

Epigenetic pathways in type 2 diabetes and its complications

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This article is available from:
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Abstract

Diabetes has reached epidemic proportions throughout the world. Increasing evidence suggests that complex interactions between genes and the environment might play a major role in the pathogenesis of this multifactorial disease and its complications, and this might be a result of the involvement of epigenetic factors. Recent studies show that epigenetic factors, including DNA methylation and histone modification, may affect the susceptibility for type 2 diabetes and the progression of their complications. However, molecular mechanisms linking environmental factors and type 2 diabetes still remains limited.

Keywords: Epigenetics, Type 2 diabetes, DNA methylation, Histones.

Introduction

Diabetes is undoubtedly one of the most challenging health problems in the 21st century. The estimated worldwide prevalence of diabetes among adults was 366 million in 2011; by 2030 this will have risen to 552 million. Type 2 diabetes is the predominant form and accounts for at least 90% of cases. 80% of people with diabetes live in low- and middle-income countries; the greatest numbers of people with diabetes are between 40 to 59 years of age [1, 2].

Type 2 diabetes mellitus is a polygenic multifactorial disease characterised by hyperglycaemia and altered lipid metabolism due to impaired insulin secretion from pancreatic β -cells. Today, it is well established that combinations of non-genetic and genetic risk factors influence the susceptibility for type 2 diabetes. While obesity, physical inactivity, and aging represent non-genetic risk factors for type 2 diabetes, genome-wide association studies have identified more than 40 polymorphisms associated with an increased risk for the disease [3-7].

Recent studies show that epigenetic factors, including DNA methylation and histone modification, may affect the susceptibility for type 2 diabetes [8]. However, molecular mecha-

nisms linking environmental factors and type 2 diabetes still remains limited. This review will provide some insights into epigenetic mechanisms associated with type 2 diabetes.

Overview of epigenetic mechanisms

Epigenetic is presently described as the study of changes in gene expression that occur not by changing the DNA sequence, but by modifying DNA methylation and remodeling chromatin. In recent years, major advances in the understanding of epigenetic mechanisms have established them as key players in several cellular processes including cell differentiation, aging, DNA replication, and repair [9-12].

The major epigenetic mechanisms are DNA methylation, histone modifications and modulation of gene transcription and translation by non-coding RNAs, including miRNAs. DNA methylation is a genomic modification that can influence gene activity. It occurs almost exclusively at the cytosine of CpG dinucleotides, which tend to cluster in regions called "CpG islands". The primary function of DNA methylation is to actively silence genes and DNA regions in which transcription is not desired [13].

The modifications of the histones result in conformational changes of the chromatin that alter the access of promot-

ers for transcription factors. These modifications, including acetylation, methylation, phosphorylation, and ubiquitination, alter the interaction between the histones, DNA and nuclear proteins, therefore affecting gene transcription and regulate gene silencing or expression [13].

A third mechanism involves the expression of short noncoding RNAs, whose expression can lead to translational silencing through the specific binding and eventual degradation of transcribed RNA. MicroRNAs (miRNAs) can also regulate DNA methylation and histone modifications [14].

Epigenetic pathogenesis for Type 2 diabetes

Epigenetic research into of type 2 diabetes (T2D) is still a very young field. The role of epigenetic mechanisms in the etiology of these disorders and related metabolic abnormalities such as obesity, dyslipidemia, hypertension, and hyperglycemia is not well elucidated. 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 (**Figure 1**).

Important evidence for a role of epigenetic factors in the pathogenesis of T2D comes from a data-mining analysis of more than 12 million Medline records [15]. The study found that methylation and chromatin are top hits, implicitly related to T2D.

The epigenetic of T2D is the interaction between gene activation and epidemiology, where gene activation can be in the form of DNA methylation, histone modification or RNA

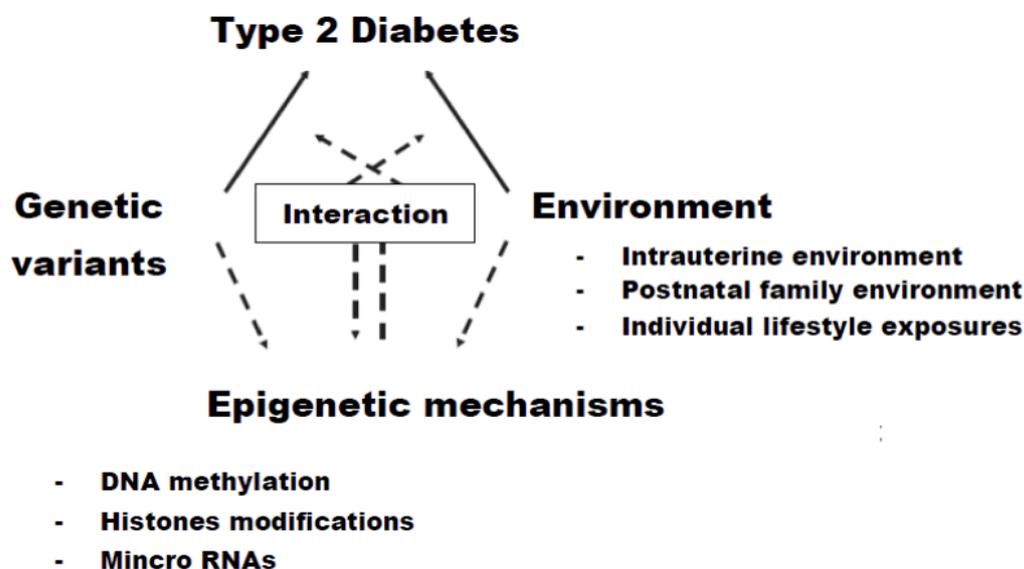
activation. This could be affected by different epidemiological factors, namely age, obesity, nutrition, physical activity and intrauterine environment [16-18].

Epigenetic mechanisms such as DNA methylation and histone modifications are increasingly considered to be important in phenotype transmission and the development of TD2. In differentiated mammalian cells, the addition of methyl groups to DNA occurs on cytosine residues, and these modifications are mostly established in the context of cytosine guanine dinucleotides (CpGs), a reaction that is carried out by various members of a single family of enzymes. DNA methylation is commonly associated with gene silencing and contributes to X chromosomal inactivation, genomic imprinting and transcriptional regulation of tissue- specific genes during cellular differentiation [16].

Although data mining analysis has suggested a role for epigenetic factors in the pathogenesis of type 2 diabetes [19], there are only a limited number of studies that have examined epigenetic changes in target tissues from patients with type 2 diabetes.

Functional study, evaluating epigenetics in human T2D tissue concerns Peroxisome proliferator-activated receptor gamma coactivator 1 alpha (also known as PGC-1a, and encoded by *PPARGC1A*), a transcriptional coactivator of mitochondrial genes involved in normal ATP-production and insulin secretion from the pancreatic beta cells, showed that the level of DNA methylation is increased in a promoter region of *PPARGC1A* in pancreatic islets from patients with T2D, as compared with islets from healthy human donors [20].

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



However, association between insulin sensitivity and *PPARG-C1A* gene expression in skeletal muscle has been investigated in previous studies with conflicting results. More recently, a paradoxical positive relationship between *PPARGC1A* DNA methylation and insulin action in skeletal muscle was demonstrated [21].

Moreover, a global analysis of DNA methylation in skeletal muscle revealed that people with a family history of T2DM have differential DNA methylation of genes involved in muscle function, insulin, and calcium signaling [22].

Furthermore, a link between histone modification and metabolism is evident from the observation that loss of histone demethylase (JHDM2A) function leads to obesity and decreased expression of metabolically relevant genes, including peroxisome proliferator-activated receptor alpha (PPARA) and uncoupling protein 1 (UCP1). Similar to DNA methylation, histone modifications also provide a molecular link between a sedentary lifestyle and the development of T2DM [19]. Recently, Jufvas A et al. have revealed a large genome-wide differences in the level of specific histone H3 methylation in adipocytes from subjects with overweight or T2D compared with normal-weight and non-diabetic subjects [23].

Clearly, the contribution of epigenetic regulation to the manifestation of metabolic disease remains to be completely described.

Epigenetic modifications and diabetic complications

Diabetes and metabolic disorders are leading causes of micro- and macrovascular complications such as atherosclerosis, hypertension, nephropathy, retinopathy and neuropathy. 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 [24].

Cardiovascular complications: remain the major cause of morbidity and mortality in the diabetic population. It is increasingly appreciated that exposure to high glucose is the major factor leading to these complications. Recent studies have proposed that hyperglycemia may induce epigenetic modifications of genes involved in vascular inflammation.

Such studies have led to the view that the transcriptional determinant, nuclear factor (NF)- κ B, which is readily activated by hyperglycemia, plays a pivotal role in diabetic vascular complications [24]. Furthermore, NF- κ B activation leads to the upregulation of molecules such as the chemokine, mono-

cyte chemotactic protein (MCP)-1, and adhesion molecules such as vascular cell adhesion molecule (VCAM)-1, which have been extensively investigated in atherosclerosis [25].

Epigenetic mechanisms such as posttranslational modification of histones and DNA methylation also play central roles in gene regulation by affecting chromatin structure and function. Recent studies have suggested that hyperglycemia-induced DNA methylation changes that persist into the metabolic memory state. The role of DNA methylation in the pathogenesis of cardiovascular diseases (CVDs) is not completely understood. Atherosclerosis was associated with global hypomethylation in vascular smooth muscle cells (VSMCs) of atherosclerotic lesions from humans [24].

In addition, several studies have implicated miRNAs in diabetes pathogenesis. However, the role of miRNAs in diabetes vascular complications is less studied. Evidence shows that miRNAs can affect the function of both endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) relevant to vascular diseases [27-29].

Diabetic nephropathy

In the diabetic nephropathy (DN), tubulointerstitial fibrosis, due to increased expression of extracellular matrix proteins such as collagens and fibronectins, is initiated and sustained by a number of different factors including the transforming growth factor-beta (TGF β) family. This family of inflammation mediators is documented to be aberrantly expressed in metabolic memory, implicating TGF- β as a major mediator of epigenetic events in DN [30, 31].

Diabetic retinopathy

A role for epigenetic mechanism in the pathogenesis of diabetic retinopathy (DR) has been recently proposed. The first of these manuscripts examined the control of VEGF (significant in both the early and late stages of DR) by miR-200b.

The second revealed that the activity of the matrix metalloproteinases MMP2 and MMP9 cause mitochondria DNA (mtDNA) damage and degradation of mitochondrial membranes in retinal capillary cells which in turn induces apoptosis of the same [32].

Conclusion

Diabetes is multifactorial disease involving interactions between genetic and environmental factors. Alarming estimates indicate that the rates of diabetes and associated complications are rapidly increasing, and therefore additional strategies to curb these trends are needed. Epigenetics provides a mechanism which may explain the etiology of diabetes and the diversity of phenotypes in the general population.

Although there is support for the role for epigenetics in the pathogenesis of diabetes and its complications, conclusive studies from human diabetes tissues are limited.

The perspective of epigenetic control is slowly growing from the view that genomic imprints are irreversibly fixed to the notion that epigenetic DNA modifications can be rapid, reversible, and responsive to both environmental and lifestyle inputs, it may thus be possible to test epigenetic drugs as putative novel drugs for the treatment of diabetes and its complications.

Conflict of interest

None.

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