MS.ID-IJPBS-6567
International Journal of Pharmacy and Biological Sciences-IJPBS™ (2024) 14 (3): 17-21
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Review Article | Biological Sciences | OA Journal | MCI Approved | Index Copernicus

Diet-Induced Epigenetic Changes: Mechanisms and Long-Term Health Effects

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Received: 14 Apr 2024 / Accepted: 6 Jun 2024 / Published online: 9 Jul 2024
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Abstract
A healthy lifestyle is crucial for preventing health issues linked to epigenetic mechanisms, which involve alterations in gene expression. Diet significantly impacts these changes, affecting gene expression and potentially influencing health. Studies show that both maternal and paternal diets significantly impact the epigenome and health outcomes of their children, emphasizing the importance of considering dietary factors during prenatal care. In this review, the author focuses on important epigenetic modifications and their interconnection with the diet of the host and transgenerational effects.

Keywords
Epigenetics, DNA methylation, Diet, Gene regulation

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INTRODUCTION
Maintaining a healthy lifestyle requires a well-balanced diet. Dietary and nutritional imbalances can disrupt normal physiological functions and cause a variety of health problems, many of which are linked to epigenetic mechanisms. Epigenetics refers to heritable changes in gene expression that do not affect the DNA sequence but are frequently mediated by modifications such as DNA methylation, post-translational modifications of histone proteins and non-coding RNA (ncRNA)-associated silencing mechanisms. These epigenetic modifications are critical for regulating gene expression. Numerous studies have shown that diet and nutrients have a significant impact on epigenetic modifications. For example, dietary components like folate, methionine, and vitamins B6 and B12 are important donors of methyl groups required for DNA methylation. Furthermore, bioactive compounds in foods, such as polyphenols and flavonoids, can influence histone acetylation and methylation, affecting chromatin structure and gene accessibility. These epigenetic changes can have short- or long-term effects on health, potentially leading to serious health problems if the nutritional imbalance persists or worsens.

DNA methylation
DNA methylation involves the addition of a methyl group to the cytosine residue of CpG dinucleotides, a process catalysed by DNA methyltransferases (DNMTs) using S-adenosylmethionine (SAM) as a methyl group donor. This epigenetic modification is critical for regulating gene expression, genomic stability, and various cellular processes.
There are two types of DNA methylation processes: de novo methylation and maintenance methylation. De novo methylation is the formation of methylation patterns on previously unmethylated DNA regions, which typically occurs during early development and cellular differentiation. This process is primarily mediated by DNMT3A and DNMT3B (Yang *et al*. 2001). Maintenance methylation, on the other hand, ensures that existing methylation patterns are faithfully preserved during DNA replication and cell division. DNMT1 is the key enzyme that recognizes hemi methylated DNA and restores full methylation status, preserving epigenetic memory across cell generations.

Furthermore, the regulation of DNA methylation states is dynamic and includes both methylation and demethylation processes. The Ten-Eleven Translocation (TET) family of enzymes catalyses active demethylation, converting 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) and other oxidation products before replacing 5mC with unmodified cytosine. This dynamic regulation enables reversible changes in response to developmental cues and environmental stimuli, emphasizing the complexities of epigenetic regulation (Maiti, 2013).

Understanding the mechanisms and effects of DNA methylation and demethylation is critical because abnormal methylation patterns are associated with a variety of diseases, including cancer, neurological disorders, and cardiovascular disease. Epigenetic research continues to shed light on the complex interplay of genetic and environmental factors in health and disease.

Histone modifications

Histone epigenetic modifications, including acetylation, methylation, phosphorylation, ubiquitination, sumoylation, ADP-ribosylation, citrullination, and biotinylation, are important post-translational changes that affect gene expression and chromatin structure without altering the underlying DNA sequence. These modifications significantly impact the regulation of many biological processes, including transcription, DNA repair, and cell cycle control. Among the given modifications, acetylation, methylation, and phosphorylation are the most studied and have a major impact on gene regulation.

Acetylation

Acetylation is a significant post-translational modification of histones, which typically occurs at lysine residues. Acetyl-Coenzyme A (Acetyl-CoA) is the acetyl group donor in this process, and it is transferred by enzymes known as histone acetyltransferases (HATs). Acetylation is commonly found on specific lysine (K) residues, such as H3K9, H3K14, H3K18, H3K23, and H3K27. This modification is critical for regulating gene expression because it alters chromatin structure and increases DNA accessibility (Gujral *et al*., 2020).

Histone acetylation removes the positive charge from lysine residues, reducing the interaction between histones and negatively charged DNA. This reduction in histone-DNA binding causes a more relaxed chromatin structure, allowing transcription factors and other regulatory proteins easier access to the DNA. Consequently, acetylation is frequently associated with active gene transcription.

Histone acetylation is a dynamic and reversible process governed by the opposing actions of HATs and histone deacetylases (HDACs). The balance of these enzymes determines the acetylation status of histones, and thus the transcriptional activity of associated genes.

Histone acetylation is critical in many cellular processes, including DNA repair, replication, and chromatin assembly. Its dysregulation has been linked to a variety of diseases, including cancer, where abnormal acetylation patterns can cause altered gene expression profiles.

Methylation

This process involves the addition of one or more methyl groups to the histone N-terminal residues, such as lysine (K) or arginine (R) of histones H3 and H4. Depending on the specific histone protein, position of the K/R in the N terminal tail of the histones, and the pattern of methylation (mono-, di-, tri-methylation), this modification can influence gene activation or repression. For example, trimethylation of H3K4 (H3K4me3) is associated with active transcription, while trimethylation of H3K9 (H3K9me3) is linked to transcriptional repression. In this process, enzymes known as histone methyltransferases (HMTs) transfer the methyl group from S-adenosyl-l-methionine (SAM) to histone residues such as lysine or arginine. Similarly, histone demethylation is a dynamic process regulated by enzymes like LSD1 (lysine-specific demethylase 1), contributing to chromatin regulation in various cancers (Hayami *et al*., 2010).

Phosphorylation

Histone phosphorylation involves the addition of a phosphate group (PO4) to specific amino acids, primarily serine, threonine, and tyrosine residues, on histone proteins. This process is catalysed by kinases and reversed by phosphatases. The addition of a phosphate group can change the charge and conformation of histones, impacting their interaction with DNA and other nuclear proteins. The donor for the phosphate group to histone proteins is adenosine triphosphate (ATP). During the phosphorylation process, kinases transfer the gamma phosphate group from ATP to the hydroxyl group of specific serine, threonine, or tyrosine residues on histone proteins. This reaction results in the formation of a phosphoester bond and the conversion of ATP to adenosine diphosphate (ADP).

Histone phosphorylation is a dynamic process that plays a crucial role in various cellular processes,

including cell cycle progression, transcriptional regulation, and DNA repair. For instance, phosphorylation of histone H3 at serine 10 (H3S10) by Aurora B kinase is critical for mitotic chromosome condensation and gene expression regulation (Leis and Kaplan, 1982). Phosphorylation of histones, such as histone H2B and H3, has been implicated in various cellular processes, including cell differentiation, DNA condensation, and cell cycle progression (Dastidar *et al*., 2013). Moreover, histone phosphorylation has been associated with the regulation of gene expression, chromatin remodelling, and cellular signalling pathways (Li *et al*., 2013).

Noncoding RNA

Non-coding RNAs (ncRNAs), including long non-coding RNAs (lncRNAs) and microRNAs (miRNAs), play crucial roles in epigenetic regulation by influencing chromatin structure, gene expression, and various cellular processes. These ncRNAs are transcribed from the genome but do not encode proteins, making them essential regulators of gene expression through epigenetic mechanisms (Mercer *et al*.,2009, Gebert *et al*., 2019, Mattick and Makunin, 2006, Morris, 2011). These non-coding RNAs can impact DNA methylation, histone modifications, and chromatin remodelling, thereby regulating various cellular processes (Chen & Xue, 2016; Peschansky & Wahlestedt, 2013; Morris, 2011; Morris, 2009).

Effect of Diet on epigenetic modifications

The following studies reveals the interconnection between the maternal diet, epigenetic modifications and gene expression, providing insights into how environmental factors can influence genetic outcomes in offspring.

Effect of diet on Agouti Mouse

In the Agouti Mouse Model experiment (Wolff *et al*.,1998, Dolinoy *et al*.,2006, Dolinoy *et al*.,2010, Michaud *et al*.,1994), pregnant agouti mice (Avy/a) were given a diet that contained additional methyl donors, including folic acid, vitamin B12, choline, and betaine. This dietary intervention was formulated to explore the capacity of nutritional factors to trigger epigenetic modifications. The addition of supplements led to a rise in DNA methylation at the intracisternal A particle (IAP) retrotransposon located upstream of the agouti gene. The process of methylation resulted in the inactivation of the agouti gene, causing a visible change in the colour of the coat. The change in colour shifted from yellow, which signifies a low level of methylation, to brown, which indicates a high level of methylation. The brown mice displayed a noticeable alteration and showed a decreased susceptibility to metabolic and health problems, such as obesity, diabetes, and cancer.

The dietary methyl donors supplied the essential substances at the molecular level for DNA methyltransferases, the enzymes accountable for incorporating methyl groups into DNA. This process enhanced the methylation of CpG sites within the IAP, which is essential for the suppression of the agouti gene. The suppression of this gene's abnormal expression was a direct consequence of these epigenetic modifications, fundamentally changing the mice's observable characteristics and illustrating a distinct connection between the diet of the mother and the regulation of epigenetic processes.

The wider ramifications of this experiment are substantial. This highlights the significant influence that the nutritional status of mothers can have on the epigenome of their offspring, resulting in enduring changes that can be passed down to future generations. This model demonstrates how environmental factors, such as diet, can lead to heritable epigenetic changes that affect both physical characteristics and the susceptibility of future generations to health issues and diseases.

Paternal diet effects on metabolism of offspring

In a groundbreaking study (Carone *et al*.,2010) investigating the impact of paternal diet on offspring epigenetics, researchers explored how a low-protein diet in male mice could influence the health and gene expression of their progeny. Male mice were fed a low-protein diet prior to mating, a dietary intervention aimed at understanding how paternal nutritional status could affect epigenetic inheritance. The study's findings were significant: the offspring of these males exhibited notable alterations in the expression of genes involved in lipid and cholesterol metabolism, particularly within the liver, suggesting profound metabolic changes.

At the molecular level, the low-protein diet induced distinct changes in the DNA methylation patterns and small RNA profiles in the sperm of the males. These small RNAs included microRNAs (miRNAs) and tRNA fragments, which are known to play crucial roles in post-transcriptional regulation of gene expression. The altered epigenetic landscape in the sperm was directly transmitted to the offspring, resulting in changes to their gene expression profiles and metabolic phenotypes. This transmission indicates that paternal dietary intake can leave a lasting epigenetic imprint on the next generation.

The broader implications of this study are far-reaching. It underscores the significant role of paternal diet in shaping the epigenome of offspring, providing compelling evidence that environmental exposures and nutritional status of fathers can influence the health outcomes of their descendants. This has important ramifications for understanding the heritability of metabolic diseases and developing dietary recommendations for prospective fathers to improve the health of future generations. The study highlights the need for a broader perspective on prenatal care that includes paternal as well as maternal influences.

Effects of restricted maternal diet

In a thorough investigation into the effects of maternal nutrition on the health of their offspring, female rats were fed a high-fat diet prior to and during pregnancy (Lillycrop *et al*., 2005). This dietary intervention sought to replicate the conditions of excessive maternal nutrition and investigate its lasting impact on offspring. The results indicated that the descendants of the rats fed a high-fat diet showed a significant rise in vulnerability to obesity, insulin resistance, and disturbances in lipid metabolism, indicating notable metabolic dysfunctions.

The high-fat diet caused significant alterations in the epigenetic profile of the offspring at the molecular level. More precisely, there were changes in the patterns of DNA methylation and histone acetylation at important metabolic genes, such as PPARγ (peroxisome proliferator-activated receptor gamma) and GLUT4 (glucose transporter type 4). PPARγ is a crucial controller of the formation of fat cells and the processing of fats, while GLUT4 plays a vital function in the absorption of glucose in fat tissue and muscles. The high-fat diet caused epigenetic changes in these genes, leading to their abnormal expression and increasing the offspring's susceptibility to metabolic disorders like obesity and insulin resistance.

The wider ramifications of this experiment are significant. This highlights the crucial significance of the mother's diet in influencing the metabolic well-being of her offspring through epigenetic mechanisms. These findings indicate that the nutritional status of the mother during pregnancy can cause long-lasting changes in the epigenome, which can impact the future health of the offspring. Therefore, implementing dietary interventions during pregnancy could be an effective strategy to reduce the likelihood of metabolic diseases in the offspring. This study emphasizes the significance of incorporating maternal nutrition as a crucial element of prenatal care in order to achieve optimal health outcomes for future generations.

CONCLUSION

In conclusion, the complex interplay among nutrition, epigenetic changes, and health emphasizes how critical a balanced diet is to preserve bodily processes and averting illness. The reviewed research emphasizes the impact of certain dietary components on epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNA activity. These alterations can have substantial health consequences in both the short and long term, especially when there are imbalances in nutrition during critical periods like pregnancy. The research conducted on the Agouti mouse model, paternal diet, and maternal diet restrictions demonstrate the capacity of dietary interventions to cause heritable epigenetic alterations that impact the health of offspring. This evidence substantiates the necessity of comprehensive dietary guidelines for both prospective mothers and fathers in order to enhance the well-being of future generations. Gaining knowledge about the epigenetic influence of diet can provide insights for preventing diseases and promoting health by tailoring nutrition and utilizing epigenetic treatments.

Acknowledgements

The author thanks the Department of Genetics and Genomics, Yogi Vemana University, Kadapa, for providing the facilities to write this manuscript.

Conflict of Interest

The author declares no conflict of interest.

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