The Role of Epigenetics in Type 2 Diabetes

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Type 2 diabetes (T2D) is characterised by high levels of blood glucose resulting from a combination of factors, including insulin resistance, a decrease in insulin secretion, and an increase in glucose production by the liver. Epigenetic changes have been shown to influence these factors through changes in changes in gene expression patterns.

diabetes epigenetic inheritance functional foods

1. Introduction

1.1. Background on Type 2 Diabetes and Its Treatment Approaches

Diabetes is the seventh-leading cause of global mortality, and has surpassed pandemic proportions. From less than 1 million deaths in the year 2000, the disease was responsible for almost 7 million deaths in 2021 [1]. Type 2 diabetes (T2D) is specifically characterised by high levels of glucose in the blood resulting from a combination of factors, including insulin resistance, a decrease in insulin secretion, and an increase in glucose production by the liver [2]. T2D causes significant morbidity and mortality worldwide, and is associated with a number of serious health complications, such as cardiovascular disease, kidney disease, and blindness [3][4].

Owing to the fact that a high consumption of unhealthy diets, and sedentary lifestyles have been greatly implicated, the current treatment approaches for T2D include lifestyle modifications (e.g., healthy diet and physical activity), oral medications, and insulin therapy [5][6]. Lifestyle modifications are considered the cornerstone of T2D management, and are often the first line of treatment for individuals with prediabetes or newly diagnosed T2D. In addition to lifestyle changes, oral medications, such as metformin, sulfonylureas, and dipeptidyl peptidase-4 (DPP-4) inhibitors are commonly used to improve insulin sensitivity, increase insulin secretion, and decrease glucose production [7][8]. For individuals who require more intensive therapy, insulin therapy may be recommended.

While these traditional approaches have been effective in managing T2D, they have limitations, and may not be effective for all individuals. As such, there is a growing interest in developing alternative strategies for preventing and managing T2D, including the use of functional foods with demonstrated preventive epigenetic effects [9].

Even though the disease has no known cure, a combination of lifestyle modification and drug therapy in diagnosed individuals has shown great success in reducing mortality and increasing quality of life. More important, as advocated by the World Health Organisation, is the preventive narrative in reducing the global burden of the

disease. Diet has been a cornerstone in the prevention of diabetes since the era of classical Greece, as declared in the tenet “Let food be thy medicine and medicine be thy food”, by Hippocrates.

1.2. Dietary Lifestyle as a Risk Factor for Type 2 Diabetes

The risk of developing type 2 diabetes has been largely linked to either environmental, lifestyle, or genetic factors [10]. Concrete data have linked lifestyle factors such as diet [11], heavy smoking [12], opioid use [13], physical inactivity (sedentarism), obesity [14][15], and alcoholism [16][17] to type 2 diabetes. Individual diets (food) and some dietary combinations have the potential to differentially impact the risk of developing type 2 diabetes [18][19]. Numerous studies have shown that the type of food people consume could be associated with the development of diabetes. In a cross-sectional study, Shu et al. demonstrated an association between consuming a Western diet, and the risk of type 2 diabetes mellitus among middle-aged Chinese adults [20]. Moreover, several cohort and preclinical studies have highlighted diet as a contributory factor in the predisposition to type 2 diabetes mellitus [11][21][22][23]. A high-fibre diet, low glycaemic index diet, and high amylose diet have been associated with a lesser predisposition to type 2 diabetes, when compared to their counterparts [24][25][26]. Nuts have also been shown to be beneficial in preclusion to type 2 diabetes. On the other hand, refined grains and sugar-sweetened beverages tend to promote a predisposition to type 2 diabetes [27]. For instance, clinical trials of short- and medium-term durations on postprandial glucose excursion in normal patients, insulin sensitivity in obese patients, and glucose handling in diabetic patients confirmed the superiority of a whole-grain diet over refined grains in maintaining a near-euglycemic state [28]. Studies have also shown that people who consume fermented dairy products are less likely to develop type 2 diabetes than those who consume non-fermented ones [29][30].

1.3. The Concept of Epigenetics, and Its Role in Chronic Diseases

Epigenetics is the study of changes in gene function that occur without a change in the underlying DNA sequence [31]. These changes are caused by modifications to DNA and its associated proteins, such as histones, which play a crucial role in regulating gene expression. There are several different types of epigenetic modifications, including DNA methylation, histone modification, and non-coding RNA-mediated regulation, all of which can have a significant impact on gene expression [32]. Epigenetic changes can occur in response to a variety of environmental and lifestyle factors, such as diet, physical activity, and exposure to toxins. These changes can be transmitted from one generation to the next, and may play a key role in the development and progression of chronic diseases, including T2D [33].

Studies have demonstrated that epigenetic changes can lead to alterations in the expression of genes involved in glucose metabolism, insulin secretion, and inflammation, which are all important factors in the development and progression of T2D [34]. Additionally, epigenetic changes can increase the risk of T2D by altering the expression of genes involved in fat metabolism, which can lead to obesity and insulin resistance [35]. Epigenome-wide association studies have substantially linked DNA methylation to diabetes [35]. Using human pancreatic islets, Daneshpajooh et al. also demonstrated that diabetes and impaired insulin secretion could result from epigenetic modifications that alter gene expression [36]. In addition, epidemiological findings in offspring born to Dutch Hunger

Winter mothers during World War II have provided some evidence of the predisposition to diabetes due to intra-uterine perturbations [37]. On the other hand, several pieces of evidence also highlight the mechanistic role of epigenetics in the dietary mitigation of type 2 diabetes. For instance, Li et al. show that a diet high in folates reduces blood glucose levels and improves insulin sensitivity, by altering the DNA methylation patterns in the adipose tissues of genes associated with type 2 diabetes [38]. The role of epigenetics in chronic diseases such as T2D highlights the importance of environmental and lifestyle factors, such as diet, in disease prevention and management.

2. The Role of Epigenetics in T2D

2.1. Overview of Epigenetic Changes Associated with T2D

T2D is associated with epigenetic changes that can impact the expression of genes involved in glucose metabolism, insulin signaling, and inflammation. These epigenetic changes include the following:

i. DNA methylation: DNA methylation is a chemical modification that involves the addition of a methyl group to the DNA molecule. Methylated DNA in mammals is usually in the form of 5-methylcytosine. In lower organisms (*Drosophila melanogaster*, fungi, and bacteria), the majority of the methylated DNA is in the form of N6-methyladenine [39]. While N6-methyladenine has been associated with over-expression, 5-methylcytosine has been linked with gene repression [40][41]. In T2D, DNA methylation changes have been observed in genes involved in insulin secretion and glucose metabolism, leading to alterations in their expression and function [42]. Maternal high-fat diet consumption in mice during gestation and lactation has been demonstrated to cause insulin resistance and glucose intolerance in their F_1 offspring, through the promotion of *Irs2* DNA methylation, and a decrease in *Map2k* DNA methylation [43]. DNA methylation has been hypothesised to act by disrupting the binding of transcription factors to recognition elements (containing a CG nucleotide), leading to the silencing of gene expression [44]. These aberrations in DNA methylation (whether hypo- or hyper-methylations) are oftentimes secondary to DNA methyltransferases gene (DNMT1, DNMT3A, and DNMT3B) dysregulation/mutations.

ii. Histone modification: Histones are proteins that interact with DNA to help package it into a compact structure. Histone modifications include the phosphorylation, methylation, acetylation, and ubiquitination of histone molecules. This leads to conformational changes that remodel chromatin, thereby altering the activity and interactions of transcription factors, nuclear proteins, and histone molecules; this, in turn, affects gene transcription and its sequelae [45]. In T2D, changes in histone modification have been observed in genes involved in insulin sensitivity, glucose metabolism, and inflammation [46].

iii. Non-coding RNA-mediated regulation: Non-coding RNAs, such as microRNAs, are short RNA molecules that do not encode for proteins, but play a crucial role in regulating gene expression. For instance, the parental intake of five functional food oils has been shown to modulate miRNA expression in both the parent and offspring [47]. In addition, functional foods have also been shown to modulate the expression of lncRNA in parents and offspring [38]

[48][49][50]. Essentially, in T2D, changes in the expression of non-coding RNAs have been observed in genes involved in insulin secretion and glucose metabolism, leading to alterations in their function [51][52].

These epigenetic changes associated with T2D can also interact with other factors, such as obesity and physical inactivity, which are known to increase the risk of T2D [35]. The complex interplay between these factors highlights the importance of a holistic approach to the prevention and management of T2D, which takes into account both the genetic and environmental factors.

Furthermore, epigenetic changes in genes involved in insulin secretion and sensitivity, glucose metabolism, inflammation, and adipocyte differentiation and function can have a profound impact on the development of type 2 diabetes (T2D). Insulin secretion and sensitivity can be decreased due to these epigenetic changes, leading to insulin resistance, which is a defining characteristic of T2D. Additionally, alterations in glucose metabolism can result in an increase in glucose production by the liver, and elevated blood-glucose levels, due to changes in glucose uptake, utilisation, and storage in peripheral tissues. Inflammation is also impacted by these epigenetic changes, resulting in a persistent state of low-grade inflammation that is associated with the progression of T2D. Moreover, changes in the differentiation and function of adipocytes can lead to altered lipid storage and an increased risk of obesity and insulin resistance. These various changes accumulate over time, resulting in a progressive decline in glucose metabolism and insulin sensitivity, which can increase the likelihood of developing T2D and its associated health complications.

2.2. Epigenetic Inheritance of T2D

Based on the sustainability of a conferred metabolic disease along subsequent generations of offspring, an epigenetic transfer may be termed transgenerational, intergenerational or multigenerational [53]. Such epigenetic change(s) could be important therapeutic target(s) for reducing diabetes, because of the typical epigenetic signature of being modifiable and reversible. Numerous clinical observations and in vivo laboratory experiments involving animals have proved beyond conjecture that there is a generational link of type 2 diabetes between parents and their subsequent descendants. Compelling animal studies involving embryo transfer experiments [54], and discordant human siblings born to parent before and after the development of maternal diabetes [55] have given credence to the association between gestational diabetes and the development of later-life type 2 diabetes. Later generational phenotypic expressions (e.g., type 2 diabetes) consequent on “developmental programming” due to early-life environmental insults, especially the over- and under-nutrition of specific nutrients, have demonstrated the risk of a generational diabetic link between offspring and their parents [56][57][58]. Crudo et al. demonstrated a transgenerational association between late-gestation glucocorticoid intervention in F1 pregnant guinea pigs, and global DNA methylation and the expression of crucial metabolic genes in subsequent generations of offspring [59]. In an earlier study, maternal under-nutrition had been associated with transgenerational increased neonatal adiposity in the offspring of exposed women [60]. Furthermore, using a mouse model, Pavlinkova and colleagues have demonstrated the association between paternal diabetes and sperm quality, and expression patterns in the offspring of later generations [57]. With the foregoing observations, and many more reports in the

literature, it is almost impossible to rule out the transmission of type 2 diabetes from parents to their subsequent generational offspring.

Accordingly, the underlying mechanisms responsible for the transmission of type 2 diabetes have been explored since the early 1990s. Diets have been shown to programme type 2 diabetes, by altering the structural and functional metabolic systems in adipose tissues, muscles, and the pancreas and liver [61][62][63]. Epigenetics have evolved as the underlying molecular mechanisms through which these dietary disturbances during intra-uterine life are registered and “reminisced” during later generations as metabolic dysfunctions such as type 2 diabetes. These metabolic dysfunctions occur through upstream modifications in epigenetic signatures which influence gene expression without tampering with the DNA sequence. For example, studies have shown that diet influences the expression of intestinal fatty acid binding protein (IFABP) mRNA, which will in turn affect all downstream processes affected by its protein [64]. IFABP is known to be an expressed product of the FABP2 gene, which is responsible for a myriad of fatty acid trafficking processes across several metabolic pathways. This report indicates that diet can modify the epigenetic memory of specific genes, which in turn affects the expression of proteins responsible for the handling of specific metabolic pathways involving the homeostasis of blood glucose and body weight. This, in the long run, impacts the development of heritable type 2 diabetes mellitus.

Therefore, understanding the specifics of these changes is crucial for the development of new strategies for preventing and managing the disease, including the use of functional foods with preventive epigenetic effects.

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