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A Comprehensive Review on Impact of Altered Epigenetics on the Development of Diabetes

Vijayakumar Sakthivel[1], Savitha Niren[2], Shiny Paul[3], Sridevi Gopathy[4], Ghousia Sayeed[5], Ponnulakshmi Rajagopal[1*]

[1]*Department of Central Research Laboratory, Meenakshi Ammal Dental College and Hospitals, Meenakshi Academy of Higher Education and Research (MAHER), Chennai-600 095, India*

[2]*Department of Physiology, Chettinad Institute of Medical Sciences, Chettinad Academy of Research and Education, Manami- Nallur, India*

[3]*Shridevi Institute of Medical Sciences and Research Hospital, Tumkur, India*

[4]*Department of Physiology, SRM Dental College, Bharathi Salai, Ramapuram, Chennai, Tamil Nadu, India*

[5]*Department of Periodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai India*

Abstract

In earlier days, researchers were concluding the origin of the disease based on genetic or environmental factors. In the past few years, Epigenetics has been considered as source of certain diseases which could not be ascertained by traditional sources. Recently, more focus has been given to epigenetics, for diseases for which autoimmune disorders, Cardiovascular disease, Cancer, Diabetes, neurodegenerative etc. The original and categorical descriptions of epigenetic alterations, as well as the function of epigenetics in biology and the relationship between epigenetics and the environment, are clarified in the current review. It appears that the significance of epigenetics in human disease is examined by concentrating on a few diseases with complex characteristics. Finally, we have provided an outlook for this field's future. This review explains the relationship between the epigenetic markers and the environment which influences diabetes.

Keywords: *Biomarker; circRNAs; Diabetes; lncRNAs; miRNAs, DNA Methylation, Gene Expression, Health and Well-being, Histone Modification, Noncoding RNA, Novel Methods.*

Introduction

The study of epigenetics focuses on how an organism's actions and surroundings can modify an organism's genetic makeup. Unlike genetic alterations, epigenetic modifications are reversible and do not alter the DNA sequence; nonetheless, they may impact the way the body interprets a DNA sequence. To put it simply, epigenetics is the study of heritable signals that are not found in DNA and that enable a cell to "remember" past experiences [1, 2]. Since epigenetic marks are reversible, it can be considered as possible targets for novel therapeutic approach [3]. Conrad Waddington established an epigenetics research centre to investigate the relationships between developmental biology and genetics, and he developed the term "epigenetics." [4]. There are several epigenetic markers which regulates gene expression which include DNA methylation, Histone Modification, Non-Coding RNA. With several such changes to the gene expression, the epigenetic markers help in managing some diseases, such as

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****Corresponding Author: drponnulakshmi.researchscientist@madch.edu.in***

Diabetes. Since epigenetic marks establish a connection between the environment and gene expression, they make excellent candidates for biomarkers for the early diagnosis of late problems [5,6]. Histone alterations, non-coding RNAs, and DNA methylation are examples of epigenetic modifications. More than 100 different types of modifications, such as methylation, acetylation, phosphorylation, sumoylation, ubiquitylation, citrullination, biotinylation, crotonylation, and ADP ribosylation, have been reported so far.

DNA Methylation

Gene expression variations that are heritable are epigenetic modifications happen without altering the gene sequence. In simple words, it may explained as follows: DNA methylation is a biological process that involves the addition of a methyl group (CH_3) to the fifth carbon atom of a cytosine nucleotide within a DNA molecule (CpG dinucleotide) sites. This epigenetic modification can significantly influence gene activity by altering the interaction between DNA and proteins, such as transcription factors and chromatin remodelling complexes, without altering its sequence.

Several years back more studies were conducted about the epigenetic changes during usual development and in diseases like cancer, and cardiovascular disease. Studies in epigenetics have increased and also have become more complicated with DNA Methylation, histone modification, non-coding RNA, DNA sequence etc. DNA methyl transferases (DNMTs), a set of enzymes which catalyze DNA methylation is known as an important marker in epigenetic silencing of the transcription (Figure 1). Through the interaction of DNMTs with other modifications and with parts of the machinery mediating those marks, DNA methylation may regularise the chromatin status. Gene expression and DNA methylation status showed a significant inverse relationship, indicating that this relationship may be a future target for therapy [7].

Epigenetic modifications which include DNA methylation are identified as a mechanism where the environment intermingles with the genome and there are proofs that such changes that happen in DNA methylation would be the cause of the incidence and occurrence of both type 1 and type 2 diabetes. Epigenetic modifications, including altered DNA methylation and gene expression, in pancreatic islets may play a role in reduced insulin secretion in type 2 diabetes. Moreover, environmental factors can contribute to insulin resistance in adipose and skeletal muscle tissues by modifying epigenetic markers (8A- 8). Epigenetic modifications in various organs have been linked to type 2 diabetes. Early-life nutrition, physical activity, and environmental factors can influence these epigenetic changes, which may serve as therapeutic targets. New drug therapies are being developed to address these epigenetic alterations (8B-9).

Many methylations quantitative trait locus (mQTL) studies have also investigated the genome-wide interaction between SNPs and DNA methylation in cis and trans in target tissues for type 2 diabetes. Human studies, including case-control analyses and intervention trials, have identified epigenetic alterations in genes such as PDX1, CDKN1A, and GLRA1, which are associated with increased risk for T2D. Furthermore, genetic association studies (mQTLs), Mendelian randomization analyses, and epigenetic editing experiments collectively provide strong evidence that epigenetic mechanisms contribute significantly to the development of T2D (8C - 10).

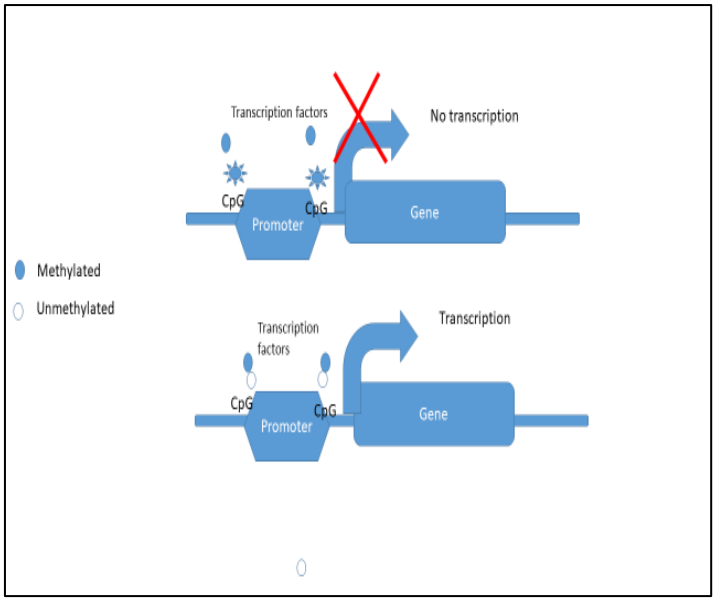

Figure 1. Basics of DNA Methylation

The DNA strand's methyl group transfer from cytosine residues to guanine residues (CpG dinucleotides) is influenced by DNMTs. CpG islands are collections of these CpG dinucleotides. Mammal genomes have CpG islands, which are found close to gene promoters and makeup 1-2% of the genome, or roughly 300–3,000 base pairs. Once the CpG dinucleotides are Methylated and become 'mCpG' that bind with transcriptional repressors they silence the gene expression. A further connection between DNA methylation and the histone code is made possible by methyl-CpG-binding proteins (MBDs), which interact primarily with methylated DNA and regulate transcription [11]. Research on human Type 2 Diabetes case-control and involvement in non-diabetic subjects revealed epigenetic changes in candidate genes (PDX1, CDKN1A, and GLRA1) that were determined to be responsible for the disease's induction.

Nevertheless, evidence from mQTL investigations, epigenetic editing research, and Mendelian randomization analysis of DNA methylation data in T2D prospective cohorts all point to a significant involvement of epigenetics in the development of T2D [12]. Based on the methylation of specific DNA sites in the blood (e.g., TXNIP, ABCG1, and SREBF1), which has been linked to the development of T2D, recent research findings suggest that these sites may be developed into biomarkers that predict it. Future studies can do research based on this input for advancing further so that new therapies would evolve and biomarkers so that we can prevent T2D by predicting it much earlier so it can be treated. DNAm is an inherited marker linked with high-order DNA structure and the control of gene expression. In the end, research on disease-related dysregulation in DNA may lead to new understandings of the pathophysiology of type 2 diabetes (T2D), identify new therapeutic targets, and facilitate the development of predictive biomarkers in non-invasive tissues. DNAm is capable of being modified according to environmental factors and is related to genetic variants [13,14].

Histone Modification

The importance of the study given to Histone modification is compared to DNA methylation. Modifications to the histones are catalysed by certain enzymes that mostly work at the histone N-terminal tails of amino acids such as arginine or lysine, as well as serine, threonine, tyrosine, etc. Histone acetylation frequently increases gene expression.

Depending on where the targeted amino acid residues are located in the histone tail and/or how many changing (such as methyl) groups are included, histone methylation can be either transcriptionally permissive or repressive [15]. Additionally, current investigation indicates that histone alteration is crucial for the onset and course of Diabetic Kidney Disease [16].

Histones are positively charged, alkaline, extremely preserved proteins that are composed of linker histones (H1 and H5) and core histones (H2A, H2B, H3, and H4). A conserved central motif domain and an unstructured amino-terminal tail define similar structures seen in the four core histones. The primary method of controlling chromatin structure is through post-translational modification (PTM) of histones, which primarily affects the amino acid residues lysine, arginine, serine, tyrosine, and threonine. PTM also has an impact on transcriptional activity. Histone modification is mediated by the enzymes acetyltransferases, methyl transferases, deacetylases and demethylases, which are referred to as epigenetic writers; proteins that detect acetylated proteins at enhancers and promoters are referred to as epigenetic readers, such as bromodomain-containing protein 4 [17].

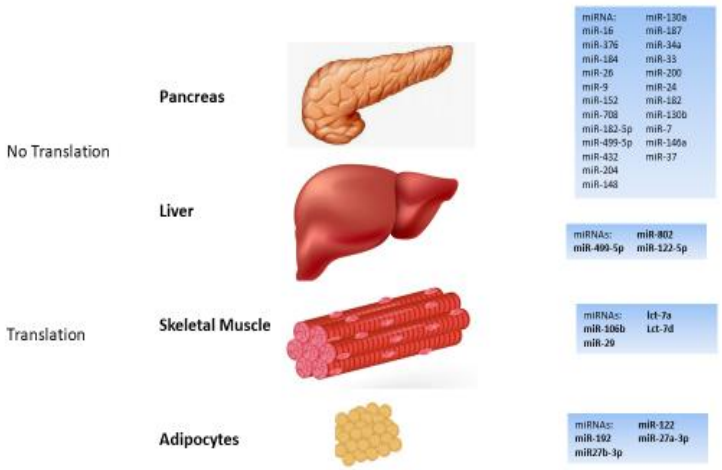

Figure 2. The Picture Illustrates the Target Organs and Cells, the Streamlined Process of miRNA and lncRNA in Post-transcriptional Control of Gene Expression

Non coding RNA

miRNA

Controlling gene expression is one of the functions of microRNAs (miRNAs), a type of non-coding RNAs. The majority of miRNAs are transcribed from DNA sequences into primary miRNAs, which are further processed into mature and precursor miRNAs [18,19]. The discovery of the first microRNA (miRNA), lin-4, in *Caenorhabditis elegans* 1993 opened new avenues in molecular biology [19, 20]. The ~22-nt RNAs known as microRNAs (miRNAs) regulate the posttranscriptional suppression of mRNA targets throughout a variety of eukaryotic lineages. These little RNAs influence how the majority of mRNAs are expressed in humans and other mammals and these are described in detail in Table 1 [21-23]. Figure 2 depicts the target organs and cells, the streamlined process of miRNA and lncRNA in post-transcriptional control of gene expression, and the alterations in the clinical state of diabetes that arise from these modifications.

Table 1. Mouse Phenotypic Alterations and miRNA Biogenesis Following the Deletion of Few Members of a Broadly Preserved miRNA Family

Marker	Function	
miR-204/211 (2)	miR-204- Enhanced glucose tolerance and decreased pathology in the diabetic model	[21]
miRNA, lin-4	Lin-4	[19,20]
pri-miRNA	Managed into pre-miRNA by microprocessor complex, comprising of an RNA binding protein DiGeorge Syndrome Critical Region 8 (DGCR8) - pre -miRNAs are generated - > transferred to cytoplasm by exportin 5 (XPO5/RanGTP complex -> administered by RNase III endonuclease dicer	[23]
5' and 3' strands	In an ATP-dependent way, two strands from developed miRNA duplex can be loaded to Argonaute (AGO) family of proteins (AGO1-4 in humans).	[24]

Epigenetic regulation of Glut 4

Skeletal muscle cells, adipocytes, and cardiomyocytes are known to contain GLUT4. Insulin-stimulated glucose absorption into muscle and fat cells is mostly caused by it. Roughly 80% of glucose is taken up by muscle cells [25]. Insulin has the effect of abruptly stimulating glucose absorption to muscle and adipose tissue, which is necessary for optimal glucose homeostasis. A key modulator of this process is the GLUT4 glucose transporter, whereby insulin brings to the plasma membrane from an intracellular pool [26].

In ERβ-deficient cells, treatment with a Sp1 inhibitor did not affect Glut4 expression. Instead, it was shown that the variations in Glut4 expression were caused by a decrease in Sp1 recruitment to the Glut4 promoter. This CpG is a component of a Sp1-binding site, and methylation of this region decreased Sp1 binding [27]. Humans can absorb glucose into their muscles up to 100 times faster during acute exercise than at rest. Research only demonstrates a roughly doubled in GLUT4 translocation to the muscle cell walls when transitioning from rest to exercise, despite the fact that deletion of glucose transporter type 4 (GLUT4) has persuasively demonstrated that GLUT4 is essential for exercise to increase muscle glucose uptake [28]. More investigation is required to determine the influence of the Glut 4 update on diabetes.

Relationship with Diabetics

Studies have been conducted on the involvement of epigenetic mechanisms, particularly DNA methylation and histone changes, in the growth of the pancreas, which causes diabetes, as well as the possible use of epigenetic modulators in the cure of diabetes [29]. Around 400 genetic variants linked to Type II diabetes or determining quantitative glycemic traits, known as β-cell function and insulin resistance, have been discovered in the early 21st century thanks to a number of gene discovery efforts, stretching from candidate genes to agnostic analyses, particularly genome-wide association studies (GWAS), exome, and whole-genome sequencing [30,31,32, 33, 34]. Such variants contain a good effect on discovering the bio-mechanisms and pathways in the pathogenesis of Type 2 Diabetes. Most of the variants seem to be present near genes are not suspected to have a part in pathogenesis of TypeIIDM earlier or Type 2 Diabetes risk which is disturbing β-cell function than insulin sensitivity in outer tissues [35, 36, 37, 38].

The majority of exon variants are found in intronic or regulatory regions or intergenic segments, with the exception of a small number that alter the amino acid sequence and affect the function of the gene, such as p.Pro12Ala of the peroxisome proliferator-activated receptor-gamma gene (PPARG) or

p.Glu23Lys of the islet ATP-dependent Kir6.2 potassium channel gene (KCNJ11) [39, 40, 41]. It should be noted that these findings indicated non-coding mutations will impact human phenotypes. Adjusting the epigenetic effects to modulate these mechanisms of trained immunity may provide new options for treating inflammatory disorders like diabetes or atherosclerosis, which have been linked to trained immunity [42].

Long-lasting hyperglycemia produces anomalous epigenetic marks that continued even after the normoglycemic milieu was created and preserved, suggesting a role for epigenetics in metabolic memory (Figure 3 & Figure 4). These markers may function as biomarkers for the early detection of microvascular and macrovascular issues.

Conclusion

Given that epigenetic alterations may be reversed, they could potentially be excellent targets for innovative therapeutic techniques [43]. The reversibility of many epigenetic modifications suggests that synergistic therapy with epigenetic drugs could potentially enhance the management of diabetes complications. Several key epigenetic targets, such as HDAC and DNMT3a, have been identified. Moreover, set 7, an inhibitor of histone methyltransferase, represents a promising novel therapeutic approach for diabetes mellitus [44, 45]. These epigenetic modifications play a crucial role in regulating histone deacetylation and methylation processes. Additionally, several other important therapeutic targets involved in diabetes management warrant further exploration. Overall, it is anticipated that continued research in the field of epigenetics will lead to the identification of novel drug biomarkers and targets, facilitating the early and effective management of diabetes and its associated complications.

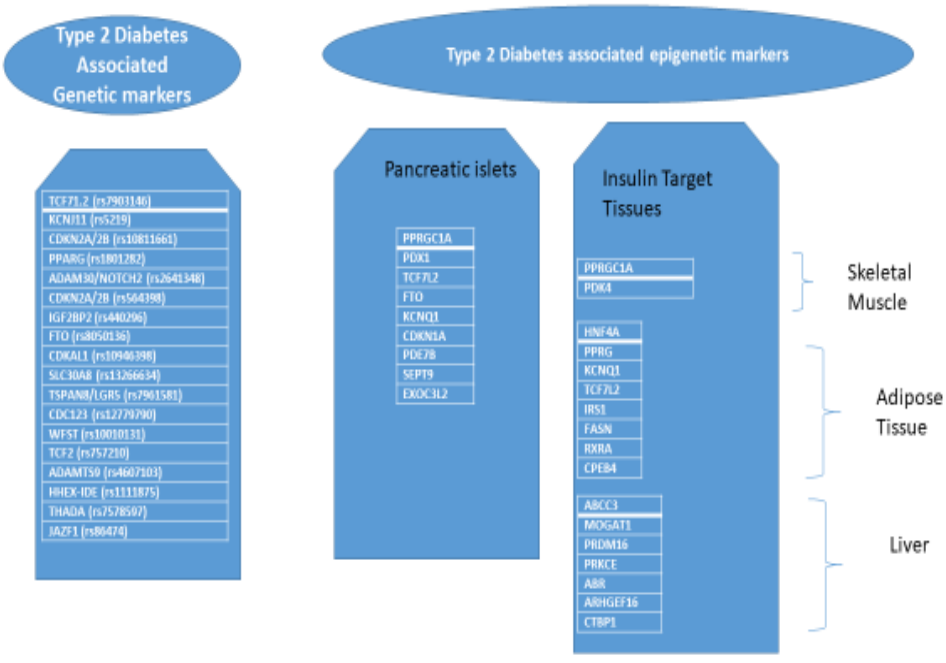

Figure 3. Genetic and Epigenetic Markers Linked to Type II DM

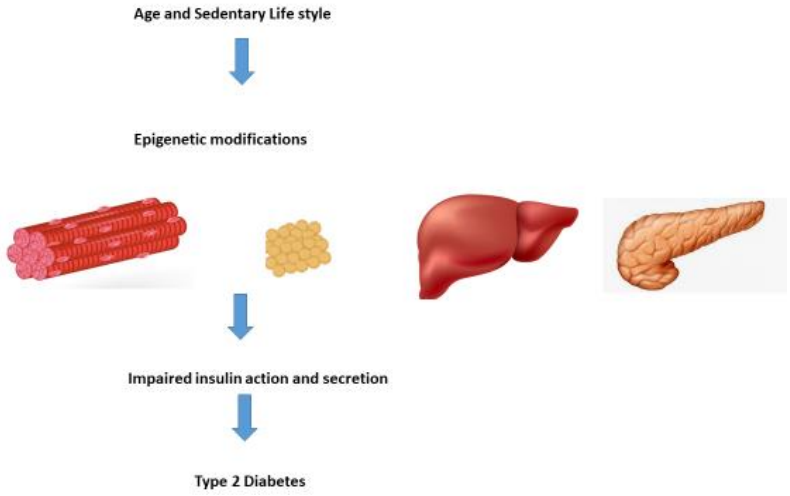

Figure 4. Generic Flow Chart Showing Induction of T2D by Epigenetic Modifications

Conflict of Interest

The authors hereby declare that there is no conflict of interest.

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