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Nutriepigenomics and Its Application in the Management of Type 2 Diabetes

Nutriepigenomics, or nutritional epigenomics, is an emerging field that studies how nutrients and dietary patterns influence gene expression through epigenetic modifications. In the context of diabetes, this field is particularly relevant due to the significant impact of diet on disease management and the prevention of complications.

Diabetes, especially type 2 diabetes mellitus (T2DM), is influenced by a combination of genetic and environmental factors, including diet. Epigenetic modifications, such as DNA methylation[1], histone modification, and microRNA-mediated regulation, play a key role in how environmental factors affect gene expression without altering the DNA sequence.

Nutrients and bioactive compounds can modify epigenetic patterns and, consequently, influence glucose metabolism by regulating genes involved in insulin sensitivity and glucose production, chronic inflammation characteristic of diabetes (which can be modulated by anti-inflammatory nutrients), and oxidative stress through dietary antioxidants that may reduce oxidative damage in metabolically active tissues. Examples of nutrients capable of influencing epigenetic regulation include folic acid, along with other B vitamins, polyphenols (resveratrol, catechins), omega-3 fatty acids, and dietary fibers, which can modulate gut microbiota. The gut microbiota, in turn, interacts with epigenetic modifications.

EPIGENETICS IN HEALTH AND DISEASE

The decoding of the human genome was completed in 2003 through the Human Genome Project. This milestone represented a significant advancement in biology and medicine, revolutionizing our understanding of genetics and its influence on health and disease. It led to the ability to diagnose previously undiagnosable diseases and advanced pharmacogenetics. However, despite knowing the complete human genome sequence, many unanswered questions remain. There is considerable variability in disease risk and responses to medical treatments. While individual genome differences explain about 30% of disease risk variability, the remaining 70% is influenced by environmental factors such as diet, physical activity, environmental pollutants, temperature, toxic habits (e.g., smoking, alcohol, or drug use), social relationships, and health care access. The molecular mechanism through which environmental factors regulate cellular function is called epigenetic mechanisms, and the science that studies them is epigenetics.

The word epigenetics was first defined in 1942 by the Scottish biologist Conrad Hal Waddington as the science that studies the molecular mechanisms connecting the genotype with the environment to give rise to the phenotype. Following this definition, numerous studies emerged, demonstrating the existence of a molecular mechanism beyond genetics. A highly representative example of this molecular mechanism comes from observing the different phenotypes found when studying identical twins. Identical twin pairs share the same genetic material, but in many cases, notable differences can be observed in their predisposition to developing diseases. These differences are influenced by variations in lifestyle and differential exposure to certain environmental factors ***(Figure 1)***. Another piece of evidence supporting the existence of a molecular mechanism that regulates gene expression beyond genetics comes from the study of children conceived during the Dutch Hunger Winter. This severe food crisis affected the Netherlands in the final months of World War II, between the winter of 1944 and the spring of 1945, and had a devastating impact on the »

FIGURE 1. Identical twins separated at birth. Phenotypic differences due to having grown up in different environments and with different habits.

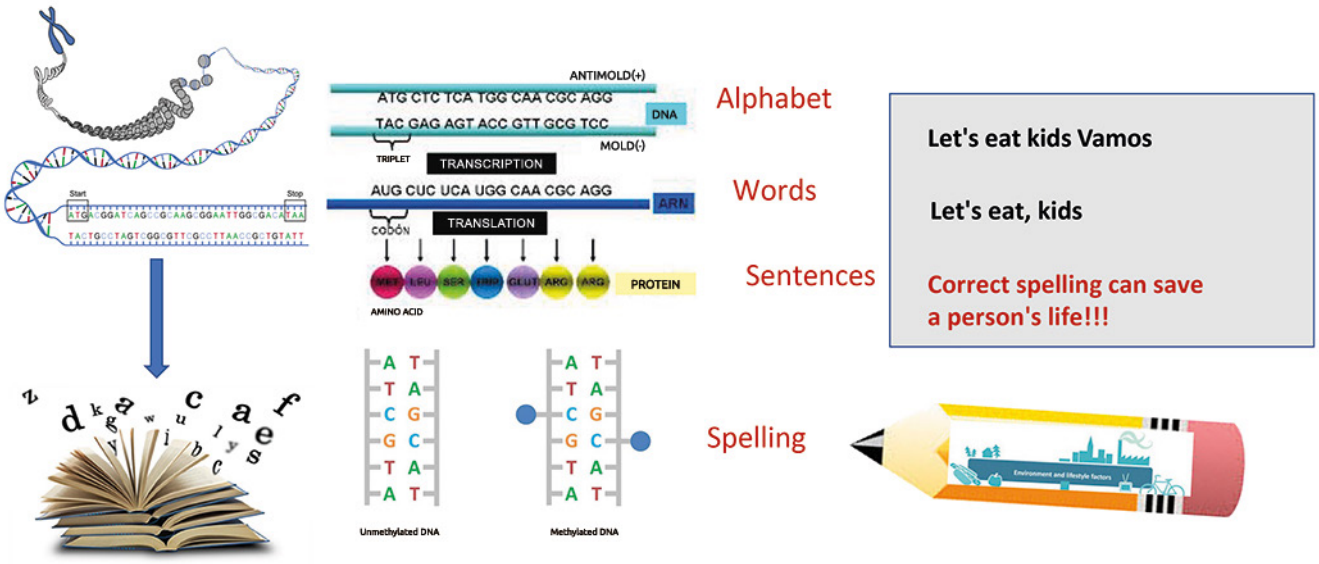

FIGURE 2. Epigenetics is the spelling of the "book of life," which is the DNA containing the genes.

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EVIDENCE SHOWS THE EXISTENCE OF A DIFFERENTIAL DNA METHYLATION PATTERN ASSOCIATED WITH VARIOUS DISEASES, INCLUDING METABOLIC DISORDERS SUCH AS TYPE 2 DIABETES AND OBESITY

Dutch population, directly affecting their health. Individuals exposed to famine in the womb or during early childhood showed a higher prevalence of cardiovascular diseases, type 2 diabetes mellitus, and metabolic disorders in adulthood. Increased rates of psychiatric disorders, such as schizophrenia and anxiety disorders, were also observed. However, siblings born outside this period did not exhibit the same disease risks.

Epigenetic regulation can be thought of as the punctuation of the book of life—our genome—while genetics serves as the alphabet that forms sentences. According to the central dogma of molecular biology, the proteins encoded by genes could be considered the sentences. However, the meaning of a sentence can change depending on where punctuation marks are placed. For example, we can say, "Let's eat kids" or "Let's eat, kids." Both sentences contain the same words, but their meanings are entirely different. The "pen" that writes this punctuation is our lifestyle and environment ***(Figure 2)***.

There are several epigenetic mechanisms, including DNA methylation, histone modification, and non-coding RNAs (microRNAs and long non-coding RNAs). Among these, DNA methylation is the most abundant and well-studied. These epigenetic mechanisms regulate gene expression throughout an organism's life, acting as switches that turn genes on or off. Whether these marks are correctly placed within gene sequences significantly impacts health.

Epigenetic marks can be quantified using various techniques, such as whole-genome sequencing (Next-Generation Sequencing, NGS), partial-genome methylation microarrays, or targeted pyrosequencing to analyze specific genes. In the case of DNA methylation marks, this quantification provides valuable information for predicting disease risk, making more precise diagnoses, and monitoring treatment responses. In this regard, research has identified differential DNA methylation patterns associated with various diseases, including metabolic disorders such as type 2 diabetes and obesity.

One crucial aspect of epigenetic marks is that, unlike genetic mutations, they are reversible. This characteristic presents an opportunity to develop therapeutic strategies aimed at modulating epigenetic marks. Such therapeutic strategies can be based on nutrition.

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AN EPIGENETIC DIET COULD SERVE AS A COMPLEMENTARY ADJUVANT THERAPY TO HYPOGLYCEMIC DRUGS, WITH MINIMAL SIDE EFFECTS AND LOW TOXICITY FOR LONG-TERM ADMINISTRATION

NUTRITION AND EPIGENETICS IN TYPE 2 DIABETES MELLITUS

The epigenetic machinery is highly dependent on nutritional factors. DNA methylation enzymes, which donate methyl groups, utilize methyl groups derived from one-carbon metabolism compounds such as folic acid, vitamin B12, and choline. Additionally, micronutrients such as zinc, retinoic acid, selenium, and other bioactive compounds like polyphenols can influence the donation of methyl groups. Due to the connection between nutritional factors and epigenetic regulation, the field of nutriepigenomics, or nutritional epigenomics, has emerged as the science that studies the effects of nutrients on human health through epigenetic changes.

It has been identified that people with diabetes often have lower levels of certain vitamins with antioxidant properties, such as vitamins A, C, and E. This reduction may be due to the increased demand to combat oxidative stress associated with glucose metabolism alterations. Additionally, retinol-binding protein plays an important role in the regulation and function of adipokines. Moreover, deficiencies in thiamine, pyridoxine, and biotin are commonly observed in individuals with diabetes. Research suggests that diabetes may interfere with the absorption of various nutrients, including vitamins B9 and B12, making their regular supplementation necessary. Vitamin D insufficiency has also been associated with an increased risk of developing diabetes and related complications, such as cardiovascular diseases.

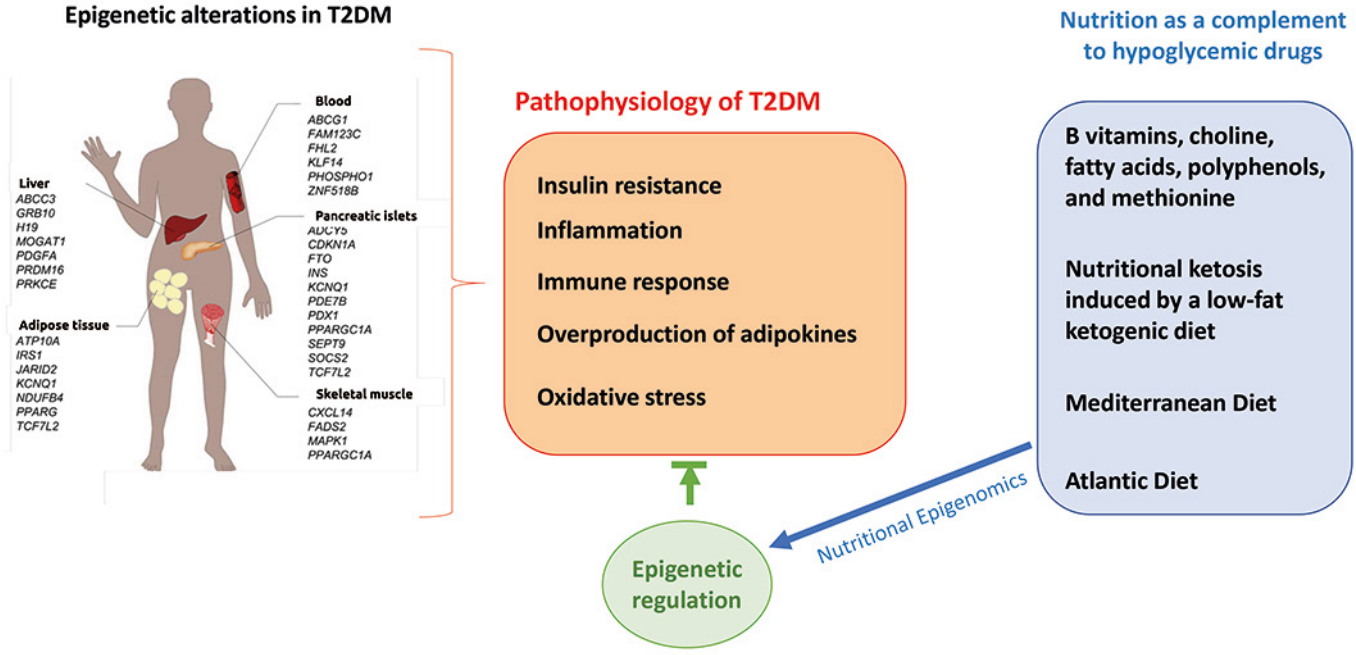

FIGURE 3. Impact of Nutritional Epigenomics in Type 2 Diabetes therapy.

» Therefore, supplementation with vitamins and bioactive nutrients capable of modulating the epigenetic machinery could be a useful adjunct to pharmacological therapy for type 2 diabetes mellitus (T2DM). The development of functional foods and targeted supplements can leverage epigenetic mechanisms to optimize diabetes treatment. Folic acid and other B vitamins participate in the methylation cycle, modulating gene expression. Studies have shown that folate deficiency can exacerbate insulin resistance and oxidative stress, both of which are related to diabetes. Compounds such as resveratrol and catechins have anti-inflammatory and antioxidant properties that act on the epigenetic machinery. These compounds improve insulin sensitivity in experimental and human models. Additionally, omega-3 fatty acids are associated with reduced inflammation and improved insulin sensitivity, partly mediated by epigenetic changes in key lipid metabolism genes. Of note, the consumption of foods and nutrients that maintain a healthy microbiota can help modulate the epigenetic machinery. The interaction between microbiota and epigenetics is bidirectional and critical for metabolic health. A balanced microbiota can act as a positive epigenetic modulator, reducing the risk of T2DM and other metabolic diseases by regulating key genes through bioactive metabolites and epigenetic modifications. In this context, a diet rich in fiber and polyphenols can restore a healthy microbiome, promoting epigenetic changes that protect against these diseases (Figure 3).

On the other hand, specific dietary patterns can also benefit the epigenetic regulation of T2DM by providing all the nutrients mentioned above, which could act synergistically when consumed as part of an overall diet, rather than as individual supplements. Examples include studies showing the effect of nutritional ketosis induced by a very low-calorie ketogenic diet (VLCKD) on DNA methylation patterns associated with obesity. These studies found that genes modified epigenetically after the nutritional intervention were associated with functions involved in the pathogenesis of obesity and diabetes, such as adipose tissue function, muscle function, inflammation, and insulin resistance. Another example is the Mediterranean Diet and the Atlantic Diet. Both diets are characterized by the consumption of foods containing bioactive compounds capable of modulating the epigenetic machinery and could be considered epigenetic diets (Figure 3). An epigenetic diet could be useful as an adjunctive or complementary therapy to hypoglycemic drugs, with minimal side effects and low toxicity in chronic administration.

CONCLUSION AND NEW CHALLENGES

Nutritional epigenomics opens new opportunities to understand and treat »

» diabetes through approaches that integrate genetics, epigenetics, and nutrition, promoting more personalized and effective medicine. However, further research is needed in basic-translational and long-term clinical studies to integrate these advancements into clinical practice. Challenges remain, such as the complexity of interactions between genes, nutrients, and the environment, the need for long-term human studies, and the development of precise tools for personalizing nutritional interventions. D

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SUMMARY

Nutritional epigenomics, or nutriepigenomics, is an emerging field that studies how nutrients and dietary patterns influence gene expression through epigenetic changes. In the context of diabetes, nutritional epigenomics offers an innovative approach to prevent and manage the disease by understanding and modulating how nutrients affect gene expression through epigenetic mechanisms. The development of functional foods and targeted supplements can leverage epigenetic mechanisms to optimize diabetes treatment. However, further basic-translational and long-term clinical research is needed to integrate these advancements into clinical practice.

NUTRIEPIGENOMICS OR NUTRITIONAL EPIGENOMICS IS THE SCIENCE THAT STUDIES THE EFFECTS OF NUTRIENTS ON HUMAN HEALTH THROUGH EPIGENETIC MODIFICATIONS

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