

Epigenetics: A Molecular Link Between Environmental Factors and Type 2 Diabetes

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Although obesity, reduced physical activity, and aging increase susceptibility to type 2 diabetes, many people exposed to these risk factors do not develop the disease. Recent genome-wide association studies have identified a number of genetic variants that explain some of the interindividual variation in diabetes susceptibility (1–5). There is also a growing body of literature suggesting a role for epigenetic factors in the complex interplay between genes and the environment. Nevertheless, our knowledge about the molecular mechanisms linking environmental factors and type 2 diabetes still remains limited. This perspective will provide some insights into epigenetic mechanisms associated with type 2 diabetes.

An overview of epigenetic regulation. Although there is no uniform definition of epigenetics, it has been described as heritable changes in gene function that occur without a change in the nucleotide sequence (6). Epigenetic modifications can be passed from one cell generation to the next (mitotic inheritance) and between generations of a species (meiotic inheritance). In plants, it is well established that epigenetic modifications can be inherited from one generation to the next (7). However, there is only limited information about the inheritance of epigenetic traits between generations in animals (8,9). Notably, epigenetic effects may also be affected by the environment, making them potentially important pathogenic mechanisms in complex multifactorial diseases such as type 2 diabetes (Fig. 1). Epigenetic factors include DNA methylations, histone modifications, and microRNAs, and they can help to explain how cells with identical DNA can differentiate into different cell types with different phenotypes. This perspective will focus on the roles of DNA methylation and histone modification in the pathogenesis of type 2 diabetes.

Cytosine residues occurring in CG dinucleotides are targets for DNA methylation in vertebrates, and DNA methylation is associated with transcriptional silencing (e.g., on the inactive X chromosome). This silencing can be achieved by either repressing the binding of transcription factors (Fig. 2A) or by recruiting proteins that specifically bind to methylated CGs (methyl-CG-binding proteins, e.g.,

MeCP2), which can further recruit histone deacetyltransferases (HDACs) and corepressors (Fig. 2B) (10).

DNA methylation requires the activity of methyltransferases. There are two groups of DNA methyltransferases: DNMT1, which copies the DNA methylation pattern between cell generations during replication (maintenance methylation), and DNMT3a and DNMT3b, which are responsible for de novo methylation of DNA (10). The process leading to demethylation of DNA is still poorly understood; for a recent review see Patra et al. (11).

Genomic DNA in eukaryotic cells is packed together with special proteins, termed histones, to form chromatin. The basic building block of chromatin is the nucleosome, which consists of ~147 base pairs of DNA wrapped around an octamer of histone proteins that is composed of an H3-H4 tetramer flanked on either side with an H2A-H2B dimer. Although the core histones are densely packed, their NH₂-terminal tails can be modified by histone-modifying enzymes, resulting in acetylation, methylation, phosphorylation, sumoylation, or ubiquitination (12). These modifications are important for determining the accessibility of the DNA to the transcription machinery as well as for replication, recombination, and chromosomal organization.

HDACs remove and histone acetyltransferases (HATs) add acetyl groups to lysine residues on histone tails (12–14). Although, it is well established that HAT activity and increased histone acetylation correlate with increased gene transcription, the exact mechanisms promoting transcription are less clear (15). Native lysine residues on histone tails contain a positive charge that can bind negatively charged DNA to form a condensed structure with low transcriptional activity. An early suggestion was that histone acetylation removes these positive charges, thereby relaxing chromatin structure and facilitating access to the DNA for the transcriptional machinery to initiate transcription (13,15). However, different models have recently been proposed, including the histone code hypothesis, where multiple histone modifications act in combination to regulate transcription (15,16). Histone acetylation may also recruit bromodomain proteins that can act as transcriptional activators (13). Histone methylation can result in either transcriptional activation or inactivation, depending on the degree of methylation and the specific lysine and/or arginine residues modified (17,18). Histone methyltransferases and histone demethylases mediate these processes (18).

New techniques have made it easier to analyze DNA methylation and histone modifications on a genome-wide scale (19,20). These techniques may be useful when studying the impact of epigenetics on the pathogenesis of type 2 diabetes.

Epigenetic changes induced by aging. Aging is associated with an increased risk of type 2 diabetes. Correspondingly, oxidative capacity and mitochondrial function

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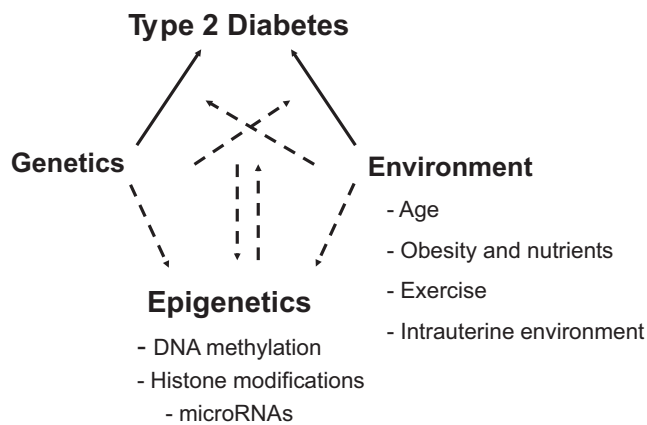


FIG. 1. Model proposing a role for epigenetic mechanisms in the pathogenesis of type 2 diabetes.

decline with age as well as in patients with type 2 diabetes (21–26). The mechanisms behind these defects may be both genetic and environmental (27–31). Recent data further suggest that the epigenetic pattern may change during the course of life, affecting key genes in the respiratory chain (32–34). *COX7A1*, which is part of complex 4 of the respiratory chain and which shows decreased expression in diabetic muscle, is a target of age-related DNA methylation (23,34). Whereas DNA methylation of the *COX7A1* promoter is increased in skeletal muscle of elderly compared with young twins, the opposite pattern is found for *COX7A1* gene expression (34). Additionally, the transcript level of *COX7A1* in skeletal muscle is associated with increased in vivo glucose uptake and $V_{O_{2max}}$ (34). These data demonstrate how age can influence DNA methylation, gene expression, and subsequently in vivo metabolism. The interaction between non-genetic and epigenetic mechanisms may further be affected by genetic factors. Indeed, a polymorphism introducing a possible DNA methylation site, a CG dinucle-

otide, and a putative transcription factor binding site in the *NDUFB6* promoter is associated with increased DNA methylation, decreased gene expression, and decreased in vivo metabolism with increasing age (33). This study provides an example of interactions between genetic (polymorphism), epigenetic (DNA methylation), and non-genetic (age) factors in the determination of human metabolism.

Hepatic insulin resistance is another important characteristic of both aging and type 2 diabetes. Glucokinase is a key enzyme in hepatic glucose utilization, and its activity is decreased in the liver of diabetic patients (35). Mutations in the glucokinase gene can cause a monogenic form of diabetes (maturity-onset diabetes of the young [MODY] 2) (36). Moreover, in aged compared with young rats, the liver displays reduced levels of glucokinase expression and enzyme activity in parallel with increased DNA methylation of the glucokinase promoter (37). When hepatocytes of aged rats were cultured in vitro and the DNA was chemically demethylated, there was a substantial increase in glucokinase expression, suggesting an important role for DNA methylation in the age-related regulation of this gene. Similar studies in humans with diabetes are still lacking.

Although aging is associated with gene-specific hypermethylation, many mammalian tissues demonstrate global hypomethylation of DNA and decreased methyltransferase (DNMT1 and DNMT3a) expression with increased age (33,34,37–45). Global hypomethylation of DNA is seen in repetitive sequences and may promote genomic instability during aging. Increased age is also associated with hypomethylation of specific genes, e.g., proto-oncogenes, thereby increasing susceptibility to cancer, especially if combined with hypermethylation of tumor suppressor genes. Further studies examining the effects of aging on genome-wide epigenetic patterns in target tissues may help to improve our understanding of

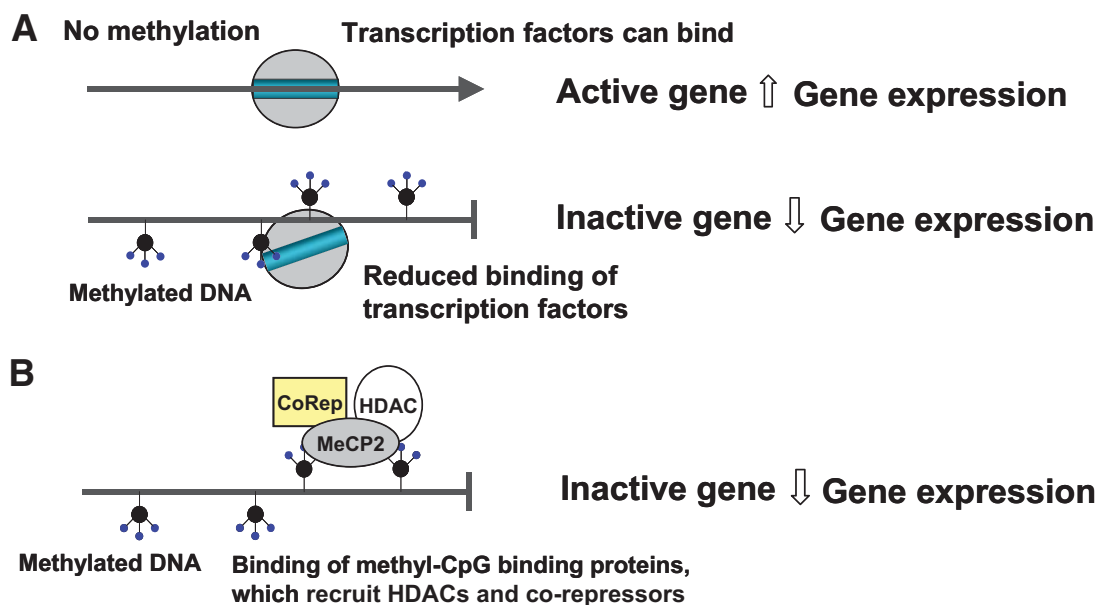


FIG. 2. Effects of DNA methylation on gene expression. **A:** Whereas low levels of DNA methylation at gene promoters have been proposed to generate active genes through increased binding of transcription factors, elevated DNA methylation at promoters may inhibit binding of transcription factors resulting in inactive genes. **B:** DNA methylation at gene promoters may also repress gene transcription via specific proteins that bind to methylated CpGs (methyl-CpG binding proteins, e.g., MeCP2), and these proteins may then recruit HDACs and transcriptional corepressors (e.g., NCoR), resulting in an altered chromatin structure and inactive genes.

of the molecular mechanisms influencing the pathogenesis of type 2 diabetes.

Links between obesity, energy metabolism, nutrients, and epigenetic modifications. The prevalence of type 2 diabetes is increasing rapidly worldwide, partly due to the epidemic in obesity seen among most ethnic groups. The fact that loss of function of the histone demethylase, *Jhdm2a*, is associated with obesity, decreased expression of metabolically active genes (e.g., peroxisome proliferator-activated receptor- α and medium-chain acyl-CoA dehydrogenase) in skeletal muscle, and an impaired cold-induced uncoupling protein 1 expression in brown adipose tissue in rodents suggests a relationship between epigenetic mechanisms and obesity (46). Another class of enzymes involved in epigenetic control of metabolism is the nicotinamide adenine dinucleotide (NAD⁺)-dependent sirtuins (class III HDACs), which target both histone and nonhistone proteins (47). The most well-characterized member, SIRT1, regulates several metabolic pathways including adipogenesis, mitochondrial biogenesis, glucose utilization, fat oxidation, and insulin secretion. Moreover, ATP-citrate lyase is an enzyme that regulates the conversion of citrate to acetyl CoA, which is a metabolite required for acetylation of histones by HATs. It has recently been suggested that glucose availability can affect histone acetylation in an ATP-citrate lyase-dependent manner, further linking energy metabolism to epigenetic regulation (48).

Leptin is a hormone secreted from adipocytes that regulates appetite and energy homeostasis. It is predominantly expressed in mature adipocytes, and leptin expression can therefore be used as a marker of differentiating preadipocytes. The leptin promoter is embedded within a CG-rich region, called a CpG island. Although there is a high degree of DNA methylation of the leptin promoter and no leptin expression in preadipocytes, the promoter is demethylated in parallel with induction of leptin expression in differentiated cells (49,50). Although a high-fat diet increases DNA methylation of one CpG site in the leptin promoter of rat adipocytes (51), it remains to be examined whether food intake and obesity are associated with epigenetic regulation of leptin expression in human adipocytes.

Environmental exposures to nutrients may change gene expression and alter disease susceptibility through epigenetic modifications. Similar mechanisms are operative in the agouti mouse; the agouti gene encodes a paracrine-signaling molecule that promotes melanocytes to produce yellow rather than black coat pigment and makes mice prone to develop obesity, diabetes, and tumors (52–54). The degree to which the agouti gene is methylated regulates agouti expression and thereby coat color and risk for disease. Moreover, supplementation of the diets of pregnant mice with methyl donors such as folic acid, vitamin B12, choline, or betaine increases DNA methylation of the gene in the offspring, resulting in low agouti expression and a brown coat color (55). The effect of maternal methyl-donor supplementation on coat color is also inherited in the F2 generation through germline epigenetic modifications (56).

Pdx1/insulin promoter factor (IPF)-1 is a transcription factor regulating pancreas development and β -cell differentiation, and mutations in this gene can cause a monogenic form of diabetes (MODY 4) (36). Intrauterine growth retardation due to uteroplacental insufficiency has recently been associated with progressive epigenetic silencing of *Pdx1*, impaired β -cell function, and type 2 diabetes

in adult offspring (57). Whether *PDX1* is a target for similar epigenetic mechanisms in humans born to mothers with uteroplacental insufficiency remains unknown. However, the prenatal environment has been associated with insulin resistance and a risk for type 2 diabetes in humans (58–60), and the prenatal nutrient supply may induce epigenetic changes in humans. Indeed, individuals from the The Dutch Hunger Winter Families Study who were prenatally exposed to famine in 1944–1945 showed less DNA methylation of the imprinted *IGF2* and *INSIGF* genes and increased DNA methylation of the *GNASAS*, *MEG3*, *IL10*, *ABCA1*, and *LEP* genes in parallel with impaired glucose tolerance compared with their unexposed same-sex siblings (60–63). Moreover, a high-fat diet during pregnancy in rats is associated with impaired glucose homeostasis and mitochondrial and cardiovascular dysfunctions in adult rats, possibly due to epigenetic modifications (64–66). In future studies it will be interesting to study the effects of short- and long-term weight gain and weight loss on epigenetic changes in relevant tissues.

Histone modifications induced by exercise. Poor physical fitness and a low VO_{2max} predict risk of developing type 2 diabetes (67). Mitochondrial dysfunction, changes in muscle fiber-type composition, and insulin resistance are potential mechanisms linking poor physical fitness with an increased risk for disease. Exercise induces the expression of a number of genes that regulate glucose uptake in skeletal muscle, including GLUT isoform 4 (GLUT4), (68). *GLUT4* expression is further regulated by the transcription factor myocyte enhancer factor 2 (MEF2).

At rest, it has been proposed that MEF2 interacts with HDAC5 in the nucleus (69). Histone tails at the *GLUT4* gene are thereby deacetylated by HDAC5, resulting in a condensed chromatin structure and subsequently reduced *GLUT4* expression (69). After exercise, HDAC5 is phosphorylated by AMP-activated protein kinase, dissociated from MEF2, and exported from the nucleus to the cytosol (69–71). MEF2 may then interact with the coactivator protein PPAR γ coactivator-1 α (PPARGC1A) and HATs in the nucleus, resulting in acetylated histones at the *GLUT4* gene, enhanced transcriptional activity, and increased *GLUT4* expression (69,72,73). It is possible that other histone modifications also influence the regulation of *GLUT4* expression in skeletal muscle. Ca⁺/calmodulin-dependent protein kinase (CaMK) also seems to modulate MEF2 activity via histone acetylation in response to acute exercise (74). Moreover, gene expression of *MYST4*, a HAT, correlates positively with the percentage of type 1 fibers and VO_{2max} in human skeletal muscle (75). Together, these data suggest that some of the biological changes induced by exercise could be due to histone modifications, a research area that deserves further exploration.

Epigenetic changes in patients with type 2 diabetes. Although data mining analysis has suggested a role for epigenetic factors in the pathogenesis of type 2 diabetes (76), there are only a limited number of studies that have examined epigenetic changes in target tissues from patients with type 2 diabetes. The transcriptional coactivator PPARGC1A coordinates gene expression that stimulates mitochondrial oxidative metabolism in multiple tissues (77). Whereas DNA methylation of the *PPARGC1A* promoter is elevated in pancreatic islets from patients with type 2 diabetes compared with that of healthy control subjects, *PPARGC1A* expression is reduced in diabetic islets and correlates inversely with the degree of DNA

methylation (78). Importantly, *PPARGC1A* expression correlates positively with glucose-stimulated insulin secretion in human pancreatic islets (78), suggesting that epigenetic mechanisms may regulate gene expression and, subsequently, insulin secretion in human islets.

Moreover, there have been some efforts to understand the epigenetic regulation of insulin gene expression in pancreatic β -cells. In β -cells, the insulin gene displays hyperacetylation of H4 and hypermethylation of H3 at lysine 4, typical of active genes; however, these epigenetic marks are not seen at the insulin gene in other cell types, e.g., HeLa cells (79,80). Furthermore, in a β -cell line, the HAT p300 and the histone methyltransferase SET7/9 are recruited to the insulin promoter to activate the gene (80). Interestingly, it has been suggested that HDACs influence pancreatic development in rodents because treatment with HDAC inhibitors during embryonic development enhances the pool of β -cells (81). However, it remains to be established whether any of these epigenetic marks in the insulin gene are affected in β -cells from patients with type 2 diabetes.

Although pancreatic islet β -cell proliferation declines after birth, β -cell proliferation may play a role in the islets adaptation to increased insulin demands imposed by insulin resistance. In support of this, an increased expression of *Ink4a/Arf* (*Cdkn2a* locus) was associated with reduced β -cell regeneration in aging mice (82). The elevated *Ink4a/Arf* expression in elderly mice further coincided with reduced levels of histone H3 lysine 27 trimethylation at *Ink4a/Arf* and the histone methyltransferase, Ezh2, together with decreased Bmi-1 binding and a loss of H2A ubiquitylation at *Ink4a/Arf* (83,84). Interestingly, a common variant at the *CDKN2A* locus has been associated with an increased risk for type 2 diabetes (1–4). However, whether this variant is associated with decreased β -cell proliferation in human islets remains unknown.

Monogenic diabetes and epigenetic factors. Most forms of MODY are caused by mutations in genes encoding transcription factors, including *HNF1A*, *-4A*, and *-1B* as well as *IPF1/PDX1* and *NEUROD1*, some of which regulate transcription of their target genes through associations with HATs and HDACs.

HNF1 α activates transcription through two different mechanisms: 1) recruitment of the general transcription machinery and 2) chromatin remodeling of promoter regions (85). The chromatin remodeling involves recruitment of HATs (e.g., p300/CBP), resulting in hyperacetylation of histones at specific promoters, including *GLUT2* and pyruvate kinase, in β -cells (86–88). Interestingly, a missense mutation (R263L) in the *HNF1A* gene that is associated with a MODY phenotype results in reduced affinity for p300 (89). Moreover, MODY mutations in the *HNF1B* gene influence the capacity of HNF1 β to bind proteins with HAT activity and may thereby affect the chromatin structure (90).

Whereas Pdx1 influences glucose-induced expression of insulin in β -cells, this regulation requires an interaction between Pdx1 and p300 and thereby hyperacetylation of histone H4 at the insulin gene promoter (91–93). It has been suggested that a low glucose level decreases insulin expression due to recruitment of HDAC1 and HDAC2 by Pdx1 (94). Insulin transcription also involves methylation of histone H3 at the insulin promoter, possibly by Pdx1 recruiting methyltransferase SET9 (95). Several *PDX1* mutations associated with diabetes in humans modulate the affinity of PDX1 for both p300 and DNA. If operative in

humans in vivo, this suggests that HAT activity and, therefore the chromatin structure of target genes may influence the risk for diabetes (92). *NEUROD* plays an important role in the development of the pancreas and regulates the transcription of insulin (36). One mutation in *NEUROD*, which results in a truncated protein and diabetes, also prevents it from binding to p300/CBP (96). Collectively, the data described above suggest mechanisms by which chromatin modifications can influence the risk of diabetes, which thereby opens new possible avenues for therapeutically preserving β -cell function.

DNA methylation and transient neonatal diabetes. Transient neonatal diabetes (TND) is a rare form of diabetes that begins in the first 6 weeks of life in growth-retarded neonates (97). Although insulin therapy is only required for an average of 3 months, the majority of these patients develop type 2 diabetes later in life. Three different chromosome 6 anomalies have been described in TND: hypomethylation at chromosome 6q24, paternally inherited duplication of 6q24, and paternal uniparental isodisomy of chromosome 6 (97,98). Interestingly, it has recently been shown that mutations in a zinc-finger transcription factor, *ZFP57*, are associated with TND and hypomethylation of regions on 6q24, including the imprinted genes *PLAGL1* and *HYMAI* (98).

Epigenetic changes associated with diabetic complications. One major event in the progression of diabetic complications is vascular inflammation with increased expression of inflammatory genes. Enhanced oxidative stress, dyslipidemia, and hyperglycemia have also been suggested to influence the development of diabetic complications. Recent studies have proposed that hyperglycemia may induce epigenetic modifications of genes involved in vascular inflammation. Nuclear factor- κ B (NF- κ B) is a transcription factor regulating expression of genes involved in inflammatory diseases, including atherosclerosis and diabetic complications (99). Poor glycemic control increases NF- κ B activity in monocytes and thereby gene expression of inflammatory cytokines (100,101). This regulation involves an interaction between NF- κ B and HATs (e.g., CBP/p300), resulting in hyperacetylation of target genes including the tumor necrosis factor (*TNF*)- α and cyclooxygenase-2 promoters (99). The histone H3 lysine 4 methyltransferase SET7/9 can also influence the recruitment of NF- κ B p65 to gene promoters and thereby its regulation of proinflammatory genes (102). Moreover, vascular smooth muscle cells from diabetic *db/db* mice show decreased levels of histone H3 lysine 9 trimethylation (H3K9me3) and elevated levels of histone H3 lysine 4 dimethylation (H3K4me2) at the promoters of inflammatory genes, e.g., *IL-6* and *MCP-1*, in parallel with decreased levels of the H3K9me3 methyltransferase Suv39h1 and a histone demethylase, the lysine-specific demethylase 1 (LSD1) (103,104). Interestingly, whereas overexpression of Suv39h1 in vascular smooth muscle cells from diabetic *db/db* mice reversed the diabetic phenotype, gene silencing of SUV39H1 in normal human vascular smooth muscle cells increased the expression of inflammatory genes (104). NF- κ B and *IL-6* also represent genes with altered histone H3 lysine 9 dimethylation in lymphocytes from patients with type 1 diabetes (105). Together, these studies suggest that hyperglycemia may induce epigenetic changes of proinflammatory genes, which subsequently regulate gene expression and thereby the development of vascular inflammation. However, improved glycemic control for 3–5 years in diabetic patients did not reduce the

risk of macrovascular complications (106,107). One reason could be that the effects of hyperglycemia may be long-term and that epigenetic modifications induced by hyperglycemia may persist for more than 5 years. Moreover, because the time-averaged mean levels of glycemia, measured as A1C, only explain part of the variation in risk of developing diabetic complications, it was recently hypothesized that transient exposures to hyperglycemia may induce sustained epigenetic changes and thereby NF- κ B-regulated gene expression and increased risk for vascular complications over a longer period of time (108,109). Indeed, a transient exposure to hyperglycemia (16 h) induces epigenetic changes in the promoter of the NF- κ B subunit *p65* and subsequently *p65* expression and NF- κ B activity in aortic endothelial cells. These changes persist for 6 days during culture at normal glucose levels. Interestingly, when genes that reduce mitochondrial superoxide production (e.g., uncoupling protein-1) are overexpressed, the changes induced by the transient hyperglycemia are prevented (109). It was further shown that both a histone methylase (SET7) and a histone demethylase (LSD1) may regulate the epigenetic changes in the NF- κ B *p65* promoter induced by transient hyperglycemia (110). In fact, epigenetic modifications induced by transient hyperglycemia may explain the hyperglycemic memory that has been proposed in epidemiological studies. In the future it may be possible that drugs using and/or affecting epigenetic mechanisms, e.g., HDAC inhibitors, can be used in the treatment of diabetic complications (13,111,112). In support of this idea, a recent study showed that myocardial infarction and ischemia induce HDAC activity in parallel with decreased histone acetylation of histone H3 and 4 in the heart (113). The use of chemical HDAC inhibitors during myocardial infarction reduced the infarct area as well as cell death (113).

Conclusions. The use of genome-wide technologies to study gene expression and genetic variation in patients with type 2 diabetes has increased rapidly over the recent years, generating long lists of new type 2 diabetes candidate genes. However, the use of global techniques to study epigenetic modifications in these same patients has been limited. Epigenetic changes associated with type 2 diabetes are therefore still poorly understood. Nevertheless, epigenetics may play an important role in the growing incidence of type 2 diabetes, and over the next few years, it will be a great challenge to dissect the role of histone modifications and DNA methylation in the pathogenesis of the disease and its complications. Two additional important questions are whether the epigenetic changes induced by today's sedentary lifestyle can be inherited by coming generations and whether these changes are reversible. Currently, several epigenetic drugs are being tested in clinical trials or are already being used (e.g., anticancer or antiepileptic drugs); it may thus be possible to test epigenetic drugs as putative novel drugs for the treatment of diabetes and its complications.

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