Spotlight on epigenetics as a missing link between obesity and type 2 diabetes

ABSTRACT

Type 2 diabetes (T2D) is a complex disorder that is caused by a combination of genetic, epigenetic, and environmental factors. β-cell failure and insulin resistance in peripheral tissues that are induced by lipid overload are main hallmarks of T2D. The mechanisms that link obesity-driven alterations of lipid metabolism and T2D are still elusive, thereby impeding the development of effective prevention and treatment strategies. Although genetic variants that have been identified in high-throughput studies comprise an appreciable proportion of the genetic component of T2D, they explain < 20% of the estimated heritability of T2D. A growing body of evidence suggests an intrinsic role for epigenetic modifications in the pathogenesis of T2D. The epigenetic regulation of gene expression in tissues that play a key role in the obesity-related development of T2D has been demonstrated, including *PDX1* in pancreatic islets, *PPARGC1A* in skeletal muscles, *ADIPOQ* in adipose tissue, and *TXNIP* in the liver. The present review summarizes our current knowledge of crosstalk between the epigenetic control of gene expression, particularly *via* DNA methylation, toxic lipid mediators, and the pathogenesis of obesity-related T2D.

INTRODUCTION

Type 2 diabetes (T2D) is a complex metabolic disorder, the worldwide prevalence of which is growing rapidly. According to the International Diabetes Federation, over 400 million people have T2D globally. By 2040, an estimated one in every 10 adults (642 million) will develop diabetes [1]. Chronically elevated blood glucose levels that are caused by both insulin resistance in target tissues (i.e., the liver, skeletal muscles, and adipose tissue) and the dysregulation of insulin secretion from pancreatic β-cells, in addition to elevated glucagon secretion by pancreatic α-cells, are main hallmarks of T2D [2].

To date, genome-wide association studies (GWASs) have identified at least 400 genetic risk variants at 250 loci that are associated with T2D, underscoring the importance of genetic susceptibility to the disease [3]. However, these genetic variants explain only a small fraction (10–15%) of T2D heritability, suggesting a major role for environmental (lifestyle) factors [4]. An unhealthy lifestyle, metabolic alterations, and being overweight or obese are well-known risk factors for T2D. An estimated 70–90% of patients with T2D are overweight or obese [5]. The molecular mechanisms that link obesity-driven alterations of fatty acid (FA) metabolism and T2D are still elusive, thereby impeding the development of effective prevention and treatment strategies.

Both obesity and T2D are conditions that are caused by an interplay between genetic and environmental factors. The epigenetic control of gene expression has been suggested to be one of the possible underlying mechanisms of obesity, lifestyle changes, and the etiology of T2D [6]. The term "epigenetics" is used to describe changes in gene function that occur without changes in the nucleotide sequence, including such mechanisms as DNA methylation, histone modifications, and non-coding RNA. These factors that influence chromatin structure and DNA accessibility lead to reinterpretation of the DNA sequence and switching "on/off" gene transcription at certain times and locations. Among other epigenetic players, DNA methylation (i.e., the covalent addition of a methyl group at the C5 position of cytosine residues typically at CpG sites) has been the most extensively studied in the context of obesity-related T2D to date [6-8]. Studies that have utilized epigenome-wide approaches allowed the discovery of 94 CpGs that are associated with body mass index (BMI) and 49 CpGs that are associated with waist circumference. The top networks presented a common link between obesity and both T2D and metabolic syndrome. Some of the identified genes, such as *SREBF1*, *ABCG1*, *SLC7A11*, and *CPT1A*, also presented different methylation patterns and were associated with lipid traits [9]. Additionally, several studies have reported that the DNA methylation status of specific genes or repetitive se-

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quences is altered in response to metabolic changes (e.g., dietary intervention or exercise) and detected inverse associations between BMI and global DNA methylation levels [10]. The epigenetic regulation of DNA and histones in response to environmental stimuli also serves as a plausible explanation of "metabolic memory," defined as the persistence of tissue dysfunction and T2D-related complications although glycemic control has been pharmacologically achieved [11]. The present review discusses crosstalk between the epigenetic regulation of gene expression, particularly *via* DNA methylation, toxic lipid mediators, and obesity, and the development of T2D.

OBESITY-RELATED TYPE 2 DIABETES AND DNA METHYLATION IN PANCREATIC ISLETS

In obesity-related T2D, pancreatic islet cells are chronically overstimulated by both hyperglycemia and toxic lipid metabolites. This leads to β-cell mass decay and β-cell failure and thus insufficient insulin secretion that is caused by the greater demand of insulin-resistant tissues [2]. Pancreatic β-cells exhibit a remarkable ability to tune their secretory functions in response to alterations of tissue insulin demands. Glucose, amino acids, neurohormonal signals, lipid mediators, and endocannabinoid signaling have been shown to modulate insulin release from pancreatic β-cells [12-13].

Studies of pancreatic β-cell dysfunction in diet-induced obese mice have shown that the transition to prediabetes and early diabetes states largely depends on transcriptional adaptive changes. The genes that are particularly affected in pancreatic islets from obese diabetic mice (a total of 1,508 differentially expressed genes) are related to the cell cycle, cell proliferation, adenosine monophosphate-activated protein kinase (AMPK) signaling, mitochondrial metabolism, and cholesterol metabolism [14]. Studies of human pancreatic islets revealed that differential gene expression in islets from T2D donors compared with islets from non-diabetic donors was accompanied by changes in DNA methylation patterns [15-17]. Initial studies of human pancreatic islets were candidate-driven and examined particular genes that have a known function in β-cell metabolism or other cell metabolism. Such research found a correlation between excessive promoter region hypermethylation and the lower expression of such genes as *INS* (which encodes insulin), *PDX1* (which encodes pancreatic and duodenal homeobox 1, a transcription factor that plays a key role in pancreatic development and mature β-cells where it regulates insulin expression), *GLP1R* (which encodes the GLP1 receptor that stimulates insulin secretion), and *PPARGC1A* (which encodes the mitochondrial regulator PGC1α – peroxisome proliferator-activated receptor γ [PPAR γ] coactivator 1) in islets from T2D donors [18,8].

Since next-generation sequencing (NGS) and high-throughput array-based methods have been introduced for DNA methylation analyses, the focus has turned to epigenome-wide association studies (EWASs). To date, EWASs have reported over 50 unique CpGs for T2D in peripheral blood, 15 CpGs in the pancreas, 10 CpGs in adipose tissue, and two CpGs in the liver [4]. Additionally, EWASs have been able to discern a functional meaning of the observed aberrations of DNA methylome by comparing correlations of DNA methylation with specific regulatory elements of genes that are associated with obesity-related T2D. The first study that utilized this methodology to investigate islet DNA covered ~27,000 CpG sites, representing less than 1% of the CpG sites in the entire human genome. In this study, 276 CpG sites that were affiliated with 254 gene promoters showed differential methylation patterns between normal and diseased samples. Remarkably, 96% of these CpGs presented lower methylation levels, whereas only 10% were hypermethylated [15]. Another study of the T2D islet methylome assessed methylation at ~450,000 CpG sites. Alterations of the DNA methylation profile were observed in approximately 1649 CpG regions of 853 genes, including *TCF7L2*, *FTO*, and *KCNQ1*. Of the group of genes that presented significantly different DNA methylation patterns within their promoter regions, 102 were also differentially expressed in T2D islets compared with islets from non-diabetic donors. Moreover, functional analyses showed that the candidate genes that were identified (e.g., *CDKN1A*, *PDE7B*, and *SEPT9*) affect insulin secretion in β-cells and glucagon secretion in α-cells [16]. The array-based methods that were used in the studies cited above covered only ~ 0.1% of the overall CpG sites [15] and 1.7% of the CpG sites [16] in the human genome, respectively. Recently, to better characterize the DNA methylation landscape in human pancreatic islets, the first whole-genome bisulfite sequencing study was performed in islets from T2D donors (BMI = 28.0 ± 2) and control subjects (BMI = 24.9 ± 0.3). This study covered the majority of CpG sites in the human genome (~24 million sites) and identified 25,820 differentially methylated regions (DMRs) in islets from individuals with T2D. A total of 457 genes were identified that presented both DMRs and significant changes in expression in T2D islets, including loci with a known function in islet biology (e.g., *PDX1*, *ADCY5*, and *SLC2A2*), and identified novel genes that are controlled by DNA methylation in T2D [17].

IMPACT OF FREE FATTY ACIDS ON DNA METHYLATION IN PANCREATIC ISLETS

Accumulating evidence shows that pancreatic islets are highly influenced by free fatty acids and lipid species. The effects of lipid mediators on Langerhans islets depend *inter alia* on the time of exposure and type of lipid mediator (e.g., long-chain FAs and phospholipids) [19-20]. Palmitic acid (16:0) is the most abundant saturated FA in the human body, comprising 38% of the total circulating FAs in lean or obese humans. Palmitic acid can be provided in the diet or synthesized endogenously *via de novo* lipogenesis [21]. Chronically high levels of palmitate in plasma induce negative effects on β-cell function through various mechanisms, including the formation of toxic ceramide species, reactive oxygen species, endoplasmic reticulum stress, and apoptosis [19]. Perturbations of palmitate metabolism that were induced by the inhibition of stearoyl-CoA desaturase 1 (SCD1) affected autophagosome-lysosome fusion, leading to an aberrant stress response and β-cell failure. SCD1 is a key regulatory enzyme that catalyzes the biosynthesis of monounsaturated FAs (palmitoleate [C16:1n-7] and oletate [C18:1n-9]) from saturated FAs (preferentially palmitate [C16:0] and stearate

[C18:0]) [22]. Studies have also supported a role for palmitate in the epigenetic regulation of gene expression in pancreatic islets. RNA sequencing that was performed to map transcripts in human pancreatic islets found 1,325 modified genes in palmitate-treated islets [23]. An *in vitro* study of genome-wide mRNA expression and DNA methylation patterns identified 1,860 differentially expressed genes in palmitate-treated human islets. Furthermore, 290 of these genes presented a corresponding change in DNA methylation, including candidate genes for T2D (e.g., *TCF7L2* and *GLIS3*). Of the genes that were differentially expressed by palmitate treatment in human islets, 67 were associated with BMI, and five (i.e., *RASGRP1*, *MIA2*, *CDKN1A*, *TNFRSF103*, and *RAB7L1*) were associated with both BMI and T2D [24]. Analyses of gene expression profiles in clonal INS-1 832/13 β-cells after exposure to palmitate showed an increase in the expression of 982 genes and a decrease in the expression of 1032 genes compared with untreated cells. Additionally, the mRNA expression of *Insig1*, *Lss*, *Peci*, *Idi1*, *Hmgcs1*, and *Casr* was reversibly altered by exposure to palmitate and associated with changes in histone modifications. These findings indicate that these genes can be a subject to epigenetic regulation [25].

METABOLIC STRESS, DNA METHYLATION, AND COMPROMISED IDENTITY OF PANCREATIC ISLET CELLS

The most plausible mechanism to explain the effects of gluco- and lipotoxicity on pancreatic islet decompensation in T2D is massive β-cell death. However, recent genetic and epigenetic studies indicate that both β-cell demise and the loss of pancreatic endocrine cell identities may be major causes of the development of obesity-related T2D [26-27]. Alterations of cell proliferation, survival, transdifferentiation, dedifferentiation, or migration that are related to remodeled cell-cell contacts may result in the reorganization of pancreatic islet microarchitecture. Moreover, dietary ω-3 polyunsaturated FAs were shown to affect the cellular organization of pancreatic islets during organ development. Thus, lipid signaling emerges as a key determinant of pancreatic endocrine organization [28].

The maintenance of identity of insulin- and glucagon-secreting cells in pancreatic islets is determined by the stable expression of transcription factors. Transcription factors that have been shown to be involved in maintaining the functional identity of adult α- and β-cell include PDX1, v-maf avian musculoaponeurotic fibrosarcoma oncogene homologs A and B (MAFA and MAFB), forkhead box protein O1 (FOXO1), aristaless-related homeobox (ARX), paired box protein 6 (PAX6), and homeobox proteins NKX2.2 and NKX6.1, among others [29]. Importantly, many of these transcription factors are closely related to the regulation of cellular metabolism. Specifically, PDX1, MAFA, FOXO1, and NKX6.1 are inactivated by hyperglycemia, providing a plausible mechanism for compromised β-cell identity in T2D [26]. Notably, 20.9–43.9% methylation was found in the *PDX1*, *MAFB*, *NKX6.1*, and *NKX2.2* gene regions. Thus, DNA methylation may differentially regulate the expression of these transcription factors in different islet cells [17]. Additionally, high glucose exposure decreased the mRNA expression and increased the DNA methylation of *Pdx1* in clonal β-cells. Ten 10 CpG sites in the distal *PDX1* promoter region and enhancer regions exhibited significant increases in DNA methylation in islets from patients with T2D compared with nondiabetic donors [30]. The plasticity of differentiated endocrine cells can be increased in the pancreas by eliminating α- and β-cell epigenetic constraints. Pancreatic β-cell identity was shown to be maintained by the DNA methylation-mediated repression of the *Arx* gene. β-cells that were deficient in methyltransferase 1 (Dnmt1), an enzyme that propagates DNA methylation patterns during cell division, were converted to α-cells through *Arx* promoter region hypomethylation [31]. The treatment of human islets with the histone methyltransferase inhibitor Adox resulted in the mis-expression of *PDX1* in α-cells and the induction of glucagon-insulin dual-positive cells [32]. These studies strongly suggest that epigenetic mechanisms in certain contexts can act as important regulators of the establishment of pancreatic islet cell identity.

ROLE OF DNA METHYLATION IN THE DEVELOPMENT OF OBESITY-RELATED TYPE 2 DIABETES IN SKELETAL MUSCLES

Skeletal muscles are considered the main site of the development of insulin resistance because they are responsible for most (≤ 80%) insulin-stimulated glucose uptake [33]. Physiologically, the binding of insulin to insulin receptors in skeletal muscles drives molecular cascades, including Akt pathway activation. Consequently, glucose transporter 4 (GLUT4) is translocated to the plasma membrane, followed by glucose uptake [34]. Toxic secondary lipid messengers, such as diacylglycerols and ceramides, that accumulate in peripheral tissues in obese individuals have been implicated in the development of T2D [35]. One of the mechanisms of the FA-induced development of insulin resistance, demonstrated by us and others, includes an increase in the protein kinase C (PKC) response to diacylglycerol accumulation that results in impairments in insulin signaling and glucose uptake in skeletal muscles [36-37]. Several recent studies indicate that obesity-driven epigenetic changes may modulate muscle cell metabolism and thus contribute to the pathogenesis of T2D. The largest EWAS to date analyzed skeletal muscle biopsies of the *vastus lateralis* from 271 individuals with normal and impaired glucose tolerance, impaired fasting glucose, or newly diagnosed T2D. The analyses of deep RNA-sequencing and genotyping data, integrated with epigenomic data, identified genomic traits for T2D that regulated the transcriptional activity of several genes, including *ANK1*, which is enriched with single-nucleotide polymorphisms (SNPs) that are located within a super-enhancer region (> 3 kb from the transcription start site) [38]. *ANK1* isoforms were recently reported to be associated with sarcoplasmic reticulum assembly, which is crucial for *GLUT4* translocation to the plasma membrane and insulin-stimulated glucose uptake [39]. Moreover, *ANK1* is thought to interact with insulin receptor substrate 1 (IRS1), another critical point in the insulin signaling cascade in skeletal muscles [40].

Another large-scale study was performed to find potential associations between DNA methylation and BMI. Of 278 CpG sites that were identified in blood samples to be strong-

ly associated with BMI with epigenome-wide significance, 187 had similar methylation patterns among the analyzed peripheral tissues (i.e., skeletal muscles, adipose tissue, the liver, and the pancreas). These data strongly support the hypothesis that the observed level of DNA methylation is a consequence of adiposity [41]. Furthermore, based on the proximity of methylation markers to the nearest gene, the authors identified 210 candidate genes that were associated with BMI and DNA methylation. Gene-set enrichment analyses revealed that many of the identified genes (e.g., *ABCG1*, *LPIN1*, *HOXA5*, *LMNA*, *CPT1A*, *SOCS3*, *SREBF1*, and *PHGDH*) participate in the development of insulin resistance and lipid metabolism [42].

EFFECT OF FATTY ACID EXPOSURE AND A HIGH-FAT DIET ON DNA METHYLATION IN SKELETAL MUSCLES

Excess lipids and their metabolically active derivatives participate in the pathogenesis of T2D, causing insulin resistance and impairing glucose metabolism in skeletal muscles. One of the master metabolic regulators in skeletal muscles is PGC1α, which is encoded by the *PPARGC1A* gene that was identified in a GWAS as one on the top hits with regard to T2D pathogenesis [3]. Based on a combination of methylated DNA immunoprecipitation and an Affymetrix promoter array approach, 838 differentially methylated promoter regions were found in samples from T2D patients compared with healthy controls. The authors found that higher *PPARGC1A* promoter region methylation was associated with a decrease in gene expression in samples from T2D donors [42]. Moreover, acute FA (palmitate or oleate) or tumor necrosis factor α (TNFα) exposure directly led to alterations of *PPARGC1A* promoter region methylation [43]. In skeletal muscle biopsy samples that were taken from monozygotic twins who were discordant for T2D, differences in DNA methylation were found between diabetic and non-diabetic twins in promoter regions of *IL8*, *CDKN2A*, *DUSP9*, *HNF4A*, *HHEX*, *KCNQ1*, *KLF11*, *PPARGC1A*, and *SLC30A8*. In the same study, alterations of DNA methylation were found in subcutaneous adipose tissue in T2D twins in promoter regions of *ADCY5*, *CAV1*, *CIDEC*, *CDKN2A*, *CDKN2B*, *DUSP9*, *HNF4A*, *IDE*, *IRS1*, *KCNQ1*, *MTNR1B*, *TSPAN8*, and *WFS1* [44]. Obesity leads to a decrease in FA β-oxidation and contributes to ectopic and intramuscular lipid accumulation [33]. Recently, the lower expression of *CPT1B*, which encodes carnitine palmitoyltransferase-1B, was shown to result in higher *CPT1B* promoter region methylation in cultures of primary skeletal muscle cells from obese patients [45]. Furthermore, an increase in methylation in the promoter region of *CPT1B* prevented the binding of such transcription factors as PPARα, consequently leading to a decrease in the expression of *CPT1B* [45]. Another gene that is crucial for skeletal muscle homeostasis is *PDK4*, which encodes pyruvate dehydrogenase kinase 4, a kinase that is involved in glucose and lipid metabolism. Methylation of the *PDK4* promoter region was lower in T2D and inversely correlated with *PDK4* gene expression. Furthermore, *PDK4* expression was positively correlated with BMI and the levels of blood glucose, insulin, C peptide, and glycated hemoglobin [46]. Five days of overfeeding resulted in alterations of the methylation of more than 7000 CpG sites in skeletal muscles from young men with a low birth weight [47]. Interestingly, the observed changes were not fully reversed by a control diet, even after 8 weeks. These data suggest that changes in methylation at selected loci might accumulate over time [47]. In another study, an increase in methylation in the *PPARGC1A* promoter region was observed after 5 days of a high-fat diet. After introducing a control diet, the pattern of *PPARGC1A* promoter region methylation was reversed and similar to controls [48]. Altogether, these data indicate that excess fat and changes in diet can influence and define epigenetic patterns and thus modulate the risk of T2D.

EFFECT OF ACUTE WEIGHT LOSS AND EXERCISE ON DNA METHYLATION IN SKELETAL MUSCLES

Skeletal muscles are a highly adaptive organ that undergoes robust changes in response to weight loss and/or exercise. One of the master metabolic switches that is activated in response to exercise is the AMPK pathway. This pathway plays a pivotal role as a metabolic fuel gauge [49]. Regular exercise exerts a beneficial effect on the oxidative capacity of skeletal muscles and whole-body glucose tolerance and lipid oxidation *via* AMPK activation [50]. Hence, it is a key element in the prevention and management of T2D and obesity [51]. Recent studies showed that even a single bout of exercise leads to epigenetic remodeling and changes in transcriptome profiling in peripheral tissues that account for improvements in metabolic health. However, the detailed mechanisms that orchestrate exercise-induced epigenetic changes remain largely unknown. Recent studies showed that short-term acute exercise leads to dose-dependent changes in the gene expression of *PPARGC1A*, *PDK4*, and *PPARδ*, which corresponded to the hypomethylation of respective gene promoter regions in skeletal muscles [42]. Multi-omic analysis (i.e., transcriptome, methylome, and microRNA) of skeletal muscle biopsies from obese T2D subjects after 16 weeks of either resistance or endurance training revealed significant alterations of gene expression that were linked to epigenetic changes [52]. Endurance training resulted in the hypomethylation of the nuclear receptor factor (*NRF1*) promoter region and FA transporter (*SLC27A4*), hypermethylation of FA synthase, and exon hypomethylation of 6-phosphofructo-2-kinase and Ser/Thr protein kinase. Functional analyses revealed lower intramyocellular lipid levels and higher capillarity, GLUT4, hexokinase, and mitochondrial enzyme activity in endurance-trained T2D obese patients. Resistance training also caused GLUT4 promoter region hypomethylation, but this change was not associated with GLUT4 protein content. Thus, DNA methylation-driven expression changes are most pronounced with endurance training and associated with improvements in the metabolic performance of skeletal muscles [52]. In another study, participants with or without a family history of T2D underwent 6 months of endurance training [53]. Skeletal muscle biopsies were taken before and after the exercise intervention. The authors found that the DNA methylation of *RUNX1* and *MEF2A*, two distinct transcription factors, decreased after the exercise intervention. Moreover, a decrease in *THADA* promoter region methylation was observed, and the increase in *THADA* expression was associated with T2D [54]. Exercise also influenced both DNA methylation and the expression of several genes (i.e., *ADIPOR1*, *ADIPOR2*, and *BDKRB2*, which encode receptors for adiponectin and

bradykinin, respectively, and are considered important regulators of skeletal muscle metabolism) [53].

Another study examined the combined effect of a short-term (9-day) high-fat diet and resistance exercise by genome- and epigenome-wide profiling. Significant changes in DNA methylation and subsequently gene expression traits were found. The authors concluded that exercise did not prevent the inflammatory process that was induced by the high-fat diet but provoked muscle adaptation and protected against muscle atrophy [55].

Notably, recent rodent studies focused on the role of exercise in the transgenerational risk of obesity and T2D. One study found that a high-fat diet before and throughout pregnancy led to an increase in methylation of the *Ppargc1a* promoter region, decreased mRNA expression in skeletal muscles from neonatal and adult offspring, and led to age-associated metabolic dysfunction. A maternal exercise intervention prevented high-fat diet-induced *Ppargc1a* hypermethylation and enhanced the expression of *Ppargc1a* and its target genes in skeletal muscles of offspring [56]. Future studies of the effects of exercise on promoter region methylation and gene expression at the genome-wide and epigenome-wide levels need to be conducted.

Gastric bypass surgery in morbidly obese patients (BMI > 35) resulted in acute weight loss and improved glucose tolerance and cardiovascular function. Improved metabolic performance was associated with an increase in *PPARGC1A* expression, resulting from a decrease in *PPARGC1A* promoter region methylation [57]. Another recent study found that sorbin and SH3 domain containing 3 (*SORBS3)* expression in skeletal muscle was regulated by the methylation of its promoter region, altered in obesity, and restored to normal levels through gastric bypass surgery-induced weight loss [58]. Previous studies found that *SORBS3* gene expression was significantly associated with BMI, percent body fat, and fasting insulin and glucose levels [58]. Collectively, the post-surgery data furthered our understanding of changes in DNA methylation that is associated with obesity and T2D.

ASSOCIATIONS BETWEEN OBESITY-RELATED TYPE 2 DIABETES AND DNA METHYLATION IN ADIPOSE TISSUE AND THE LIVER

Adipose tissue, in addition to being a storage depot for fuel (primarily in the form of triglycerides), also functions as an endocrine organ in the body. Adipocytes secret adipokines, such as leptin, adiponectin, interlukin-6 (IL-6), TNFα, and plasminogen activator inhibitor-1 (PAI-1), which play pivotal roles in the maintenance of energy expenditure homeostasis, immunity, appetite control, and glucose metabolism regulation. Two Wnt signaling molecules, WNT3a and WNT4, are specifically secreted by adipose tissue during the development of insulin resistance and play an important role in crosstalk between insulin-resistant tissues and pancreatic β-cells [59]. Obesity represents the abnormal accumulation of adipose tissue. An increase in the accumulation of adipose tissue is associated with deleterious effects, including excess FA secretion, the development of a state of chronic low-grade inflammation, and abnormal adipocyte hormone signaling, which ultimately have detrimental effects, including insulin resistance [60]. Obesity and T2D are also strongly associated with hepatic lipid accumulation and abnormal liver function. In a normal state, the liver regulates blood glucose levels in both fasting and satiated states. After meal ingestion, the liver stores glycogen in response to insulin stimuli, whereas glucagon that is released during fasting increases glycogenolysis and gluconeogenesis in the liver to prevent hypoglycemia. In T2D, the action of glucagon is enhanced, leading to greater hepatic glucose production and release and consequently hyperglycemia [33]. The liver is an important site for one-carbon metabolism where methyl groups are utilized in the metabolic pathways [61]. Several studies are being conducted to investigate associations between T2D, obesity, and changes in DNA methylation in adipose tissue and the liver.

To shed further light on the epigenetic mechanisms that underlie T2D, studies analyzed adipose tissue from monozygotic twins who were discordant for T2D and unrelated case-control cohorts using genome-wide expression and DNA methylation data. The differences in methylation between the discordant monozygotic twins were modest. The data suggested that the DNA methylation pattern in human adipose tissue is highly heritable [44,62]. However, the expression of 31 gene sets was shown to be either downregulated or upregulated in adipose tissue from diabetic *vs.* nondiabetic co-twins. Among the differentially expressed genes were those that are involved in oxidative phosphorylation, lipid metabolism, and inflammation [62]. The SCD1-dependent regulation of inflammatory gene expression in adipocytes involves changes in DNA methylation. Changes in methylation at CpG promoter sites were correlated with the differential expression of interleukin-10 receptor α (*Il10ra*), interleukin-4 receptor α (*Il4ra*), interleukin-6 signal transducer (*Il6st*), and transforming growth factor β1 (*Tgfb1*) [63]. Importantly, when DNA methylation was analyzed in adipose tissue from unrelated subjects, 15,627 CpG sites, representing 7046 genes (including *PPARG*, *KCNQ1*, *TCF7L2*, and *IRS1*), were found to be differentially methylated in diabetic individuals compared with nondiabetic controls [62]. In obese patients, DNA methyltransferase 1 is activated in adipose tissue and hypermethylates the promoter region of the *ADIPOQ* gene (which encodes adiponectin), leading to a decrease in gene expression [64]. Interestingly, two SNPs (rs17300539 and rs266729) that are located at CpG sites within the adiponectin promoter region were significantly correlated with serum adiponectin levels [64]. The significant differences in CpG site methylation were also observed in adipose tissue from obese subjects compared with lean subjects. More than 2800 genes were identified where both DNA methylation and expression correlated with BMI. These include sites that have been annotated to genes that were previously linked to T2D and/or lipid metabolism (e.g., *FTO*, *TCF7L2*, *IRS1*, *IRS2*, *FASN*, and *PPARGC1B*) [65]. Thus, obesity-driven epigenetic modifications may appear before the development of T2D and define its progression.

A healthy lifestyle, including a balanced diet and physical activity, reduces the risk of developing T2D. Transcriptomic and epigenomic changes in human adipose tissue in

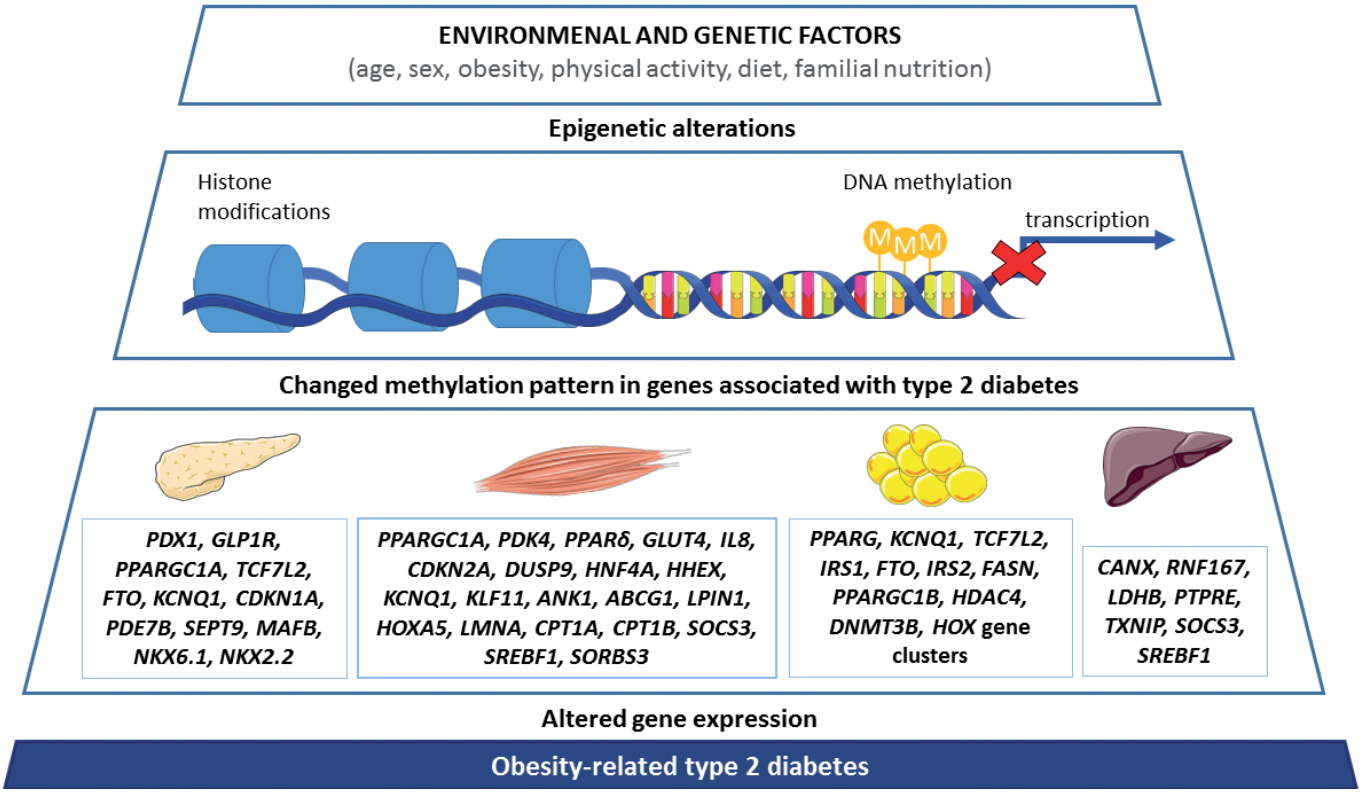

Figure 1. The scheme illustrating how environmental and genetic factors can affect gene expression patterns in specific tissues (pancreas, skeletal muscle, adipose tissue and liver) *via* epigenetic mechanisms, and thereby contribute to development of T2D.

response to exercise, diet, and major weight loss have also been investigated. The DNA methylation profile in subcutaneous adipose tissue from 23 healthy men before and after a 6-month exercise intervention was investigated. A total of 17,975 individual CpG sites, in or near 7663 genes, that presented alterations of DNA methylation were found after the exercise intervention. Specific candidate genes for obesity (18 genes) and T2D (21 genes) were also detected, including *TCF7L2* and *KCNQ1* [66]. Dietary fat composition was also shown to affect DNA methylation in adipose tissue. A study of the effects of saturated FA (SFA) and polyunsaturated FA (PUFA) overfeeding on adipose tissue in healthy young subjects revealed that DNA methylation patterns were differentially affected, depending on the diet [67]. Moreover, 3601 differentially methylated CpG sites in subcutaneous adipose tissue were found after gastric bypass surgery. These sites were annotated to such genes as *HDAC4*, *DNMT3B*, *KCNQ1*, and *HOX* [68]. A recent study of obese T2D patients with non-alcoholic fatty liver disease (NAFLD) identified 59 differentially methylated CpG regions that were associated with fasting insulin and glucose levels and T2D. This study also investigated the impact of DMRs that were identified in the study on the expression for transcripts that are located in the genomic region around these CpGs (within the *cis* distance of 500 kb upstream and 100 kb downstream of the gene). They found 30 correlations (nine negative correlations and 21 positive correlations) between DNA methylation and mRNA expression at a level of significance of $p < 0.05$. The genes encode calnexin (*CANX*), ring finger protein 167 (RNF167), and lactate dehydrogenase B (LDHB) [69]. Obesity has also been shown to accelerate liver aging through epigenetic mechanisms and thus contribute to the development of insulin resistance [70]. Furthermore, aging might affect DNA methylation by increasing the gene expression of *DNMT3A* and *DNMT3B* in the liver [71]. Importantly, bariatric surgery was shown to reverse NAFLD-associated CpG methylation patterns in the liver in obese T2D subjects [72]. This study found that *PTPRE* gene expression was downregulated in the liver after gastric bypass surgery, and this change was associated with *PTPRE* promoter region hypermethylation. Interestingly, previous studies found that the *PTPRE* gene, which encodes protein tyrosine phosphatase ε, promoted the development of insulin resistance in skeletal muscles. Further studies are needed to discern the role of *PTPRE* in restoring hepatic insulin sensitivity after acute weight loss [73]. Altogether, these studies provide convincing evidence that weight loss, overeating, and the type of diet can affect the epigenome in human adipose tissue and the liver and influence the expression of genes that are involved in energy balance and food intake regulation, thereby affecting whole-body metabolism. A schematic overview of the effect of epigenetic alterations on gene expression in tissues relevant for T2D pathogenesis is depicted in figure 1.

CONCLUSION

Accumulating data show that epigenetic mechanisms plausibly contribute to understanding and fighting obesity-related T2D. The role of epigenetics in T2D is firmly established. With the rapid development of new high-throughput approaches, diabetes research has substantially accelerated

in identifying genetic variants and epigenetic modifications that contribute to the pathogenesis of T2D. Exposure to environmental factors from the prenatal stage to adulthood can lead to (epi)genomic changes that influence the risk of developing T2D. Epigenetics are also involved in inflammatory components of T2D, and inflammation plays an important role in the development of T2D. GWASs and EWASs have identified genes and novel metabolic pathway targets that deserve further attention to elucidate mechanistic relationships with insulin resistance in peripheral tissues and pancreatic islet failure. Collectively, the studies that are discussed in this review indicate an important role for epigenetics in the pathogenesis of T2D. The importance of epigenetic factors in the pathogenesis of T2D creates the possibility of developing novel strategies to both treat and prevent diabetes. New therapies that are based on epigenetic modulators are being designed to reduce the global burden of T2D. Nonetheless, the road toward translating basic research into clinical application is long and challenging. Future studies should consider non-CpG methylation and the methylation of repetitive regions that are thought to play a role in the development of T2D. Distinct methylation patterns that are observed in peripheral tissues as a response to obesity or acute weight loss should be considered in prospective longitudinal studies of T2D patients.

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Epigenetyczna regulacja ekspresji genów – nowy mechanizm łączący otyłość z rozwojem cukrzycy typu 2

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Słowa kluczowe: cukrzyca typu 2, epigenetyka, metylacja DNA, insulinooporność, dysfunkcja komórek β trzustki

STRESZCZENIE

Cukrzyca typu 2 (T2D) jest chorobą, której patogeneza jest złożona i determinowana poprzez interakcje genomu, epigenomu, i środowiska. Jednym z głównych czynników ryzyka wystąpienia T2D jest otyłość, której konsekwencją jest rozwój insulinooporności tkanek obwodowych oraz dysfunkcji komórek β trzustki. Molekularne mechanizmy leżące u podstaw T2D związanej z otyłością nie zostały w pełni poznane, co uniemożliwia opracowanie skutecznych metod prewencji i leczenia T2D. Warianty genetyczne zidentyfikowane w badaniach wielkoskalowych wyjaśniły jedynie część podłoża genetycznego tej choroby. Z tego względu, wiele obecnych badań jest skierowanych na określenie roli mechanizmów epigenetycznych w kontroli ekspresji genów kluczowych dla rozwoju T2D. W ostatnich latach pokazano, że ekspresja genów takich jak: *PDX1* w wysepkach trzustkowych, *PPARGC1A* w mięśniach szkieletowych, *ADIPOQ* w tkance tłuszczowej i *TXNIP* w wątrobie, regulowana jest poprzez zmiany epigenetyczne. Niniejsza praca podsumowuje obecny stan wiedzy na temat udziału kwasów tłuszczowych i mechanizmów epigenetycznych, w szczególności metylacji DNA, w patogenezie T2D związanej z otyłością.