and Giralt M: Inflammation of brown/beige adipose tissues in obesity and metabolic disease. J Intern Med 284: 492-504, 2018.
115. Yoshimoto N, Hayashi K, Hishikawa A, Hashiguchi A, Nakamichi R, Sugita-Nishimura E, Yoshida-Hama E, Azegami T, Nakayama T and Itoh H: Significance of podocyte DNA damage and glomerular DNA methylation in CKD patients with proteinuria. Hypertens Res 46: 1000-1008, 2023.
116. Su M, Yu T, Yu Y, Cheng Q, Zheng Y, Liao R and Zeng Z: hsa-miR-607, lncRNA TUG1 and hsa_circ_0071106 can be combined as biomarkers in type 2 diabetes mellitus. Exp Biol Med (Maywood) 247: 1609-1618, 2022.
117. Trang K and Grant SFA: Genetics and epigenetics in the obesity phenotyping scenario. Rev Endocr Metab Disord 24: 775-793, 2023.
118. Jiang Z, Zhao M, Voilquin L, Jung Y, Aikio MA, Sahai T, Dou FY, Roche AM, Carcamo-Orive I, Knowles JW, *et al*: Isthmin-1 is an adipokine that promotes glucose uptake and improves glucose tolerance and hepatic steatosis. Cell Metab 33: 1836-1852.e11, 2021.
119. Kannel WB and McGee DL: Diabetes and cardiovascular disease. The framingham study. JAMA 241: 2035-2038, 1979.
120. Lowe LP, Liu K, Greenland P, Metzger BE, Dyer AR and Stamler J: Diabetes, asymptomatic hyperglycemia, and 22-year mortality in black and white men. The Chicago heart association detection project in industry study. Diabetes Care 20: 163-669, 1997.
121. Gu K, Cowie CC and Harris MI: Mortality in adults with and without diabetes in a national cohort of the U.S. population, 1971-1993. Diabetes Care 21: 1138-1145, 1998.
122. Morgan CL, Currie CJ and Peters JR: Relationship between diabetes and mortality: A population study using record linkage. Diabetes Care 23: 1103-1107, 2000.
123. Wei M, Gaskill SP, Haffner SM and Stern MP: Effects of diabetes and level of glycemia on all-cause and cardiovascular mortality. The San Antonio heart study. Diabetes Care 21: 1167-1172, 1998.
124. Hao J and Liu Y: Epigenetics of methylation modifications in diabetic cardiomyopathy. Front Endocrinol (Lausanne) 14: 1119765, 2023.

125. Prandi FR, Lecis D, Illuminato F, Milite M, Celotto R, Lerakis S, Romeo F and Barillà F: Epigenetic modifications and Non-coding RNA in Diabetes-mellitus-induced coronary artery disease: Pathophysiological link and new therapeutic frontiers. Int J Mol Sci 23: 4589, 2022.
126. Zhou Y, Suo W, Zhang X, Yang Y, Zhao W, Li H and Ni Q: Targeting epigenetics in diabetic cardiomyopathy: Therapeutic potential of flavonoids. Biomed Pharmacother 157: 114025, 2023.
127. Temple NJ: Fat, sugar, whole grains and heart disease: 50 years of confusion. Nutrients 10: 39, 2018.
128. Silveira Rossi JL, Barbalho SM, Reverete de Araujo R, Bechara MD, Sloan KP and Sloan LA: Metabolic syndrome and cardiovascular diseases: Going beyond traditional risk factors. Diabetes Metab Res Rev 38: e3502, 2022.
129. Henry RM, Kostense PJ, Dekker JM, Nijpels G, Heine RJ, Kamp O, Bouter LM and Stehouwer CD: Carotid arterial remodeling: A maladaptive phenomenon in type 2 diabetes but not in impaired glucose metabolism: The Hoorn study. Stroke 35: 671-676, 2004.
130. Samsu N: Diabetic nephropathy: Challenges in pathogenesis, diagnosis, and treatment. Biomed Res Int 2021: 1497449, 2021.
131. Papadopoulou-Marketou N, Paschou SA, Marketos N, Adamidi S, Adamidis S and Kanaka-Gantenbein C: Diabetic nephropathy in type 1 diabetes. Minerva Med 109: 218-228, 2018.
132. Wong YH, Wong SH, Wong XT, Yap QY, Yip KY, Wong LZ, Chellappan DK, Bhattamisra SK and Candasamy M: Genetic associated complications of type 2 diabetes mellitus. Panminerva Med 64: 274-288, 2022.
133. Chen J, Liu Y, Xia S, Ye X and Chen L: Annexin A2 (ANXA2) regulates the transcription and alternative splicing of inflammatory genes in renal tubular epithelial cells. BMC Genomics 23: 544, 2022.
134. Liu Z, Liu J, Wang W, An X, Luo L, Yu D and Sun W: Epigenetic modification in diabetic kidney disease. Front Endocrinol (Lausanne) 14: 1133970, 2023.
135. Kushwaha K, Garg SS and Gupta J: Targeting epigenetic regulators for treating diabetic nephropathy. Biochimie 202: 146-158, 2022.
136. Bechtel W, McGoohan S, Zeisberg EM, Müller GA, Kalbacher H, Salant DJ, Müller CA, Kalluri R and Zeisberg M: Methylation determines fibroblast activation and fibrogenesis in the kidney. Nat Med 16: 544-550, 2010.
137. Bates J, Vijayakumar A, Ghoshal S, Marchand B, Yi S, Kornyeyev D, Zagorska A, Hollenback D, Walker K, Liu K, *et al*: Acetyl-CoA carboxylase inhibition disrupts metabolic reprogramming during hepatic stellate cell activation. J Hepatol 73: 896-905, 2020.
138. Lu J, Li XQ, Chen PP, Zhang JX, Liu L, Wang GH, Liu XQ, Jiang TT, Wang MY, Liu WT, *et al*: Activation of acetyl-CoA synthetase 2 mediates kidney injury in diabetic nephropathy. JCI Insight 8: e165817, 2023.
139. Li X, Li C and Sun G: Histone acetylation and its modifiers in the pathogenesis of diabetic nephropathy. J Diabetes Res 2016: 4065382, 2016.
140. Lazar AG, Vlad ML, Manea A, Simionescu M and Manea SA: Activated histone acetyltransferase p300/CBP-Related signalling pathways Mediate Up-Regulation of NADPH oxidase, inflammation, and fibrosis in diabetic kidney. Antioxidants (Basel) 10: 1356, 2021.
141. Briest F, Noerenberg D, Hennch C, Yoshida K, Hablesreiter R, Nimo J, Sasca D, Kirchner M, Mansouri L, Inoue Y, *et al*: Frequent ZNF217 mutations lead to transcriptional deregulation of interferon signal transduction via altered chromatin accessibility in B cell lymphoma. Leukemia 37: 2237-2249, 2023.
142. Feng X, Yang X, Zhong Y and Cheng X: The role of ncRNAs-mediated pyroptosis in diabetes and its vascular complications. Cell Biochem Funct 42: e3968, 2024.
143. Guo J: Effect of miR-21 on renal fibrosis induced by Nano-SiO_2 in diabetic nephropathy rats via PTEN/AKT pathway. J Nanosci Nanotechnol 21: 1079-1084, 2021.
144. Dhas Y, Arshad N, Biswas N, Jones LD and Ashili S: MicroRNA-21 silencing in diabetic nephropathy: Insights on therapeutic strategies. Biomedicines 11: 2583, 2023.
145. Liu S, Wu W, Liao J, Tang F, Gao G, Peng J, Fu X, Zhan Y, Chen Z, Xu W and Zhao S: MicroRNA-21: A critical pathogenic factor of diabetic nephropathy. Front Endocrinol (Lausanne) 13: 895010, 2022.
146. Sur S, Steele R, Shi X and Ray RB: miRNA-29b inhibits prostate tumor growth and induces apoptosis by increasing bim expression. Cells 8: 1455, 2019.
147. Dieter C, Lemos NE, Girardi E, Ramos DT, Pellenz FM, Canani LH, Assmann TS and Crispim D: The rs3931283/PVT1 and rs7158663/MEG3 polymorphisms are associated with diabetic kidney disease and markers of renal function in patients with type 2 diabetes mellitus. Mol Biol Rep 50: 2159-2169, 2023.
148. Jiang S, Li H, Zhang L, Mu W, Zhang Y, Chen T, Wu J, Tang H, Zheng S, Liu Y, *et al*: Generic diagramming platform (GDP): A comprehensive database of high-quality biomedical graphics. Nucleic Acids Res 53: D1670-D1676, 2025.
149. Johnstone SE, Gladyshev VN, Aryee MJ and Bernstein BE: Epigenetic clocks, aging, and cancer. Science 378: 1276-1277, 2022.
150. López J, Añazco-Guenkova AM, Monteagudo-García Ó and Blanco S: Epigenetic and epitranscriptomic control in prostate cancer. Genes (Basel) 13: 378, 2022.
151. Garcia-Martinez L, Zhang Y, Nakata Y, Chan HL and Morey L: Epigenetic mechanisms in breast cancer therapy and resistance. Nat Commun 12: 1786, 2021.
152. Hanahan D: Hallmarks of cancer: New dimensions. Cancer Discovery 12: 31-46, 2022.
153. Fan H, Yang F, Xiao Z, Luo H, Chen H, Chen Z, Liu Q and Xiao Y: Lactylation: Novel epigenetic regulatory and therapeutic opportunities. Am J Physiol Endocrinol Metab 324: E330-E338, 2023.
154. Nagaraju GP, Dariya B, Kasa P, Peela S and El-Rayes BF: Epigenetics in hepatocellular carcinoma. Semin Cancer Biol 86: 622-632, 2022.
155. Panera N, Mandato C, Crudele A, Bertrando S, Vajro P and Alisi A: Genetics, epigenetics and transgenerational transmission of obesity in children. Front Endocrinol 13: 1006008, 2022.
156. Galicia-Garcia U, Jebari S, Larrea-Sebal A, Uribe KB, Siddiqi H, Ostolaza H, Benito-Vicente A and Martín C: Statin Treatment-induced development of type 2 diabetes: From clinical evidence to mechanistic insights. Int J Mol Sci 21: 4725, 2020.
157. Grady WM, Yu M and Markowitz SD: Epigenetic alterations in the gastrointestinal tract: Current and emerging use for biomarkers of cancer. Gastroenterology 160: 690-709, 2021.
158. Li X, Lu L, Hou W, Huang T, Chen X, Qi J, Zhao Y and Zhu M: Epigenetics in the pathogenesis of diabetic nephropathy. Acta Biochim Biophys Sin (Shanghai) 54: 163-172, 2022.
159. Khan RMM, Chua ZJY, Tan JC, Yang Y, Liao Z and Zhao Y: From Pre-diabetes to diabetes: Diagnosis, treatments and translational research. Medicina (Kaunas) 55: 546, 2019.
160. Ling C, Bacos K and Rönn T: Epigenetics of type 2 diabetes mellitus and weight change-a tool for precision medicine? Nat Rev Endocrinol 18: 433-448, 2022.
161. Asano T, Fujishiro M, Kushiyama A, Nakatsu Y, Yoneda M, Kamata H and Sakoda H: Role of phosphatidylinositol 3-kinase activation on insulin action and its alteration in diabetic conditions. Biol Pharm Bull 30: 1610-1616, 2007.
162. Chen X, Pan X, Zhang W, Guo H, Cheng S, He Q, Yang B and Ding L: Epigenetic strategies synergize with PD-L1/PD-1 targeted cancer immunotherapies to enhance antitumor responses. Acta Pharm Sin B 10: 723-733, 2020.
163. Filip K, Lewińska A, Adamczyk-Grochala J, Marino Gammazza A, Cappello F, Lauricella M and Wnuk M: 5-azacytidine inhibits the activation of senescence program and promotes cytotoxic autophagy during trdmt1-mediated oxidative stress response in insulinoma β-TC-6 cells. Cells 11: 1213, 2022.
164. Thakur V, Gonzalez MA, Parada M, Martinez RD and Chattopadhyay M: Role of histone deacetylase inhibitor in diabetic painful neuropathy. Mol Neurobiol 61: 2283-2296, 2024.
165. Wang Y, Zhou F, Li M, Zhang Y, Li N and Shao L: MiR-34a-5p promotes hepatic gluconeogenesis by suppressing SIRT1 expression. Exp Cell Res 420: 113336, 2022.
166. Özel M, Baskol M, Akalın H and Baskol G: Suberoylanilide hydroxamic acid (SAHA) reduces fibrosis markers and deactivates human stellate cells via the epithelial-mesenchymal transition (EMT). Cell Biochem Biophys 79: 349-357, 2021.
167. Samidurai A, Olex AL, Ockaili R, Kraskauskas D, Roh SK, Kukreja RC and Das A: Integrated asnalysis of lncRNA-miRNA-mRNA regulatory network in rapamycin-induced cardioprotection against ischemia/reperfusion injury in diabetic Rabbits. Cells 12: 2820, 2023.