Epigenetic Diabetic Vascular Complications

Ali Ahmadzadeh-Amiri 1 and Ahmad Ahmadzadeh-Amiri 2 , *

 Authors Information

Abstract

Diabetic vascular complications (DVC) influence several vital organ systems including cardiovascular, renal, ocular and nervous systems making it a major public health problem. Although extensive researches were performed in this field, the exact mechanisms responsible for these organ damages in diabetes remain obscure. Several metabolic disturbances have been involved in its complication and change in genes associated with these pathways occurred. Gene expression to produce a biologically active protein can be controlled by transcriptional and translational alteration on the head of genes without change in nucleotide composition. These epigenetic adjustments are steady, but possibly reversible and can be transmitted to future generation. Gene expression can be regulated by three epigenetic mechanisms including DNA methylation, histone modifications and noncoding microRNAs (miRNAs) activity. Epigenetic studies must be directed to better realize the role of epigenetic changes to the etiology of DVC and knowledge of epigenetic would play a pivotal role in the application of individualized medicine. Application and development of high technology sequencing combined with more sensitive and advanced methodologies for epigenome studying help to determine specific epigenetic events that stimulate gene responses in patients with diabetes mellitus.

Keywords: Diabetes Mellitus; Epigenetic; Vascular Complications

1. Context

Vascular complications of diabetes mellitus (DM) are categorized as either microvascular complications, such as diabetic retinopathy, diabetic nephropathy and diabetic neuropathy or macrovascular complications, including diabetic cardiovascular complications (1-3). Global burden of high prevalence diabetes are worldwide own to cardiovascular interventions and renal failure therapy (1). Long-term diabetes, poor control of blood glucose and elevated blood pressure are the major risk factors for diabetic complications (4). Some evidence showed that part of excessive risk of DVC may be due to genetic factors, independent of conventional clinical variables (5-8).

Epigenetic modifications are an emerging area in the pathogenesis of many diseases including diabetic microangiopathy. Epigenetic-induce gene expressions caused by systems other than those that alter the underlying DNA sequence, including DNA methylation, histone modification, and microRNAs, help to illustrate how cells with equal DNA can differentiate into different cell types with different phenotypes (9-12). Modified epigenetic can be transmitted from one cell generation to the next and also between generations of humans. Environmental factors can adjust genetic and epigenetic effects, making them important pathogenic mechanisms in complex diseases such as DM or DVC (13-15). Epigenome is precisely arranged and preserved by chemical modifications of the chromatin template. Epigenetic regulation also made by miRNAs through gene modifying enzymes for transcriptional control (16-18). The present review centered on the knowledge of epigenetic studies of DVC and collected data regarding susceptibility epigenetic alterations that impact DVC.

2. Evidence Acquisition

A PubMed literature search limited to English language from 2005 to 2015 was performed using the following search terms; epigenetic and diabetic retinopathy, nephropathy, neuropathy and diabetic macrovascular complications. Herein, qualitative results obtained from reviewed articles are presented and discussed.

3. Results

3.1. DNA Methylation

Addition of a methyl group on 5 regions of cytosine residues of CpG dinucleotides Island leads to DNA methylation. This region has regulatory role of most genes and commonly associated with transcriptional suppression. Life style and environmental exposures affect the methylation process and lead to inadvertent change that can be passed on for several generations (13, 14). Gene suppression occurred with DNA methylation at promoter CpG islands that was reported in the background of cancer and tumor repressor genes (19). Recent diabetic study showed that the insulin promoter DNA was methylated in embryonic stem cells and specifically demethylated in pancreatic β cells, indicating epigenetic adjustment of insulin expression (20). Another attractive recent study displayed increment of DNA methylation of the promoter of the peroxisome proliferator-activated receptor-γ (PPARγ) coactivator 1α gene (PPARGC1A) in diabetic islets (21). Hypermethylation of PPARGC1A promoter of nonCpG nucleotides was also occurred in skeletal muscles of patients with diabetes. Newly, DNA methylation profiling was performed in diabetic pancreatic islets and nondiabetic donors by Volkmar

(22). A recent study discovered 276 CpG loci related to promoters of 254 genes representing significant disparate DNA methylation in diabetic islets. These results showed that methylation changes were not available in blood cells of diabetic individuals, but compatible transcriptional changes were present for a subgroup of differentially methylated genes. Remarkably, a genome wide DNA methylation analysis has been performed in nephropathic patient of type 1 diabetes mellitus (23). DNA methylation profiling by investigators were performed in bisulphite converted DNA from cases and controls using genome wide DNA methylation approach providing the direct handling of 27578 individual cytosines at CpG loci centered on the promoter regions of 14495 genes. This finding demonstrated that 19 CpG sites were correlated with development of diabetic nephropathy. This consists of one CpG site that located in18 bp upstream of the transcription beginning site of UNC13B, in which SNP rs13293564 associated with diabetic nephropathy. This high operating platform was able to effectively inquire the methylation condition of individual cytosines and discern 19 next CpG sites related to risk of diabetic nephropathy. Briefly, these diversities in DNA methylation require further follow-up in repetition studies using greater cohorts of diabetic patients with and without nephropathy (24). Multiple evidences indicate that epigenetic modifications play a pivotal role in disease progression and treatment by means of methylation at specific CpG islands. Recently, Dnmt inhibitors 5-aza-20-deoxycytidine (5-Aza-CdR; decitabine; Dacogen) and 5-azacytidine (5-Aza-CR; azacitidine; Vidaza) have been approved by FDA for cutaneous T cell lymphoma and myeloid cancers. Moreover, a recent study indicated that methylation of VEGFR promoter could affect the effectiveness of VEGF-specific tyrosine kinase inhibitors on proliferating tissues (25). This is a promising target for diabetic patients encountering loss of vision due to retinopathy as VEGF is a major proliferative factor in the development of diabetic retinopathy.

3.2. Histone Modification

Chromatin, a composite structure of histones and nucleic acid plays an important role in gene expression. Histones have tetrameric structure, the nucleosome, histone 2A and B (H2A and H2B), H3 and H4 that act as spools around which DNA winds (26). Importantly, N-terminal of histones is susceptible for posttranslational alterations and can be acetylated, methylated and phosphorylated. Commonly, acetylation leads to gene activation and loosens the chromatin composition permit recruitment and binding of transcription factor and RNA polymerase II (27). Histone acetylating and deacetylating enzymes; histone acetyltransferases (HATs) add acetyl group while histone deacetylases (HDAC) regulate acetylation. Methylation with greater variation can be associated with either gene activation or repression and can happen at both lysine and arginine residues. Histone 3 (H3K4) of lysine is associated with gene activation, while histone 3 H3K9 of lysine is associated with gene suppression (28-30).

Regulation of several diabetic target genes have been shown to be related to histone acetyltransferases (HATs) and histone deacetylases (HDACs) (31, 32). Alteration in level of inflammatory gene expression occurred by adjusting NF-γB transcriptional activity. They also found that changes in monocytes histone

acetylation within the promoters of inflammatory genes were prominent in diabetes versus controls (33-35). Remarkably, histone acetylation at inflammatory gene promoters in a CREB/p300 (HAT)-dependent manner can be affected by oxidized lipids so that gene expression drives increased (36). In addition, PARP and NF-γB signaling was performed by p300 pathways in diabetic retina, kidney and heart, and led to extracellular matrix (ECM) components augmentation resulting in DVC (37-42). Research in epigenetic showed that HDACs play a crucial role in TGF-β1-mediated ECM generation and renal parenchymal fibrosis (43-45). While, lysine acetylation is a temporary histone modification, it is presumably that histone methylation can be more constant and can play pivotal roles in diabetes vascular complications. Human blood monocytes and lymphocytes studies demonstrated that cell-specific histone methylation patterns are relatively stable within cell types irrespective of age or gender (46-48). Stable histone methylation patterns that maintained in healthy individuals over a time in a cell type-specific manner can be impaired in a disease state, as revealed by epigenomic studies. Histone methyltransferase (HMT) SET7/9 impress regulating NF-γB expression and inflammatory gene expression through promoter H3K4 methylation in response to inflammatory diabetic stimulus (49-51). Furthermore, blood pressure control and fluid reabsorption are associated to dynamic regulation of H3K79 methylation (52-56). In addition, risk of diabetic complications increased as H3K4me and recruitment of SET7/9 to the insulin promoter region are augmented (38, 56). Hyperglycemic memory may implicate epigenetic modifications through a transient hyperglycemia (57, 58). Myocardial infarction makes HDAC activity along to decreased histone acetylation of histone H3/4 in the heart. Use of chemical HDAC inhibitors can reduce the risk of cell death and the infarct area (59). Inhibition of p65 acetylation-dependent NF-kB activation can occur by epigallocatechin-3-gallate, a strong HAT inhibitor; which could be considered potentially to inhibit the development of diabetic retinopathy (60). Regarding the effect of environmental and dietary factors on epigenetic modifications, many natural compounds have been found to have beneficial effects (61, 62). Resveratrol, a natural extract of red grapes, is involved in the adjustment of histone deacetylases (63). Curry spice such as curcumin, is shown to regulate a number of histone modifying enzymes and miRNAs, and our previous work showed that its curcumin improves retinal abnormalities in the setting of diabetic retinopathy (64-66).

3.3. miRNA

MicroRNAs (miRNA); 22-nucleotide noncoding RNAs can control gene expression posttranscriptionally by binding to supplementary sequences in the 3 untranslated areas of target mRNAs (16, 67). Posttranscriptional silencing can be occurred with miRNAs (68, 69). Principally, tissue response to environmental stimuli adjusted by miRNAs without changing DNA sequence with a prompt and returnable means of gene modulation. Epigenetic regulation of miRNAs may occur by histone modifications and changes in chromatin structure that result in miRNA transcription and expression (70). Moreover, noncoding RNAs and miRNAs may interact with transcriptional coregulators and use epigenetic control via transcriptional regulation (71, 72). Table 1 shows major organ systems adversely affected by diabetes through miRNA expression. MiRNAs can modulate genes implicated in biological processes such as cholesterol biosynthesis, fat metabolism, adipogenesis and insulin secretion, all of which are critical ways in the pathogens of diabetes (73-75). Special miRNAs consist of miR-192, miR-

216a, miR-217 and miR-377, have been involved in TGF-β signaling, which were implicated to DN (76-79). Suppression of miR-133a and miR-1 play an important role to muscle impairment in diabetic conditions (80-84). In addition, miR-1 and miR-133 were contributed in normal cardiac function (85, 86). Normal heart muscle hypertrophy from high levels of glucose exposure may develop from low levels of miR-133a (87, 88). Over-expressed miR-133 can impel QT interval prolongation in patients with diabetes (89). However, down-regulation of both miR-1 and miR-133a occurred in insulin-deficiency and in cardiac hypertrophy and heart failure (90, 91). Remarkably, a recent study found correlation between miR-126 levels and the onset of DVC was contradictory (92). Therefore, it appears that miRNAs and other epigenetic factors play crucial roles in the development of diabetes and its complications. Interestingly, the miRNA profile of insulin resistant tissues altered a long time before the onset of DM.

Table 1. miRNA and Diabetic Vascular Complications

4. Conclusions

It is apparent that diabetes can cause epigenetic alteration. One of the important epigenetic changes is DNA methylation and related chromatin alterations induced by elevated glucose in cells of multiple organs, which leads to metabolic recollection of diabetic vascular complications. Histone core alterations are returnable. Present estimation showed that approximately 30% of human genes are regulated by miRNAs. Provide evidence indicates that insulin production, secretion and action affected by miRNAs. Alteration in miRNA expression profiles occurs in many diabetic tissues such as liver, pancreas, heart and kidney. Mutually, alteration in tissue miRNA levels can raise diabetes progression. Moreover, novel advance in emergence of how to aim miRNAs in vivo may give exquisite guides for future diabetes and complications managements. Generally, epigenetic modifications are not instance; however, their unceasing response to environmental alteration, e.g. diabetes and chances of inherited transmission raise those interesting goals for long standing illness