Review

Epigenetic changes in diabetes


Diabetes is a multifactorial disease with numerous pathways influencing its progression and recent observations suggest that the complexity of the disease cannot be entirely accounted for by genetic predisposition. A compelling argument for an epigenetic component is rapidly emerging. Epigenetic processes at the chromatin template significantly sensitize transcriptional and phenotypic outcomes to environmental signaling information including metabolic state, nutritional requirements and history. Epigenetic mechanisms impact gene expression that could predispose individuals to the diabetic phenotype during intrauterine and early postnatal development, as well as throughout adult life. Furthermore, epigenetic changes could account for the accelerated rates of chronic and persistent microvascular and macrovascular complications associated with diabetes. Epidemiological and experimental animal studies identified poor glycemic control as a major contributor to the development of diabetic complications and highlight the requirement for early intervention. Early exposure to hyperglycemia can drive the development of complications that manifest late in the progression of the disease and persist despite improved glycemic control, indicating a memory of the metabolic insult. Understanding the molecular events that underlie these transcriptional changes will significantly contribute to novel therapeutic interventions to prevent, reverse or retard the deleterious effects of the diabetic milieu.

Conflict of interest

The authors report no conflicts of interest.

The epigenetic component of diabetes

The responsive epigenome

Since the initial publication of the chartered human genome, the focus of genetic research has increasingly shifted toward the characterization of molecular foundations of transcriptional regulation (1, 2). The various cell types of multicellular eukaryotes display strikingly extensive morphological and functional diversity defined by distinct patterns of gene expression, despite identical genetic content (3). Elaborate combinations of nongenetic mechanisms significantly extend the information potential of the genome. This epigenetic facet of transcriptional regulation is not restricted to cellular differentiation, but also encompasses mechanisms of gene expression exhibited by nondividing cells.

Genomic organizational complexity is significantly influenced by modular interaction of constituent assemblies, composition of which is dependent upon cellular context, microenvironment and circumstance. Chromatin is a dynamic constituent assembly of DNA and various nucleoproteins, and the central template of epigenetic processes. Functional modulation of these components greatly influences the steady-state dynamics of chromatin architecture and gene expression. The recent amalgamation of chromatin-associated events with the DNA sequence-dependent model of transcriptional regulation has emerged from a fundamental shift in the way the field of epigenetics is described and investigated. The growing accessibility of genome-wide sequencing technologies that allow comprehensive analysis of epigenetic phenomena has driven a multitude of recent discoveries that have influenced the scope and capacity of epigenetic research to evolve rapidly. The centrality of epigenetic processes to transcription-driven maintenance,
instruction and regulation of phenotypic characteristics are increasingly appreciated. This contrasts early epigenetic investigations that narrowly focused on heritable aspects of these processes (4).

Modulation and compartmentalization of the genome into transcriptionally accessible (euchromatin) and repressive (heterochromatin) domains dictate gene expression and characterize the epigenomic landscape (5). Integration of epigenetically recorded information to this dynamically interactive system greatly influences gene expression and cellular phenotype (5). Precise regulation of gene transcription requires synchronized activities of core transcriptional machinery and additional complexes that collaborate to structurally reorganize chromatin. For transcription to both initiate and perpetuate, the degree of chromatin accessibility must sufficiently allow the formation of the pre-initiation complex composed of general transcription factors and RNA Polymerase II (RNAPII) in physical association to the DNA template (6, 7). Chromatin accessibility is defined by several coordinated epigenetic mechanisms including DNA CpG methylation, chromatin modifying enzymes and their post-translational modifications, RNA interference, and effector complexes responsible for the local remodeling of chromatin. It is the specific combination and temporal associations of these factors at a particular locus that ultimately dictates the transcriptional competency of a gene (3, 8, 9).

Epigenetic processes at the chromatin template significantly sensitize transcriptional and phenotypic outcomes to signaling information associated with metabolic state, requirements, history, and extracellular interactions, which can be assimilated into this coordinated system (10). More recently, deregulated epigenetic transcriptional control has been implicated in pathogenesis of human disease (11–13), and epigenetic regulators have accordingly emerged as therapeutic targets (14). Changes in epigenetic regulation of gene expression represent potentially important pathogenic mechanisms behind complex diseases such as diabetes.

Diabetes and associated complications: a role for epigenetics

Diabetes is a multifactorial disease, with numerous pathways influencing its progression. In all forms of the disease, the diabetic milieu is characterized by hyperglycemia and a relative or absolute lack of insulin signaling (15). Type 1 diabetes mellitus (T1DM) results from autoimmune destruction of pancreatic β-cells responsible for insulin production, whereas type 2 diabetes mellitus (T2DM) essentially results from the imbalance of blood glucose levels and glucose utilization. Despite strong familial clustering of T2DM (16, 17) and identification of several common variants, genome-wide association studies provide limited capacity to predict T2DM (18). Thus the complexity of T2DM cannot be entirely accounted for by genetic changes. The observed familial clustering of T2DM may be attributable to a significant epigenetic component. For instance gestational metabolic programming by environmental cues are important determinants of T2DM predisposition (19). This is exemplified by follow-up studies of Pima Native Americans that demonstrate significantly higher predisposition to T2DM for individuals born to diabetic mothers than offspring of nondiabetics and importantly siblings born prior to maternal T2DM diagnosis (20, 21). Second, childhood and adult lifestyle factors are strongly associated with T2DM risk and a shared family environment including dietary factors and exercise could promote common environmentally derived epigenetic changes.

Prolonged exposure to poor glycemic control leads to a host of diabetes-specific pathologies across multiple organ systems including microvascular complications of peripheral nerves, renal glomeruli and the retina (22). Additionally macrovascular complications including accelerated atherosclerosis and cardiomyopathy are associated with both T1DM and T2DM (23). These vascular complications are largely driven by transcriptional changes in gene regulation mediated by the diabetic milieu. In particular, upregulation of inflammatory pathways as well as genes involved in fibrosis and extracellular matrix deposition are implicated. Mitochondrial overproduction of reactive oxygen species (ROS) is proposed as a central activator of four major pathways of hyperglycemic damage: stimulation of the polyol pathway, increased flux through the hexosamine pathway, activation of protein kinase C signaling, and accumulation of advanced glycation end-products (24). The overproduction of ROS induced by hyperglycemia is recognized as a major agonist of clinical complications associated with diabetes (25). To this end, overexpression of antioxidant enzymes in transgenic diabetic mice ameliorates the development of retinopathy (26), cardiomyopathy (27) and nephropathy (28).

Metabolic memory

The concept of metabolic memory refers to the persistence of diabetic vascular complications after glucose normalization. This phenomenon is supported by reports from experimental animal models and cell culture, as well as clinical observations of both T1DM and T2DM patients. Studies of this phenomenon have predominantly focused on the harmful effects conferred by hyperglycemia.

Experimental models of metabolic memory

Animal and cell culture studies have highlighted the deleterious and persistent long-term effects of hyperglycemia and the requirement for early intervention. Examination of alloxan-induced diabetic dogs revealed that early insulin therapy intervention and improved glycemic control prevented progression to diabetic retinopathy 5 years from the development of diabetes. In contrast, animals subjected to poor glycemic control for 2.5 years before insulin therapy still developed retinopathy after 5 years of diabetes (29). Similarly rats
with streptozotocin-induced diabetes exhibited retinal oxidative and nitrative stress resulting from periods of hyperglycemia, and late reinstitution of glycemic control failed to inhibit the progression of diabetic retinopathy (30). A separate study of sucrose-fed diabetic rats that received islet transplantation 6 weeks after development of diabetes exhibited reduced progression of retinopathy compared with islet transplantation following 12 weeks of diabetes (31). With regard to inflammation associated with diabetic vascular disease, aortic endothelial cells from mice subjected to a hyperglycemic clamp for 3 h displayed significantly increased expression of the pro-inflammatory NFκB p65 subunit (encoded by RELA) that persisted for up to 6 days beyond normalization of blood glucose (32). Consistent with these observations, primary human endothelial cells exposed to transient high glucose concentrations exhibited activation of inflammatory pathways that were maintained following a return to physiological glucose conditions (32). Similar transient glucose exposure significantly increased expression of fibronectin and collagen IV that persisted in human endothelial cells despite reinstitution of normoglycemia (33).

Observations from epidemiological studies

Evidence from large-scale clinical trials clearly demonstrate that the duration of prior exposure to hyperglycemia influences the development and progression of diabetic complications in human patients. The ‘metabolic memory’ hypothesis where diabetic patients, despite improved glycemic control, develop complications as a result of prior poor glycemic control was established from results of the Diabetes Control and Complications Trial (DCCT) (34) and the Epidemiology of Diabetes Intervention and Complications (EDIC) follow-up observational study (35). The DCCT examined T1DM patients and compared the effects of intensive therapy to maintain blood glucose levels as close as possible to normal using strict insulin regimens, to conventional therapy for blood glucose control. At the conclusion of this study, the EDIC trial examined the long-term effects on diabetic complications of the original DCCT cohort. Both groups received therapy for blood glucose control that was at a level in the medium range between the intensive and conventional group of the DCCT study. At the conclusion of the DCCT, glycosylated hemoglobin (HbA1c) levels differed by approximately 2% between the two groups. However, toward the end of the EDIC study, HbA1c levels of both groups had converged to comparable levels (35). Intriguingly, despite this normalization of HbA1c, effects of the intensive therapy conducted for 6.5 years during the DCCT were persistently beneficial for at least 10 years with regard to microvascular complications. Recent investigations revealed that subjects who received continuous intensive treatment throughout both trials were at significantly lower risk of macrovascular complications including atherosclerosis (36, 37), cardiovascular disease and stroke (38).

Clinical studies have addressed the long-term benefits of glycemic control in patients with T2DM. The UK Prospective Diabetes Study (UKPDS) compared conventional dietary glucose control with intensive insulin therapy over 10 years and initially reported lower incidence of microvascular complications in the group that received intensive therapy (39). In accordance with the metabolic memory hypothesis, lower incidence of macrovascular complications in the intensive therapy group was observed when compared to the conventional treatment group 10 years post-trial (40). Together these trials indicate that early episodes of poor glycemic control initiate deleterious effects on the microvasculature that persist despite intensive treatment regimens and normalization of blood glucose in both T1DM and T2DM. The precise processes underlying this phenomenon are currently unclear. Understanding the molecular mechanisms that govern these lasting effects of hyperglycemia is a key objective toward treatment of the complications associated with diabetes.

Histone modifications associated with diabetes

The role of histone modifications in transcriptional regulation

The dynamic chromatin complex of DNA, nucleosomal histone proteins and additional modifying complexes serve not only the function of efficient DNA packaging, but also additional regulatory mechanisms of gene expression. Post-transcriptional covalent modification of chromatinized proteins has emerged as an exciting field of research revealing a multitude of reactions that contribute to the regulation of chromatin organization and transcriptional control. The repeating unit of the chromatin polymer is the octameric nucleosome comprised of approximately 147 bp of DNA two H3 and H4 homodimers and two H2A/H2B heteroderimers (41–45) (Fig. 1). Compaction of nucleosomal DNA forms transcriptionally repressive heterochromatin, where access of core transcriptional machinery to the DNA is prevented (46, 47). The relaxed configuration of euchromatin permits core transcriptional machinery access to the DNA sequence conferring transcriptional competency (48–50). Largely unstructured N-terminal tails extending from each histone protein harbor amino acid residues that are substrates for a variety of post-translational enzymatic modifications (3, 51). Methylation, acetylation, phosphorylation, ubiquitination and sumoylation of specific residues of predominantly H3 and H4 histones are associated with distinct transcriptional states through various mechanisms. Contrasting the histone acetylation characteristic of transcriptional activity (52–55), methylation of histone lysine and arginine residues can be associated with either transcriptional activation or repression, depending on the position of the residue and the degree of modification (56).

Histone modifications such as acetylation and deacetylation of lysine residues by histone acetyltransferases (HATs) and histone deacetylases (HDACs), respectively, directly affect chromatin structure by
Fig. 1. Structural chromatin configurations dictate transcriptional competency. The typical nucleosome is comprised of approximately 147 bp of DNA (solid black line) encircling an octamer of two copies of each of the four core histone proteins H2A, H2B, H3 and H4. Distinct transcriptional outcomes are associated with post-translational modification of specific histone residues, in concert with chromatin remodeling events. Modification patterns at lysine and arginine residues of histone tails can be associated with both gene activation and repression, depending on the residue position and modification type. The relaxed configuration of euchromatin permits core transcriptional machinery access to the DNA sequence conferring transcriptional competency. Compaction of nucleosomal DNA forms transcriptionally repressive heterochromatin, where access of core transcriptional machinery to the DNA is prevented.

Disrupting charge states of histone tails, altering their contact with adjacent histones as well as their affinity for DNA (41), leading to the unfolding of stable chromatin structures and a subsequent increase in accessibility to transcriptional machinery and associated factors (57). Second, histone modifications are implicated as high affinity-binding sites for recruitment of non-histone effector proteins, functional molecules responsible for the local remodeling of chromatin (58). Distinct modifications recruit specific functional complexes that subsequently confer differential transcriptional responses through spatial reorganization of nucleosomes (59–61). The catalog of protein complexes and binding domains that interact with various modified histones is increasingly expanding (62, 63). Enzymes responsible for the transfer and removal of histone modifications demonstrate strong specificity toward amino acid positions within histone tails (64). Furthermore, examples of functional interplay between post-translational modifications on histone tails within a single nucleosome or across adjacent nucleosomes are reported (65). A code that accounts for the combinatorial nature and cross talk of histone modifications has been proposed to significantly extend the level of complexity and information potential of the genetic code by dictating the transcriptional competency of a gene (3, 66, 67).

Histone modifications under diabetic conditions

Examples of changes to histone modifications have been observed under diabetic conditions that could account for altered gene expression associated with the disease. Monocyte expression of inflammatory cytokines in response to high glucose concentrations involves interaction between NFκB and HATs that leads to hyperacetylation and transcriptional activation (68–70). Methylation of lysine 9 of histone H3 (H3K9) is linked with altered expression of genes relevant to autoimmune and inflammatory pathways in lymphocytes from patients with T1DM (71). Gene silencing of the H3K9 methylation-writing enzyme Suv39h1 in human smooth muscle cells (SMCs) increased expression of inflammatory genes (72). Similarly, SMCs from diabetic db/db mice exhibit altered histone methylation patterns at promoters of key inflammatory genes such as MCP-1 and IL-6, including depletion of H3K9 methylation and enrichment for H3K4 methylation (72, 73). Increasingly studies have focused on identifying chromatin-controlled gene expression patterns that could allow genes to retain a memory of recent transcriptional competency and activity. The db/db SMCs revealed a persistent atherogenic and inflammatory phenotype compared to db/+ SMCs throughout ex vivo cell culture for up to 8 weeks, implying a metabolic memory of previous exposure (72).

Studies of glycemic variability have begun to elucidate the molecular processes that govern the sustained deleterious effects of hyperglycemia on the vasculature described by clinical studies. Transient exposure of primary human and bovine endothelial cells to high glucose concentrations induced transcriptional activation of the NFκB subunit p65 (encoded by RELA).
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and downstream activation of inflammatory NFκB-dependent promoters (32, 74). Despite restoration of physiological glucose concentrations, increased RELA expression persisted for 6 days suggesting a metabolic memory of prior hyperglycemic exposure and endothelial dysfunction (Fig. 2). Further investigation revealed that the sustained glucose-sensitive enrichment of H3 histones mono-methylated at lysine 4 (H3K4me1) and reduction of H3 histones methylated at lysine 9 at the RELA promoter paralleled the persistent gene expression profile. Structural and biochemical studies indicate that the Set7 (also Set9) lysine methyltransferase catalyses the transfer of a single methyl group to H3K4 (75–77) and can inhibit the transcriptionally repressive Suv39h1-mediated H3K9 methylation (76). Specific knockdown of this enzyme attenuated RELA promoter H3K4me1 enrichment and persistent gene expression in response to high glucose concentrations.

Thus Set7 may operate as a sensor of the hyperglycemic insult to activate and maintain transcriptional changes that could partly explain metabolic memory and the persistence of complications despite the restoration of glycemic control (Fig. 2). Accordingly, recent experimental findings demonstrate that high glucose concentrations promote nuclear localization of Set7 in human endothelial cells (78). Interestingly, this enzyme also participates in H3K4 methylation-dependent transcriptional activation of a subset of glucose-responsive genes in β-cells and primary islets (79) and TGF-β-mediated expression of extracellular matrix genes associated with mesangial fibrosis (80). It is therefore tempting to speculate roles for Set7 in the activation and persistence of altered gene expression associated with diabetic complications across numerous organs and tissues.

Characterization of glucose-responsive genes such as IL-8 and HMOX1 revealed both H3K4me1-dependent and H3K4me1-independent mechanisms of transcriptional regulation by Set7 (78). Indeed the detection of Set7 methyltransferase activity toward lysine residues of non-histone proteins including transcription factors has revealed previously unknown mechanisms of transcriptional regulation that may be important for diabetes and its complications (81). For instance Set7-mediated methylation and subsequent modulation of STAT3 transactivity in response to IL-6 stimulation (82) could play a role in the development and progression of diabetic nephropathy (83, 84).

Interestingly, overexpression of either manganese superoxide dismutase (MnSOD) or uncoupling protein 1 (UCP-1) (encoded by SOD2 and UCP1 respectively) prevented RELA activation by the inhibition of hyperglycemia-induced ROS accumulation (32, 74). Experimental observations have revealed mechanisms of epigenetic regulation of these genes that may be relevant to the diabetic phenotype. In particular, hyperglycemia induced tri-methylation of histone H4 at lysine 20 (H4K20me3) at proximal and distal regulatory regions of SOD2 in retinal endothelial cells. This modification significantly contributed to downregulation of SOD2 that interestingly remained repressed following reinstitution of normal glucose. Furthermore, paralleling previous observations of endothelial hyperglycemic memory, NFκB-p65 was also implicated in this sustained response (85). Similarly, UCP1 expression in brown adipose cells is regulated by dynamic changes in histone methylation. Specifically the Jhdm2a demethylase binds the UCP1 promoter to facilitate removal of the transcriptionally repressive H3K9me2 modification (86).

![Fig. 2](image-url). The Set7 lysine methyltransferase is a central mediator of endothelial hyperglycemic memory. High glucose concentrations promote nuclear translocation of Set7 in human vascular endothelial cells. This results in transcriptional activation of RELA, paralleling Set7 and H3K4me1 enrichment at the RELA promoter, and subsequent activation of downstream NFκB-p65-dependent genes. These changes were sustained for 6 days following restoration of physiological glucose conditions, indicating a memory of recent hyperglycemic exposure.
Covalent post-replicative methylation of DNA at the 5′ position of the cytosine ring of CpG dinucleotides is a classic example of epigenetic transcriptional regulation. DNA methylation is strongly associated with stable silencing of regulatory and coding regions by specific recruitment of chromatin remodeling complexes to establish transcriptionally repressive chromatin (87–89) and by preclusion of transcription factor binding (90). This modification necessitates the activity of DNA methyltransferases (DNMTs) through both de novo methylation by DNMT3A and DNMT3B, and maintenance methylation by DNMT1 whereby in the latter DNA methylation patterns are propagated across cell generations (91). Limited studies have addressed the role of DNA methylation in the pathology of diabetes, however several examples of altered methylation patterns have been observed for the diabetic phenotype.

The role of DNA methylation in gestational changes associated with diabetes

Altered patterns of DNA methylation provide strong candidacy to mechanistically link changes in gene expression to the developmental environment (92) (Fig. 3). Regulatory regions of mammalian genes are subject to dynamic methyl modifications during development (93). The local intrauterine and early postnatal environments can drive epigenetic changes early in life with persistent effects on metabolic gene expression profiles that may predispose individuals to T2DM. Early clinical findings demonstrated a strong correlation between low birth weight and later incidence of the disease (94). Similar findings were reported for analysis of the Helsinki Birth Cohort (95). A study conducted on a rat model of intrauterine growth retardation (IUGR) revealed that among other epigenetic processes, expression of pancreatic and duodenal homeobox 1 (PDX1) is silenced by DNA-methylation-driven transcriptional repression during transition from IUGR to diabetes in adults (96). Indeed PDX1 is a transcription factor that functions as a critical regulator of β-cell differentiation, growth and insulin secretion (97, 98). Changes in PDX1 are linked to T2DM and β-cell dysfunction in human and animal models (99–101). DNA methylation patterns of differentiated murine β-cells are established from a state of global hypermethylation to confer tissue-specific gene expression (102), suggesting a role for this modification in the regulation of insulin expression. Analysis of similar experimental models of growth restriction revealed DNA hypermethylation and decreased expression of hepatic insulin growth factor-1 (IGF-1) (103) and the rat hippocampal glucocorticoid receptor (hpGR) genes (104). Similarly, direct environmental factors such as nutrition can be epigenetically assimilated through gestation and early post-natal development to direct metabolic gene expression. Dutch and Chinese middle-aged men exposed to maternal starvation at developmentally crucial periods of gestation were found to have much higher rates of T2DM (105, 106). Some evidence suggests that DNA methylation may link prenatal famine to diabetes through decreased...
methyltion of the imprinted IGF2 gene (105) and sex-specific hypermethylation of GNASAS and LEP (107). Animal studies have provided useful insight to additional DNA-methylation-regulated loci relevant to obesity and the diabetic phenotype that could be established through childhood and adulthood (108). For instance, high fat diets induce hypermethylation of the hepatic glucokinase and t-type pyruvate kinase promoters in obese rats (109). It is therefore reasonable to speculate a contribution of DNA methylation to the changes in gene expression observed in adult diabetic patients (110). Though this is an exciting area of research, reported studies of DNA methylation patterns of tissues derived from diabetic patients are limited. Compared to healthy control subjects, DNA hypermethylation at the peroxisome proliferator-activated receptor-γ coactivator 1α (PPARγCoA1) promoter and concomitant transcriptional repression was observed in pancreatic islets isolated from patients with T2DM (111). Genomewide promoter methylation analysis of skeletal muscle from patients with T2DM revealed similar observations (112). Expression of this gene is linked with insulin secretion and a recently described polymorphism in the coding region is associated with increased risk for T2DM (113). Combined with the aforementioned correlation of PDX1 promoter hypermethylation to islet dysfunction and development of T2DM in animal models (96), this observation suggests a link between DNA methylation and pancreatic dysfunction in diabetes.

DNA methylation in diabetic complications and metabolic memory

Studies have begun to examine the potential role of DNA methylation in the development and progression of diabetic complications (Fig. 3). Global DNA hypermethylation of peripheral blood leukocytes from patients with chronic kidney disease is associated with inflammation and increased mortality (114). Similarly, peripheral blood monocytes from diabetic patients with increased risk of cardiovascular disease exhibit significant changes in global DNA methylation relative to healthy controls (115). Studies of SMCs from human atherosclerotic lesions, human endothelial cells and animal models including high-fat fed ApoE-null mice identified associations between atherosclerosis and DNA hypomethylation (116–119). Changes to the DNA methylation status of key genes related to kidney disease were detected in saliva of diabetic patients with end-stage renal disease (120). Similarly, T1DM patients with diabetic nephropathy exhibit hypermethylation of the UNC13B promoter (121), a gene recently associated with diabetic nephropathy and proposed to regulate hyperglycemia-induced glomerular apoptosis (122).

Covalent methylation of cytosines is a robust modification in vivo that remains stable through experimental procedures such as DNA extraction (123). Not only does this permit thorough investigation of the modification in epigenetic studies per se, but also provides strong candidature for the involvement of DNA methylation in the establishment of long-term metabolic memory. However, limited studies have addressed the role of this modification in persistent changes in gene expression associated with diabetes. The progression of diabetic retinopathy is associated with mitochondrial DNA damage, and this has been linked with metabolic memory (124, 125). In vivo studies of streptozotocin-induced diabetic rats demonstrated persistent changes in the expression of DNA replication machinery associated with mitochondrial DNA after 3 months of strict glycemic control that followed 3 months of poor glycemic control. Significantly, continued hypermethylation and decreased transactivation of the POLG promoter was observed in the retina despite reinstition of euglycemia. Similar results were reported for bovine endothelial cells in vitro under a model of hyperglycemia variability (126).

Summary and conclusions

Investigations of the epigenetic processes underlying altered transcriptional regulation in the context of diabetes have increased rapidly over recent years particularly with the use of high-throughput sequencing technologies (127). Comprehension of the temporal and spatial molecular mechanisms that underlie synthesis of the final gene product is crucial to understanding the link between genomic regulation and the diabetic phenotype. Within this context, evidence for the general involvement of epigenetic mechanisms in transcriptional regulation has driven the proposition of a histone code (3, 66, 67). Whether these observations constitute a true histone code is often debated, as a strict code implies that definite patterns of post-translational histone modifications translate to a rigid functional outcome. Unlike the causal nature of the genetic code, it is more likely that combinatory patterns of histone modifications generate a biased chromatin landscape that generally correlates to a particular result. Specifically, certain combinations of modifications appear to subtly shift the chromatin context to favor competency for a specific transcriptional outcome (128). It is therefore critical that epigenetic modifications are not considered in isolation, but as interactive constituents of the chromatin landscape.

Epigenetic modifications including aberrant DNA methylation are associated with predisposition to T2DM through impaired intrauterine development and nutrition. Clinical and experimental studies have identified the importance of early and strict glycemic control in prevention or retarding the development and persistence of chronic diabetic complications. Emerging evidence indicate a key role for deregulated epigenetic transcriptional control in the pathogenesis of chronic complications associated with the diabetic phenotype. Continued exposure to the insults of the diabetic milieu is linked to altered expression of key genes across various organs and tissues that underlie the pathogenesis of diabetic complications. Studies of cell culture, animal models of diabetes as well as human samples have begun to distill the epigenetic mechanisms that connect the microenvironment of the cell to functional changes associated
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with the disease. These observations include changes to histone modifications and DNA methylation and have been reported for the relatively vulnerable microvasculature of the retina and kidney as well as macrovascular complications. Mechanisms underlying these transcriptional events have begun to be elucidated in cell culture and experimental animal models. Histone methyltransferases including the activating Set7 and repressive Suv39h1 are implicated in this process and future epigenomic profiling will undoubtedly uncover other potential therapeutic targets. The emerging field of microRNA (miRs) research may also provide insight in to changes in gene expression associated with diabetes. Several genes that participate in crucial pathways that are deregulated in diabetes are regulated by miRs (129, 130), most significantly TGF-β signaling in diabetic nephropathy (131, 132). Furthermore, examination of epigenetic mechanisms of miR precursor expression may reveal further pathways to be targeted for therapeutic intervention.

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