Role of Epigenetics in Type 2 Diabetes Mellitus in Tropics

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Type 2 Diabetes Mellitus (T2D) is a prevalent disease with devastating complications especially in the tropical communities. T2D likely to result from many genes interacting with different environmental factors to produce a wide variation in the disease's clinical course. Epigenetics addresses the relationship between genes, environmental exposure, and disease development. Additionally, epigenetics concerns heritable gene expression changes without changes in the DNA sequence itself, affecting how cells "read" genes. Many factors affect epigenetic modifications, such as age, lifestyle, family history, and disease status .

Epigenetics plays a vital role in the pathology of T2D. Recent research surrounding epigenetics has shown that exposure of the fetus to various abnormal intrauterine environmental states like hyperglycemia and famine can also increase the risk of developing T2D. Since methylation of CpG islands may be heritable, epigenetic activity occurring in the developing fetal genome may result in lasting effects on our metabolic control. These lasting effects most likely introduce critical factors in the development of T2DM later in life. Thus, the influence that epigenetic mechanisms exert may be immensely important not only as a means by which environmental factors impact development of T2D but also in its role in establishing one's risk profile for developing T2D even before birth.

The nutritional quality and quantity provided to a developing embryo serves as a strong predictor of the development several risk factors associated with T2D postnatally. There is a growing interest in certain functional foods with epigenetic effects that potentially prevent T2D. This may be especially beneficial for tropical poor communities where treatment of T2D is an economic burden.

INTRODUCTION

Diabetes mellitus is a metabolic disorder which is on the rise globally. It is caused by a combination of hereditary and environmental causes, and the treatment of its crippling complications is extremely expensive. By 2030, the incidence of T2D is predicted to approach 366 million patients worldwide [1]

Types of diabetes mellitus

(1) Type 1 diabetes (T1D)

(2) Type 2 diabetes (T2D)

(3) Latent autoimmune diabetes in adults (LADA) and Maturity-onset diabetes of the young (MODY): Like T2D, LADA is diagnosed in adulthood and progresses gradually. It also has certain symptoms and treatments with type 1 and type 2. Conversely, MODY results from genetic alterations that impact the body's ability to produce insulin [2].

(4) Type 3 diabetes(T3D): There is a link between Alzheimer's disease (AD) and T2D. Type 3 diabetes (T3D) is defined as chronic insulin resistance and deficit in insulin utilization, which results in cognitive dysfunction in the brain. Over time, insulin resistance and imbalance gradually

(5) impair brain function, resulting in AD [3].

(6) Gestational diabetes (GDM)

Etiology of type 2 diabetes mellitus

Pathophysiology of T2D involves genetic susceptibility, non-genetic and epigenetic variables, such as environmental factors, and individual behaviors including food intake and physical activity [4].

Genome-wide association studies (GWAS) has demonstrated links between Single Nucleotide Polymorphisms (SNPs) and T2D in large cohort and family studies, supporting genetic theory [5]

Non-genetic risk factors for obesity including lack of physical activity, high caloric diets and advanced age. Nonetheless, a large number of individuals with type 2 diabetes do not meet the criteria for obesity and have low insulin resistance. Therefore, modifications in environmental-epigenetic interactions were incorporated in addition to T2D heredity as an explanation [4]. So, what is the mean of "epigenetic ؟"

WHAT ARE EPIGENETICS

Since the Greek word "epi" (επι) means "above, over," it follows the biological processes, such as genetic transcription and metabolic phenotyping, are controlled by epigenetic modifications rather than changes to DNA sequences. Any inherited (one mitotic cell division at least) alteration in phenotyping or characteristic without any change in DNA sequence is known as epigenetics. In other word influencing the way cells "read" genes. This definition forms the foundation for understanding how the environment affects islet cell activity and the predisposition to diabetes [6]

Principal categories of epigenetic changes

Histone modifications

The genetic material found in a cell is contained within chromatin, a DNA-protein complex made up of histone cores and linear DNA. Histone core consists of 4 dimers of every histones H2A, H2B, H3, and H4, is circumfluent by 147 base pairs of DNA to form nucleosome **(Figure 1).** These histones' N-terminal tails can be changed, which changes the compaction of chromatin and attracts transcriptional regulators to control the expression of certain genes [7].

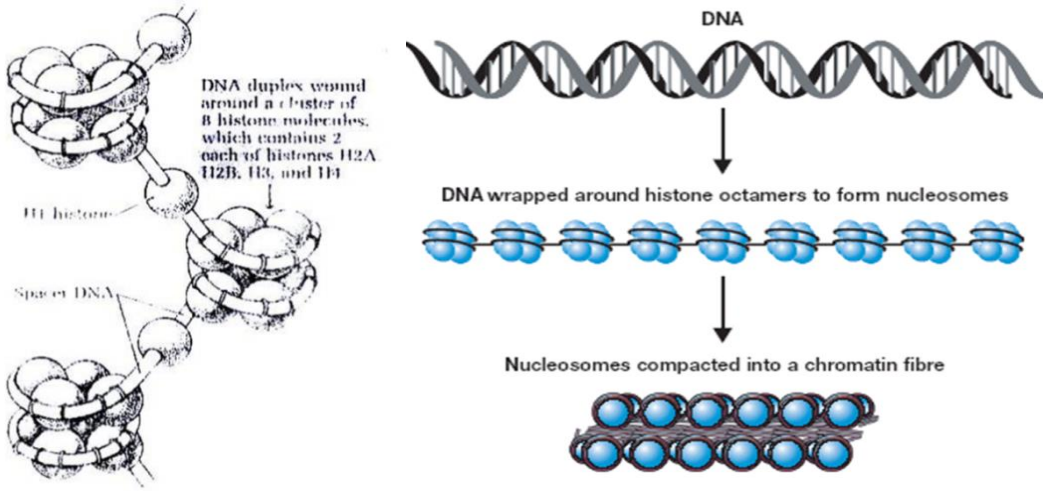

Figure 1: Chromatin structure

Pasquali et al., [8] mapping specific histone marks and the bound profiles of pancreatic beta cells transcription factors, extensive maps of the genome of diverse chromatin states (limited number of histone marks) in pancreatic beta cells, from promoters to active enhancers, have been constructed. Examples of activating marks are H3K27Ac , a marker of active enhancers, and H3K4me3, which is linked to active enhancers at genes enriched in CpG islands; H3K27me3 is commonly used to indicate repressed chromatin states [6].

DNA methylation

DNA methylation is second key epigenetic change, the CpG (genomic regions that contain a high frequency of cytosine and guanine nucleotides, connected with a phosphodiester bond) sequence comprises palindromic DNA small stretches which are found on both DNA strands. 5-methyl cytosine is the result of methylating the DNA on the 5th cytosine carbon by using DNMTs to transfer a methyl group from the donor S-adenosyl methionine to the DNA. The majority of CpG dinucleotides in the human genome are methylated; gene bodies and the gene regulatory region dictate how much DNA methylation can influence gene expression [9].

The impact of DNA methylation is dependent on where it occurs in a gene. Furthermore, methylation within the gene body has diminished RNA polymerase's capability to transcribe the gene. Methylation in the gene regulatory region's promoter or first intron is essential for regulating transcription initiation and gene silencing [9].

The human genome contains around 30 million CpG dinucleotides, or 1% of all nucleotides. This is significantly less than predicted, suggesting that during evolution, CpGs were actively chosen against. The bulk of CpGs are spread extensively over the genome in other circumstances, but a minute percentage—1-2%—are organized into dense arrays known as "CpG islands" (CGIs). CGIs are defined as genomic regions that span greater than 500 dinucleotides and have greater than 50% CpG content [10].

The active demethylation that produces the 5mC derivatives, 5' -hmC, 5'-fC, and 5'-caC is catalyzed by the TETs enzymes. The remaining 5caC is then removed by the base excision repair enzyme thymine DNA glycosylase (TDG). During replication, all oxidative byproducts could be eliminated (passive demethylation). since DNMT1 does not identify oxidative derivatives **(Figure 2)** [6].

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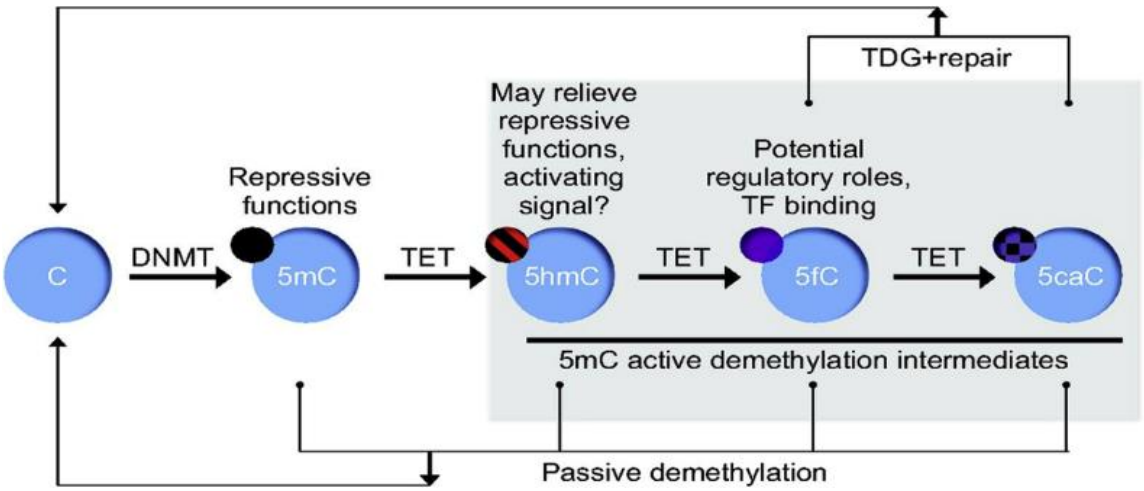

Figure 2: Process of oxidation and demethylation

Non-coding RNAs (ncRNAs)

ncRNAs were the third class of epigenetic regulators. The 1990s saw a rise in interest in ncRNAs, long non-coding RNAs (lncRNAs), and microRNAs (miRNAs) [11].

Mature miRNAs consists of 21–25 nucleotide single-stranded molecules that are processed by the ribonuclease Dicer in humans. They have strong sequence homology to the 3′ UTR of one or, more frequently, many protein-encoding RNAs.

Part of the RNA-induced silencing complex (RISC) complex in which they bind their targets is the Argonaute protein, which is the enzyme cleaves miRNA targets. lncRNAs are RNAs that are longer than 200 nucleotides and typically shorter than mRNAs. However, it is different from mRNAs, as they are enhanced in cell's nucleus fraction and go through splicing and polyadenylation [12].

ROLE OF EPIGENETICS IN TYPE 2 DIABETES MELLITUS

Different genes interacting with different environmental conditions led to type 2 diabetes. Epigenetics plays a crucial part in the pathophysiology of T2D. Blood glucose regulation requires stable β-cell function. Epigenetic changes are crucial for preserving the β-cell's physiology and functionality [13]. Epigenetic dysregulation in diabetes patients can result in decreased expression of genes necessary for β-cell function; also, ectopic expression of genes not intended for expression might cause β-cell identity loss **(Figure3)**. Genetic, non-genetic, and environmental factors all affect the pancreatic islets' transcriptome and DNA methylation. These changes result in changes to the survival and function of cells, which induce onset of T2D [4]

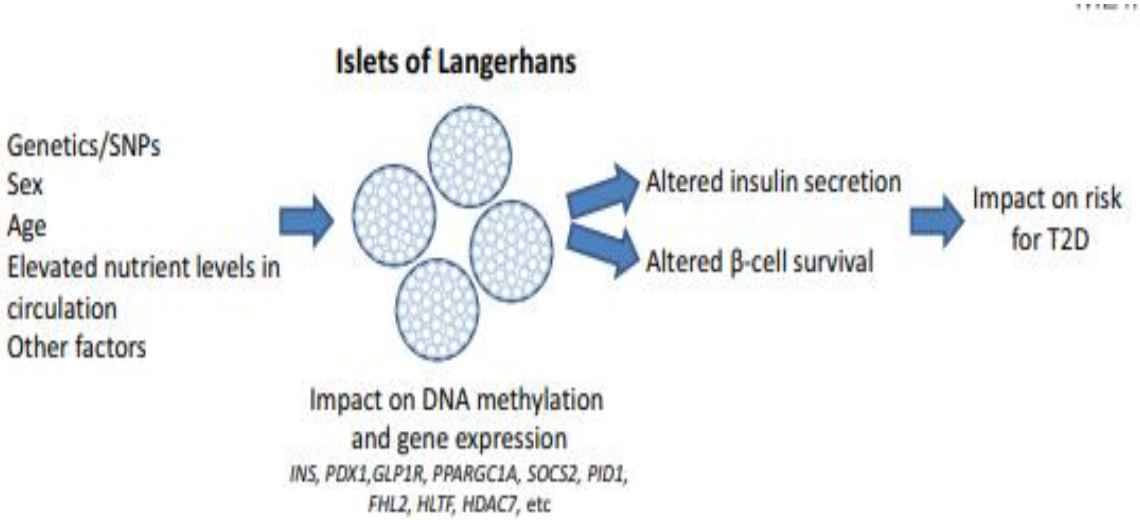

Figure 3: DNA methylome islets of Langerhans

Studies that uncover genetic variants linked to DNA methylation, or methylation quantitative trait loci (mQTLs), provide additional support for this hypothesis, 500,000 SNPs and 450k array methylom data were combined to examine from 89 healthy individuals beta cells. More than 100,000 mQTLs were found by the research, and over 6% of the SNPs were found to be substantially correlated with methylation at particular CpG sites [4].

These mQTLs are interestingly linked to insulin secretion and gene expression. The idea that SNPs can influence islet gene expression through modified DNA methylation was further corroborated by causal inference tests (CITs) **(Table 1)**. The finding that 25% of all genomic SNPs include an addition or deletion at the CpG site serves as additional evidence of the connection between the concepts of epigenetics and genetics. These so-called CpG-SNPs affect the possibility of methylation at specific

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locations. x related to methylation at certain CpG sites; 19 of the 40 SNPs associated with T2D risk that were discovered at the time were really CpG-SNPs [14].

Interestingly all of the CpG-SNPs that were studied were related to variable CpG-SNP site DNA methylation in human islets. However, some of the CpG-SNPs were also connected with differential mRNA splicing, insulin and glucagon production, and gene expression. Together, these two investigations demonstrate that SNPs raise the risk of T2D by compromising beta-cell function is occurring due to altering DNA methylation at CpG sites **(Figure 4)** [4].

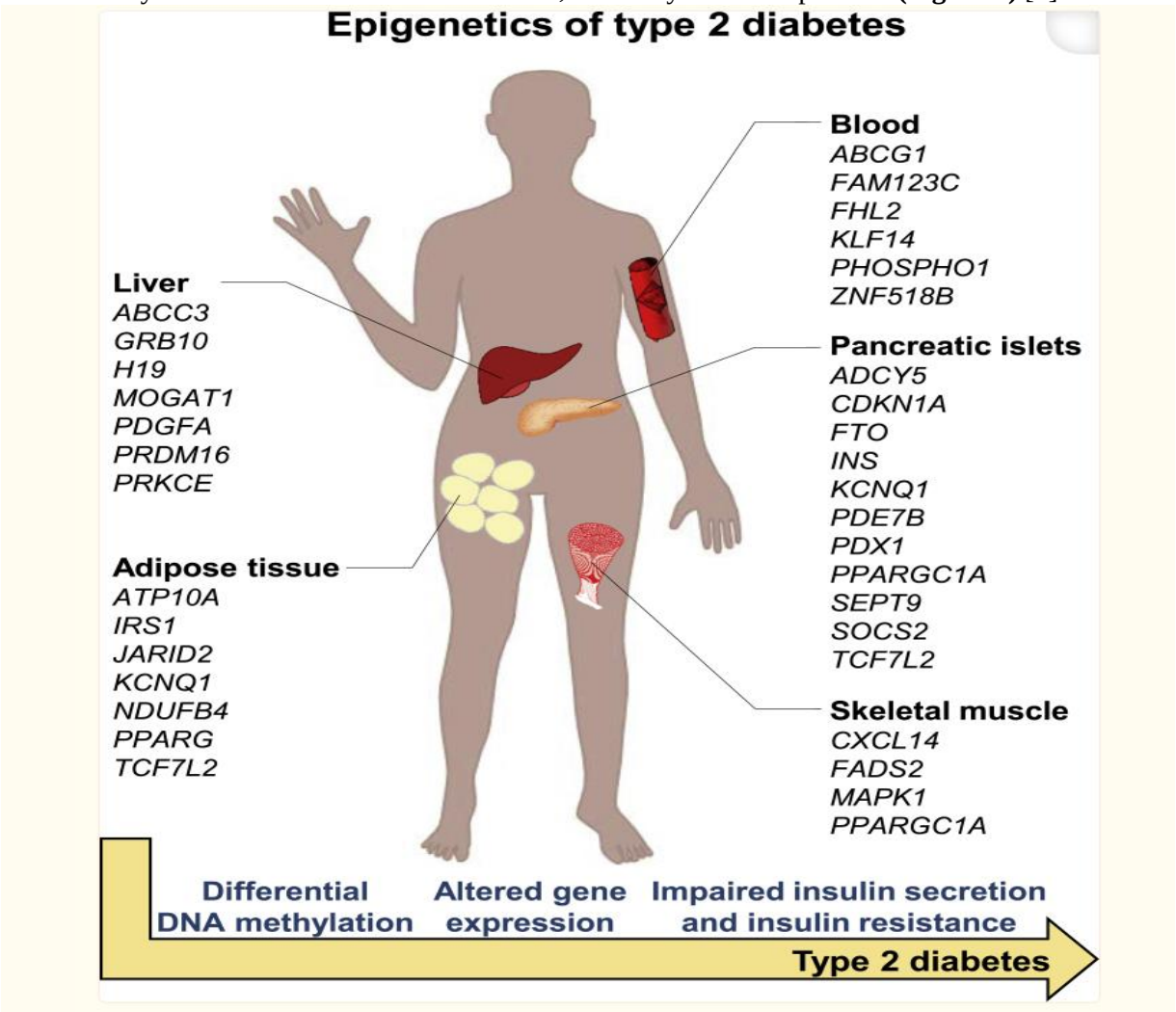

Figure 4: Epigenetics and type 2 diabetes.

In Human Tissues, Differential DNA Methylation Is Associated with T2D [15].

Table 1: Changes in DNA methylation in type 2 diabetes [16]

Genes/Susceptibility factors	Methylated status	Insulin-sensitive organs	Effects
PPARGC1A	Hypermethylation	Human pancreatic islets	Influenced glucose-stimulated insulin secretion
KCNQ1	Hypermethylation	Human pancreatic islets	Increased the risk of T2DM
Insulin gene	Demethylation	Human and mouse islet cell	Inhibited the function of beta cell
Insulin gene	Hypermethylation	Human pancreatic islets	Increased the levels of HbA_{1c}
PDX-1	Hypermethylation	Human pancreatic islets	Associated with the insulin secretion
GLP1R	Hypermethylation	Human pancreatic islets	Positively associated with BMI and HbA_{1c}
MEG3-DLK1 microRNA	Hypermethylation	Human pancreatic islets	Caused the increase of β cell apoptosis
Ageing	Hypermethylation	Rat pancreatic islets	Associated with molecular inflammation
NDUFB6	Hypermethylation	Human skeletal muscle	Influenced insulin sensitivity
COX5a	Hypermethylation	Rat skeletal muscle	Associated with mitochondrial dysfunction
COX7A1	Hypermethylation	Human skeletal muscle	Associated with glucose uptake in vivo
Gastric bypass surgery	Hypomethylation	Human skeletal muscle	Remodeled the promoter methylation of PGC-1α and PDK4
Acute exercise	Hypomethylation	Human skeletal muscle	Activated contraction-induced gene
Ionizing radiation	Hypermethylation	Mice skeletal muscle cells	Increased the risk of insulin resistance
Insulin and glucose exposure	Hypermethylation and hypomethylation	Human skeletal muscle	Altered the DAPK3 methylation
Gck	Hypermethylation	Rat liver	Involved in the development of insulin resistance
TNFα	Hypermethylation	Mice liver and adipose tissue	Associated with the reduction of inflammation
Metformin transporter genes	Demethylation	Human liver	Improved hyperglycaemia and obesity
In-utero malnutrition	Hypermethylation	Mice liver	Influenced the expression of lipogenic genes
Loss of MBD2	Hypermethylation	Mice liver	Protected mice from insulin resistance
IGFBP1 and IGFBP7	Hypermethylation	Human peripheral blood	Associated with insulin resistance
Alu repeats	Hypermethylation	Human peripheral blood leukocytes	Associated with insulin resistance
LINE-1	Hypomethylation	Human peripheral blood	Increased the risk of metabolic worsening
MCP-1	Hypomethylation	Human peripheral blood	Increased the serum MCP-1 level
TCF7L2	Hypermethylation	Human peripheral blood	Positively associated with fasting glucose
TXNIP	Hypomethylation	Human peripheral blood	Increased HbA_{1c} and fasting glucose
NR4A1	Hypomethylation	Human peripheral blood	Decreased the blood glucose
Aging	Hypermethylation	Human brain and blood	Remodeled DNA methylation

By causing an initial "disruption" to chromatin, epigenetic dysregulation can be caused by a variety of risk factors, including hyperglycemia, inactivity, aging, parental obesity, mitochondrial dysfunction, and an aberrant intrauterine environment. Thus, epigenom might be impacted at many points over a person's lifetime [17].

Histone modifications and/or DNA methylation disrupt the accessibility of genes

to the transcriptional machinery by causing either a relaxed/open or condensed/closed chromatin state. Histone acetylation generally causes chromatin to open up, resulting in gene activation, whereas DNA methylation, primarily of cytosines in gene promoters, condenses DNA and results in gene silencing. As miRNAs, ncRNAs control the phenotypic of cells by either upregulating or downregulating the production of gene transcripts **(Figure 5)**. On the other hand, ncRNAs might be epigenetically controlled [18].

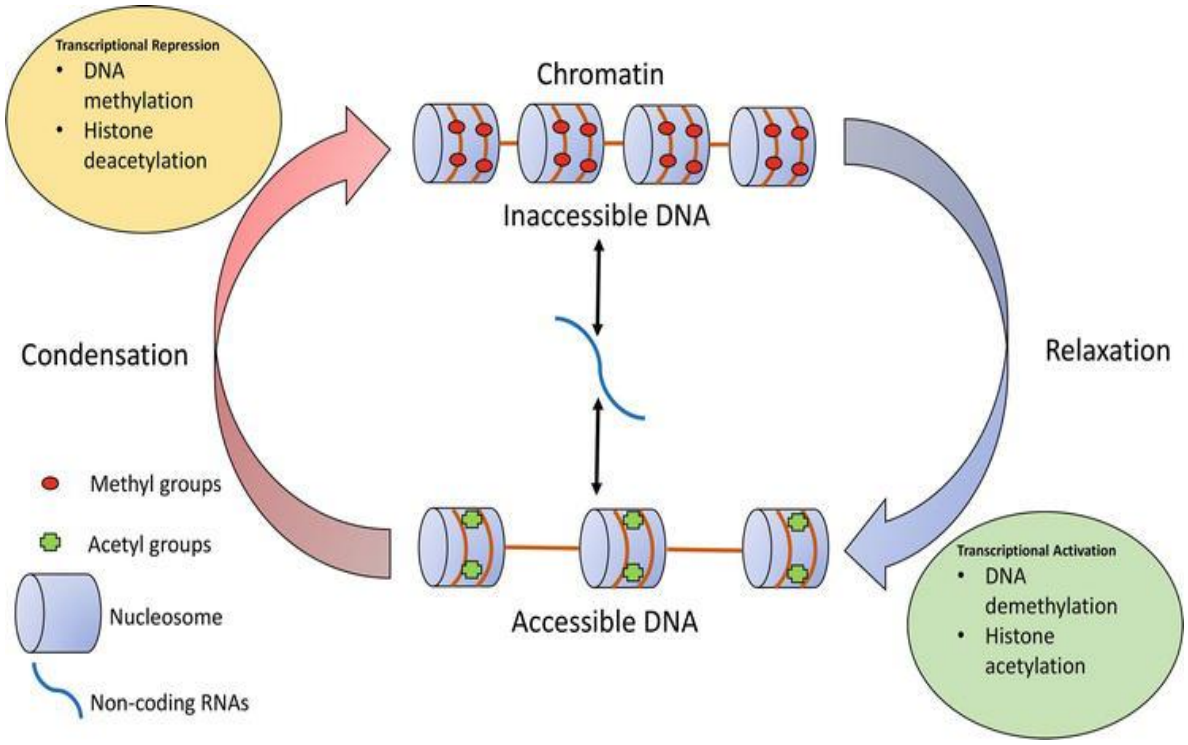

Figure 5: Epigenetic regulation of gene expression.

Epigenetic changes resulting to β-cell dysfunction, insulin secretion disturbance, and pancreatic function impairment, leading to well manifested disease in the whole organism, So an incidental chain is established by the environment inducing disease in the following series: environment ⟶ chromatin ⟶ genes ⟶ cells ⟶ organs ⟶ organism **(Figure 6)** [9].

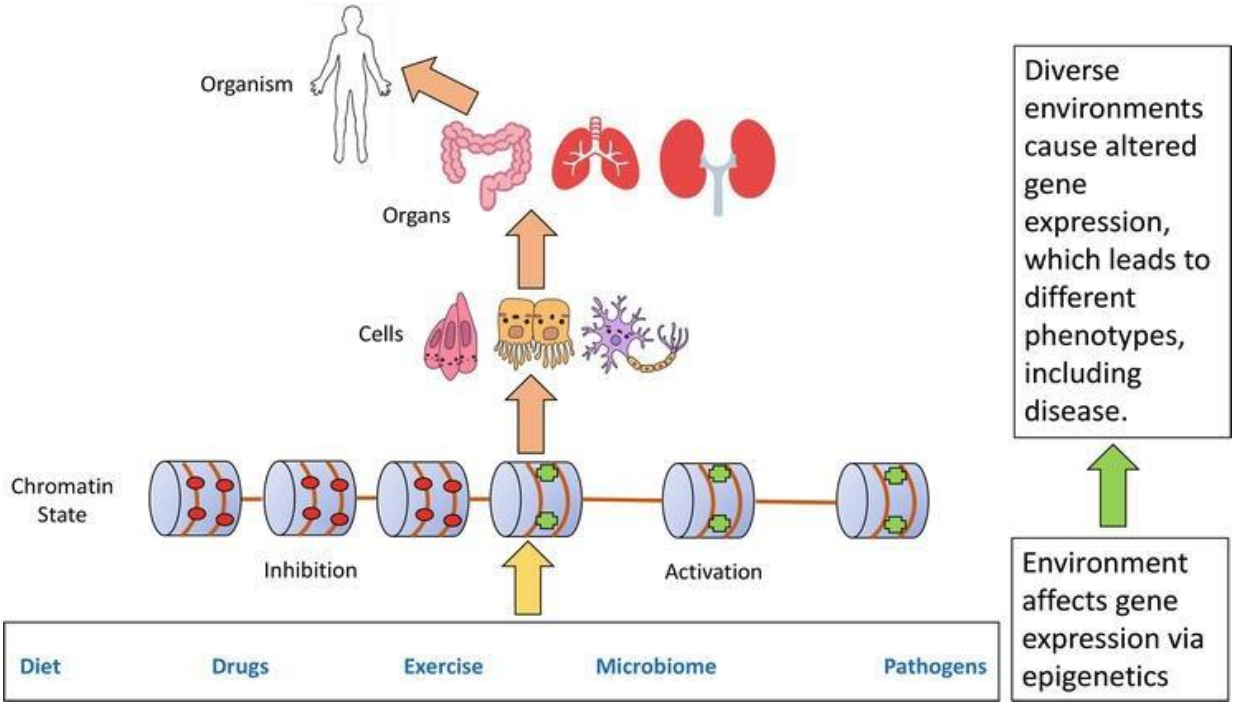

Figure 6: Genetic and environmental interactions during disease development.

From two Sweden population-based cohorts recent study included 533 type 2 diabetic patients measuring DNA methylations in 800.000 genomic sites of individuals, they found that the four subgroupings differed in terms of the amount of DNA methylation at 4.465 locations.

Variations in epigenetics among the four subgroups of T2D [2]

1 - Severe insulin-deficient diabetes (SIDD)

Early onset, insufficient insulin secretion, and inadequate metabolic regulation are the hallmarks of SIDD. 56 genomic locations have been shown to have DNA methylation, which is linked to a lower risk of heart attack and stroke.

2 - Severe insulin-resistant diabetes (SIRD)

SIRD is distinguished by significant insulin resistance, obesity, and a late onset. It includes 74 locations where DNA methylation is present, and it is related to an higher risk of kidney disease, heart attack, and stroke.

3 - Mild obesity-related diabetes (MOD)

Early onset, a relatively moderate form of hyperglycemia and obese patients, are the hallmarks of MOD. 4.135 locations on DNA are methylated. It is related to a lower risk of kidney disease, heart attack, and stroke

4 - Mild age-related diabetes (MARD)

Good metabolic control and late-onset diabetes are characteristics of MARD. It revealed 200 places where DNA was methylated. It is related to higher risk of renal illness, heart attacks, and strokes.

ROLE OF EPIGENETICS IN DIABETES COMPLICATIONS

In diabetic patients with cardiovascular complications circulating miR-126 levels were found significantly higher than those having other diabetic complications [21]**.** lncRNAs interaction and enhancers suggest

epigenetic role in trans-gene regulation. GWAS identifiy SNP in lncRNAs leading to functional alteration associated with cardiovascular complications in diabetics. So, lncRNAs dysregulation significantly participate to diabetic vascular complications [22]. The phenomenon of metabolic memory in type 2 diabetes can be explained by the long-lasting effects of epigenetic modifications, since maintaining excellent glucose control has long-term advantages and a history of hyperglycemia causes diabetic problems even when good glucose control is achieved **Figure 7** [22] .

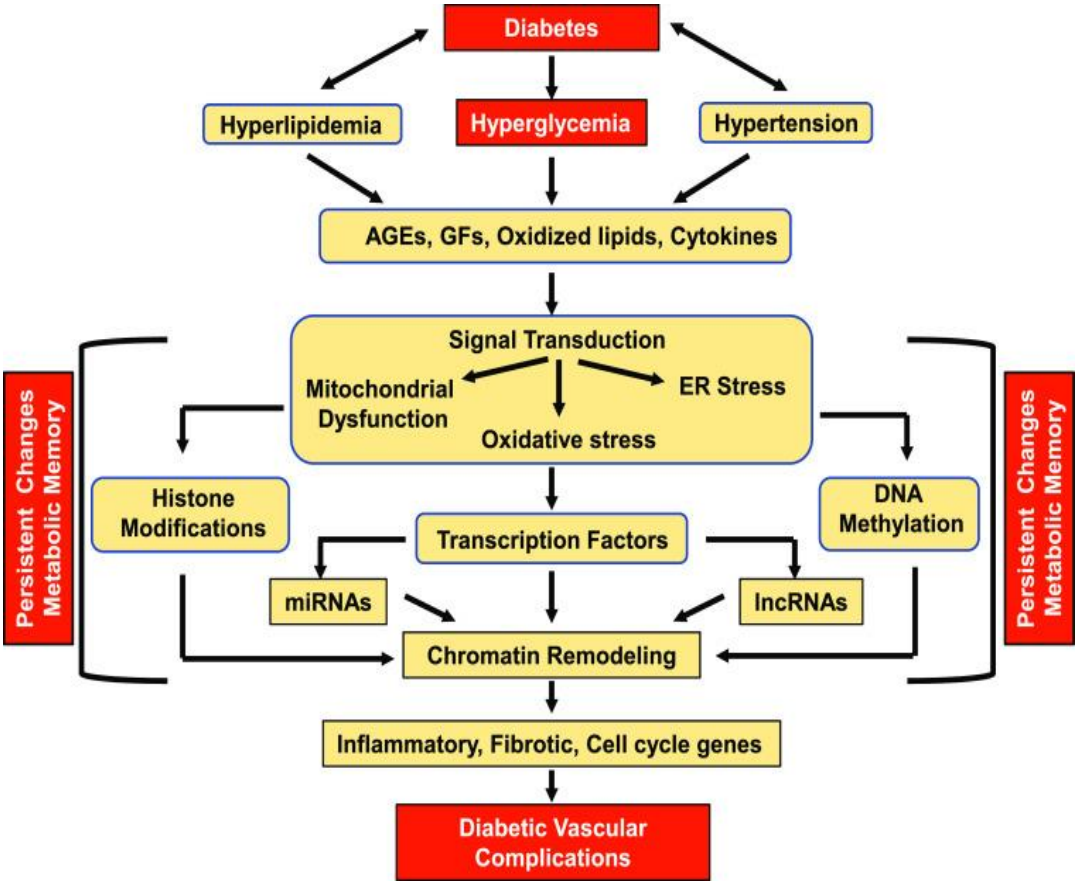

Figure 7: the role of epigenetic processes in metabolic memory and vascular complications of diabetes

Diabetic retinopathy

The complete DNA genome associated with diabetic retinopathy was studied by *Argadh et al. in 2015* [23]. At more than 300 CpG sites, the DNA methylation rates were investigated. The results show that people with diabetic retinopathy had higher levels of methylation, and that these rates also significantly predict how severe the retinopathy would be. 46 genes with CpG island methylation were associated with proliferative retinopathy, which is consistent with exudative and ischemia damage. According to *Argadh et al.* [23], regulatory genes hypomethylation is connected with enhancement of the expression of genes, which is correlated with higher proliferative retinopathy. Histone modifications, miRNAs, lncRNAs, and DNA methylation and demethylation all control a large number of genes related to angiogenesis. These modifications can drive pathophysiological pathways that result in an inflammatory response and vascular problems [24].

Diabetic Kidney Disease (DKD).

The synthesis of fibrotic genes and inflammatory genes in renal cells is stimulated by TGF-β1 through the activation of NF-κB, an important process in the pathophysiology of diabetic kidney disease. In podocytes, tubular epithelial cells, and renal Mcshistone alterations are involved in these processes. TGF-β1 reduced restrictive H3K9me2/3 at profibrotic gene promoters and elevated permissive alterations H3K4me1/3 and H3K9ac in mesangial cells. control of genes linked to inflammation, cell proliferation, and fibrosis utilizing DKD cell and mice models. Numerous long non-coding RNAs (lncRNAs) have shown dysregulated expression in renal cells cultured in diabetic environments (e.g., treated with TGF-β1 and in animals with diabetic kidney disease). Up-regulation of miR-21 in glomerular tissue appears to be a compensatory mechanism to prevent kidney failure in diabetic individuals [22]

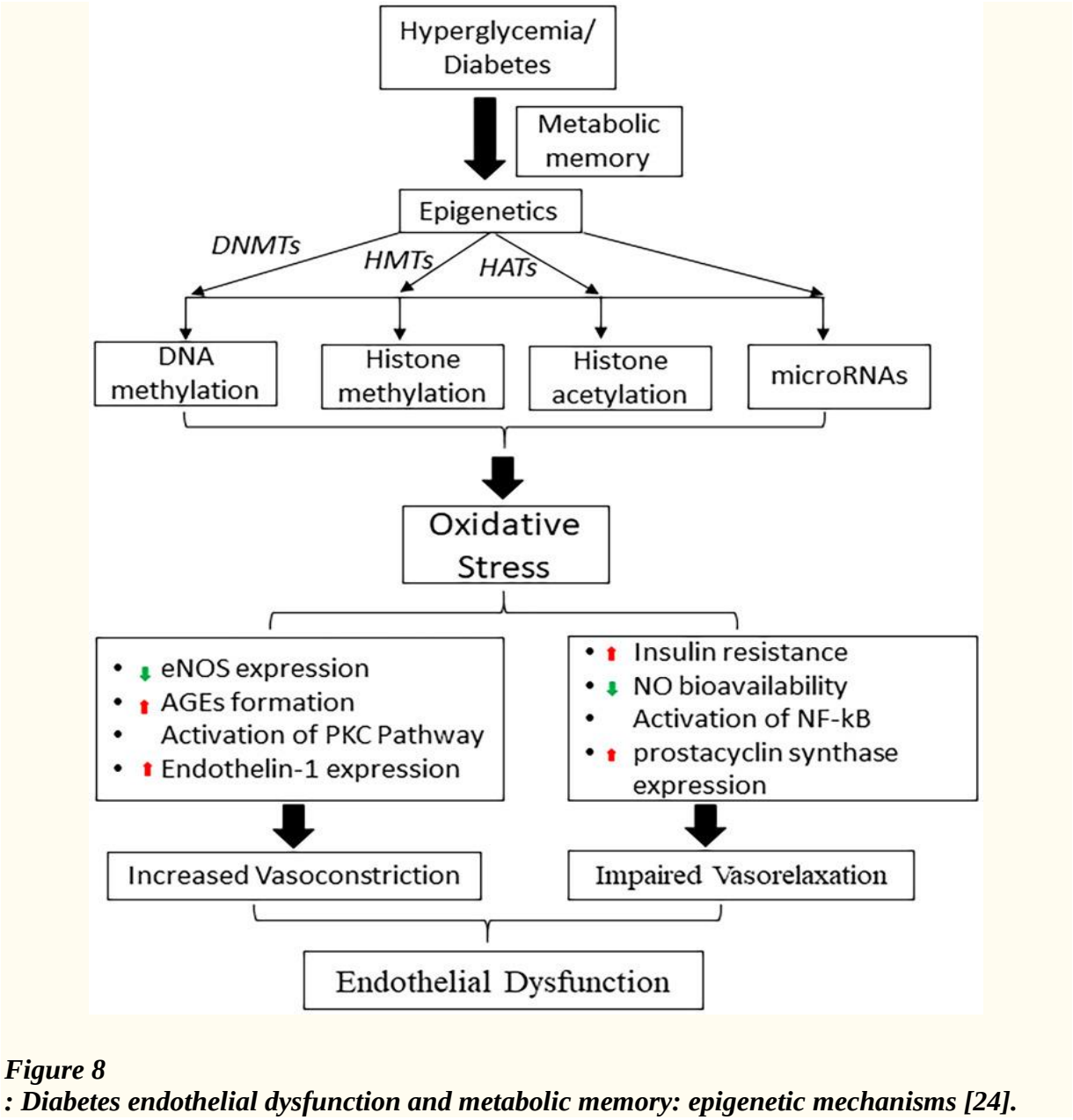

Figure 8
: Diabetes endothelial dysfunction and metabolic memory: epigenetic mechanisms [24].

The non-healing diabetic wounds' epigenetic processes

Due to aberrant gene-environment interactions and diabetes oxidative stressors, in reaction to an injury, the cutaneous process of wound healing is unbalanced. The process of cutaneous wound healing is hampered by the dysfunction of endothelial cells (ECs) **(Figure 8)** and the buildup of glycosylated products. This process has been linked to a number of epigenetic changes, mostly methylation of DNA and histone alterations [25].

The gene for endothelial nitric oxide (eNOS) is tightly controlled by epigenetic modifications.Under physiological conditions, endothelial cells exhibit persistent eNOS activation through a significantly hypomethylated promotor region that spans symmetric strands and CpG dinucleotides.

According to *Yan et al.* [26], endothelial cells differ from nonendothelial cells in their chromatin structure of eNOS. In particular, it has even been demonstrated that eNOS levels are elevated by histone deacetylase (HDAC) inhibitors. Therefore, the deregulation of eNOS levels observed in diabetic wounds provides direct evidence for the function that epigenetic control will play in wound healing [27].

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EPIGENETICS AND PRENATAL PREDISPOSITION TO DIABETES MELLITUS

Although the development of T2DM is influenced by both heredity and environment, recent research suggests that the fetus's environment during pregnancy may create certain epigenetic modifications to the fetus's DNA that may increase the fetus's susceptibility to developing T2DM later in life. Therefore, the development of T2DM is influenced by epigenetics. Numerous investigations on animals have demonstrated that a mother's diet permanently alters the methylation of her offspring. One such study showed that mice raised by mothers with GDM exhibit hypermethylation and epigenetic downregulation of the H19 and IGF2 genes, which is linked to insulin insensitivity (**Figure 9)** [28].

Children born to mothers going through famine have been shown to have differential methylation of the IGF2 gene and other genes linked to type 2 diabetes (T2DM). This finding suggests that epigenetics is the mechanistic link between prenatal nutrition and the development of T2DM later in life [29]

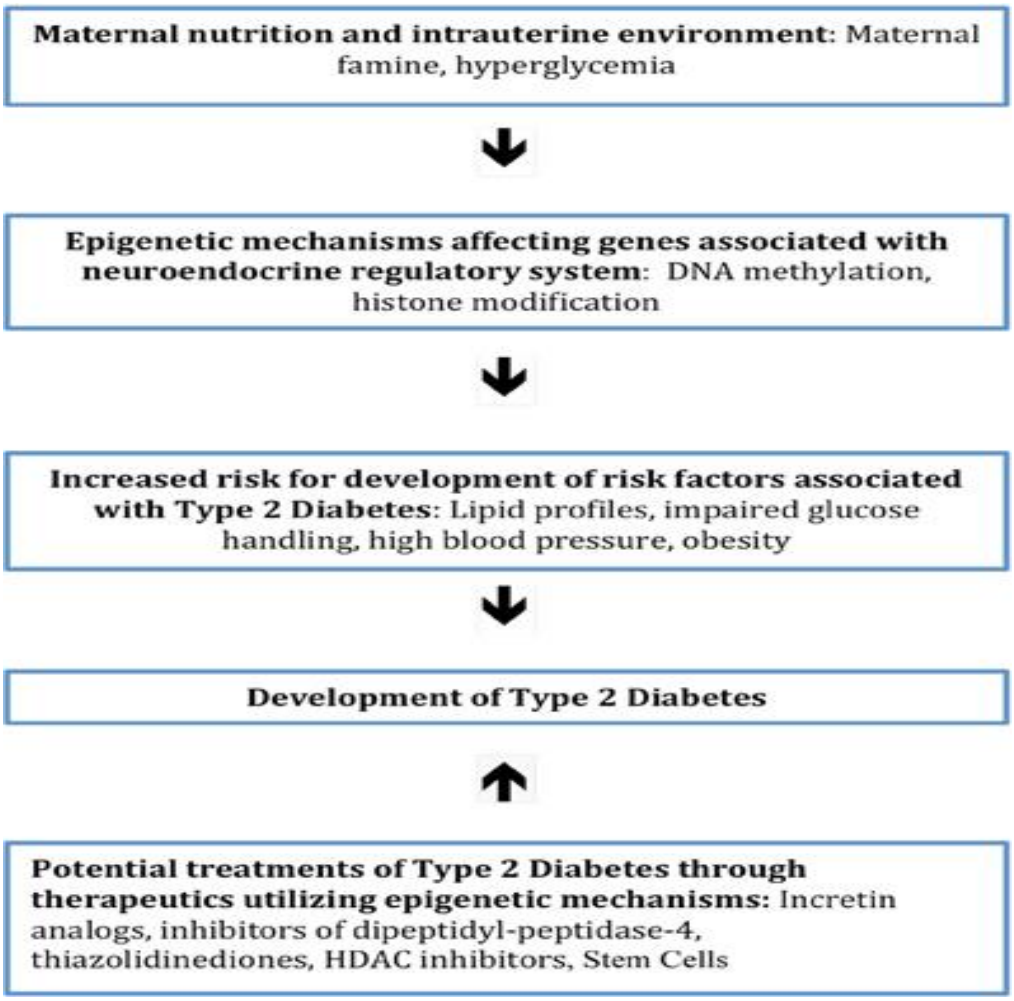

Figure 9: intrauterine environment and higher risk of T2DM development.

It has been shown that perinatal perturbations (as malnutrition and other metabolic disorders) in parents (F0) will predispose their offspring (F1) to have risk of diabetes after breath. Therefore, an appropriate functional food could prevent intergenerational epigenetic alteration(s) that might worsen the susceptibility to diabetes. This theory is supported by the finding that supplying the relevant dietary component during intrauterine life inhibits the development of diabetes risk factors in offspring [30]. **Figure 10,** shows an example of how three generations are impacted by the environment at once. The spermatozoa methylome and the in-utero environment are two aspects of the environment that affect the parents during conception. Eventually, these factors may also have an impact on the developing fetus and its reproductive cells. There is currently little proof that people can inherit epigenetic changes across four generations or more [15].

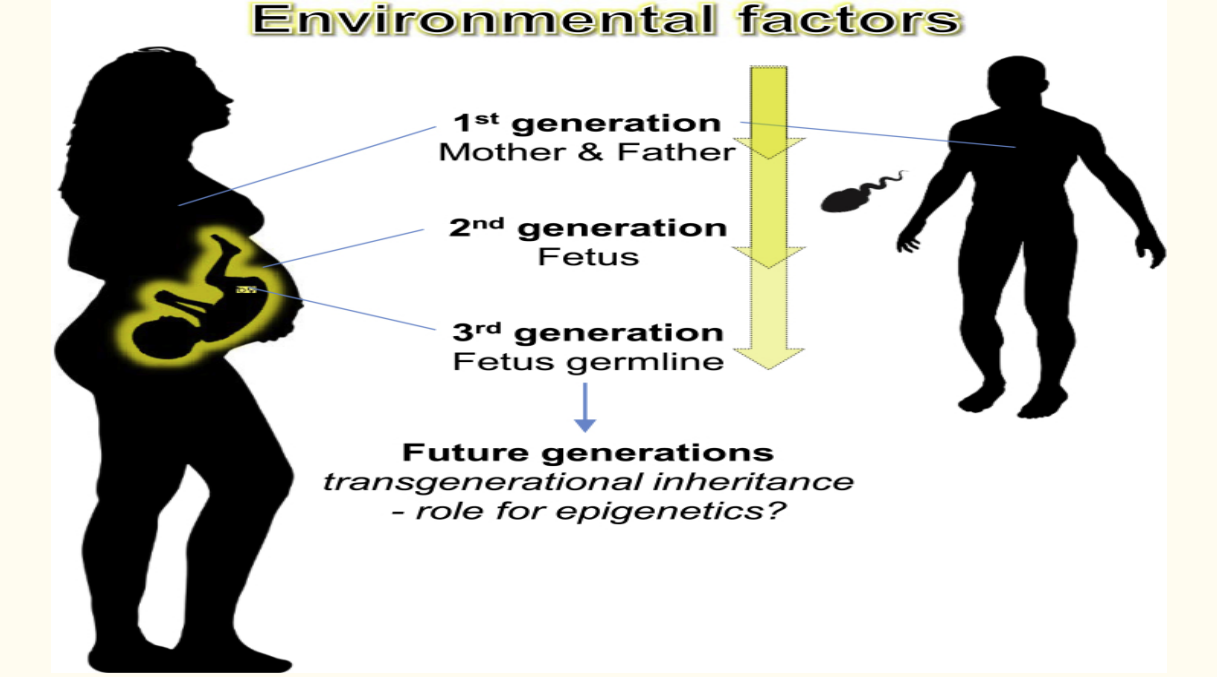

Figure 10: Transgenerational inheritance role of epigenetics

A recent study on IUGR rats described pancreas and duodenal homeobox 1 (Pdx1) expression. One transcription factor is Pdx1 which has a homeodomain and is involved in the formation of β cells as well as the exocrine and endocrine pancreases. Pdx1-mRNA expression in IUGR rats was shown to have decreased by 50% within 24 hours of early diagnosis. The pancreatic β cell that has been isolated suggests that it lowers the amount of H3 and H4 at the Pdx1 promoter. In these epigenetic alterations, the acetylation of H3 and H4 was associated with the binding of (USF1) to the PDX1 promoter region. In IUGR rats, an increase in histone deacetylation causes an increase in H3K9 dimethylation and a decrease in H3K4 trimethylation. Thus, chromatin was produced**; Figure 2** [9].

NUTRITION'S PREVENTIVE EPIGENETIC EFFECTS IN TYPE 2 DIABETES

Many functional meals could protect offspring against a genetic tendency toward diabetic [31]*:*

Whole Foods

Whole foods including camel milk and germinated brown rice. Whole foods are described as unaltered meals with broader health benefits (i.e., combating diabetes in offspring brought on by parents) *Mahmoud et al.* [32], *have* shown that whole camel milk, rich in camel whey protein, shields diabetic mothers' infants from the onset of diabetes and its aftereffects. Furthermore, gamma oryzanol-rich whole-grain germinated brown rice increases adiponectin levels. In addition to suppressing glucose production, it increases insulin sensitivity. Histones H3 and H4 undergo post-translational acetylation, as well as changes in DNA methyl marks, were responsible for the anti-diabetic effect on susceptible offspring. These modifications demonstrate the epigenetic influence of functional meals on subsequent generations [33].

Functional Foods with Epigenetic Effects that Prevent Type 2 Diabetes [31]

i. Berries:

Bioactive substances called anthocyanins and ellagitannins, which are found in berries like blueberries, blackberries, and Strawberries is linked to reducing

inflammation, improving insulin sensitivity, and managing glucose metabolism to prevent type 2 diabetes.

When taken as a supplement, it changes the patterns of DNA methylation of genes linked to inflammation and insulin signaling in people with type 2 diabetes (T2D), which raises the possibility that blueberries can prevent T2D via epigenetic mechanism [34].

ii. **Cruciferous Vegetables**:

Broccoli, cauliflower, and cabbage are examples of cruciferous vegetables. They include bioactive substances called sulforaphane and indole-3-carbinol, which increase insulin sensitivity and reduce inflammation, hence avoiding type 2 diabetes. Cruciferous vegetables may be able to prevent type 2 diabetes through epigenetic mechanisms because, they alter the DNA methylation patterns of genes connected to insulin signaling and inflammation in T2D patients [35].

iii. **Green Tea**:

It is a great source of catechins, such as epicatechin and epicatechin gallate, which are thought to act as epidrugs and have protective epigenetic effects in type 2 diabetes. By means of their associations with certain epigenetic markers, like DNA methylation and histone modifications these drugs improve insulin sensitivity and regulate glucose metabolism. Apart from restricting the elevated manifestation and functionality of DNA methyltransferases epigallocatechingallate inhibits the neural-tube abnormalities caused by maternal diabetes. As a result, neural tube closure-related gene expression is restored and DNA hypermethylation is suppressed. indicating that green tea may help manage and prevent type 2 diabetes through epigenetic processes [36].

iv. **Omega-3 Fatty Acids**:

Flaxseeds and salmon fish are rich sources of omega-3 fatty acids, which have been associated to a lower risk of type 2 diabetes via enhancing insulin sensitivity and decreasing inflammation. Research has indicated a potential correlation between the methylation of inflammatory genes in type 2 diabetes (T2D) and omega-3 fatty acid intake. This suggests that omega-3 fatty acids may have an epigenetic effect in the prevention of T2D [37].

v. **Spices:**

Curcumin and cinnamon aldehyde, two bioactive chemicals found in spices like turmeric and cinnamon, improve insulin sensitivity and control inflammation and glucose metabolism to prevent type 2 diabetes. Additionally, curcumin controls DNA methyltransferase I, histone acetyltransferases, histone deacetylases, and miRNAs [38].

Yun et al. [26], *discovered* that curcumin's potential in type 2 diabetes is due to histone modification. High blood sugar levels activate the NF-B signaling pathway, which in turn activates genes that are linked to inflammation. Curcumin, on the other hand, increases HDAC activity, namely HDAC2, and decreases HAT leading to reduction of proinflammatory cytokine production in high glucose-induced cells. Thus, the function of curcumin supply in controlling DNA methylation, miRNAs and histone acetylation, of genes related to inflammation and insulin signaling in people with type 2 diabetes indicating that curcumin may have a function in preventing T2D through epigenetic processes [39].

EPIGENETIC THERAPEUTIC TARGETS

Combining epigenetic medications with complementary therapy may help with diabetes complications. Owing to a large number of epithelial changes that can be reversed in nature. Therefore, With the advent of epigenetic modifications like DNMT3a and HDAC, molecules have an epigenetic effect called epidrugs, a number of important targets have also been identified [25].

Histone deacetylase inhibitors (HDACi)

Given its role in the development of diabetes, HDACs represent a novel therapeutic target for the management of type 2 diabetes and it was developed for insulin signaling regulation of and β- cell function. HDACi include trichostatin A, suberoylanilide Hydroxya, valproicacid, sodium butyrate and Givinostat [40].

Simultaneous histone acetylation that causes MyoD and Mef2a to bind encourages the release of GLUT4. GLUT4 transports glucose from the cell's exterior to its interior. Under the effect of HDACs NKHDAC2 and 4 as well as DNAMT3 A/3B, histone protein has been shown to exhibit both hypermethylation and deacetylation **(Figure 11)**. This has led to a reduction or suppression of GLUT4 expression. These enzymes have been suppressed by HDAC and DNAMT3A/3B inhibitors, which help to reverse the mechanism so that it is normal [25].

Sirtuin 1

It is examined in bacteria and is a member of the sirtuin family, also referred to as NAD-dependent deacetylase. The human cell's nucleus and cytoplasm contain the majority of the seven types of sirtuins that have been identified in humans.

It deacetylates PGC-1α and uncouples proteins, among other functions in metabolic diseases. SIRT1-induced PGC-1α deacetylation led to mitochondrial improvement through GLUT4 induction, adiponectin, and mitochondrial biogenesis, all of which increased insulin sensitivity and prevented type 2 diabetes. Adiponectin is a protein hormone with anti-diabetic properties; insulin resistance and type 2 diabetes are associated with decreased expression of this hormone [25].

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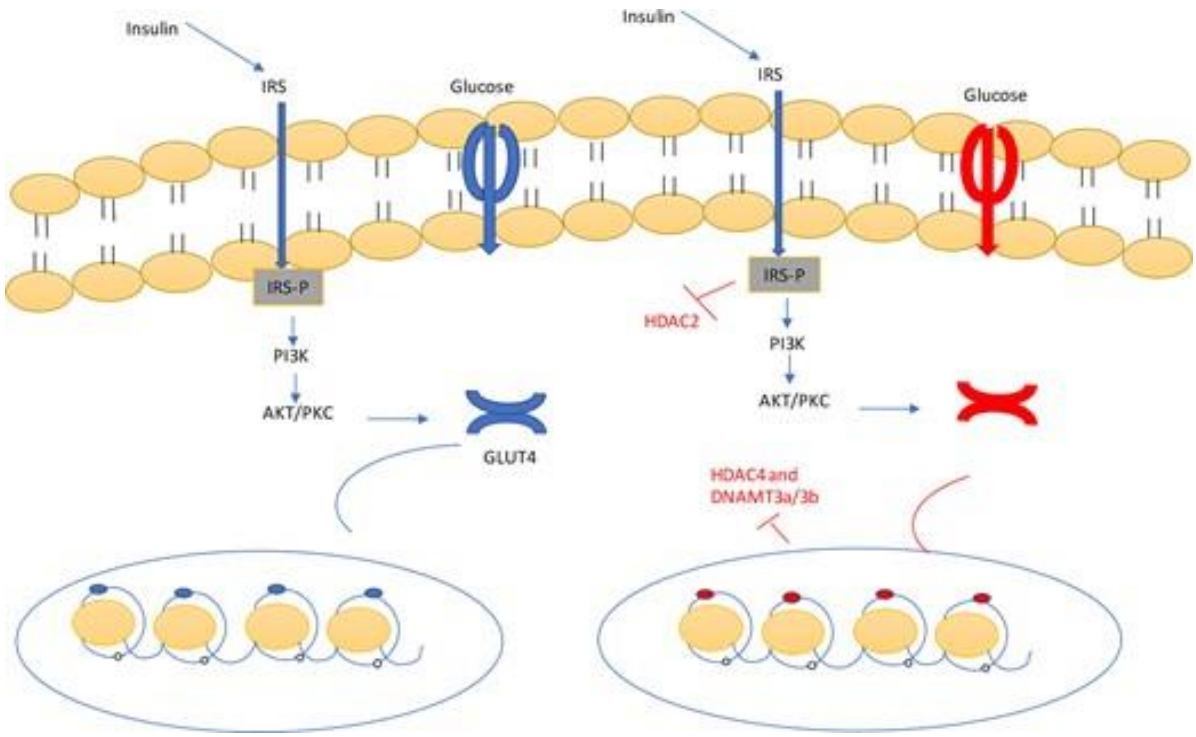

Figure 11: binding of Insulin to tits receptor, phosphorylating the receptor and initiating the PI3K/AKT pathways.

Protein tyrosine phosphatase 1B (PTP-1B)

PTP-1B is a member of the family of PTP enzyme, which has 435 amino acids and is encoded by 50 kDa PTpn1 genes. PTP1B's unphosphorylated form is involved in cell differentiation, proliferation, and death, among other processes. PTB1B controls the interaction between IRS1 and IRS2, which controls insulin action on liver and other organs. Insulin receptor attachment results in IR phosphorylation, which in turn activates secondary messengers that aid in regulating blood glucose level. As a result, PTB1B plays an important role in insulin resistance and being essential therapeutic target in the treatment of type 2 diabetes [41].

The Set 7

An innovative treatment for diabetes mellitus, Set 7 is an inhibitor of histone methyltransferase that aids in controlling the processes of histone deacetylation and methylation. Set7 is a chromatin-modifying enzyme that regulates transcription factor NF-kB, inflammation, oxidative stress, and endothelial dysfunction. It is upregulated in diabetes patients. Therefore, Set7 expression in circulating monocytes could be a useful indicator of vascular injury. Therefore, the creation of pharmaceutical strategies that target Set7 offers a possible means of reducing vascular inflammation and oxidative stress in the context of diabetes mellitus [25,42].

Translational Potential of Epigenetic Changes: Future Perspectives

Current epigenetic medications' nonspecific genomic effects may be partially mitigated by using epigenetic engineering to alter epigenetic markers at the locus-specific level. Enhancing the delivery, effectiveness, and selectivity of RNA-based therapies, like siRNAs or nuclease-resistant antisense oligonucleotides, will require more studies that target epigenetic modifiers and lncRNAs/miRNAs.Combining genotypes and traditional medicines with epigenotypes, epigenetic medications, and biomarkers can enhance treatment of vascular diabetic complications and metabolic memory [22].

EPIGENETIC DRIFT VERSUS EPIGENETIC CLOCK

Research on monozygotic (MZ) twins has revealed that while infancy they are epigenetically identical, as they age, the epigenomes of the older MZ twins differ significantly, suggesting that patterns of epigenetic modifications in MZ twin pairs diverge. Twin studies also show that repetitive sequences generally become more hypomethylated with aging, with methylation increases reported at unique regulatory locus-specific areas **(Figure 12***)*. Entropic decay of DNA methylation is detected during aging. Different diseases may affect different organs and tissues due to variations in tissue-dependent DNA methylation. "Epigenetic drift" refers to a large number of stochastically occurring methylation alterations that result in inter individual divergence during aging. It has been discovered that some CpG sites experience consistent methylation changes as people age, making it possible to employ these sites in epigenetic clock algorithms to precisely measure biological age and forecast chronological age [39].

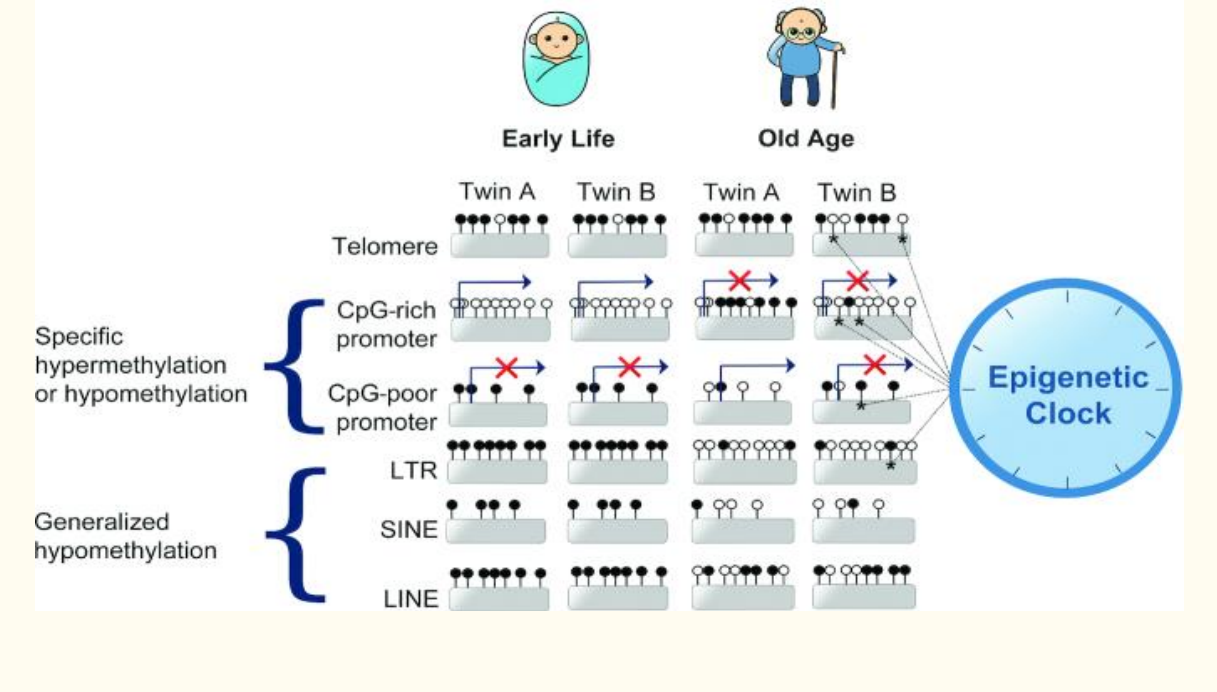

Figure 12: DNA methylation patterns of monozygotic twins diverge during aging.

CONCLUSION

Epigenetics plays a vital role in the pathology of DM, especially T2D.Recent research surrounding epigenetics has shown that exposure of the fetus to various abnormal intrauterine environmental states like hyperglycemia and famine can also increase the risk of developing T2DM. Since methylation of CpG islands may be heritable, epigenetic activity occurring in the developing fetal genome may result in lasting effects on our metabolic control. These lasting effects most likely introduce critical factors in the development of T2DM later in life. Thus, the influence that epigenetic mechanisms exert may be immensely important not only as a means by which environmental factors impact development of T2DM but also in its role in establishing one's risk profile for developing T2DM even before birth.

The nutritional quality and quantity provided to a developing embryo serves as a strong predictor of the development several risk factors associated with T2DM postnatally.

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