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Review Article

Epigenetic modifications and their role in the development and disease progression of type 2 diabetes

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ABSTRACT

Type 2 Diabetes is one of the major public health issues and a complex metabolic disorder strongly associated with genetic predisposition influenced by environmental factors and epigenetic regulation. This review paper illustrated the role of epigenetics in the pathogenesis, progression, and detection of Type 2 Diabetes. A review study was performed for the articles published in English from 2000-2019 using Pub Med, and Google Scholar databases. Main underlining mechanisms of Type 2 Diabetes were identified; insulin resistance in the peripheral tissue, and disintegrate insulin secretion. Genome Wide Association Studies suggested that epigenetic regulation such as DNA methylation, Histone modification, Non-coding RNA, microRNA is strongly related with the development of Type 2 Diabetes. Altered DNA methylation patterns in pancreatic islets, skeletal muscle, adipose tissue, from diabetic subjects compare to normal subjects was also found. Other risk factors like; obesity, age, gender, impaired glucose tolerance, periconception and intrauterine environment may also have been linked with the possibilities of epigenetic changes. Epigenetics plays a crucial role by modifying the gene expression and establish a relationship between the environment and genetic factors. Understanding the epigenetic mechanisms contributing to the development of Type 2 Diabetes is still limited.

Keywords: DNA methylation, Epigenetics, Epigenetic modifications, Type 2 diabetes

INTRODUCTION

Diabetes is a long-term condition with a significant effect on the well-being of individual, family, and societies. It is estimated, 463 million people were diagnosed as diabetic in the year 2019 worldwide, it is predicted that the number will rise to 578 million by 2030, and 700 million by 2045.[1] Three primary types of diabetes include Type 1 Diabetes (T1D), Type 2 Diabetes (T2D), and Gestational Diabetes (GDM). T2D is the most common form, consist of approximately 90% of all diabetes, with a rising trend with age, urbanization, and unhealthy lifestyle.[2] T2D is the most prevalent chronic metabolic condition in the developed countries, and T2D has escalated exponentially in the developing countries.[3] T2D is defined by a high blood glucose level resulting from insulin resistance. It is hastened by several risk factors like family history, obesity, rise blood pressure and high low-density lipoprotein (LDL) and low high-density lipoprotein (HDL) levels.[4] This complex disorder has a strong association with genetic and heritable predisposition, and some well recognized environmental factors such as food habit, physical activity, obesity; provide significant contribution to the pathogenesis, and both of these factors in disease progress possibly involves epigenetic modifications.[5]

Epigenetics is the linkage between genes, exposure to the environment, and disease development. It provides the molecular understandings of interactions between

environmental and genetic factors may involve in a disease process. Epigenetics is usually described as inherited changes in gene function that happens without changing the nucleotide sequence. Epigenetic regulation takes in the form of DNA methylation, histone modifications, and non-coding RNA.[6] Epigenetics is now one of the growing research areas in medicine as it involved in many biological processes which leads to several complex diseases, including T2D.

Recent epigenetic studies identified altered DNA methylation patterns in the pancreatic islets, skeletal muscle and adipose tissue from individuals suffering from T2D compared to normal person.[7] Compare to T1D, an autoimmune disorder, where the insulin-secreting pancreatic β cells are destroyed, in T2D insulin resistance occur in the peripheral tissues especially in the liver, skeletal muscle, adipose tissue which stimulate the pancreatic β cells to produce and secret an extra amount of insulin.[8] Although the initiation of T2D is known to be the consequences of multifactorial interplay, researchers revealed the secondary role of epigenetic mechanisms like DNA methylation, Histone modification and Non-coding RNA in the development and function of pancreatic β cell.[9] DNA methylation is the predominantly reviewed epigenetic change, and Genome-wide association studies (GWAS) have identified diverse DNA methylation patterns in the candidate genes that have vital roles in T2D.[10] The perspective of epigenetics in the disease pathogenesis was hardly studied in Bangladesh, especially for the non-communicable diseases like T2D. Considering the need, it is high time for epigenetic research to flourish in Bangladesh. The aim of this review paper is to provide the introductory idea of epigenetics as a link between environment, genetics, and development of T2D. In particular, this study will concentrate on the effect of DNA methylation to the pathogenesis, progression, and detection of T2D.

MATERIALS AND METHODS

Information sources: Database of Pub Med, and Google Scholar were searched to find articles related to the research interest.

Search strategy: The search was led by a list of pre-selected keywords. The search strategy was focused to review, and research articles; full text availability, and publication date was confined to 2000-2019. Keywords for search were confined to; type 2 diabetes, epigenetic changes, DNA methylation, obesity, parental obesity, β cell dysfunction, insulin resistance, environmental factors, diabetic complications, epigenetic biomarker.

RESULT AND DISCUSSION

Epigenetics

Epigenetics is "the study of changes in the gene functions that are mitotically and/or meiotically heritable and that do not entail a change in DNA sequence", usually this changes occur in a group of cell type but sometimes the changes may be clonal.[5] An epigenetic trait is a heritable phenotype; an epigenator is the distinct types of extracellular stimuli that mark the changes by sending appropriate signals; epigenetic initiator receives this signal and initiate a change in specific chromosome, that may persist even after the incentives has been withdrawn.[8] The main epigenetic mechanisms that affect the cell expression and regulation are DNA methylation, Histone modification and Non-coding RNA.[9] A closely monitored DNA methylation pattern is essential for normal gene transcription and regulation throughout the life, and epigenetic modifications of genomic activities may persist from generation to generation.[7] Irregularity of epigenetic mechanisms can guide to improper gene expression resulting in direction to many diseases.

DNA methylation

DNA methylation is the addition of the Methyl group covalently to the 5' position of the cytosine and form 5-methylcytosine (5-mc) with the help of DNA methyltransferase (DNMT1) enzyme.[11] This methylation mostly occurs in CpG island, although some non-CpG methylation has been dispatched in embryonic stem cell though its function is not so clear. CpG islands are the CpG dinucleotide rich region usually affiliated with the promoter region of the gene.[8] Unmethylated CpG regions at the gene promoter site loosen the tightly packed chromatin structure and promote the recruitment of transcription factors. In contrast, dense methylation of CpG islands directly inhibit the transcription factors to bind with the promoter region, jointly with the help of methyl-CpG binding domain proteins (MBDs).[5] DNA methylation in the enhancer region may also regulate the transcription of the distal promoter by binding with transcription factors and chromatin modelling proteins.8 DNMT1 is the primary enzyme for this methylation process, and it also needs the cooperation of DNMT3a/b enzymes. Sometimes 5-mc converts into 5-hydroxymethylcytosine (5hmc) catalyzed by Ten-eleven-translocation enzyme (TETs), it also oxidizes the 5hmc to 5- formylcytosine (5fc) and finally 5- carboxylcytosine.[11]

Histone modification

In a eukaryotic cell, DNA is wrapped with unique proteins called Histone protein, formed nucleosome, the functional structure of the chromatin. The histone octamer composes of two heterodimer histone H2A, H2B, and two homodimer histone H3, H4. Nucleosomes attach with the help of histone H1. Histone modifications like acetylation, methylation, phosphorylation, ubiquitination, sumoylation, ADP ribosylation, are reversible changes that occur at the histone tails.[5] Generally, acetylation facilitates the binding of transcription factors, RNA polymerase 2 and cause the gene activation and transcription initiation. Methylation is processed by

Histone methyltransferase enzyme, frequently take place at Lysine or Arginine of the histone protein amino acid chain.[11]

Non-coding RNAs (NcRNAs)

Non-coding RNAs are small RNA molecules about 21-25 nucleotide long, also called miRNAs. It's a crucial post-translational regulator of gene expression. Suppression of a particular gene's expression depends upon the complementarity between the miRNA and the 3' UTR of the target mRNA. Epigenetic changes can also modulate miRNAs; abnormal DNA methylation of miRNA can also be found in some human cancers. Interestingly, these miRNAs also can regulate DNA methylation and histone modifications.[5] A list of common epigenetic modifications and responsible enzymes are illustrated in Table 1.

Table 1: Epigenetic modifications, responsible enzymes and effects on gene expression.

Epigenetic modifications	Enzymes	Modification	Gene expression
DNA methylation	DNMT1	Methylation	Suppression
	DNMT3A, DNMT3B	Methylation	Suppression
	TET family	De-methylation	Activation
Histone modifications	HATs HDACs	Acetylation De-acetylation	Activation Repression
	HMTs	Methylation	Activation
	HDMs	De-methylation	Activation or repression
	MSK 1	Phosphorylation	Activation

DNMT1: DNA methyltransferase 1; DNMT3A: DNA methyltransferase 3A; DNMT3B: DNA methyltransferase 3B; TET: ten-eleven translocation methylcytosine dioxygenases; HATs: Histone acetyltransferases; HDACs: Histone deacetylases; HMTs: Histone methyltransferases; HDMs: Histone Demethylases; MSK 1: Mitogen- and stress-activated kinase 1.

Complex interaction between environment, DNA methylation and development of T2D

Both endogenous and exogenous stimuli can design epigenetic changes. Endogenous factors are allied with the early development, diverse cell lineage, stem cell variations, age-related changes, whereas exogenous factors are physical and chemical such as radiation, hypoxia, temperature, exposed to hazardous agents.[12] The epigenetic modifications are reversible and adjustable. Though it adds an additional layer of complexity to understanding the genetic mechanism of T2D, but it can give us factual information about how the environmental factors contribute to the T2D pathogenesis.[13] Several documentations demonstrate the importance of environment to the development of diabetes. A significant examples is the "Thrifty phenotype hypothesis", - children born from mothers who experienced the famine at their pregnancy in the Dutch hunger winter or during the WWII, were the low birth weight and were at high risk to develop T2D.[13,14] Mechanisms that defined this hypothesis include the altered DNA modification in the β cell and decreased the amount of mitochondrial DNA.[13] Another study highlighted that intrauterine hyperglycemia could be responsible for impaired glucose and T2D to the offspring. The Pima Indian family study issued that, children born after the mother was diagnosed as diabetic, is high possibility to have a higher body mass index and T2D compared with the children born before the diagnosis of maternal diabetes.[13] It is proved that T2D has high family aggregation, which can explain by epigenetics. Family aggregation shows not only the genetic impact, but also the shared family environment and environmentally induced epigenetic modifications.[5]

As T2D is an inflammatory disease, an association of inflammation with DNA methylation is also important. Hyperlipidemia causes DNA methylation and repression of anti-inflammatory genes, moreover a genome-wide study in a mouse model by Babu et al., 2015; identified hypomethylation of inflammatory genes in T2D mouse.[15] DNA methylation also has some critical role during the developmental programming, low birth weight baby (LBW) and offspring from mother with GDM displayed immense probability to develop T2D. LBW individual showed a higher rate of methylation in promoter region of PPARGC1A transcription factor than the average weight individual.16 Also, GDM accelerate the chance of T2D in consecutive generations.[17]

Obesity, Parental obesity and T2D

Lifestyle, socioeconomic condition, food habits are contributing to obesity and T2D. Obesity is now a significant health problem worldwide and becoming a pandemic. Every year 2.8 million people die worldwide due to obesity and its complications. Nearly, 205 million men and 297 million women were obese in 2008, and it is predicted that the number will increase to 2 billion by 2030.[18] Studies have been suggested that central obesity has a greater risk to develop T2D than the general obesity.[19] Central obesity refers to accumulation of extra amount of fat in the abdomen, visceral adipose tissue and hepatic tissue results in over-saturation of abdominal adipocytes with triglyceride (TG). Central obesity is highly sensitive to catecholamine but poorly response to insulin. Central fat deposits have the easy access to the liver through the portal circulation, causes increase amount of free fatty acid into the circulation leads to

accumulation of fat in the skeletal muscle, liver; the main reason behind the insulin resistance and β cell dysfunction.[12]

Adipocyte is not only the storehouse of fat, but also a major endocrine organ producing hormones such as leptin, resistin, estrogen, cytokine TNFα. Leptin-melanocortin signaling pathway is a major regulator of energy balance and food intake; genes maintain this pathway are exclusively involved in the onset of obesity. Eight genes have been identified associated with monogenic obesity, where obesity occurs due to mutation of one single gene; leptin (LEP), leptin receptor (LEPR), brain-derived neurotrophic factor (BDNF), proopiomelanocortin (POMC), single-minded homologous1 (SIM1), and neurotrophic tyrosine kinase receptor type 2 (NTRK2). Mutation of these genes are contributing to the early onset of obesity and hyperglycemia, and about 10% of severely obese children.[18]

Maternal hyperglycemia has emerged as an essential factor that may increase the chance of diabetes or hyperglycemia to the offspring. To review the methylation pattern in some specific genes related to childhood obesity, a study resulted that; parental obesity is associated markedly with hypomethylation of mesoderm-specific transcript gene (MEST), paternally expressed gene 3 (PEG3) and Neurontin gene (NNAT) and also alter methylation pattern in pleiomorphic adenoma gene-like 1 (PLAGL1).[18] According to the study conducted by Godfrey and Coworkers; using sample from umbilical cord tissue at birth and then subjects were judged 9 years later for the adiposity, and noticed methylation of two genes; retinoid X receptor α, and endothelial nitric oxide synthase, correspond with development obesity in later childhood.[18]

DNA methylation and insulin secretion

Under normal physiological condition, increased blood glucose level after meal, stimulate the β cell to release insulin to maintain the blood glucose level. In T2D, insulin demand raises due to the insulin resistance. Failure of Pancreatic β cell plays a crucial role in the development of T2D. In a GWAS; scientists have found altered DNA methylation patterns in affected individuals, to understand the DNA methylation pattern, they analyzed 479,927 CpG sites from both T2D and normal individuals, and found altered level of methylation in a total 1649 CpG sites corresponding to 853 genes in the diabetic subjects. Genes having the diabetic loci TCF7L2, KCNQ1, THADA, FTO, IPS1, PPARG showed the modified form of methylation.[20] The regions located near the transcription sites usually hypomethylated and regions distance from the transcription site displayed the higher rate of methylation. Functional analysis of both β and α cell revealed different results such as, exocytosis during insulin secretion reduced due to the silencing of the Exoc3L gene; insulin secretion impaired when Cdkn1a, Pde7b are overexpressed in β cell, and also hampered β cell proliferation.[20]

Another study by Volkmar, et al., found 276 CpG related to 254 genes promoters with various degree of DNA methylation obtained from diabetic patients, and these genes have a role in function and survival of β cell.10 These methylated genes are highly expressed and actively transcribed in pancreatic islets. So, it can be concluded that this T2D related hypomethylation leads to the activation of previously silent genes.[10]

Incretin an essential hormone that stimulates insulin secretion in response to meal, and its receptor GLP1R (Glucagon-like peptide 1) is expressed in β cell. While investigating the epigenetics of GLP1R, one study has found, increased DNA methylation pattern for the T2D samples in compare to non-diabetic.[7]

DNA methylation and insulin resistance

Insulin resistance is characterized by diminishing cellular response to insulin, driven to elevated insulin level in fasting state, although blood glucose level may be normal or high. Insulin resistance is the primary mechanism to T2D pathogenesis and also responsible for the cardiovascular diseases, obesity, dyslipidemia, and hypertension.[21] Resistance in peripheral tissue, adipose tissue and skeletal muscle fail to utilize the blood glucose, that leads to increase secretion of Adipokines, one kind of cytokines; which further worsen the condition. Due to resistance, hepatocyte fails to stop glucose production in response to high blood glucose level.[7] Skeletal muscle is the primary tissue that uses glucose as fuel, and glucose uptake by muscle increases dramatically after physical exercise. Physical exercise is favorable to increase insulin sensitivity and decrease the chance of developing T2D. Many studies have linked DNA methylation with insulin resistance. As described by Tina Ronn and Charlote Ling, et al., they investigated a genome wide methylation in human skeletal muscle having both subjects with or without family history of T2D. Various methylation patterns have been found in the subjects with positive family history involving genes such as MAPK, Insulin, Wnt signaling, Calcium signaling as well as the genes that involved in muscle action like MAPK1, MY018B, HOXC6 and PRKAB1.[7]

Risk factors for T2D associated with DNA methylation

Risk factors of T2D can cause epigenetic dysregulation. Childhood obesity and development of T2D markedly related to paternal obesity. Some imprinted genes of newborns baby from obese parent have altered DNA methylation pattern such as; Maternally expressed 3 (MEG3), PEG3, Neuronatin and pleiomorphic adenoma gene-like 1. Hypomethylation of insulin-like growth factor 2 (IGH2) also associate with parental obesity. Unfavorable intrauterine conditions have detrimental effects on fetal development, over or undernutrition have

adverse effects on the neuroendocrine development of the fetus.[8]

Insulin resistance increases with age; again, human pancreatic islets have also affected with age-related DNA methylation. Hypomethylation of CDKN1A and hypermethylation of EX0C3L2 is escalated with age, and both of this cause reduced mRNA expression in pancreatic β call. Physical activity has a role in glucose and lipid metabolism in skeletal muscle and adipose tissue. Inactivity contributes some dysregulation in pancreatic β cell. Metabolic activities vary between male and female. Female are more sensitive and release more insulin than male. Some autosomal and X-linked genes involved in insulin secretion are distinctly methylated and expressed in β cell in female than male.[8]

Hyperglycemia is the primary risk factors for T2D. Hyperglycemia has some affiliation with inflammatory genes, causing alter chromatin remodeling and affect transcription. HbA1c a biomarker for long term hyperglycemia, positively interacts with DNA methylation of INS and PDX1 in human pancreatic islets. An elevated level of free fatty acid in the blood, have some negative effect on insulin secretion and function.[22]

Diabetic complications and the role of DNA methylation

Diabetic complications are significant causes of morbidity and mortality in the modern age. Modifications in DNA methylation at different molecular pathway of target cells lead to different complications. Diabetic associated hyperglycemia leads to activation of PKC, MAPKs, production of reactive oxygen species and nitrogen species. Each of this events stimulate production of growth factors like ANG II, TGF-β, NF-kB; that bring epigenetic changes; DNA methylation, as well as histone modification of the target tissue and finally, develop complications.[23]

DNA methylation: a potential biomarker

The most important epigenetic changes that control gene expressions is DNA methylation. Recent researches in the field of epigenetics are opening new windows to identify biomarkers for the risk and progression of complex metabolic disorders like T2D. Although, searching for a biomarker to predict T2D is still in the beginning period, but a diagnostic test to detect early colorectal cancer based on DNA methylation is now available clinically.[24] A study by Hidalgo et al., identified a CpG site in ABCG1 gene associated with DNA methylation, that was symbolic for fasting insulin.[25] Another survey from twin discordant for T2D, found DNA methylation in MALT1 and G-protein receptor 6 gene that suggested future T2D.[26] DNA methylation in some specific sites for bloodborne human genome in some young individuals who developed T2D later. Also, some unique CpG sites in adipose tissue genes related to T2D showed various methylation pattern in T2D subjects compare to normal subject.[27]

In searching for new biomarker to detect the high-risk group and to predict the future development of T2D, a research study was conducted called Botnia prospective study. The study aimed to search for DNA methylation of 5 CpG sites in blood DNA (ABCG1, PHOSPHO1, SOCS3, SREBF1 and TXNIP) from 258 individuals matched for age, gender, and fasting glucose level. Their result was fascinating; they concluded that; DNA methylation in ABCG1 at loci cg06500161 was related with future development of T2D, on the other hand, DNA methylation at PHOSPHO1 loci cg02650017 was associated with little chance to develop T2D. DNA methylation in ABCG1 loci also collaborated positively with BMI, HbA1c, fasting insulin, triglyceride level. Also, 2 CpG sites in adipose tissue ABCG1 was found positively methylated, and DNA methylation in loci cg19693031 of TXNIP was decreased in pancreatic islets, skeletal muscle, and blood in the same individual with T2D compared with control.[28]

CONCLUSION

In addition to genetic factors, epigenetics plays a crucial role by modifying the gene expression and establish a relationship between the environment and genetic factors. Disease susceptibility differs from individual to individual, and here epigenetics has some tremendous effects. Epigenome undergoes continuous changes throughout our life and dysregulation of this process caused by different factors affect individual from the early age of life as well as throughout the life. However, T2D has now became a threat for us, and understanding all epigenetic mechanisms contribute to T2D are still limited. This review illustrated some of the recent progression in epigenetic research for T2D, especially the association of DNA methylation to the pathogenesis, risk factors, and early detection of T2D. Pancreatic β cell functions, insulin secretion, insulin resistance, metabolism all of them can be influenced by DNA methylation upon certain conditions and environments. Considering this, detection of DNA Methylation level can be highly relevant for the diagnosis and treatment of T2D.

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