Journal of Health and Social Sciences Advance Publication Online
Published Online January 29, 2019 doi10.19204/2019/rlfp12

NARRATIVE REVIEW IN EPIGENETICS

Role of epigenetics in aetiology and therapies for Type 1 Diabetes Mellitus: A narrative review

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Abstract

Introduction: Some studies have demonstrated the possibility of using epigenetic modifications to manage or treat some cases of Type 1 diabetes mellitus (T1DM) in the near future. However, there are diverse opinions on the strategies suggested, necessitating this study to review epigenetic mechanisms and their possible therapeutic applications for T1DM.

Results and Discussion: Through enzyme-mediated DNA methylation, histone post-transcriptional modifications and microRNAs (miRNAs) gene expression, environmental factors may program the epigenomes of several cells during intrauterine life. In the β-cells, these biological processes may lead to altered expressions of certain insulin genes along with their promoter regions, resulting in dysfunctional insulin biosynthesis, hyperglycemia and T1DM. By

inhibiting the enzymes modulating these pathways, epigenetic changes can be reversed and normal functions of the affected genes restored, culminating in improved insulin production.

Conclusions: Epigenetic programming during intrauterine life may be responsible for the pathogenesis of some cases of T1DM. Fortunately, epigenetic mechanisms are reversible, so when detected early, could be used to prevent some cases of T1DM. It can also be used to formulate treatment procedures for T1DM.

KEY WORDS: β-cells; Diabetes Mellitus, Type 1; DNA methylation; epigenomics; genetic therapy; hyperglycemia; microRNAs.

Riassunto

Introduzione: Alcune ricerche hanno dimostrato la possibilità di usare modificazioni epigenetiche per gestire o trattare alcuni casi di diabete mellito tipo 1 nel prossimo futuro. Tuttavia, ci sono diverse opinioni sulle strategie suggerite, questo rende indispensabile la revisione dei meccanismi epigenetici e le loro possibili applicazioni terapeutiche per il trattamento del diabete mellito tipo 1.

Risultati e Discussione: Attraverso la metilazione del DNA per via enzimatica, le modificazioni post-trascrizionali degli istoni, l'espressione genica dei microRNA (miRNAs), i fattori ambientali possono programmare gli epigenomi di diverse cellule durante la vita intrauterina. Nelle cellule Beta pancreatiche, questi processi biologici possono portare ad alterare le espressioni di certi geni dell'insulina e dei loro promotori, determinando una disfunzione nella biosintesi dell'insulina, l'iperglicemia ed il diabete mellito tipo 1. Attraverso l'inibizione degli enzimi che modulano tali vie di attivazione, le modifiche epigenetiche possono essere invertite e

le normali funzioni dei geni interessati ripristinate determinando un miglioramento nella produzione dell'insulina.

Conclusioni: La programmazione epigenetica durante la vita intrauterina può essere responsabile della patogenesi di alcuni casi di diabete mellito tipo 1. Fortunatamente, i meccanismi epigenetici sono reversibili, cosi quando riconosciuti precocemente, potrebbero essere usati per prevenire alcuni casi di diabete mellito tipo 1. Tale programmazione può anche essere usata per formulare procedure terapeutiche per il diabete mellito di tipo 1.

TAKE HOME MESSAGE: Epigenetic modifications, including DNA methylation, histone post-transcriptional modifications and miroRNAs gene silencing are being suspected as among the factors responsible for the rising incidence of T1DM worldwide. Fortunately, epigenetic changes are reversible, so if understood and monitored, could be used to prevent or reverse T1DM.

Competing interests: none declared

Cite this article as: Tajudeen YO, Shemishere UB. Role of epigenetics and therapies for Type 1 Diabetes Mellitus: A narrative review. [published online ahead of print January 29, 2019]. J Health Soc Sci. doi10.19204/2019/rlfp12

DOI 10.19204/2019/rlfp12

Received: 12 Jan 2019 **Accepted:** 28 Jan 2019 **Published Online:** 29 Jan 2019

INTRODUCTION

Type 1 diabetes mellitus (T1DM), also known as insulin dependent, immune-mediated and juvenile-onset diabetes mellitus, is majorly caused by destruction of pancreatic beta cells [1, 2]. The destruction is typically mediated by an auto-immune reaction in which the cells are attacked by the body's defense mechanism [3]. Consequently, the beta cells secrete insufficient or no insulin – the hormone that transports glucose into the cells [1]. The disease can affect people of all ages, but is most common among children or youths [1, 4]. T1DM is among the most frequently occurring endocrine and metabolic conditions during the early stage of life [5]. It is irreversible, degenerative, and so affected individuals require daily insulin treatment to normalize blood glucose levels, without which the affected will die [1, 6, 7]. The onset of T1DM is often sudden and characterized by abnormal thirst and dry mouth as well as frequent urination [8]. Other clinical features of T1DM include fatigue, frequent hunger, sudden weight loss, persistent sores, recurrent infections, and blurred vision [1].

T1DM has been on the rise worldwide since the 20th century. According to Gale [9], the incidence of the disease was low in the first half of the century, but a sudden increase was recorded in the second half. Hsia et al [10] put the global incidence rate of T1DM at 4 % increase per annum in the century. A research group known as the DIAMOND Project Group also puts the global incidence rate of the disease at 2.8 % increase per annum between 1990 and 1999 [11]. In the last two decades, there has been a significant increase in the incidence of T1DM, occurring at about 5 % increase per year. Within this period, approximately 65,000 new cases are recorded

per year, mostly among children below 15 years [12]. The particular cause of the rising incidence of the disease is unknown; however, several studies suspected genetic and environmental factors such as chemical exposure, microbial infections, diets and lifestyles [13]. Recently, researchers have suggested the involvement of intrauterine epigenetic programming in the pathogenesis of diabetes mellitus (DM), including T1DM [14].

There is no specific definition for epigenetics; however, some scientists defined it as biological processes that control gene expression without altering DNA sequence [15, 16]. Some other scientists described it as the study of the marks on the genes, that is, the chemical tags (methyl and acetyl groups) on the DNA and RNA [17]. The epigenome comprises of DNA methylation, histone modifications and non-coding RNAs, all of which control transcription and, therefore, cellular activities and phenotypic expressions [18]. Changes to the epigenomes aside normal biological functions or reactions to environmental stimuli, can lead to heritable epigenetic mutations [19]. Epigenetic mutations can produce significant effects on cell functions, gene expressions and functions, which may result in or contribute to the onset of several diseases, including T1DM [19]. However, due to the relative newness of the field, awareness of the involvement of epigenetics in the pathogenesis of T1DM is poor. To this end, this study aimed at enlightening the public on the involvement of epigenetic changes in the onset of T1DM and possible reversal or preventive measures using epigenetic mechanisms.

RESULTS AND DISCUSSION

Description of epigenetics

From the literature, epigenetics could summarily be described as a molecular link between the genetic and environmental factors in the regulation of cellular events and disease pathogenesis. While the DNA controls the entire body, the epigenome modulates the DNA or rather have an overwhelming control over its expression [20]. The epigenome comprises of modification in the DNA structure and its packaging as well as the available regions that can be expressed into RNA and proteins [20]. The effects of epigenetic modifications can be cell or tissue-dependent in that the same epigenetic change may produce different effects in different tissues such as pancreas versus liver [20]. Epigenetic changes are heritable, so it can be theorized that if a particular region of the genome is modified, the effects can be passed on to the subsequent generations [21]. The epigenome interacts with genetic and environmental factors to determine the phenotypic features in individuals [22, 23].

Mechanistic links between epigenetics and T1DM

Some T1DM cases begin when environmental factors such as pollutants, diets, and microbes compromise the immune system during intrauterine life through epigenetic changes. This may lead to autoimmunity of the pancreatic beta cells, disrupting its insulin production function [24]. Environmental factors may also trigger epigenetic changes in certain genes, disrupting beta cell differentiation and maturation [24]. The most common mechanisms by which epigenetic modifications occur are DNA methylation, histone post-translational modifications and non-

coding microRNA-mediated (miRNA) gene silencing [25]. Figure 1 is the diagrammatic representation of the mechanistic links between epigenetics and Type 1 diabetes mellitus.

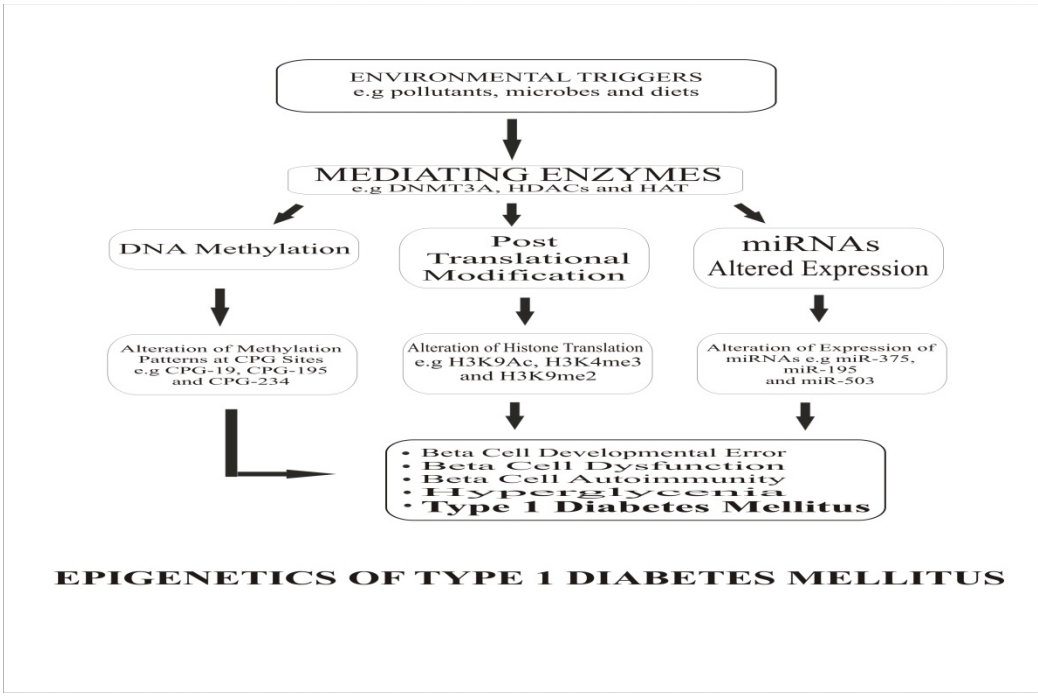

Figure 1. Link between Epigenetics and Type 1 Diabetes Mellitus.

Role of DNA methylation in T1DM pathogenesis

DNA methylation is a process by which a methyl group covalently attached to the 5′ carbon of DNA molecules at a CpG site [26]. DNA methylation usually results in gene silencing, and is known to be important in maintaining normal embryonic development, genomic imprinting, X-inactivation, and repression of aging, among others [27]. Certain epigenetic modifications that disrupt normal gene expression are now known to predispose to T1DM [28]. By targeting the mechanisms involved, researchers have prevented and cured DM in non-obese diabetic (NOD)

mice [29]. Several genes have been established to either heighten or lower the risk of T1DM; notable among the predisposing genes are human leukocyte antigen (HLA) genes. Any epigenetic change that targets these genes may induce T1DM pathogenesis by disrupting the normal expression and function of these genes, resulting in beta cell autoimmunity [30]. Similar changes in gene expression affecting the immune system in different target organs such as pancreas in the case of T1DM have been observed in individuals with various autoimmune diseases [31]. The pancreas of individuals with T1DM has been demonstrated to have an over-expression of inflammatory immune response genes [17]. Based on this finding, drugs that suppress over-expression of these genes have been demonstrated in mice to reduce inflammation, re-grow beta cells, and reverse T1DM [17].

According to Rui et al [32], DNA methylation plays an important role in maintaining the normal pancreas embryonic development and beta cell differentiation. The primary function of beta cells, which is glucose response insulin secretion is acquired after birth and is mediated through a metabolic program by DNA methyltransferase 3A (DNMT3A) [32]. This shows, in addition to its role in beta cell maturation, DNA Methylation also helps in maintaining normal function of the cell [32]. Rui and his co-researchers examined the cellular and molecular events in pancreatic islets and beta cells during the induction of DM in NOD mice. Autoimmunity was induced in the NOD mice between 3-4 weeks of age, followed by the adaptive immune responses, which destroyed the beta cells. The scientists observed a decline in beta cell population with increased infiltration of T cells into the islets of Langerhans with ageing. The CpG sites, which enhance insulin1 and insulin2 gene transcription was also observed to undergo methylation in the pre-diabetic period. Additionally, they observed over-expression of specific cytokines in the islets of

pre-diabetic NOD mice, which induced DNMTs and insulin gene methylation, affecting insulin transcription. Thus, epigenetic changes, especially those involving changes of gene function in response to immune stimuli, may be the mechanistic link between the immune system, loss of insulin gene expression, and onset of T1DM [32].

A study by Fradin et al. [33], also shed more light on the role of methylation in gene expression and disease pathogenesis. The study monitored the DNA methylation patterns of 7 CpGs in the transcription initiation region in the INS gene promoter. The scientists noted that patients with T1DM have a reduced methylation of CpG19, CpG-135, and CpG-234 and increased methylation of CpG-180 compared with controls.

Role of MicroRNA (miRNA) in T1DM pathogenesis

MicroRNAs are a group of small non-coding RNAs that negatively control gene expression by incompletely bonding to the 3′, 5′ untranslated sections of the target mRNAs [34]. This bonding results in translation repression and/or transcript degradation [35]. MicroRNAs are single-stranded molecules of about 22 nucleotide chains, and functionally regulate gene expression and cellular activities [36]. They are responsible for the expression of at least 6 out of 10 protein-coding genes, and modifications in their expressions have been linked with many diseases, including T1DM [37, 38].

T1DM begins when beta cells are exposed to certain stimuli, causing developmental errors and beta cell dysfunction [39], which in some cases are mediated by modifications in certain miRNAs. Some of these miRNAs include miR-15a/b, miR-16, miR-195, miR-503, miR-541, miR-214, miR-9, miR-124a, miR-7, miR-376 and miR-375, among others [40–42]. Although

detailed information on the roles of these miRNAs in DM pathogenesis is sketchy, it has been established that mutations in, or modification of these RNAs, could lead to β-cell dysfunction [43]. For instance, using an animal model, increased levels of blood miR-375 has been demonstrated to be associated with beta cell death, hyperglycemia, and DM [44]. Moreover, in serum samples collected from children with new-onset T1DM and age-matched healthy controls, 12 miRNAs were up-regulated in the diabetics, leading to apoptosis and poor glycemic control. The upregulated miRNAs in the T1D patients include miR-152, miR-30a-5p, miR-181a, miR-24, miR-148a, miR-210, miR-27a, miR-29a, miR-26a, miR-27b, miR-25, and miR-200a [45]. Inflammatory cytokines had also been noted to induce miR-21-5p, miR-30b-3p, miR-34, miR-101a and miR-146a-5p expressions in pancreatic islets, suggesting that miRNAs may have a role in cytokine-mediated beta-cell destruction [46, 47].

In one study, some scientists measured changes in miRNA expression in regulatory T cells of T1D-affected individuals. The cells were targeted in the study as a result of their importance in the prevention of autoimmune disease [43]. They found that miR-510 was significantly upregulated, while miR-191 and miR-342 were significantly reduced in adult peripheral T-reg cells of diabetic compared with controls [43]. These observations suggest a role for these miRNAs in the autoimmune destruction of β-cells [43]. Thus, measurement of specific miRNA levels may be useful for identifying people at risk for developing T1DM, possibly preventing the development of the disease [36].

Role of histone post-translational modification in T1DM pathogenesis

Histone post-translational modifications are alterations in the chromatin structure, affecting the expression and repression of embedded genes by enzymatic modification of the core histone [48]. The enzymes involved in this process are known as histone acetyltransferase (HAT) and histone deacetylases (HDACs) [49]. Epigenetic mechanisms in chromatin are increasingly being recognized as one of the molecular links between genes and the environment. In eukaryotic cells, chromatin structure can be modified by environmental factors such as diet, chemicals, and pathogens [50]. Post-translational modifications (PTMs) at the N-terminal amino acids of histones play an important role in modifying chromatin structure, modulating gene transcription [51]. Sometimes both DNA methylation and histone PTMs can work together to modulate epigenetic changes [51]. Histone PTMs have varying effects on gene expression depending on the position and the type of modification such as acetylation, methylation, phosphorylation, and ubiquitylation [52]. Its effects also depend on the degree of methylation, which could be either mono-, di-, or tri- [51]. Generally, histone H3-lysine 4-trimethylation (H3K4me3) and H3K9-acetylation (H3K9Ac) promote gene expression, while H3K9me2, H3K9me3, and H3K27me3 repress it [51, 53].

Some studies have reported alteration in the chromatin status of promoter/enhancer regions of key T1D susceptible genes in monocytes of T1D patients [52]. In one study, scientists compared histone H3K9me2 patterns in peripheral blood lymphocytes and monocytes obtained from T1DM patients against unaffected individuals. The results revealed a significant increase in H3K9me2 in certain genes in lymphocytes of the diabetics. Further analyses showed that the

methylated genes were strongly associated with T1DM pathogenesis and its complications [54] The study provided evidence of a link between T1DM and altered histone methylation of key diabetes-related genes, including those associated with inflammation and autoimmunity [54]. Notably, CTLA4, a known T1DM predisposing gene, revealed differential H3K9me2 methylation in T1DM lymphocytes versus normal [54]. In a similar study, data obtained from notable histone PTM profiling were analyzed [55]. The results showed marked variations in H3K9Ac levels at upstream regions of HLA-DRB1 and HLA-DQB1 within the T1DM locus in monocytes of patients with T1DM relative to controls [55]. Studies about the role of epigenetics in the aetiology of T1DM are summarized in Table 1.

Table 1. Epigenetic aetiology of Type 1 Diabetes.

Aetiology	**References**
Methylation of Human Leukocytes gene	[30,31]
Methylation of CpG sites	[32]
Epigenetic modification of MicroRNAs	[34, 35, 36, 37, 38, 40, 41, 42, 43, 45, 46, 47]
Post translational modification of histone	[48, 49, 50, 51, 52, 53]
Methylation of Histone proteins	[54, 55]

Epigenetic therapies for T1DM

When epigenetic mechanisms of a metabolic disease are fully understood, it could be used to predict the onset of the disease. It could also be used to formulate drugs or diet-related treatments

to delay the epigenetic change and even reverse it. Below are some of the potential therapeutic applications of epigenetics in diabetes management.

Epigenetic modification as biomarkers of T1DM

A biomarker can be defined as any substance, structure, or cellular process whose activities in the body can be used to predict the onset or progression of a disease [56]. Epigenetic biomarkers can be used to predict the pathogenesis of T1DM so as to adopt some modifications to prevent or treat the disease. The biomarkers must have been observed in a significant number of diabetic individuals in a population [57]. Early detection of DNA methylation and post-translational modification pattern as well as the expression of certain microRNAs related to T1DM in an individual may be used to predict T1DM. Many biological techniques, some of which have been previously mentioned, may be used to reveal these T1DM-related epigenetic changes. For example, Rakyan et al [58] used a genome-wide DNA methylation analysis of monocytes to differentiate between diabetic and non-diabetic monozygotic twins. The test revealed the presence of T1D-specific methylation variable positions (T1D-MVPs) in the T1D-affected twin, which were not found in the second.

Epigenetic blocking of methylation and post-translational modification enzymes

DNA methylation needs an enzyme known as DNA methyltranferase, while histone post-translational modification is mediated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). Blocking or deleting these enzymes may help reverse some diseases, including T1DM [59]. In fact, inhibiting the enzyme HDAC3 has been observed to prevent the progression of T1DM to diabetic cardiomyopathy (DCM).

Researchers in China observed that HDAC3 may be instrumental to the progression of T1DM DCM and, as such, determined if blocking the enzyme could reduce the disease progression. They observed that inhibition of the enzyme stopped the progression of T1DM to DCM. The scientists explained the mechanism underlining their observation using an animal model. In the study, transgenic mice with severe early onset T1DM and age-matched wild species were fed the HDAC3 inhibitor known as RGFP966 for 3 months. Afterward, cardiac functions and some relevant biomarkers were measured, which showed RGFP966 greatly prevented DCM in the diabetic mice. The diabetic mice showed improved cardiac functions as well as reduced inflammation and insulin resistance [60].

In vitro treatment of embryonic rat pancreata explanted around the 14th day of embryonic formation with some histone deacetylase inhibitors has also been reported to reduce exocrine and increase endocrine cell types [61]. In the study, deletion of class I and class II HDACs with trichostatin A was observed to increase endocrine progenitor cells and β cells, while inhibition of class I HDACs with valproic acid promotes the endocrine progenitor and α-cell [61]. These findings indicate that HDACs is important in the embryogenesis of pancreatic cell types [61].

A variety of dietary factors are now being investigated as potential HDAC and HAT inhibitors. Sulforaphane (an isothiocyanate found in broccoli sprouts) and diallyl disulfide (an organosulfur compound in garlic, have been shown to act as HDAC inhibitors [62, 63].

Epigenetic targeting of immune cells

Autoimmunity is the hallmark of T1DM and several cell types are involved in the pathophysiology of the disease. These cells include pathogenic T cells that wrongly recognize

beta cells as foreign and antigen-presenting cells that stimulate the pathogenic T cells. Others are macrophages that release pro-inflammatory molecules such as cytokines, and β cells that are the target of attack [64]. The wrong recognition of beta cells may due to some epigenetic modifications in certain genes embedded in the cells. Drugs or diets can be formulated to target the programmed epigenetic codes on these cells, normalizing their expression and possibly reverse T1DM. A few drugs have been formulated along this direction notable among which is the epigenetic drug called I-BET151.

I-BET151 was formulated by a group of scientists at Harvard Medical School and GlaxoSmithKlin and has been reported to target macrophages among several immune cells [7]. The drug modulates macrophage to repress certain pro-inflammatory genes by suppressing NFkB-mediated gene activation. I-BET151 also raises the expression of some molecules with anti-inflammatory properties [7]. Reduction in T cells was also observed following the application of the drug, which likely contributed to the reversal of the islet inflammation [65].

Some other drugs can be manufactured to alter the T1DM-pathways of other immune cells. For example, drugs can be manufactured to neutralize the cytokines, or block the interaction of T cells and antigen-presenting cells [66]. Other treatments may be formulated to promote the survival and regeneration of β cells as well as modification of pathogenic T cells [66]. According to Matthews et al [66], effective treatment of complex diseases like T1DM requires multifaceted approaches in which several drugs are simultaneously directed at different pathways related to the target disease.

Epigenetic targeting of environmental triggers

Environmental factors, including pollutant and microbial exposure as well as diets are the triggers of epigenetic changes across generations. In-depth understanding of epigenetic landscapes of an individual with T1DM can help formulate appropriate epigenetic diets to reduce the progression of the disease or even reverse it. Maternal restriction of methyl-donating minerals and vitamins consequent of eating too little fruits and vegetables may result to T1DM in the offspring [67]. Epigenetic treatment with methyl donating compounds such as folate may reprogram the epigenome of such diabetic individuals, normalize the expressions of the target gene and possibly reverse the disease [68]. Among methyl-donating compounds, deficiency of folate has particularly been blamed for the epigenetic programming of cells susceptible to several diseases, including T1DM. As such, folate, a water-soluble B vitamin, has been extensively investigated for its effect on DNA methylation and epigenetic programming [69]. Folate has a methyl group which it releases for the synthesis of adenosyl methionine, an important methyl donor for DNA and histone methylation processes [69]. Other methyl rich compounds include methionine, choline, betaine, and vitamin B-12 as well as other environmental factors [70, 71].

Several researchers have demonstrated the effects of diet on epigenetic programming and phenotypic presentation using the honeybees. All honeybees are the same after completing metamorphosis after which some developed to be queens while some become workers depending on whether they eat royal jelly or beebread. Royal jelly is a gelatinous substance produced by honey bees, while bee bread contains pollen and nectar or honey. The different feeds had been theorized to change DNA methylation patterns in the respective honeybee and programmed its

epigenome toward its phenotype [72]. A couple of studies reported that about 35 % of the honeybee genome are usually methylated at the CpG sites by a highly controlled DNA methylation mechanism. This indicates that honeybees use DNA methylation to control the expressions of certain genes involved in special biological functions [73, 74].

MicroRNA-based therapeutics for T1DM

As explained earlier, some T1DM cases are due to over-expression or repression of certain miRNA in insulin secreting cells and tissues. Analogues of some miRNAs have been synthesized and demonstrated both in vitro and in vivo to be useful in managing T1DM. A single miRNA can be used to target many genes sharing the same pathological pathway. Some miRNAs are cell or tissue specific and their activation or inactivation may alter the expression of genes embedded in the cells or tissue or may play a central role in their different pathways [75].

Two strategies exist for the application of miRNAs in diabetes therapeutics and are replacement and silencing strategy. Replacement therapy involves normalizing miRNA expression by adding hairpin RNA molecules analogous to the precursors of target miRNA or adding oligonucleotides that mimic the mature form of the miRNA of interest. In silencing therapy, the aim is to reduce over-expression of the suspected miRNA and restore normal expression of target genes. This is normally done by binding antisense oligonucleotides (anti-miRs) to the miRNA, resulting in the inhibition of its expression [75]. A brief recap of the therapeutic applications of epigenetics for T1DM management are presented in Table 2.

Table 2. Epigenetic therapies for Type 1 Diabetes.

Therapies	References
Use of epigenetic biomarkers	[56, 57, 58]
Blocking of methylating and post translational modification enzymes (e.g. DNA methyltransferase and Histone deacetylase)	[59, 60, 61]
Drug targeting epigenetic codes that induce autoimmunity	[7, 65, 66]
Drugs and diets targeting environmental triggers	[67, 68, 69, 70, 71, 72, 73, 74]
Replacement and silencing of miRNA	[75]

CONCLUSION

From the articles reviewed, it is clear that in addition to genetic and environmental factors, epigenetic changes may also play a role in the pathogenesis of T1DM. In fact, epigenetics serve as a link between the genetic and environmental triggers of T1DM. Epigenetic changes are reversible and, as such, can be used in the prevention and therapeutics of T1DM. We are appealing to policy makers, health organizations and individuals worldwide to fund researches in this direction.

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