Epigenetic Mechanisms of Metabolic Memory in Diabetes

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Diabetes affects 28.5 million people in the US. In addition, several million people with diabetes are estimated to be undiagnosed, thus increasing the risk for developing long-term complications, including macrovascular diseases and end-stage renal disease in a fairly significant fraction of the population. Type 1 diabetes, an autoimmune disease that mainly afflicts children, is characterized by the loss of insulin-producing beta cells. Until now, our understanding of this insidious disease relied on classic genetic approaches including genome wide association studies and single nucleotide polymorphisms. Although 40 immune response related genes have been implicated in type 1 diabetes, we are far from understanding how these genes render susceptibility to this complex disorder. Type 2 diabetes is common among people >45 years of age and characterized by the lack of serum autoantibodies, progressive insulin resistance, and beta cell insufficiency. Despite the differences in the etiology, both type 1 and type 2 diabetes are associated with microvascular complications such as diabetic nephropathy, neuropathy, and retinopathy, as well as macrovascular cardiovascular diseases including atherosclerosis, hypertension, and stroke. Tight glycemic control for 3 to 5 years may prevent cardiovascular disease but not all diabetes-related endpoints, referred to as the hyperglycemic memory or the legacy effect. Although it is unclear how the external cues such as hyperglycemia is perceived as a signal for gene transcription, several intracellular events including generation of oxidative stress and advanced glycation end products, and engagement of the mitogen activated protein kinase pathway have been implicated in metabolic memory (Figure). Recent data indicated a role for epigenetic mechanisms in a preclinical model of type 1 diabetes. Although gene-environment interactions have been implicated in the manifestation of type 2 diabetes, compelling evidence for the involvement of epigenetic mechanisms in the initiation and transmission of the metabolic syndrome to the offspring is not robust. However, accumulating evidence is consistent with a role for epigenetic mechanisms in the manifestation of hyperglycemia-induced diabetic vascular complications.

Several in vivo and in vitro models were developed to complement clinical trials of metabolic memory. Although retinal complications were observed a long time ago in diabetic dogs even after switching to normal glucose control, the underlying mechanisms remain poorly understood. A seminal paper more than 2 decades ago described that rats treated with streptozotocin, a nonspecific cytotoxic agent, induced chronic hyperglycemia and increased the expression of fibronectin mRNA in the kidney cortex, which remained elevated for several weeks even after the maintenance of near-normal glucose levels by exogenous insulin administration. To facilitate the investigation of the mechanisms of hyperglycemic memory, these authors developed an in vitro model in which human umbilical vein endothelial cells were exposed to hyperglycemia. Although the expression of both fibronectin and collagen IV was increased in cells cultured under hyperglycemic condition, cells that were switched to normal glucose level continued to display elevated expression of these genes albeit at lower levels than those cultured continuously in high glucose containing media. Although epigenetic mechanisms were postulated in metabolic memory, these possibilities were explored only recently.

Epigenetic mechanisms including DNA methylation and histone modification represent a paradigm shift in our understanding of changes in gene expression under pathological conditions. Hypomethylation of CpG (cytosine-phosphoguanine) sites at the promoter region generally correspond to gene activation. Methylation of CpG dinucleotides at the promoter region interferes with the binding of transcription factors and promotes the binding of methyl-CpG-binding domain proteins, which in turn recruit histone deacetylases, leading to gene repression. Analysis of methylation levels at the promoter of the insulin-sensitizing adiponectin gene in the placenta indicated that they could serve as an epigenetic adapter of glucose levels in utero. Elucidation of methylome landscape will advance our understanding of the regulation genes underpinning the metabolic memory.

Modification of lysine residue in the histone tail by methylation is a remarkably complex process, involving mono-, di, or trimethylation at highly conserved positions, which often clusters within specific regions resulting in the organization of chromosomes into distinct structural and functional domains. Bovine aortic endothelial cells exposed to high glucose upregulated the expression of the NFκB subunit p65 gene, accompanied by monomethylation of histone 3 at lysine 4 (H3K4m1) but not dimethylation (H3K4m2) or trimethylation of histone 3 at lysine 4 (H3K4m3). Hyperglycemia also had other epigenetic effects, including the suppression of diethylation (H3K9m2) and trimethylation of H3 at lysine 9 (H3K9m3) in this system. Relevance of histone lysine methylation to gene expression under diabetic conditions was indicated by the constitutive dimethylation of H3K9 at 2 candidate genes in peripheral blood monocytes derived from type 1 and type 2 diabetes.

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Environmental cues: Hyperglycemia, Infection, Drugs

Epigenetic modulation:
DNA methylation
Histone methylation
Histone acetylation
Non-coding RNA
Nucleosomal repositioning

Set7
LSD1
DNMT1

Metabolic responses:
Oxidative stress
MAPK
Advanced glycation end products

Regulation of gene expression

Microvascular and Macrovacular complications, Atherosclerosis, End organ disease

Figure. A model depicting the epigenetic mechanisms involved in metabolic memory. Environmental cues such as hyperglycemia can employ epigenetic mechanisms to alter gene expression, leading to diabetes-associated complications. Exposure to transient hyperglycemia is associated with metabolic changes including the engagement of the mitogen activated protein kinase (MAPK) pathway. The resulting nuclear translocation of Set7 influences gene expression as a consequence of interaction with DNA methyl transferase 1 (DNMT1), which in turn is influenced by lysine specific demethylase 1 (LSD1).

The fact that not all diabetic patients develop debilitating consequences including end-stage renal disease indicates that an important determinant in the metabolic memory is the genetic background of the responder cell. Although the genetic background has been suspected to contribute to the legacy effect, this viable possibility has not been fully elucidated. Another important piece of the puzzle in understanding the mechanisms of metabolic memory is how the extracellular cues like high levels of glucose are translated into an intracellular signal triggering the nuclear translocation of the methyltransferase Set7 enzyme engendering subsequent events (Figure). Other epigenetic mechanisms of differential susceptibility of vascular endothelial cells to hyperglycemia may include gene regulation mediated by noncoding RNA and nucleosomal repositioning (Figure). It appears that in conjunction with undefined genetic factors, epigenetic mechanisms can fine-tune the regulation of genes involved in diabetic complications. Although mortality due to ischemic cardiac disease is higher among type 1 diabetes patients than in the general population, cardiovascular complications in type 2 diabetes patients receive greater attention. Further work is necessary to fully understand the impact of epigenetic mechanisms on complications of type 1 and type 2 diabetes, which may lead to designing novel treatment strategies for both patient populations.

Disclosures
None.
References


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