糖尿病血管病变中的表观遗传现象

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【摘要】 糖尿病及相关的微血管和大血管并发症对公众健康构成了极大威胁,其高发病率和死亡率是造成社会经济负担的主要原因。最近研究指出表观遗传学可能在糖尿病血管病变中发挥重要作用,这种表型的变化并不涉及 DNA 序列的改变,然而可影响基因的表达并遗传给下一代。此外,大型临床试验 UKPDS 和 DCCT-EDIC 均证实代谢记忆的存在,即使血糖控制在理想状态,血管炎症仍能持续发生。尽管表观遗传现象尚未完全阐明,但为糖尿病的发病机制提供了新的思路,并有望成为难治性疾病的治疗靶点。

【关键词】 DNA 甲基化； 组蛋白修饰； 糖尿病血管病变； 代谢记忆

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Epigenetic phenomenon in diabetic vascular diseases

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【Abstract】 Diabetes mellitus and its associated micro- and macrovascular complications have posed a great threat to public health and become the main cause of morbidity and mortality burden to state economy. Recent studies have raised that epigenetics may play an important role in the pathology of diabetic vascular diseases, which refers to phenotype changes that are not related to the underlying DNA sequence, yet the alterations in gene expression can possibly be inherited into next generation. Furthermore, UKPDS and DCCT-EDIC demonstrate a phenomenon called metabolic memory, even if the blood glucose level is controlled in an ideal state, vascular inflammation still persists. Although epigenetics has not been fully elucidated, it provides a new insight into the pathogenesis of diabetes and is expected to become the targeted therapy for severe diseases.

【Key words】 DNA methylation； histone modification； diabetic vascular diseases； metabolic memory

Introduction The incidence of diabetes mellitus has increased at an unprecedented speed and caused widespread concern. Both type 1 and type 2 diabetes have accelerated rates of developing into vascular

complications, including microvascular complications such as diabetic nephropathy, retinopathy, neuropathy, and macrovascular complications such as cardiovascular diseases, hypertension and stroke[1]. Studies have demonstrated that diabetic vascular diseases can be triggered at the level of epigenetics[2], which includes DNA methylation, histone modifications, chromatin remodeling, genetic imprinting, random chromosome (X) inactivation, RNA interference, etc[3]. Hyperglycemia, dyslipidemia, increasing age or pharmacological intervention can lead to epigenetic changes, which in turn affect genomic stability and up-regulate or down-regulate genes expression. That is to say, epigenetics provide a link between phenotype and genotype, thus has a significant impact on diverse biological processes and are correlated with corresponding changes in pathophysiology[4-6]. In this review, we mainly elaborate the epigenetic phenomenon, particularly DNA methylation and histone modifications in diabetic vascular diseases. There are few reviews giving a comprehensive and systematic description of the pathogenesis of diabetes-related vascular complications from the epigenetic filed. Here we provide a more focused review which not only presents our own experiments data and the latest research results to improve the integrity and authority of our article, but also includes some clinical studies using inhibitors of epigenetic modifications to highlight the article values in guiding therapy.

DNA methylation   As the first epigenetic marker, DNA methylation has been extensively studied. DNA methylation is mediated by DNA methyltransferases (DNMTs) which transfer a methyl group from S-adenosyl-methionine (SAM) to the $5'$ position of the cytosine ring, generating 5-methyl-cytosine (5-mC)[7]. In mammals, this specific activation mainly occurs at the cytosine phosphate guanosine (CpG) di-nucleotides. However, parts of CpG di-nucleotides sequences, which contain high quantity of GCs, called CpG islands, mostly remain non-methylated[8]. Located at the promoters of regulatory genes, the abnormal methylation of CpG islands, generally hypermethylation, can lead to transcriptional repression or make the gene silencing[9]. The following three ways may be the underlying mechanisms either direct or indirect affecting genes expression: First, preventing transcription factors from binding to cognate DNA sequences. Second, recruiting additional inhibitory molecules, such as methyl-CpG-binding proteins (MBPs) and histone deacetylases (HDACs). Third, agglutination of chromatin structures may hinder the binding of transcription factors to its regulatory sequences[10]. Therefore, DNA methylation is associated with gene silencing, while non-methylation is associated with gene activating, and demethylation often correlates with re-activating of a silent gene[11].

Histone modifications   N-terminal amino acid residues exposed to the surface of the nucleosome are the major sites of post-translational modifications (PTM), including methylation, acetylation, phosphorylation, ubiquitination, ADP ribosylation and other covalent modifications. Different modified types of histones with different amino acid residues, often seen in lysine (K) or arginine (R), suggest the existence of " histone codes "[12], which determine the state of genes transcription either by affecting the affinity of histones and DNA duplexes to make chromatin structures loose or condensed, or by playing a gene regulatory role to affect transcription factors binding to promoter or enhancer regions. Histone lysine methylation is considered to be more stable and long lasting, it can be mediated mono-, di-, or trimethylation by specific histone lysine methyltransferases (HMTs). Lysine residues are usually methylated in H3 or H4, studies have shown that the methylation of H3 in lysine 4, 36, 79 sites activates the transcription of chromatin, while methylation in 9, 27 and H4 lysine 20 sites presents repressive marks[13]. Histone acetyltransferases (HATs) and histone deacetylases (HDACs) are both involved in the transference of an acetyl group from acetyl CoA. HATs have been considered activating marks,

which prevent the formation of highly condensed chromatin and promote genes transcription, while HDACs remove acetyl groups from lysine residues, generating counteractions[14]. The dynamic genes expression processes are regulated by a balance between the opposing activities of HMTs and histone lysine demethylases (HDMs), as well as HATs and HDACs[15].

DNA methylation under diabetic conditions
Increasing evidence shows that the level of DNA methylation varies under diabetic conditions. Recent reports manifested that β-cell dysfunction and insulin genes expression could be regulated by DNA methylation[16-17]. In another case, progressive epigenetic silencing through DNA methylation at the promoter of Pdx1 (a transcription factor that has an effect on β cell differentiation and gene activation) would lead to the development of diabetes[18]. In damaged diabetic islet, peroxisome proliferator-activated receptor-γ (PPARγ) was highly methylated at DNA CpG islands[19]. Several inflammatory genes relevant to atherosclerosis showed DNA methylation alterations in vascular smooth muscle cells (VSMCs) and endothelial cells (ECs). In addition, DNA methylation was considered to be linked with diabetic-associated cardiovascular diseases (CVDs) and chronic kidney diseases (CKDs). There was an increased level of homocysteine being identified as a risk factor for both CVDs and CKDs, activated mainly by inhibiting DNA methyltransferases, as reported in some studies[20-22]. DNA hypomethylation was generally seen in diabetic nephropathy (DN), while hypermethylation at the promoter of UNC13B (a gene known as an indicator of DN) was found in type 1 diabetes with DN[23]. Thus the role of DNA methylation in diabetic complications was still full of confusion and needed more investigations.

Results of our preliminary studies confirmed that high expression of interleukin-17 (IL-17) significantly accelerated the development of metastatic diabetes in NOD/SCID mice compared with siRNA-IL-17 and control groups, along with notably elevated levels of tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin-6 (IL-6) in peripheral blood[24-25]. In our follow-up studies, we found that diabetic rats′ aortas showed reduced DNA methylation levels at the promoters of IL-17, IL-6, TNF-α and IFN-γ compared with normal groups, in parallel with increased protein and mRNA levels of each cytokine, proved by Western blotting and real-time PCR, indicating that DNA methylation may be one of the potential mechanisms regulating diabetic vascular diseases. A new study identified that type 1 diabetes-associated DNA methylation variable positions arose early in the etiological process before diagnosis[26], suggesting it may be a useful clinical biomarker for early diagnosis of diabetes and its management.

Histone methylation-associated diabetic vascular diseases NF-κB is one of the major transcription factors activated in inflammatory pathways under diabetic conditions, which allows monocytes and macrophages to be assembled in the blood vessels and leads to macrovascular atherosclerosis[27]. Evidence indicated that the activating events of NF-κB P65 gene may be modulated by epigenetic modifications. Based on the crystal structure, Set7 acted as an unique mono-methyltransferase exactly targeting on H3K4, generating H3K4m1. Chromatin immunoprecipitation purification (ChIP) of bovine aortic endothelial cells which were previously exposed to hyperglycemia, found Set7 enriching at the NF-κB p65 gene promoter. However, when Set7 was silenced or knocked down by siRNA, NF-κB p65 gene failed to be induced under the same condition[28]. As a result, NF-κB p65 gene expression induced by hyperglycemia may be achieved through the pathway of H3K4 m1 catalyzed by Set7.

It has also been indicated that cytokines and chemokines such as IL-6, monocyte chemoattractant protein-1 (MCP-1) and macrophage colony stimulating factor-1 (MCSF-1) are detected in vascular smooth muscle cells (VSMCs) in both diabetes and atherosclerosis[29]. Until recently, researchers come up with the idea that aberrant changes of histone

modifications may influence inflammatory factors expression. H3K9m3 is a particular lysine residue trimethylated by Suv39h1，they may recruit other inhibitory complexes such as heterochromatin protein 1α（HP1α）and HDACs to further propagate suppressive marks[30]. Compared with db/+ control mice，IL-6，MCP-1 and MCSF mRNA levels were significantly increased in VSMCs of db/db mice（db/db refers to a model established for type 2 diabetes with insulin resistance），while H3K9m3 levels decreased at the promoters of inflammatory genes in accordance with reduced Suv39h1[31]. When db/db VSMCs were transfected with human Suv39H1，the over-expression and hypersensitivity could be reversed，suggesting that the enhanced inflammatory factors expression may be associated with loss of inhibitory histone modifications.

Lysine-specific demethylase 1（LSD1）is a nuclear amine oxidase that removes the methyl from H3K4m1 and H3K4m2，it can not only make loss of activated gene transcription signals，but can also demethylate H3K9m1 and H3K9m2，resulting in silent genes to be re-activated[32-33]. In high glucose，LSD1 enriched in the NF-κB P65 gene promoters，however，the occupancies of LSD1 were dramatically decreased at IL-6 and MCP-1 genes promoters in db/db VSMCs[34]. As discussed above，it is certain that LSD1 is linked to inflammatory genes expression events regardless of which one（H3K4 or H3K9）does LSD1 exactly act on. In summary，mutual suppression or mutual antagonism takes place in the process of histone methylation，respective methyltransferases and demethylases coexist a system which eventually leads to deleterious diabetic vascular diseases（Fig 1）.

Histone acetylation-associated diabetic vascular diseases In genome-wide analysis of primary human aortic endothelial cells，gene activation events were identified to be strongly correlated with hyperacetylation[35]. Islet specific transcription factor Pdx1 was found to promote β cell expression by recruiting HAT p300，while p300 inhibitor curcumin could prevent glucose-induced gene transcription and insulin secretion[36-37]. Kaur，et al found that p300 may regulate fibronectin expression via NF-κB and
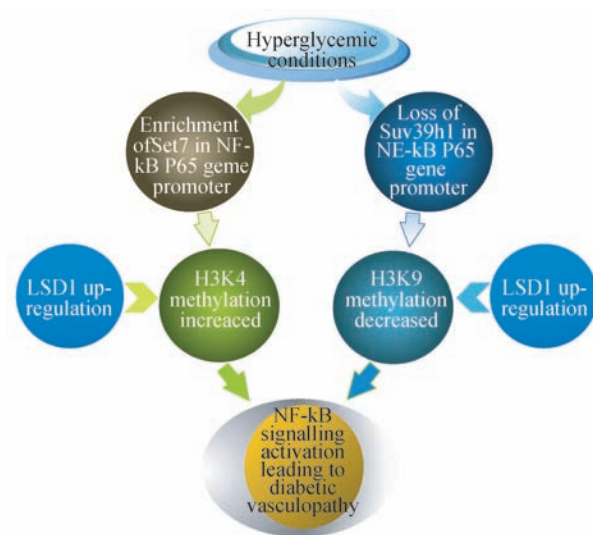

Fig 1   Proposed histone methylation mechanisms of hyperglycemia on vascular cells

poly ADP-ribose polymerase（PARP）activation in diabetes，leading to structural alterations such as basement membrane thickening and extracellular matrix（ECM）proteins like fibronectin and collagen deposition in tissues in chronic diabetic complications[38]. Studies further confirmed that the upregulation of glucose-induced histone methylation and acetylation were important up-stream epigenetic mechanisms，regulating genes expression of vasoactive factors and ECM proteins in endothelial cells，and were potential therapeutic targets for diabetic complications[39-40]. Moreover，IFN-γ could disrupt the expression of genes key to cellular metabolism and energy expenditure by repressing the activity of silent mating type information regulation 2 homolog 1（SIRT1）[41]. The NAD + dependent deacetylase SIRT1 has emerged as a critical coordinator of inner environment primarily by impacting deacetylation levels and thus fine-tuning the activation of key transcription factors involved in the inflammatory processes.

Interestingly，in a recent study by Zhong et al[42]，hyperglycemia was mentioned to enhance advanced glycation end products（AGEs）and reactive oxygen species（ROS），which stimulated HDACs（mainly HDAC1，HDAC2 and HDAC8）while inhibited HATs activity，resulting in an accelerated development of diabetic retinopathy.

The results are quite distinct，not only due to multiple cross-talk modifications in response to cellular "language"，but also because regulatory determinants are segregated into intricate pathways[43]. Nevertheless，HDAC inhibitors such as trichostatin A（TSA）are currently being tested as anticancer agents in clinical trials. Recent studies even demonstrated antifibrotic and renoprotective effects of HDAC inhibitors in diabetic kidneys，suggesting that HDAC inhibitors may prove to be a novel class of multitarget agents in the treatment of DN[44]. Crosson，et al provided the first evidence that suppressing HDAC activity could protect the retina from ischemic injury[45]. Although our knowledge of HDAC biology is very limited，the progress in understanding the role of HDAC inhibitors identifies epigenetic mechanism as a powerful tool for therapeutic intervention in tissue pathological lesion including diabetic vasculopathy.

Epigenetic role in metabolic memory Early or transient exposure to high glucose levels will induce long-lasting deleterious changes in the vasculature even after the patients have achieved normal glycemic control，which refers to "metabolic memory"[4] or "legacy effect"[46]. The Diabetes Control and Complications Trial（DCCT），and the subsequent Epidemiology of Diabetic Complications and Interventions Trial（EDIC）demonstrated that the progression of diabetic vascular diseases occurred in both conventional and intensive glycemic control groups，and this effect could continue to operate for more than 5 years though the glycosylated hemoglobin had normalized for a period of time[47]. The United Kingdom Prospective Diabetes Study（UKPDS）found that in type 2 diabetes lower fasting blood glucose at the time of diagnosis correlated with decreased risk of macrovascular diseases[48]，but there was no statistically significance whether tight glycemic control would lead to better outcomes. The Action in Diabetes and Vascular Disease Preterax and Diamicron Modified Release Controlled Evaluation（ADVANCE）and Action to Control Cardiovascular Risk in Diabetes（ACCORD）suggested that intensive glycemic control helped delay both micro- and macrovascular complications，but raised the question whether this strict treatment was beneficial to all diabetics[49-50].

In fact，metabolic memory phenomenon was first observed *in vitro* models more than 20 years ago. When the retina of diabetic dogs were placed in high glucose environment for 2.5 years and then switched to normal glucose level for another 2.5 years，the incidence of retinopathy was similar to the control group which in poor glucose all over the 5 years[51]. Endothelial cells cultured in high glucose could continuously express ECM proteins in spite of returning to subsequent normal glucose[52]. In addition，reinstitution of normoglycemia after previous short episodes of hyperglycemia still had good effects on retina，whereas achieving glucose control after persistent exposure to hyperglycemia failed to appear protection[53]. *In vivo* studies on rats showed that exposure from hyperglycemia to normoglycemia possibly led to irreparable damages of diabetic neuropathy[54].

Epigenetics is reported to be the underlying mechanism contributing to metabolic memory. When endothelial cells were incubated in high glucose（30 mmol/L）for a while then replaced in normal level（5 mmol/L），H3K4m1 and Set7 continued to increase at the NF-κB p65 gene promoter，and LSD1 was recruited along with the above changes，on the contrary，H3K9m3 presented sustained reduction[28]. This effect lasted for six days，during the short period of time，NF-κB dependent proteins MCP-1 and VCAM-1 also showed elevated expression levels[55]. When streptozotocin（STZ）-induced rats were either in poor glycemic control（PC，GHb＞11%）or in good glycemic control（GC，GHb＜6%）for 12 months，or in PC for 6 months and then in GC for 6 months，termination of hyperglycemia provided no benefits to retinal capillary cells，HDACs remained active and HATs kept compromised，revealing histone acetylation was important in this legacy effect，too[42]. Besides，epigenetic pathways of AGEs and ROS were manifested to play a key role in the persistent genes expression[56]. Although none of the experiments can solely clarify the phenomenon，when taken

together，the evidence strongly suggests that epigenetics are associated with metabolic memory，at least can partly explain it.

　　Conclusions　Hyperglycemia can incur epigenetic changes through provoking variousbiological pathways to dysregulate genes expression in vessels，and the persistent changes imply that epigenetics may be a contributor to metabolic memory. Epigenetics not only reveals the pathogenesis of diabetes in the levels of etiology and pathology，but also represents a new treatment to interfere or overcome diabetes and its severe complications because of the reversible modifications. In fact，some epigenetic drugs are being studied for cancer and other diseases，such as DNA methylation inhibitors and HDACs inhibitors. We have every reason to believe that epigenetics will become the most powerful and reliable tool to conquer diabetes and vascular complications.

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