

NEPHROPATHIC AND DIABETIC NEPHROPATHIC EVALUATION VIA EPIGENETICAL MODIFICATION

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ABSTRACT

Epigenetics, is the study of changes in gene expression but do not involve changes to the DNA sequence which in turn affects how cells read the genes. DNA methylation is also the process where the addition of a methyl group to part of the DNA molecule, which prevents certain genes from being expressed. Epigenetics also works through the histone modification, Acetylation of specific lysine residues on core histones is believed to result in uncoiling of the DNA. There are various diseases, including cancer, heart disease, diabetes, and mental illnesses are influenced by epigenetic mechanisms, and epigenetic therapy offers a potential way to influence them directly. When genes are silenced, their expression is reduced. Epigenetics play a major role against nephropathic and diabetic nephropathic conditions via epigenetical modifications in the specific genes.

KEYWORDS: DNA methylation, histones, uncoiling, diabetic nephropathy.

1. INTRODUCTION

Diabetic nephropathy is distinguished by proteinuria, hypertrophy in glomerular region, reduced glomerular filtration rate, and fibrosis in renal which results the loss of renal function.^[1] It was founded that 20% and 40% of patients with diabetes mellitus ultimately evolve nephropathy.^[2] It multiplies the risk of death, mainly due to causes in cardiovascular system, and is expressed by increased urinary albumin excretion (UAE) in the absence of other renal diseases. The categorization of Diabetic nephropathy is done into

stages: microalbuminuria (UAE 20 g/min and 199 g/min) and macroalbuminuria (UAE 200 g/min).^[3]

It is observed that globally, ~347 million people have diabetes and this number expected to increase more than 430 million by 2030.^[4] In elderly people, it was considered as a mild disorder. But now it becomes a major cause of morbidity and mortality affecting the youth and middle aged people.^[5] In India diabetes is getting rapidly the status of a potential infestation currently more than 62 million diabetic individual diagnosed. India (31.7 million) was having the top world with the highest number of people with diabetes mellitus in 2000. It is predicted that by 2030, In India around 79.4 million individuals may be afflicted by diabetes mellitus, which manifest significant increase. Currently, India faces a speculative future in relation to the prospective burden that diabetes may impose upon the country.^[6] On the basis of globally report, more males are diagnosed. It was founded in 2013 report that 14 million times more men affected with diabetes than women.^[7] Now a day's, nephrotoxicity is one of the most leading problem the reason behind that a lot of the drugs transport within the tubular cells is the first fundamental stage in the onset of the nephrotoxic process^[8] and the poor control of diabetic in patients can increase the microvascular complications (i.e. retinopathy, nephropathy and neuropathy), Diabetic nephropathy is closely associated with diabetic retinopathy, Patients with diabetic retinopathy have increased connective tissue growth factor (CTGF) in the vitreous and microvascular pericytes of the retina.^[9] Since diabetic retinopathy might be a reflection of systemic microvascular damage^[10], its presence and severity might influence plasma CTGF, which would also be reflected in the (filtered) CTGF level in urine.^[11] Relation between the diabetes and cancer has recently received more attention because of the alarming increase in the occurrence of diabetes.^[12] Type 2 diabetes increases the risk of pancreatic, colon and breast and some other type of cancers while type 1 diabetes causes or increases the risk of cervical, pancreatic, stomach and endometrial cancer.^[13] The risk of cancer increased if the level of glucose is high and the insulin level is high. High level of glucose supplies the high demand of tumor cell for glucose. And insulin is hormonal stimulator cause cellular proliferation. Hyperinsulinemia most likely favors cancer in diabetic patients as insulin is a growth factor with preeminent metabolic but also mitogenic effects, and its action in malignant cells. Obesity, hyperglycemia, and increased oxidative stress may also contribute to increased cancer risk in diabetes.^[14] Diabetes increases the production of free radicals which is a strong stimulus for the release of pro-inflammatory factors and cause nephropathy.^[15] Evidence suggests that factors associated with the

pathophysiology of diabetic complications and metabolic memory might also be influenced by epigenetic mechanisms in chromatin such as DNA methylation, histone lysine acetylation and microRNAs, and they can help to explain how cells with identical DNA can differentiate into different cell types with different phenotypes.^[16] Key histone modifications and the related histone methyltransferases and acetyltransferases have been implicated in the regulation of inflammatory and pro-fibrotic genes in renal and vascular cells under diabetic conditions.^[17] Nephrotoxicity is the major side effect which is caused by many of the drugs mainly anticancer and some antibiotics. This limits the action of these drugs.

1.1 Nephropathy:- Nephropathy is induced by injecting 5 mg/kg body weight of cisplatin. This results an increase in creatinine in serum and tubular damage in the outer stripe of the outer medulla in rats. The malondialdehyde (MDA) i.e renal content is transiently increased.^[18] Cisplatin's chief dose-limiting side effect is nephrotoxicity because kidney accumulates cisplatin to a higher degree than other organs perhaps via mediated transport. Functionally, reduced renal perfusion and a concentrating defect characterize its nephrotoxicity.^[19] *Azadirachta indica* can be considered a potential candidate for protection of nephrotoxicity induced by cisplatin.^[20] And the critical importance of OCT2 in the renal handling and related renal toxicity of cisplatin and provides a rationale for the development of new targeted approaches to mitigate this debilitating side effect.^[21]

1.2 Diabetic Nephropathy:- For screening purposes, Diabetes is induced by injecting a single dose of STZ (55mg/kg, intraperitoneally, dissolved in ice-cold sodium citrate buffer (0.01M, pH 4.4).^[22] And it results histopathological changes in the proximal tubules cells which contain organic cation (OCTs) and organic anion transporters (OATs), which regulate transepithelial transport of both organic cation and anion substrates OAT1 and OAT3 have been shown to play a major role in the basolateral uptake of OAs into the renal proximal tubular cell.^[23] And the factors involved in the pathologic glomerular microvascular alterations in response to hyperglycemia and the possible use of anti-angiogenic therapies for the treatment of diabetic nephropathy.^[24] In human and animal models that hyper secretion of TGF- β 1 triggered by diabetes might be a major cause of these processes, thereby contributing to diabetic nephropathy. Furthermore, in patients with diabetes, the level of intraglomerular TGF- β 1 mRNA was positively correlated with the staining intensity of collagen type IV in the mesangium, glomerular basement membrane, and Bowman's capsule. Recently, it was demonstrated that diabetic patients had increased renal production of TGF- β 1 protein.^[25]

2. Epigenetic mechanism involved in diabetes

DNA methylation analysis based on bisulfite conversion:-Exposing DNA to bisulfite rapidly leads to the deamination of unmethylated cytosines which will be converted to 6-sulfonyluracil. At high pH, 6-sulfonyluracil is desulfonated, which ultimately will translate into thymidine, while methylated cytosines will not be converted. Hyperglycaemia can lead to change DNA methylation.^[1] DNA methylation is associated with fibroblast differentiation and activation and the consequent build up of fibrotic scar tissue. The potential use of therapies that modulate this epigenetic pathway for the treatment of fibrosis in several organ systems will be beneficial.^[26]

2.1 Histone modification:-Histone acetylation and deacetylation are mediated by histone acetyltransferases (HATs) and histone deacetylases (HDACs), respectively. Acetylation of specific lysine residues on core histones is believed to result in uncoiling of the DNA and increased accessibility to transcription factor binding.^[27]

- HDACs play a regulatory role in physiological insulin signaling. HDACi increase GLUT4 translocation and augment basal and insulin-induced glucose uptake in skeletal muscle. This result was associated with decreased acetylation of IRS-1 and reduced insulin receptor-mediated tyrosine phosphorylation of IRS-1. Accordingly, inhibition of HDAC2 with TSA or RNAi-mediated knockdown inhibited deacetylation of IRS-1 and partially restored insulin signaling.^[28]
- HDAC1 over-expression mediated the reduction of the pVHL and p53 expression. The suppression of these genes resulted in the over-expression of HIF-1 α and VEGF, which was reversed by the use of the histone deacetylase inhibitor.^[29]
- Histone deacetylase inhibitors (HDACi) possess promising anti-inflammatory properties, as demonstrated by various cellular models of inflammatory diseases.^[30]
- HDACs were shown to be up-regulated in response to hypoxia mediating increased HIF-1 α signaling. HDAC inhibitors represent a new class of anti-cancer therapeutics which show great promise at inhibiting angiogenesis in pre-clinical animal models and early phase clinical trials.^[31]
- When proinflammatory transcription factors, such as NF- κ B, are activated, they bind to specific recognition sequences in DNA and then recruit coactivator molecules, such as p300, to the target gene promoters. These coactivator molecules control gene transcription, and most of them have intrinsic HAT activity. In contrast, histone

deacetylation mediates transcriptional repression by compacting chromatin, thereby limiting access to transcription factors.^[27]

2.2 Noncoding RNAs in diabetic Nephropathy

However, with the development of high-throughput platforms, the classical view of the molecular biology has changed.^[32] It has been reported that less than 2% of human genome is transcribed into RNA transcripts that can code protein.^[33] It means that most of RNAs are noncoding RNAs (ncRNAs) separated into long ncRNAs (more than 200 nucleotides in length) and small ncRNAs (less than 200 nucleotides).

2.3 miRNA

MicroRNAs (miRNAs) are obviously very small noncoding RNA molecules that are capable of silencing mRNA targets. Some miRNAs are considered to have renal functions because they are enriched in kidney only.^[34] Besides, miRNAs may have cell type and tissue-specific functions since different miRNA expression patterns were found in renal cortex and medulla.^[35] Many miRNAs involved in DN have been identified.^[36] Compared with nondiabetic control mice, several miRNAs (miR192, miR-200b/c, miR21, and miR-1207-5p) are upregulated in TGF- β 1-treated murine mesangial cells and in renal glomeruli of mouse models of diabetes. TGF- β 1 pathway is a master regulator of renal fibrosis, which plays an important role in DN.

2.4 lnc RNA

Long noncoding RNAs are defined as a large and diverse group of non-protein-coding transcripts longer than 200 nucleotides.^[37] Based on the association with nearby protein coding genes, the lncRNAs can be bifurcated into six groups: antisense (located in antisense orientation to a protein-coding gene), sense (overlapping a protein coding gene), bidirectional promoter (transcribed within 1 kb of promoters antisense to the protein coding transcript), intergenic (between two protein-coding transcripts), intronic (transcribed from an intron of a protein-coding gene), and enhancer (transcribed from an enhancer region of a protein-coding gene).^[38] Circular RNAs also have been identified as they form covalently enclosed circular structure, which usually come from splicing of a protein-coding gene.^[39] According to the mechanism of lncRNAs, they can be classified into four categories—signal, decoy, guide, and scaffold.^[40] By collection of the evidence has demonstrated that the RNA i.e noncoded (ncRNA) affects pre-mRNA processing, translation and transcription.^[41]

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