

MINI REVIEW

# Complications of diabetes: an unsolicited epigenetic memory



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## ABSTRACT

Diabetes is a multifactorial disease, characterized by hyperglycemia and insulin resistance. Diabetic microvascular end points such as retinopathy, cardiomyopathy and nephropathy; and macrovascular complications such as myocardial infarction and stroke are causing premature death in diabetic populations. Despite strong familial clustering is associated with diabetes, the essential role of epigenetic component in the development of diabetes and its complications is inevitable. Several clinical trials and experimental animal studies show the persistence of diabetic vascular complications even after the normalization of glucose in diabetic patients, indicating the role of epigenetic or metabolic memory. Although previous researches on diabetes implicated the role of reactive oxygen species in the pathogenesis and development of diabetic complications, lifestyle factors including diet and exercise and environmental factors are strongly associated in inducing epigenetic changes related to diabetic risk.

**Keywords:** *epigenetics, diabetes, metabolic memory, type 1 diabetes, type 2 diabetes, DNA methylation, histone modification*

## Introduction

Epigenetics represents all heritable or non-heritable changes in gene function that occur without a change in the sequence of nucleotide. Methylation of DNA, modifications of histones, and interference of RNA are the main epigenetic control over the alteration of gene function.<sup>1</sup> Epigenetic changes are specific to tissues and crucial for the development and differentiation of the various cell types in an organism. Epigenetic changes, such as alteration in DNA and chromatin structures can be inherited through mitosis (transferred from one cell division to another) or meiosis (passed to the next generation of the species).<sup>1</sup>

Methylation of DNA mostly occurs at the cytosine nucleotide present in the genomic region called CpG islands, where cytosine is adjacent to guanine and they are rich in cytosine and guanine nucleotides. Nearly 40 % of the mammalian gene promoters contain CpG islands, which are about 300–3,000 base pairs in length. The enzyme DNA methyltransferase (DNMT) adds a methyl group at the fifth position of cytosine nucleotides using s-adenosyl methionine as the methyl donor. The methylation of cytosine nucleotides in the CpG island results in silencing of the genes possibly through restricting the binding of transcriptional factors at promoter region

whereas, the hypomethylation of CpG islands results in enhanced gene transcription.<sup>2,3</sup>

Histone modification is another epigenetic modification regulating the expression of genes. Eukaryotic DNA is tightly packed with the help of histones to a fundamental unit called nucleosomes. A nucleosome consists of 146 base pairs of DNA wrapped around an octamer of histones, containing two copies each of the histones H2A, H2B, H3 and H4. The histones present in the nucleosome can undergo many types of reversible modifications, such as methylation, acetylation, phosphorylation, and ubiquitination. The acetylation and deacetylation of histones occurs at a specific lysine residue present in the histones. The acetylation of histones is carried out by the enzymes histone acetyltransferases (HAT) that results in the change of allosteric interactions in the nucleosome that ease the binding of transcriptional factors to the DNA. The deacetylation of histones is carried out by the enzymes histone deacetylases (HDAC), resulting in producing a heterochromatin that leads to the inhibition of gene transcription.<sup>4,5</sup> The methylation of histone is carried out by the enzymes histone methyltransferases using s-adenosyl methionine as a methyl donor. Only, lysine (K) and arginine (R) residues (both contain amino groups) present in the histones H3 and H4 are found to be

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methylated. The methylation at H3K4, H3K48, and H3K79 are associated with gene activation. Whereas, the methylation at H3K9 and H3K27 are associated with gene inactivation.<sup>4</sup>

Epigenetic regulation of gene expression is attained at the post-transcriptional level by microRNAs (miRNA), which are 21–25 nucleotide long, single-stranded non-coding RNAs. The miRNAs binds to messenger RNA (mRNA) and destroys it through forming RNA-induced silencing complexes (RISC). miRNAs plays a major role in the regulation of cellular differentiation, proliferation and apoptosis.<sup>6,7</sup>

### Metabolic memory in diabetes

The persistence of diabetic vascular complications even after the normalization of glucose in diabetic patients is referred as “metabolic memory”. Large-scale clinical trials such as Diabetes Control and Complications Trial (DCCT)<sup>8</sup> and the Epidemiology of Diabetes Intervention and Complications (EDIC) follow-up observational study<sup>9</sup> show in diabetic patients that despite improved glycemic control, the patients develop complications as a result of prior poor glycemic control. However, recent investigations revealed that subjects who received continuous intensive treatment throughout the trials were at significantly lower risk of macrovascular complications including atherosclerosis cardiovascular disease and stroke.<sup>10–12</sup> Experiments in diabetic dogs<sup>13</sup> and in diabetic rats<sup>14</sup> showed that the improved glycemic control failed to prevent the progression to diabetic retinopathy. Similarly, in-vitro studies in aortic endothelial cells from mice and in primary human endothelial cells prove that the activation of pro-inflammatory genes were continued for several days after the normalization of glucose concentration.<sup>15</sup>

### Epigenetic regulation in diabetes

DNA methylation of long interspersed nucleotide element 1 (LINE-1) sequences measured in the peripheral blood of diabetic patients was significantly associated with a higher risk for metabolic worsening, and these results highlight the important role for epigenetic biomarkers as predictors of type 2 diabetes mellitus risk.<sup>16</sup> Lymphocytes from patients with type 1 diabetes mellitus showed an altered methylation at lysine 9 of histone H3 (H3K9) and which is correlated with the expression of genes involving autoimmune and inflammatory pathways.<sup>17</sup> A decreased methylation at H3K9 and enhanced methylation at H3K4 were observed at the promoters of inflammatory genes such as MCP-1 and IL-6 in

smooth muscle cells obtained from diabetic db/db mice.<sup>18,19</sup> Moreover, the smooth muscle cells from the db/db mice retained the inflammatory phenotype up to eight weeks in ex vivo cell culture, indicating the metabolic memory.<sup>19</sup> High glucose concentration in monocytes causes interaction between NF $\kappa$ B and HATs that leads to hyperacetylation and transcriptional activation of genes related to inflammatory cytokines.<sup>20,21</sup>

The Set7 lysine methyltransferase may operate as a sensor for hyperglycemic insult and in mediating the metabolic memory in human endothelial cells.<sup>22</sup> High glucose in human vascular endothelial cells induces the nuclear translocation of Set7, resulted in enhanced methylation at H3K4 and a decreased methylation at H3K9 of the RELA promoter leading to the activation of NF $\kappa$ B-p65-dependent genes.<sup>22</sup> In retinal endothelial cells, hyperglycemia induced trimethylation of H4K20 at the regulatory regions of SOD2 leading to a decreased expression of SOD2 even after restoring the normal glucose values.<sup>23</sup> Moreover, the expression of UCP1 in brown adipose cells is decreased after Jhdm2a demethylase binds to the UCP1 promoter leading to the formation of transcriptionally repressive methylation at H3K9.<sup>24</sup> Helsinki Birth Cohort and other clinical findings show a strong correlation between low birth weight and later incidence of the diabetes.<sup>25,26</sup> Hypermethylation at the promoter of peroxisome proliferator-activated receptor- $\gamma$  coactivator 1 $\alpha$  (PPARGC1A) was associated with the transcriptional repression in pancreatic islets isolated from patients with type 2 diabetes mellitus.<sup>27,28</sup> In experimental animal models, hypermethylation-induced suppression of pancreatic and duodenal homeobox 1 (PDX1)<sup>29</sup>, and hepatic insulin growth factor-1 (IGF-1)<sup>30</sup> have been observed.

### Concluding remarks

Type 1 diabetes mellitus is caused by autoimmune destruction of pancreatic  $\beta$ -cells; whereas type 2 diabetes mellitus is mainly caused by the improper control of blood glucose and its utilization. Despite strong familial clustering is associated with type 2 diabetes mellitus, the essential role of epigenetic component in the development of type 2 diabetes mellitus is inevitable.<sup>31,32</sup> Although previous research studies on diabetes essentially indicate the role of mitochondrial reactive oxygen species in the pathogenesis and development of diabetic complications,<sup>33</sup> emerging studies pointing towards the indispensable role of epigenetic or metabolic memory caused by the prior existence of hyperglycemia in diabetic patients.<sup>5</sup> Recent studies in

humans show that short term high fat overfeeding introduced widespread DNA methylation changes affecting over 6,500 genes in human skeletal muscle<sup>34</sup>, and genome-wide DNA methylation analysis identified several candidate genes influencing insulin secretion in human pancreatic islets from type 2 diabetic patients.<sup>35</sup> Treatment with epigenetic modulators, which can have the potential to erase the epigenetic or metabolic memory associated with the prior existence of hyperglycemia, and can postpone the development of diabetic complications. Recently, inhibition of HDAC3 has been suggested for type 1 and type 2 diabetes; however, diabetic treatments with epigenetic modulators are still at an infancy stage.<sup>36,37</sup> Overall, in evaluating the risks for diabetes, the epigenetic changes induced from the lifestyle factors including diet and exercise in adults and in children and environmental factors should be strongly considered.

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### Conflict of interest

None.

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