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REVIEW

# Glucose metabolism partially regulates β-cell function through epigenomic changes

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## ABSTRACT

The β-cell relies predominantly on glucose utilization to generate adenosine triphosphate, which is crucial for both cell viability and insulin secretion. The β-cell has evolved remarkable metabolic flexibility to productively respond to shifts in environmental conditions and changes in glucose availability. Although these adaptive responses are important for maintaining optimal cellular function, there is emerging evidence that the resulting changes in cellular metabolites can impact the epigenome, causing transient and lasting alterations in gene expression. This review explores the intricate interplay between metabolism and the epigenome, providing valuable insights into the molecular mechanisms leading to β-cell dysfunction in diabetes. Understanding these mechanisms will be critical for developing targeted therapeutic strategies to preserve and enhance β-cell function, offering potential avenues for interventions to improve glycemic control in individuals with diabetes.

## INTRODUCTION

The regulation of metabolic homeostasis in mammals is closely tied to complementary actions of insulin, glucagon and somatostatin. These hormones are secreted from pancreatic β-cells, α-cells and δ-cells, respectively, and are controlled by endocrine, paracrine and metabolic regulatory mechanisms[1]. Pancreatic β-cells are primarily responsible for maintaining glucose homeostasis; loss and/or dysfunction of pancreatic β-cells results in diabetic phenotypes[1]. Type 1 diabetes is a disease caused by immune-mediated loss of insulin producing β-cells, resulting in a life-long intrinsic inability to maintain glucose homeostasis[2,3]. Currently, the prevailing treatment option is insulin replacement therapy. Although there is general acceptance that autoimmunity is the fundamental cause of type 1 diabetes, many important questions remain about the potential contribution of inherent β-cell dysfunction that might contribute to disease initiation and/or progression[2]. Type 2 diabetes is caused by a complex combination of genetics and environmental factors, and is associated with obesity, insulin resistance and islet dysfunction, including the loss of normal glucose-stimulated insulin secretion (GSIS)[1,4].

A fundamental feature of pancreatic β-cells is to maintain blood glucose levels by sensing the glucose as a metabolic fuel. Recent investigations in both type 1 diabetes and type 2 diabetes patients have shown the importance of maintaining mitochondrial function and appropriate metabolic pathways for this process to work optimally[2,5–8]. However, the precise impact of alterations in metabolic flux on the progression of type 1 diabetes and type 2 diabetes remains unclear. Recent studies have suggested that altered intermediates of glucose metabolism can contribute to adverse gene expression changes through altered acetylation or methylation of histone lysine residues[9,10]. The purpose of this review article is to evaluate the latest research on the cellular and molecular mechanisms of glucose metabolism that induce epigenetic changes that ultimately alter insulin secretion capacity. Greater insight of the dynamic relationship

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between glucose metabolism and the epigenome will be necessary to understand some of the underlying mechanisms leading to β-cell dysfunction in diabetes.

## GLUCOSE METABOLISM TRIGGERS ENERGY PRODUCTION AND GSIS

The process of glucose metabolism in islet β-cells is finely tuned to maintain glucose homeostasis, ensuring that blood glucose levels are kept within a narrow euglycemic range. In response to elevated blood glucose levels, glucose enters the β-cells through glucose transporter 1 and glucose transporter 3 in humans, and glucose transporter 2 in rodents[2,11,13]. On entry into the cell, glucose undergoes glycolysis, which involves a series of enzymatic reactions that break glucose down into pyruvate[14]. Unlike many other cell types, pancreatic β-cells primarily utilize aerobic metabolism (oxidative phosphorylation) for energy production; pyruvate enters the mitochondria where it undergoes further oxidation to produce additional adenosine triphosphate (ATP). The production of ATP leads to $K_{ATP}$-channel closure, which in turn causes membrane depolarization and the consequent activation of voltage-gated $Ca^{2+}$ channels[11,12]. The increase in intracellular calcium then triggers insulin granule docking and exocytosis (Figure 1).

## ALTERATIONS IN METABOLIC FLUX CONTRIBUTE TO β-CELL FAILURE

β-Cells dynamically respond to conditions of increased metabolic demand or stress. For example, high glucose levels can

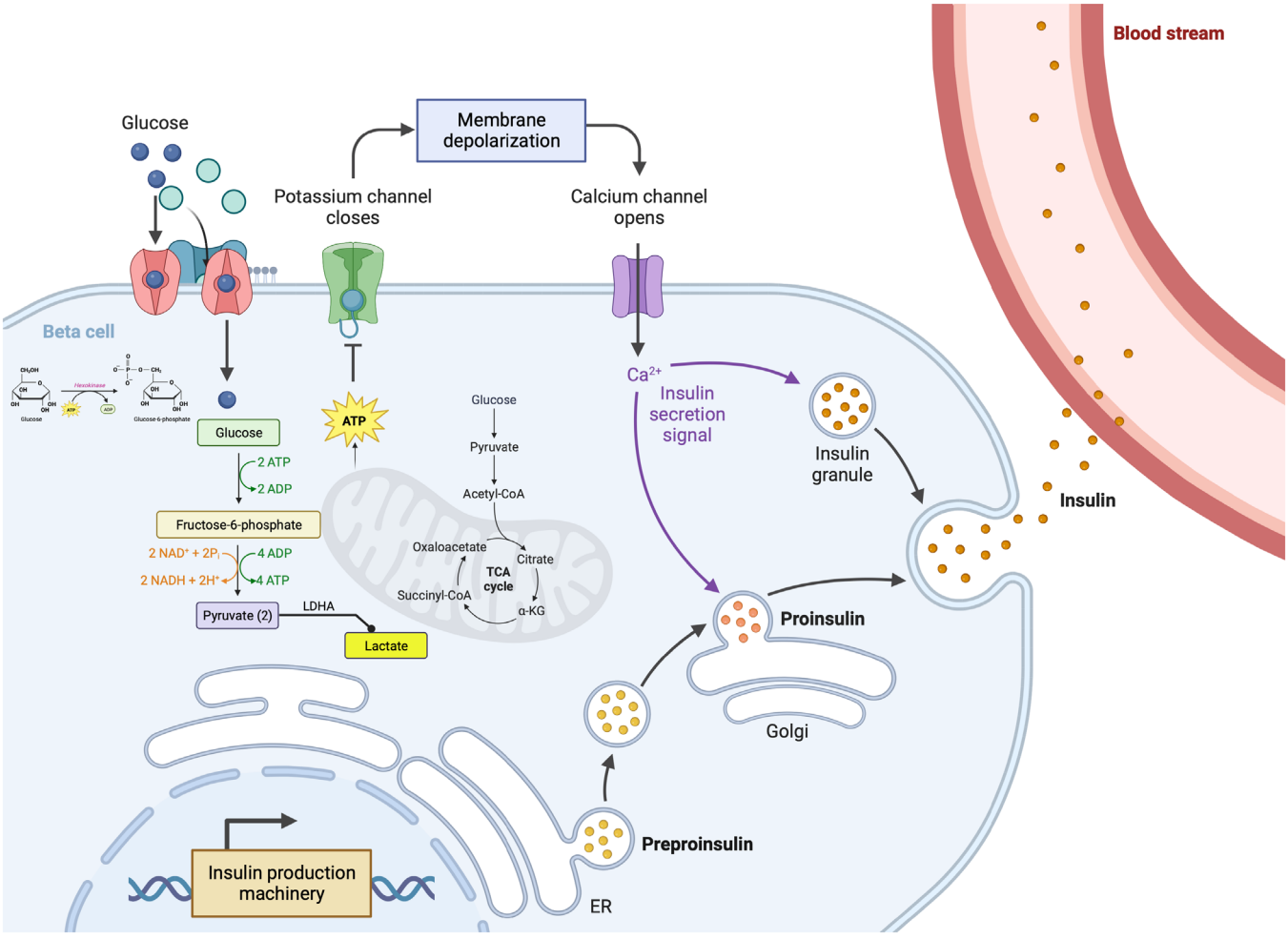


**Figure 1** | Overview of glucose stimulated insulin secretion in the β-cell. Glucose enters the cell through glucose transporters (e.g., glucose transporter 2 in mice) and undergoes phosphorylation by hexokinase. Subsequently, glucose enters the glycolytic pathway, leading to the generation of two pyruvates from one glucose molecule. Pyruvate can be converted into acetyl-coenzyme A or lactate. Adenosine triphosphate (ATP), produced through glycolysis and the mitochondria through the tricarboxylic acid (TCA) cycle, induces membrane depolarization by closing potassium channels. This depolarization event opens calcium channels, initiating the docking and exocytosis of insulin granules. Created with BioRender.com. ER, endoplasmic reticulum; LDHA, lactate dehydrogenase A. ADP, adenosine diphosphate.

lead to elevated glycolytic flux, and increased production of ATP and other metabolic intermediates. Furthermore, during increased metabolic activity or in situations where oxygen availability is compromised, β-cells can shift to anaerobic glycolysis, and pyruvate can become converted to lactate in the absence of sufficient oxygen. Although metabolic flexibility is essential for β-cells' ability to adapt to changing environmental conditions, over time, these changes in metabolic pathways can eventually mediate β-cell failure. Chronic exposure to high glucose levels and elevated levels of free fatty acids, as seen in type 2 diabetes, can contribute to glucotoxicity and lipotoxicity, resulting in impaired mitochondrial function. Several mitochondrial enzymes have been shown to be impacted in type 2 diabetes patients, including pyruvate dehydrogenase, citrate synthase, isocitrate dehydrogenases (IDH1 and 2) and ATP synthase. Depending on the individual, dysregulation of these enzymes could be a consequence or cause of β-cell dysfunction. For example, IDH2 messenger ribonucleic acid and protein expression are decreased in two diabetic mouse strains with β-cell dysfunction, suggesting they are impacted by a diabetic environment[15]. However, inhibition of IDH2 can also result in the suppression of insulin secretion in isolated islets and in mice, suggesting mutations in IDH2 could contribute to an underlying vulnerability of β-cells to stress conditions[1,15]. In addition to mitochondrial dysfunction, lipid toxicity can also induce fatty acid oxidation, which can lead to the impairment of GSIS. The inhibition of fatty acid translocase cluster determinant 36 lowered intracellular peroxide levels in INS-1 cells, and rescued the decreased GSIS response,[16,17] showing that – at least in the short term – β-cell dysfunction can be reversed. These examples show the importance of preserving normal metabolic pathways to maintain and enhance β-cell function in diabetes.

## ALTERED GLUCOSE METABOLISM CAN LEAD TO EPIGENETIC CHANGES

Altered glucose metabolism can also have profound effects on the epigenome. Metabolism is considered a key regulator of the epigenome, given that nearly all chromatin-modifying enzymes rely on essential metabolites as cofactors to facilitate their catalytic functions. Consequently, shifts in glucose metabolism dynamically shape the availability of these vital cofactors, influencing the enzymatic processes involved in epigenetic modifications. As described below, these epigenetic modifications, such as deoxyribonucleic acid (DNA) methylation and histone modifications, will influence gene expression in β-cells to have a significant impact on the development or progression of β-cell dysfunction in diabetes[10,18,19].

## DNA AND HISTONE METHYLATION

DNA methylation is a major mechanism for regulating gene expression. There are several DNA methylases that are classified based on their functions and targets. DNMT1 is responsible for maintaining existing DNA methylation patterns during DNA replication, whereas DNMT3a and DNMT3b are involved in the establishment of new DNA methylation patterns in response to environmental cues. DNMT3L modulates the activity of DNMT3a and DNMT3b, and is important for establishing genomic imprinting. S-adenosyl methionine is a critical cofactor for DNA methyltransferases, and high glucose levels can lead to increased flux through the one-carbon metabolism pathway, potentially increasing S-adenosyl methionine levels and impacting DNA methylation patterns (Figure 2). Several studies in rodents and humans have highlighted the importance of DNA methylation in preserving β-cell identity and function. In rodents, two complementary studies showed the importance of DNMT1 in maintaining β-cell identity; disruption of DNMT1 expression or targeting in β-cells resulted in the derepression of α-cell lineage genes[20,21]. In humans, Ling *et al.*[22] showed that an increase in DNA methylation at the PPARGC1A promoter in type 2 diabetes human islets was associated with reduced insulin gene expression and secretion. This group also identified a cohort of patients with type 2 diabetes that had increased DNA methylation and decreased expression of the essential pancreatic master regulator, PDX1[23]. Additionally, Kameswaran *et al.*[24] shed light on the importance of appropriate imprinting for maintaining β-cell function. That study showed that the imprinted DLK1-MEG3 locus was downregulated in islets from individuals with type 2 diabetes, and the decreased expression correlated with hypermethylation of the MEG3 promoter. Collectively, these findings underscore the potential for altered glucose metabolism to exert profound effects on DNA methylation, thereby influencing gene expression and, consequently, β-cell function.

Consistent with the aforementioned studies cited, lysine-specific histone demethylase 1A (LSD1/KDM1A) plays a pivotal role in essential cellular processes[25]. The demethylase activity of LSD1 relies on flavin adenine dinucleotide as a cofactor, establishing a strong connection between cellular metabolism and the nutrient environment[26]. LSD1 is a component of transcriptional complexes within the nucleus that regulates nutrient responses in various cell types, including hepatocytes, adipocytes and pancreatic β-cells[27]. Systemic inhibition of LSD1 results in a reduction of hyperphagia and weight gain, improvement in insulin sensitivity, and prevention of hyperglycemia in obesity models[25]. Furthermore, β-cell-specific deletion of LSD1 (*Pdx1-CreERT*, *MIP-CreERT*) led to insulin hypersecretion, aberrant expression of nutrient-response genes and histone hyperacetylation[28]. Additionally, genetic variants linked to type 2 diabetes were concentrated at sites bound by LSD1 in human islets. This suggests that LSD1 plays an important role in coupling the nutrient state to the regulation of the islet epigenome and adaptive downstream gene expression[28].

Histone methylation is another important epigenetic modification that can be influenced by cellular metabolism, as the availability of S-adenosyl methionine is also crucial for histone methyltransferase activity. Consistently, mice carrying a deletion in the histone arginine methyl transferase, PRMT1, showed

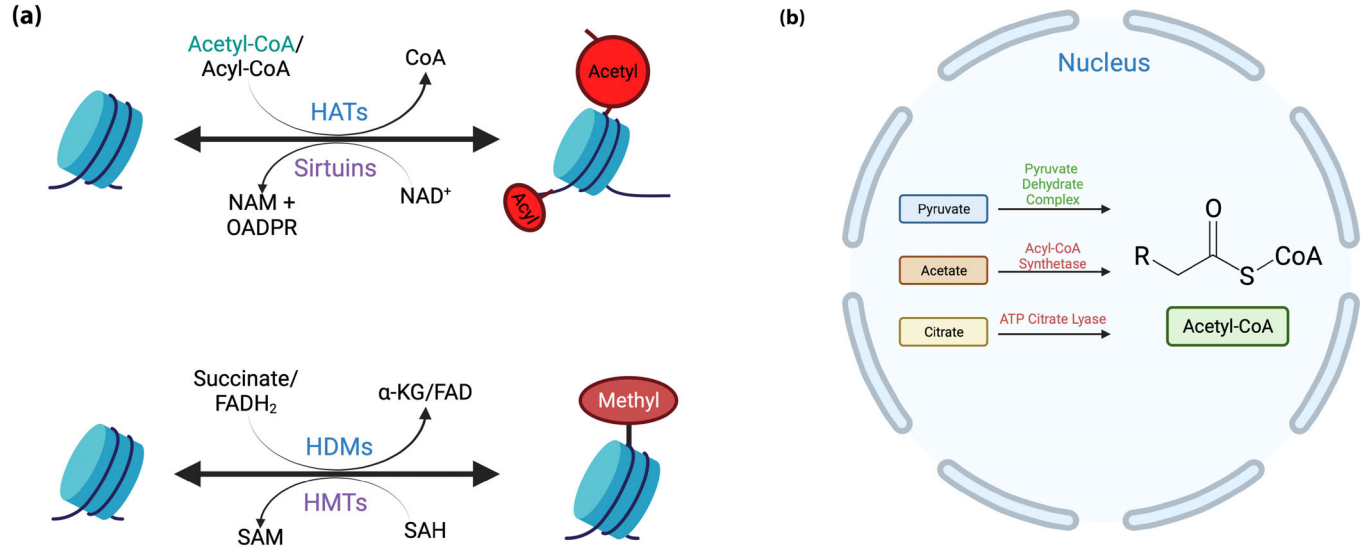


**Figure 2** | Metabolic intermediates are cofactors for the chromatin-modifying enzymes. (a) Metabolic intermediates are essential cofactors for chromatin modifying enzymes. (b) Acetyl-coenzyme A production can be catalyzed from pyruvate, acetate and citrate by different enzymes. CoA, coenzyme A; $FADH_2$, rlavin adenine dinucleotide; HAT, histone acetyltransferases; HDM, histone demethylase; HTM, histone methyltransferase; $NAD^+$, nicotinamide adenine dinucleotide; NAM, nicotinamide; OAADPR, O-acetyl-ADP-ribose; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine; α-KG, α-ketoglutarate. Created with BioRender.com

impaired expression of genes important for β-cell function and identity[29].

## HISTONE ACETYLATION

The primary regulation of histone acetylation levels typically involves histone acetyltransferases (HATs) and histone deacetylases (HDACs). Three primary families of HATs have been identified (GNAT, MYST and p300/CBP) that each require acetyl-coenzyme A (acetyl-CoA) as the acetyl group donating cofactor[9]. Maintenance of appropriate histone acetylation has been shown to be essential for β-cell proliferation and function in numerous studies[25,28,30-34]. HDACs are metalloenzymes classified into three main classes based on their protein sequence homologies with yeast deacetylase enzymes[9,35]. One group of HDACs, known as class I HDACs, consists of HDAC1, HDAC2, HDAC3 and HDAC8. These are closely associated with the yeast reduced potassium dependency 3 transcriptional regulator. The class II HDACs, is comprised of HDAC4, HDAC5, HDAC7, HDAC9 (class IIa), and HDAC6 and HDAC10 (class IIb), with domains resembling yeast histone deacetylase I. Many different studies have investigated the role of HDACs in β-cells with mixed results. HDAC inhibition in cell lines and rodent islets has been shown to prevent cytokine-induced toxicity in β-cells[36-38] and enhance β-cell proliferation[39]. Furthermore, mice carrying an inducible β-cell specific (*MIP-CreERT*) deletion of HDAC3 showed increased glucose tolerance and insulin secretion[40]. However, mice carrying a constitutive β-cell-specific (*Rip-Cre*) deletion of HDAC3 caused an impairment of β-cell function[41]. This was consistent with a study that showed that the administration of HDAC inhibitors to the rodent β-cell line β-TC3 led to a loss of β-cell identity, with a concomitant elevation in α-cell marker expression within β-cells[42], and a more recent study that reported HDAC inhibition using the pan-HDAC inhibitor, trichostatin A, appeared to impair pancreatic β-cell function through an epigenome wide reprogramming[43]. The discrepant results from all these studies suggest that the function of HDACs is more nuanced than appreciated, and a balance of the different HAT and HDAC activities – perhaps in response to external conditions – might function as a rheostat for sensing the metabolic condition of cells and translating it into an appropriate cellular response.

## DEPENDENCE OF HISTONE ACETYLATION ON METABOLIC INTERMEDIATES

Although the primary regulation of histone acetylation levels typically involves HATs and HDACs, acetyl-CoA derived from exported citrate also contributes to the histone acetylation process. Acetyl-CoA is an essential substrate for HATs that can impact the balance of histone acetylation; during high-glucose conditions there is an increased flux through glycolysis, leading to higher acetyl-CoA levels. This implicates acetyl-CoA as another metabolite that links cellular metabolism to epigenetic regulation (Figure 2a).

Acetyl-CoA is necessary for both lipid synthesis in the cytosol and histone acetylation in the nucleus[44,45]. Acetyl-CoA functions as a central metabolic intermediate produced during nutrient catabolism, and acts as the substrate for acetylation

reactions involving proteins and metabolites, including histone acetylation[46]. The enzyme, ATP citrate lyase (ACLY), converts citrate to acetyl-CoA for several different cellular pathways, including having a role in augmenting histone acetylation, thereby facilitating chromatin structure and transcriptional activation of cell-specific genes[45] (Figure 2b).

As ACLY plays a critical role in cellular metabolism, it is tightly regulated to meet the metabolic demands of the cell and regulate appropriate cell-specific gene expression. The regulation of ACLY has predominantly been investigated in the context of cancer cells, where it is activated by acetylation and AKT-mediated phosphorylation, and degraded by ubiquitinylation[47]. Recently, in β-cells, ACLY has been identified as a novel substrate for PTPN2[48]. That study reported that increased tyrosyl phosphorylation of ACLY caused a detrimental effect on metabolic activity and insulin secretion, a result that could be attributed to both its role in the generation of acetyl-CoA and regulation of gene expression. Furthermore, the observed changes were compounded by a reduction in citrate production[48] (Figure 3). Several inhibitors targeting ACLY have also shown promising outcomes in diverse therapeutic areas, demonstrating that inhibition of ACLY has the potential to modulate inflammation and reduce the progression of atherosclerotic diseases[49] (Figure 3). Further exploration into the mechanisms underlying the translocation of metabolic enzymes into the nucleus, as well as their involvement in epigenetic regulation in the β-cells, will provide novel information related to the metabolic regulation of cellular functions.

## CONCLUSIONS AND PERSPECTIVES

β-Cell dysfunction in diabetes involves a complex interplay of molecular changes that affect diverse cellular processes. As discussed in this review, in diabetic conditions, altered glucose metabolism can have profound effects on the epigenome of the β-cell by altering the availability of metabolites that serve as cofactors for enzymes involved in epigenetic processes. Understanding these molecular changes will be crucial for developing targeted therapeutic strategies to preserve and enhance β-cell function in diabetes. Research in this area has the potential to identify interventions that can protect β-cells from stressors, promote their regeneration and ultimately improve glycemic control in individuals with diabetes.

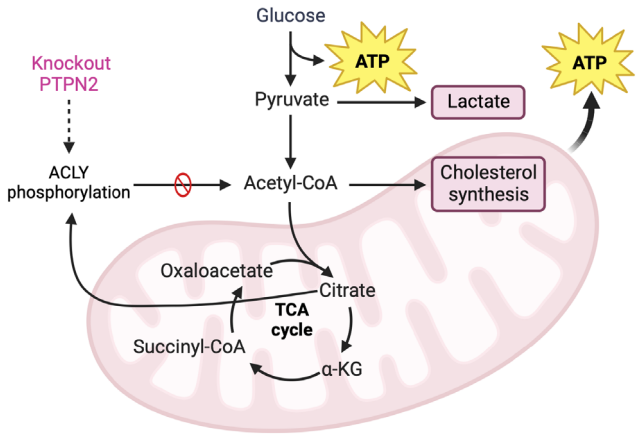


**Figure 3** | Acetyl-coenzyme A (acetyl-CoA) is regulated by adenosine triphosphate (ATP) citrate lyase (ACLY) activity in the cytosol. Schematic of acetyl-CoA metabolism in the cytosol. Acetyl-CoA produced by pyruvate dehydrate complex and ACLY. PTPN2, phospho-tyrosine phosphatase 2; TAC, tricarboxylic acid. Created with BioRender.com.

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## DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: N/A.
Informed consent: N/A.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

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