ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 11| Issue: 2| February 2025|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2025: 8.691 || ISI Value: 1.188

NUTRITIONAL EPIGENETICS

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Article DOI: https://doi.org/10.36713/epra20096
DOI No: 10.36713/epra20096

ABSTRACT

Introduction: *in recent years great progress has been made in the understanding of epigenetic mechanisms in the regulation of gene expression as a consequence of gene-environment interactions. Nutrition, as well as other environmental factors, represent a crucial factor that can induce epigenetic modifications not only in directly exposed organisms, but also in subsequent generations through transgenerational inheritance of epigenetic traits.*
Objective: *to detail current information related to epigenetic regulation, the most predominant epigenetic mechanisms, the influence of nutrition on the epigenetic state, as well as related patterns, behaviors and properties.*
Methodology: *a total of 52 articles were analyzed in this review, including review and original articles, as well as clinical cases, of which 31 bibliographies were used because the other articles were not relevant to this study. The sources of information were PubMed, Google Scholar and Cochrane; the terms used to search for information in Spanish, Portuguese and English were: epigenetics, nutrition, genes, methylation, DNA.*
Results: *epigenetics studies heritable changes in gene expression that do not alter the DNA sequence, but rather its regulation. These changes, such as DNA methylation and histone modifications, affect health and the development of diseases such as cancer and metabolic disorders. Environmental factors, such as diet, influence epigenetic regulation. Nutrients such as omega-3 fatty acids and polyphenols can modify these mechanisms, promoting protective effects against chronic diseases. Thus, nutritional epigenetics becomes a key area for the development of therapies and preventive strategies.*
Conclusions: *epigenetics shows how environmental factors, such as diet and lifestyle, influence gene expression without altering the DNA sequence, through mechanisms such as DNA methylation, histone modifications and gene silencing. These processes explain how cells with the same DNA can have different phenotypes. Nutrients present in diets such as Mediterranean or DASH, as well as bioactive compounds such as polyphenols, carotenoids, omega-3 fatty acids and selenium, modulate epigenetic regulation and have protective effects against chronic diseases such as cancer, cardiovascular disease and obesity. These advances offer new therapeutic possibilities, highlighting the potential of nutritional epigenetics in the prevention and treatment of diseases, as well as in the improvement of health and healthy aging.*
KEYWORDS: *epigenetics, nutrition, genes, methylation, DNA.*

INTRODUCTION

Up-to-date scientific evidence has shown the value of diet and lifestyle habits for the perfect functioning of the human body. A balanced and healthy diet, physical activity and psychological well-being have a direct beneficial effect on health and may play an important role in the development and prognosis of some diseases. In the last 20 years, great progress has been made in the understanding of epigenetic mechanisms in the regulation of gene expression as a consequence of gene-environment interactions. The observation that nutritional molecules can modulate the epigenome initiated the new nutrigenomic subdiscipline, nutritional epigenetics. The concept that epigenetic memory and programming are driven by our diet has several implications for the interpretation of disease risk, including disease prevention. Nutrition, as well as other environmental factors, represents a crucial factor that can induce epigenetic modifications not only in organisms directly exposed, but also in subsequent generations through transgenerational inheritance of epigenetic traits(1,2).
This paper provides useful, current and interesting information related to epigenetics and nutrition.

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METHODOLOGY

A total of 52 articles were analyzed in this review, including review and original articles, as well as cases and clinical trials, of which 31 bibliographies were used because the information collected was not important enough to be included in this study. The sources of information were Cochrane, PubMed and Google Scholar; the terms used to search for information in Spanish, Portuguese and English were: epigenetics, nutrition, genes, methylation, DNA.

The choice of bibliography exposes elements related to epigenetics and nutrition; in addition to this factor, an approach to epigenetic regulation, the most predominant epigenetic mechanisms, the influence of nutrition on the epigenetic state, as well as related patterns, behaviors and properties are presented.

DEVELOPMENT

Epigenetics has been defined in multiple ways, as heritable changes in gene function that are not attributable to alterations in DNA sequence, or as a set of mechanisms that define the phenotype of a cell without affecting the genotype, as well as the structural adaptation of chromosomal regions to register, signal or perpetuate altered states of activity(3-5).

There are several epigenetic mechanisms such as:

- DNA methylation and demethylation.
- Histone modification.
- Non-coding RNA-associated gene silencing (ncRNA).
- ATP-dependent chromatin remodeling complexes.
- Polycomb repressor complexes and Trithorax activator complexes.
- Loss of imprinting.
- Nuclear dynamics and three-dimensional organization of the genome: as well as the effect of nutrients on post-transcriptional regulation of genes.

Epigenetic regulation of gene expression appears to show long-term and far-reaching effects on health. A remarkable peculiarity of epigenetic modifications is that they are heritable between mother and daughter cells (mitotic inheritance) and between generations (meiotic inheritance). Epigenetics is one of the explanations for how cells and organisms with identical DNA can exhibit such remarkable phenotypic distinctions. Diet and environmental factors can potentially modify the level and capacity of epigenetic regulation, so some current studies in the field of epigenetics could explain correlations between lifestyle and its association with disease. Aberrant epigenetic sequences are associated with several digestive diseases, such as Barrett's esophagus, cirrhosis, inflammatory bowel disease, as well as multiple gastrointestinal malignancies. Epigenetic modifications of DNA provide hope and the promise of new biomarkers for early detection of cancer, as well as prediction, prognosis and response to treatment. Reversal of epigenetic changes is one of the main potential targets in the trend of therapeutic strategies and drug design(6-9).

The most predominant epigenetic mechanisms will be described below:

DNA Methylation

DNA methylation, carried out by DNA methyltransferase enzymes, involves the incorporation of a methyl group directly to a cytosine nucleotide within a cytosine-guanine (CpG) sequence, which are commonly surrounded by other CpGs forming what is known as a CpG island. CpG islands are frequent targets for epigenetic DNA methylation, especially those within promoter areas. In fact, it has been reported that about 70% of gene promoter regions are located within these CpG islands. Methylated cytosines in a promoter region attract gene repressor proteins and decrease the interaction between DNA and transcription factors. Cytosine methylation also promotes the creation of heterochromatin, which causes nucleosome packing and blocks the interaction of the transcriptional machinery with DNA. Thus, DNA methylation in promoter areas results in gene suppression. In cancers, a remarkable hypermethylation of tumor suppressor genes and hypomethylation of proto-oncogenes is commonly observed, contributing to tumor development. This epigenetic mechanism also plays an essential role in the regulation of tissue-specific genes, genomic imprinting and X-chromosome inactivation(10-12).

Post-Translational Modifications of Histone Proteins

These modifications include acetylation, methylation, phosphorylation and ubiquitination, processes catalyzed by various enzymes, each of which changes the interactions between DNA and histones in nucleosomes. Histone acetylation generally occurs at positively charged lysine residues, weakening the interactions between DNA and histones, leading to chromatin opening and facilitating transcription. For example, acetylation of lysines 9 and 27 on histone 3 (H3K9ac and H3K27ac, respectively) is linked to transcription activation. Histone methylation, on the other hand, is more complex, as it does not alter histone protein charge and may involve the addition of 1 to 3 methyl groups to lysine and 1 to 2 methyl groups to arginine. For example, methylation of lysine 4 on histone 3 (H3K4me) is associated with transcription activation, whereas trimethylation of lysine 27 on histone 3 (H3K27me3) is associated with transcription repression.Histone phosphorylation involves the addition of a negative phosphate group to the histone tail, but less is known about its function other than H2A(X) phosphorylation, which plays a role in DNA damage response and subsequent DNA repair. Histone ubiquitination refers to the addition of a large molecule of ubiquitin to lysine residues. Examples of histone ubiquitination include H2AK119ub, which is associated with gene silencing, and H2BK123ub, which is involved in transcription. In contrast to the relatively direct effect of histone acetylation on gene expression, the effects of other histone modifications are more complex and are highly dependent on the state of nearby DNA molecules(13-15).

Folate, vitamin B-12, methionine, choline and betaine can influence DNA methylation and histone modification by altering one-carbon metabolism. Two metabolites derived from this metabolic process can affect DNA methylation and histones: S-adenosylmethionine (AdoMet), which acts as a methyl donor in

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methylation reactions, and S-adenosylhomocysteine (AdoHcy), which is an inhibitor of methyltransferases. Therefore, theoretically, any nutrient, bioactive component or condition capable of modifying AdoMet or AdoHcy levels in tissues can modify DNA and histone methylation. In addition, other water-soluble B vitamins, such as biotin, niacin and pantothenic acid, also play important roles in histone modification. Biotin acts as a substrate in histone biotinylation. Niacin participates in ADP-ribosylation of histones by being a substrate for poly(ADP-ribose) polymerase, as well as in histone acetylation by being a substrate for Sirt1, which acts as a histone deacetylase (HDAC). Pantothenic acid is part of CoA, which generates acetyl-CoA, which provides the acetyl group in histone acetylation. Bioactive components present in food directly impact enzymes involved in epigenetic mechanisms(16-18).

Non-Coding RNA (ncRNA)-Associated Gene Silencing

The most recently understood epigenetic mechanism is gene switching associated with non-coding RNA. A non-coding RNA (ncRNA) is a functional RNA molecule that is transcribed, but not converted into proteins. Previously considered a residue in the genome, recent discoveries indicate that cncRNA molecules play an essential role in epigenetic gene regulation and probably explain the remarkable difference in phenotypes between species and within human populations, despite the great similarity in encoded proteins. Among the most prominent ncRNA molecules are microRNAs (miRNAs) and small interfering RNAs (siRNAs), which are less than 30 nucleotides, as well as long non-coding RNAs (lncRNAs), which contain 200 nucleotides or more. Although the full extent of their role in epigenetics is still under investigation, there is evidence to suggest that ncRNAs influence DNA methylation and histone modifications, as well as gene silencing. Both RNAi and lncRNAs have been shown to regulate gene expression through heterochromatin formation(19,20).

Influence of Nutrition on Epigenetic Status

It has been recognized for hundreds of years that food can interfere with an individual's state of health and has been used for the management of different conditions and diseases over the years.

Gradually, more and more empirical evidence is being found to support the influence of nutrition on epigenetic state and a growing understanding of the mechanisms by which this might happen. This is not surprising, since methyl and acetyl groups, which constitute the main epigenetic marks, are at the heart of nutritional metabolism. Nutrition can affect the epigenetic state through the availability of substrates for epigenetic reactions as well as through direct effects on proteins. Today, the scientific community is showing increasing interest in how our genes respond to the different foods consumed by humans. However, the molecular basis that explains how dietary nutrients or dietary patterns modify gene expression has not yet been fully unraveled. The most widely accepted hypothesis is that epigenetic regulation is responsible for these processes. Epigenetics studies how environmental factors, such as lifestyle, physical activity, exposure to toxins and diet, can modulate gene expression without altering our DNA sequence.Epigenetic modifications are frequent in various diseases, such as obesity, type 2 diabetes, metabolic syndrome, insulin resistance and cancer. It is noteworthy to point out that these epigenetic markers can be reversed by various therapeutic strategies, such as those following a low-calorie diet, bariatric surgery or physical activity in the treatment of obesity. Also, nutrients can function as a source of epigenetic modifications and reverse specific epigenetic markers associated with diseases. Thus, nutritional epigenetics has emerged as a key underlying mechanism in the interaction between genes and diet, providing evidence of the modulatory role of nutrition in aging and the development of age-related diseases(4,21-24).

Related Patterns, Behaviors, and Properties

Healthy eating habits are usually based on the incorporation of foods that promote well-being, such as plant-based products, fresh fruits and vegetables, whole grains or whole-grain cereals, nuts, which are sources of omega-3 fatty acids and low in saturated fats, trans fats and added refined sugars, as well as various bioactive compounds. Examples of beneficial eating habits are the Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH). The Mediterranean diet is practiced naturally in certain areas and is deeply linked to local tradition, being considered not only a healthy diet, but also a lifestyle. The DASH diet was developed following research to improve certain conditions, such as hypertension and other cardiovascular diseases (CVD). In recent years, other potentially healthy diets have also gained prominence within traditional dietary patterns, such as the Nordic diet and the Southern European Atlantic diet (SEAD)(25,26).

Appetite and lifestyle behaviors have been associated with epigenetic processes. DNA methylation and other epigenetic mechanisms may play a role in the regulation of appetite and alcohol consumption. Epigenetic status has been linked to the amount of body fat, and a polymorphism in the gene linked to fat mass and obesity (FTO) has been reported to interact with genetic variants of DNMT3B to influence post-meal hunger and satiety levels(4).

Experimental research in animal and cellular models has shown that compounds present in the Brassicaceae family and their derivatives have beneficial health effects, such as the prevention of cancer development. This protective effect is mediated through epigenetic markers, which act as regulators and inhibitors of the expression factors present in most cancers. Glucosinolates induce modifications in DNA methylation, which reduce the risk of developing certain chronic diseases, and the chemopreventive and health-promoting properties of cruciferous vegetables could be mediated by ncRNA-related mechanisms.

Further research is required, especially in humans, to identify which epigenetic markers are generated as a result of the inclusion of these cruciferous vegetables in the diet, not only in cancer

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prevention, but also in other biological processes in chronic diseases associated with inflammation and elevated cell proliferation(1,27,28).

Carotenoids possess anticancer properties that have been shown to be driven by modifications in DNA methylation of genes responsible for proangiogenic processes. Polyphenols, comprising flavonoids and stilbenes such as resveratrol, have the ability to alter cellular epigenetic mechanisms linked to potential beneficial health effects. Polyphenols counteract unfavorable epigenetic regulation by modifying epigenetic markers, resulting in the reactivation of beneficial genes (silenced tumor suppressors, antioxidant genes and DNA repair genes) or the inactivation of detrimental genes (oncogenes involved in inflammation, cell cycle progression, proliferation, invasion, angiogenesis and metastasis). The positive action of polyphenols on the organism, mediated by epigenetic mechanisms, prevents the development of diseases such as cardiovascular diseases, metabolic syndrome, obesity and cancer, etc(21,29).

Omega-3 fatty acids and selenium present in fish and shellfish have anti-inflammatory and triglyceride-lowering properties, which are attributed to their influence on genes through epigenetic mechanisms such as DNA methylation and microRNAs. Recently, it has been recognized that omega-3 fatty acids have anti-obesity effects and are effective against metabolic syndrome, and several investigations have shown that these effects result from their epigenetic action in counteracting related metabolic changes. In addition, other benefits associated with omega-3 fatty acids and their interactions with epigenetic markers have been reported in studies related to various diseases such as cancer, Alzheimer's disease and cardiovascular disease. Some studies on the positive health effects of selenium, which are regulated by epigenetic modifications, have also been documented(1,30,31).

CONCLUSIONS

Epigenetics has proven to be a fundamental field in understanding how environmental factors, such as diet and lifestyle, influence gene expression without modifying DNA sequence. Through mechanisms such as DNA methylation, histone modification, non-coding RNA-mediated gene silencing and the three-dimensional organization of the genome, epigenetics explains how cells can express different phenotypes despite sharing the same genotype. Advances in this field provide clear evidence of how nutrients, especially those present in dietary patterns such as the Mediterranean, DASH or Nordic diet, affect epigenetic regulation, and with it, the prevention and treatment of chronic diseases, such as cancer, cardiovascular disease, metabolic syndrome and obesity. In addition, foods and their bioactive components, such as polyphenols, carotenoids, omega-3 fatty acids, selenium and compounds present in Brassicaceae, show a direct impact on epigenetic modulation, reactivating protective genes and suppressing genes that favor disease progression. The investigation of these mechanisms offers new therapeutic avenues, highlighting the reversibility of epigenetic modifications and the potential of dietary and lifestyle strategies as key tools in disease management.

In summary, nutritional epigenetics emerges as an essential factor for healthy aging, disease prevention and improvement of quality of life, opening new perspectives in personalized medicine and public health.

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Conflict of Interest Statement
The authors report no conflicts of interest.

Funding:
The authors report no funding by any organization or company.