DNA Methylation in Cancer: Epigenetic View of Dietary and Lifestyle Factors

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ABSTRACT

BACKGROUND: Alterations in DNA methylation play an important role in cancer development and progression. Dietary nutrients and lifestyle behaviors can influence DNA methylation patterns and thereby modulate cancer risk.

INTRODUCTION: To comprehensively review available evidence on how dietary and lifestyle factors impact DNA methylation and contribute to carcinogenesis through epigenetic mechanisms.

MATERIALS AND METHODS: A literature search was conducted using PubMed to identify relevant studies published between 2005 and 2022 that examined relationships between dietary/lifestyle factors and DNA methylation in cancer. Studies investigating the effects of dietary components (eg, micronutrients, phytochemicals), physical activity, smoking, and obesity on global and gene-specific DNA methylation changes in animal and human cancer models were included. Data on specific dietary/lifestyle exposures, cancer types, DNA methylation targets and underlying mechanisms were extracted.

RESULTS: Multiple dietary and lifestyle factors were found to influence DNA methylation patterns through effects on DNA methyltransferase activity, methyl donor availability, and generation of oxidative stress. Altered methylation of specific genes regulating cell proliferation, apoptosis, and inflammation were linked to cancer development and progression.

CONCLUSION: Dietary and lifestyle interventions aimed at modulating DNA methylation have potential for both cancer prevention and treatment through epigenetic mechanisms. Further research is needed to identify actionable targets for nutrition and lifestyle-based epigenetic therapies.

KEYWORDS: DNA methylation, epigenetics, nutrition, lifestyle factors, cancer progression

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Introduction

Cancer is a prominent contributor to global mortality, responsible for approximately 10 million fatalities annually.[1,2] Cancer progression from typical endothelium to sophisticated carcinomas entails a complex series of events marked by the accrual of genetic and epigenetic alterations, culminating in heightened oncogene activity and reduced activity or impairment of tumor suppressor genes.[3] Despite extensive endeavors to clarify the molecular underpinnings of cancer, a comprehensive understanding of its molecular mechanism remains elusive. The predominant epigenetic modification found in mammalian DNA is 5-Methylcytosine (5mC).[4] This modification has been verified in diverse organisms such as bacteria, plants, and mammals. Nevertheless, its biological role and genomic allocation exhibit marked differences across these taxa. The dual role of the DNA demethylation pathway in eliminating epigenetic marks and producing distinct DNA modifications with particular regulatory functions introduces an extra level of intricacy to the DNA-level epigenetic regulation.[5] The biological necessity justifies the presence of such complexity in mammals. The activation or deactivation of transcriptional programs is essential for mammalian cells to carry out cell-specific functions, transition through developmental stages, or react to external stimuli. DNA methylation, demethylation, and other epigenetic factors are substantial components of this regulatory network.[6,7]

Cancer is typified by unregulated cellular proliferation and dissemination, wherein cells have circumvented regulatory cues and acquired the ability to undergo unrestrained growth, evade programed cell death and immune surveillance, and metastasize to distant sites.[2] The alterations in the cellular function of malignant cells are instigated by genetic and epigenetic anomalies that amass gradually and culminate in malignant metamorphosis. Cancer frequently involves disruptions in epigenetic mechanisms, with mutations in crucial epigenetic regulators such as DNMT and TET enzymes, as well as other chromatin-interacting proteins detected in diverse malignancies.[8] Deficient epigenetic regulation leads to anomalous DNA methylation patterns typified by widespread hypomethylation

and localized hypermethylation. The methylation alterations exert a twofold effect on the neoplastic genome. Initially, global methylation loss facilitates transposable elements' reactivation, augments the overall mutation load, and correlates with genomic instability. Furthermore, alterations in the local abundance of 5mC can stimulate oncogenic transcriptional programs, thereby facilitating cancer onset and advancement. Apart from diverse pathophysiological conditions that impact methylation patterns and epigenetic processes, alterations in DNA methylation specific to cancer can also develop novel transcriptional programs, thereby facilitating a malignant phenotype.[9,10] The investigation of aberrant methylation and hydroxymethylation patterns in cancer progression, as well as the long-lasting effects of cancer-extrinsic factors on DNA methylation and epigenetic regulation, could provide valuable insights into the mutability of DNA methylation and epigenetic mechanisms under various conditions. This could lead to identifying new biomarkers and developing preventive, diagnostic, and therapeutic strategies. The present study provides a comprehensive review of the intricate interplay between nutrition, lifestyle factors, DNA methylation, and epigenetic modifications, along with their underlying molecular mechanisms in cancer progression. This review aims to discover the most consequential risk factors connected to cancer development and the signaling pathways involved in these processes.

Cancer-Related Epigenetic and DNA Methylation Changes

DNA methylation in mammalian cells is primarily observed in symmetric CG dinucleotides, commonly called cytosine-guanine dinucleotides (CpG) sites.[11] Nevertheless, specific cells and tissues, such as the brain and stem cells, display a relatively elevated level of 5mC in a non-CG context.[12] DNA methylation involves the enzymatic transfer of a methyl group from S-Adenosyl-L-methionine (SAM) to the cytosine base at carbon position 5, also called the "fifth DNA base."[13] This reaction is catalyzed by DNA methyltransferases (DNMTs) and introduces methylation to the genome. De novo methyltransferases DNMT3A and DNMT3B can directly deposit methylation marks on unmethylated DNA.[14,15] Maintenance methyltransferase DNMT1 can uphold these marks by identifying hemimethylated CpG sites and reinstating them to a fully methylated state.[16] 5mC is significantly observed in mammalian genomes, with an approximate methylation frequency of 5% of all cytosines in the genome.[17] It has been observed that around 70%-80% of all CpG sites in the genome undergo methylation, and this modification is distributed across diverse genomic regions.[18] Methylated sites exhibit a depletion in distinct genomic features, including but not limited to CpG islands (CGIs), enhancers, and active promoters.[18,19]

DNA methylation as a gene-expression regulator

DNA methylation contributes significantly to regulating gene expression through 2 distinct mechanisms. First, it has been observed that 5mC can modulate the binding of transcriptional factors directly.[20] Furthermore, it can recruit proteins that bind to chromatin and instigate modifications in chromatin configuration, ultimately affecting gene expression.[9] Typically, 5mC within promoter regions is regarded as a suppressive indication due to its ability to impede the binding of transcription factors (TFs), obstruct transcription initiation, and encourage the formation of a compact chromatin structure.[21,22] Research has demonstrated that regulatory regions of highly expressed genes are characterized by a higher prevalence of activating histone marks and lower DNA methylation levels.[23] Conversely, lowly expressed or silenced genes are associated with repressive histone marks and higher DNA methylation levels. However, some investigations indicate that the function of DNA methylation may extend beyond solely suppressing transcription. Even though promoter methylation is commonly linked with transcriptional repression, there have been instances of hypermethylation of gene bodies in highly transcribed genes.[24] This observation suggests that the location of the methylation or other epigenetic mechanisms may influence the impact of 5mC on gene expression. Similarly, DNA methylation may exert a distinct impact on the binding of TFs. Although methylation can inhibit the binding of some TFs, recent research has demonstrated that a subset of TFs has a preferential tendency for binding to methylated cytosines. This preferential binding can alter chromatin structure and activate target gene expression.[25,26] It is noteworthy that although 5mC has been widely recognized for its ability to establish a repressive chromatin state by recruiting the Methyl-CpG-binding domain protein complex 1 (MeCP1) and promoting histone deacetylation, recent research has indicated that TFs binding to 5mC may lead to localized demethylation and facilitate a more permissive chromatin state.[26] The primary function of 5mC is to repress transcription. However, as mentioned above, DNA methylation and its conventional repressive function may also activate gene expression. The ultimate influence of 5mC on genome regulation depends on various factors, such as its genomic location, adjacent histone modifications, TF binding, and cellular physiological state.[27] The effects mentioned above are contingent upon the context and indicative of epigenetic regulation's ever-changing nature.

Reversibility of DNA methylation and epigenetic regulation

Reversibility is a significant characteristic of epigenetic regulation. This statement implies that epigenetic modifications have the potential to be eliminated or substituted with alternative marks within the genome.[28] Although the process of 5mC deposition in the genome has been understood for a considerable period, scant knowledge was available concerning its elimination. Passive demethylation occurring during cell divisions has been traditionally associated with losing 5mC for a significant duration.[29] Passive demethylation is the phenomenon wherein the loss of 5mC can be observed during DNA replication.

Following each round of replication, hemimethylated CpG sites are generated due to the absence of modification on the newly synthesized strand. Typically, the DNMT1 enzyme facilitates the methylation of hemimethylated CpG sites, thereby preserving their fully methylated state.[30] When DNA methylation maintenance is ineffective, the restoration of symmetric CG methylation does not occur. As a consequence of passive dilution during subsequent replication rounds, the level of DNA methylation decreases.[31]

However, the phenomenon of global demethylation observed in the paternal pronucleus and Primordial germ cells during early development cannot be solely attributed to passive demethylation. Further experimental investigations have substantiated that TET enzymes function not only as active dioxygenases that facilitate the oxidation of methylated cytosines within the genome but have also validated the presence of a functional pathway for DNA demethylation.[32] The oxidation of 5mC to 5-hydroxymethylcytosine (5hmC), 5-formyl cytosine (5fC), and 5-carboxyl cytosine (5caC) in DNA is facilitated by TET proteins through a Fe (II)/α-KG-dependent process.[33] The thymine DNA glycosylase (TDG) is capable of eliminating the ultimate oxidation products, namely 5-formyl cytosine (5fC) and 5-carboxyl cytosine (5caC), from the genome. This process is followed by replacing the abovementioned products with unmodified cytosine through the base excision repair (BER) pathway.[34] TET proteins are deemed significant epigenetic regulators due to their participation in the active demethylation pathway. The TET family in mammals comprises 3 distinct enzymes, namely TET1, TET2, and TET3. TET-mediated DNA demethylation is crucial in regulating fundamental biological processes such as early developmental stages, transcription activation, bivalent promoters' establishment, enhancers' regulation, and cellular self-renewal maintenance.[35] In addition, the byproducts resulting from active DNA oxidation function as enduring epigenetic markers that perform regulatory roles within the genome.

Transcription regulatory and protein–protein interactions network in DNA methylation

The recruitment of DNA methyltransferases and establishment of methylation has garnered significant attention concerning the involvement of protein-protein interactions with other transcription repression systems.[28] The preponderance of evidence pertains to the interactions involving histone proteins and their associated covalent modifications.[36] The de novo methyltransferases exhibit partial localization toward pericentric heterochromatin, which is concurrently distinguished via the methylation of histone H3 at lysine 9 (H3K9). The co-immunoprecipitation of Dnmt3b with the Suv39h histone methyltransferase has been observed. Furthermore, the absence of Suv39h in embryonic stem cells results in the depletion of H3K9 methylation and CpG methylation at pericentric heterochromatin.[37] This implies that H3K9 methylation may be necessary for DNA methylation in certain instances. Additional protein interactions have been suggested to trigger DNA methylation by recruiting de novo methyltransferases. These include polycomb group proteins and the recruitment by site-specific transcription factors.[37] The latter has been observed in a pathological context for the Myelocytomatosis (Myc) oncogene and promyelocytic leukemia/retinoic acid receptor alpha (PML-RARA) fusion protein. Nevertheless, the demonstration of the importance of site-specific recruitment by transcription factors in normal physiology is yet to be accomplished.[38]

DNA methylation as an independent regulator of transcription

With all these interpretations, 3 well-established exceptions exist to the principle that CpG island DNA remains unmethylated. These exceptions include gene imprinting, X chromosome inactivation (XCI), and the silencing of transposable elements.[39] The events are correlated with methylation-induced gene silencing. Imprinting and Inactivation of the X chromosome both result in monoallelic gene expression. X inactivation entails the stochastic suppression of transcription from a single chromosome in females, while imprinting pertains to the suppression of one allele based on its parental origin.[40] In these instances, methylation is linked to suppressing the gene on the dormant allele.[41] The exposure of both alleles to identical conditions and transactivating factors within the nucleus implies that DNA methylation serves as a mechanism for regulating transcription distinct from the regulation mediated by transcription factors.

Lifestyle and Demographic Factors

The etiology of cancer is primarily attributed to modifiable lifestyle factors, including dietary habits, tobacco use, physical activity levels, and body weight regulation.[42] Epigenetics has been extensively postulated as a primary mechanism that facilitates the reversible impacts of dietary and lifestyle factors on cancer development (Table 1).[43] An individual's diet and lifestyle significantly influence cancer etiology. Studies suggest that dietary habits may contribute to over 30% of cancer-related mortalities in the United States.[44] Various protective mechanisms have been proposed for certain nutrients, including antioxidant, anti-inflammatory, and antiestrogenic properties. Nevertheless, the precise mechanistic pathways through which these effects act on the cells to prevent, postpone, or reverse carcinogenesis remain unclear.[45] The deposition of epigenetic marks is subject to modulation by both chronological aging and environmental exposures. The environmental, dietary, or lifestyle-induced epigenetic modifications may offer insights into the enigma of cancer disparities.[46] In addition to developmental nutrition, the impact of detrimental lifestyle factors such as smoking and alcohol consumption on disease susceptibility may be modulated by epigenetic mechanisms.[47]

Table 1. The impact of demographic factors on DNA methylation in cancer.

DEMOGRAPHIC FACTORS	FUNCTIONS	SIGNALING PATHWAYS	REFERENCE
Increasing age	Global and gene-specific hypomethylation	Decreases DNMT activity Reduces methyl donors	Riboli and Norat[50], Horvath[53]
Gender	Hypermethylation of tumor suppressor genes	Regulation of DNMTs	Toyota et al[55], Tost and Gut[57]
Physical inactivity	Hypermethylation of cell proliferation genes Hypermethylation of apoptosis genes	Alters HDACs activity Changes SIRTs activity	Brown[60], Kanzleiter et al[62]
Ethnicity	Differences in gene-specific methylation	Methylation-related genes	Wang et al[63], Xiao et al[64]

Abbreviations: DNMT, DNA methyltransferase; HDACs, histone deacetylases; SIRT, sirtuin.

Exposure to carcinogenic toxins during prenatal or early developmental stages can lead to the emergence of persistent epigenetic alterations that increase the susceptibility to cancer.[47]

On the other hand, DNA methylation levels are associated with specific demographic factors, potentially attributable to variations in lifestyle or environmental exposures among subpopulations. Demographic factors, such as age, sex, and ethnicity, have been shown to influence DNA methylation patterns in normal tissues, and recent studies have suggested that they may also play a role in cancer.[42,47] The effects of demographic factors on gene methylation and epigenetic modifications in cancer are outlined in Table 1.

Age

The aging process's biochemical mechanisms are intricate and multifaceted, involving a range of biologically significant alterations in the structures and functions of proteins, lipids, and nucleic acids. In animals, advanced age is correlated with a reduction in overall DNA methylation and an elevation in gene-specific methylation.[48] The correlation in humans is comparatively less stable, potentially attributable to marker-specific non-linear alterations that occur with age progression.[49] Empirical data suggests that the likelihood of developing prostate cancer significantly correlates with advancing age, as evidenced by a notable 30-fold rise in incidence rates among males aged 40 years and above relative to those under 40. The progressive increase in the age distribution of the present populace implies that the ailment will assume a more significant status as a public health concern in the forthcoming years.[50] The study conducted by Jung and Pfeifer elucidated the phenomenon of DNA methylation alterations that occur during mammals' aging process.[51] The authors also investigated potential mechanisms that may contribute to the site-specific modifications of DNA methylation.[51] The compelling evidence indicating alterations in DNA methylation patterns over time supports the notion that anomalous, age-related methylation of specific CpG islands represents an initial stage in cancer development.[52] The age-related reduction in DNA methylation levels in various genes may play a role in the development of pathological conditions. Unnikrishnan et al demonstrated that anti-aging interventions, such as caloric restriction, dwarfism, and rapamycin treatment, can decelerate the epigenetic clocks and prevent or reverse up to 40% of the age-related alterations in DNA methylation.[49] Horvath[53] have identified a highly stable co-methylation module associated with aging and observed it across various human tissues, such as blood and the brain. These findings suggest that blood could serve as a viable substitute for brain tissue in investigating the impact of age on DNA methylation patterns and gene expression. As the ongoing scientific investigations advance, other age-related disorders will likely manifest modifications in gene expression resulting from perturbed DNA methylation and gene expression.

Gender

Sex is another demographic factor that has been associated with DNA methylation changes in cancer.[54] Studies have shown that sex-specific differences in DNA methylation patterns exist in various cancers, including lung, liver, and bladder cancer. For example, in lung cancer, DNA methylation changes have been observed in genes involved in immune response pathways, which may contribute to the higher incidence of lung cancer in males compared to females.[55] One study reported sexual dimorphism in DNA methylation levels between men and women in repeat elements and specific promoters.[56] However, another study found that men exhibited lower levels of Alu methylation and higher levels of long interspersed nuclear element-1 (LINE1) methylation.[57]

Physical activity

The human body's overall physiology is significantly influenced by physical activity, which serves as a potent stimulus. Epigenetic mechanisms may serve as mediators for exercise-induced alterations in gene expression.[58] An increasing corpus of empirical data suggests that physical exercise regimen has a regulatory effect on DNA methylation in both muscular and adipose

tissues.[59] Certain epigenetic markers have been linked to a decreased susceptibility to chronic illnesses. According to Brown's[60] findings, the process of DNA methylation exhibited a decrease subsequent to physical exercise, specifically at approximately 60% of the loci. The study found that the alteration in DNA methylation associated with physical exercise was more pronounced in individuals of advanced age. The study conducted by Garcia et al[61] demonstrated that a period of 8 weeks of exercise training can bring about changes in the DNA methylation of certain genes and pathways in the skeletal muscles of individuals with varying levels of insulin sensitivity. The study conducted by Kanzleiter et al[62] demonstrated that DNA methylation plays a significant role in the adaptations of skeletal muscle induced by exercise. An enriched occurrence of CpG methylation was discovered in the binding sites of the myogenic regulatory factors MyoD and myogenin.[62]

Ethnicity

Several studies have reported the association between ethnicity and DNA methylation in cancer progression. Ethnicity is a complex trait that reflects the genetic, cultural, and social background of individuals. It has been shown that ethnicity influences the DNA methylation patterns in cancer cells, which may contribute to the differences in cancer incidence and mortality rates among different ethnic groups.[59] One study investigated the DNA methylation patterns of breast cancer patients from different ethnic backgrounds, including African American, Caucasian, and Hispanic/Latina. The results showed significant differences in DNA methylation profiles between these groups, suggesting that ethnicity may play a role in breast cancer development and progression.[63] Another study examined the DNA methylation patterns of prostate cancer patients from African American and Caucasian populations. The study found that African American men had higher levels of DNA methylation in certain genes compared to Caucasian men, which may contribute to the higher incidence and mortality rates of prostate cancer among African American men.[64] Understanding the complex relationship between ethnicity and DNA methylation in cancer progression may lead to the development of personalized therapies that target specific epigenetic alterations in different ethnic groups. However, more research is needed to fully understand the underlying mechanisms that link ethnicity and DNA methylation in cancer progression.

Nutrients

Evidence suggests that certain nutrients in the human diet, which are closely linked to the risk of cancer, can regulate DNA methylation (Table 2). Research has demonstrated that identical twins exhibit an identical genotype and lack discernible epigenetic variations during their initial developmental stages.[65] However, notable discrepancies in genomic methylation and histone acetylation patterns emerge during their later stages of life. The observed variations in epigenetic modifications can influence the expression of genes and the likelihood of developing certain diseases. Hypermethylation can be attributed to an overabundance or insufficient specific nutrients or food constituents.[66] This can impact the interaction between transcription factors, DNA, and chromatin configuration. Ultimately, this can lead to the suppression of genes that serve as tumor suppressors, thereby contributing significantly to the development and advancement of cancer. Table 2 outlines the impact of various nutritional factors on gene methylation alterations and epigenetic modifications in cancer.

Folate

The investigation of nutrients that act as methyl-unit carriers or coenzymes for one-carbon metabolism, which provides the ubiquitous methyl donor compound S-adenosylmethionine (SAM), has primarily focused on their association with DNA methylation.[67] Folate is a crucial nutritional component in one-carbon metabolism, providing the necessary methyl units for DNA methylation. The preponderance of data and corroborating evidence supports this assertion. Previous studies have proposed that in scenarios where folate or methionine availability is restricted, S-SAM synthesis takes precedence over DNA biosynthesis.[68] This prioritization results in the preferential utilization of one-carbon units through the methionine cycle to promote methylation reactions at the cost of DNA synthesis and repair processes.[69] The biochemical process of converting 5,10-methylene tetrahydrofolate (THF) into 5-methyl THF, which in turn facilitates the re-methylation of homocysteine to methionine, is facilitated by the enzyme methyltetrafolate reductase (MTHFR). This enzymatic reaction is irreversible in nature. The protein in question plays a pivotal role in regulating the allocation of folate toward either the synthesis of DNA precursors or DNA methylation.[70] The presence of polymorphisms at the MTHFR gene has been found to significantly impact individuals' susceptibility to various types of human cancers.[71] The reduced activity of MTHFR is anticipated to elevate the likelihood of developing cancer owing to diminished levels of 5-methyl THF in the bloodstream, DNA hypomethylation, and activation of proto-oncogenes. A decrease in DNA methylation levels may elevate the risk of neural tube (NT) defects in humans due to inhibition of methyl transfer or reduced folate intake.[72] Recent studies establish a positive correlation between the status of folate and DNA methylation during the gestational period. The findings of scientific investigations utilizing a rat model of hyperhomocysteinemia revealed that a diet supplemented with folate increased DNA methylation in the placenta.[72] In contrast, a diet deficient in folate led to decreased placental methylation. The study found a positive correlation between DNA methylation in the placenta and levels of hepatic folate and hepatic S-SAM, which serves as the sole methyl donor for DNA methylation.[73]

Table 2. The influence of nutritional factors on altering DNA methylation in cancer.

NUTRITIONAL FACTORS	FUNCTIONS	SIGNALING PATHWAYS	REFERENCE
Folate	Provide methyl groups for DNA methylation	One-carbon metabolism	Hou and Zhao[67], Figueiredo et al[70]
Vitamins B12	Stimulates DNA methylation	Reduced SAM synthesis	Hao et al[74], Chambers et al[75]
	Reduces methylation capacity	Increased SAH	
Omega-3 fatty acids	Stimulate DNA methylation	COX-2, PPARγ	Lemaitre et al[85], Berquin et al[87]
Vitamin D	Inhibits DNA methylation	PI3K	de La Puente-Yagüe et al[89], Bao et al[90]
	Suppresses histone modifications	Akt-Wnt	
	Stimulates DNMT activity	β-catenin	
	Hypomethylation of tumor suppressor genes		
Zinc	Inhibits DNA methyltransferase	Modulates methyl donors	Stoll[92], Russell et al[94]
	Induces hypomethylation state		
Polyphenols	Inhibits DNA methylation	Nrf2, NF-κB	Fang et al[79], Fang et al[80]
	Anti-inflammatory		
	Anti-oxidant		
	Anti-cancer properties		
	Activate DNMTs and HDACs		
Protein restriction	Induces global DNA hypomethylation	Regulation of DNMT	Gong et al[95], Sosa-Larios et al[97]
	Activates autophagy	AMPK, SIRT1, mTOR	
	Changes DNMT activity		

Vitamin B12

The essential micronutrient, Vitamin B12, is a cofactor in the enzymatic conversion of homocysteine to methionine during methionine synthesis. The insufficiency of vitamin B12 results in the buildup of serum homocysteine.[74] Homocysteine metabolism is closely associated with its role as a donor of methyl groups in transmethylation reactions.[75] Vitamin B12 deficiency-induced perturbations in re-methylation pathways can lead to 2 potential outcomes: reduced S-SAM synthesis and the reversible conversion of homocysteine to S-adenosylhomocysteine (SAH). As a highly effective inhibitor of methyltransferase enzyme, SAH hydrolysis to homocysteine undergoes a reversal in heightened homocysteine levels.[76] The SAM/SAH ratio has been proposed as a potential indicator of cellular methylation capacity due to its involvement in the methylation process.

Polyphenols

Polyphenols are a class of naturally occurring phytochemicals found in plants ingested in substantial quantities in the human diet. Phytochemicals have been hypothesized to play a role in preserving typical DNA methylation and gene expression patterns, as well as reversing methylation-induced suppression of tumor suppressor genes.[77] This may offer a potential alternative strategy for the prevention and treatment of cancer. Studies have demonstrated that polyphenols present in tea, berries, vegetables, apples, and wines exhibit strong anticarcinogenic properties both in vitro and in animal models.[78] These polyphenols prevent DNA instability at multiple sites along the carcinogenic pathway. Polyphenols can bind directly to the binding pocket of DNMT and indirectly reduce the concentration of S-SAM within cells. This leads to the inhibition of DNMT activity in vitro, which can reverse DNA hypermethylation and reactivate the activity of tumor suppressor genes.[79]

Polyphenolic compounds such as (−)-epigallocatechin 3-gallate (EGCG), quercetin, myricetin, and fisetin have been found to potentially reduce DNA methylation through modulation of the SAM/SAH cellular ratio, thereby indirectly inhibiting DNMT activity. Genistein, derived from soybean, and EGCG, extracted from green tea, have been identified as the most effective inhibitors of DNMT. The activity of DNMT in human esophageal cancer cells is hampered in a dose-dependent manner by EGCG and other metabolites found in green tea.[80] The gallate moiety on the D ring of EGCG exhibits a robust interaction with the cytosine-active site on the DNMT

enzyme. Additionally, the formation of hydrogen bonds between the hydroxyl groups of the A and B rings and specific amino acid residues, namely Sr1229 and Cys1225, on the protein further contributes to the high-affinity binding of EGCG and consequent inhibition of DNMT activity.[81] The compound Genistein exhibited a significant interaction with DNMT and effectively suppressed the enzymatic activity.

The phenomenon of hypermethylation of CpG islands in the promoter regions has been observed to result in the silencing of tumor suppressor genes such as p16 INK4a, retinoic acid receptor b (RARb), methylguanine methyltransferase (MGMT), mMLH1, and glutathione S-transferase p (GSTP) in cancer cells.[81] The resurgence of tumor suppressor genes is concomitant with a proportional augmentation in mRNA and protein manifestation. The study has revealed that EGCG has the potential to induce the reversal of DNA methylation and enhance the expression of MGMT, p16 INK4a, and hMLH1 in a cell line of esophageal cancer. The exposure to green tea polyphenol for 48 hours resulted in changes in cytosine methylation levels and mRNA expression, which continued to exhibit a time-dependent progression.[82] The augmentation of protein expression was observed to enhance the reversal of DNA hypermethylation. EGCG can potentially reactivate Retinoic Acid Receptor beta (RARβ) in prostate and breast cancer cells, p16INK4 in colon cancer cells, and Glutathione S-transferase Pi (GSTP) in prostate cancer cells.[83] Recent findings point out that Genistein has the potential to partially reverse DNA hypermethylation and reactivate the expression of p16 INK4, RAR b, and MGMT genes.[79] The isoflavones biochanin A and daidzein, as well as the flavonoids myricetin, quercetin, hesperetin, naringenin, apigenin, and luteolin, were found to exhibit activity in the alteration of DNA methylation and re-activation of tumor suppressor genes, albeit to a lesser extent.[84]

Omega-3 fatty acids

Omega-3 fatty acids are essential polyunsaturated fatty acids that have been shown to have anti-inflammatory and anti-cancer properties. Several studies have investigated the relationship between omega-3 fatty acids and DNA methylation in cancer progression.[85] One study investigated the effect of omega-3 fatty acids on DNA methylation in breast cancer cells. The results showed that omega-3 fatty acids could reduce the DNA methylation levels in certain genes that are involved in breast cancer development and progression.[86] Another study examined the effect of omega-3 fatty acids on DNA methylation in prostate cancer cells. The study found that omega-3 fatty acids could reduce the DNA methylation levels in certain genes that are associated with prostate cancer development and progression.[87] The mechanism by which omega-3 fatty acids affect DNA methylation is not fully understood. However, it has been suggested that omega-3 fatty acids may modulate the activity of DNA methyltransferases, which are enzymes that catalyze DNA methylation. Omega-3 fatty acids may also affect the availability of methyl donors, such as folate and vitamin B12, which are required for DNA methylation. In conclusion, omega-3 fatty acids may play a role in cancer prevention and treatment by modulating DNA methylation. However, more research is needed to fully understand the underlying mechanisms and to determine the optimal dose and duration of omega-3 fatty acid supplementation for cancer prevention and treatment.

Vitamin D

Vitamin D is a lipid-soluble vitamin that has demonstrated anti-neoplastic properties. Numerous scientific inquiries have explored the correlation between vitamin D and DNA methylation in the advancement of cancer.[88] A research investigation was conducted to examine the impact of vitamin D on DNA methylation in cells affected by breast cancer. The findings indicate that vitamin D has the potential to decrease the levels of DNA methylation in specific genes that play a role in the onset and advancement of breast cancer.[89] A further investigation was conducted to analyze the impact of vitamin D on DNA methylation in cells affected by prostate cancer. The research conducted demonstrated that vitamin D has the potential to decrease the levels of DNA methylation in specific genes that are linked to the advancement and onset of prostate cancer.[90] The precise molecular mechanism underlying the impact of vitamin D on DNA methylation remains incompletely elucidated. There exists a proposition that vitamin D has the potential to regulate the functioning of DNA methyltransferases, a class of enzymes that facilitate DNA methylation. The impact of Vitamin D on the accessibility of methyl donors, including folate and vitamin B12, that are essential for DNA methylation, is a subject of interest. In summary, the potential involvement of vitamin D in cancer prevention and treatment could be attributed to its ability to modulate DNA methylation. Further investigation is required to comprehensively comprehend the fundamental mechanisms and ascertain the most effective dosage and duration of vitamin D supplementation for the purpose of cancer prevention and treatment.

Zinc

Zinc is a vital micronutrient that performs a pivotal function in the processes of DNA synthesis, repair, and transcription.[91] A scientific inquiry was conducted to examine the impact of zinc on DNA methylation in cells affected by breast cancer. The findings of the study indicate that zinc has the potential to decrease the levels of DNA methylation in specific genes that play a crucial role in the advancement and onset of breast cancer.[92] A further investigation was conducted to analyze the

impact of zinc on DNA methylation in cells affected by prostate cancer.[93] The research revealed that zinc has the potential to decrease the levels of DNA methylation in specific genes that are linked to the advancement and onset of prostate cancer.[94] The precise molecular mechanism underlying the impact of zinc on DNA methylation remains incompletely elucidated. There exists a suggestion that zinc may act as a modulator of DNA methyltransferases, a class of enzymes that facilitate the process of DNA methylation. Zinc has the potential to modulate the bioavailability of methyl donors, including folate and vitamin B12, which are essential for the process of DNA methylation.[93] In summary, it has been suggested that zinc could potentially contribute to the prevention and management of cancer through its ability to modulate DNA methylation. Further investigation is required to comprehensively comprehend the fundamental mechanisms and ascertain the most effective quantity and duration of zinc supplementation for the prevention and management of cancer.

Low protein diet

The mediation of nutrient limitation is partially facilitated by epigenetic modifications, such as DNA methylation. Research has demonstrated that environmental exposure during the early stages of embryonic and fetal development can result in the transmission of epigenetic information to subsequent generations. The study conducted by Gong et al[95] revealed that the gene expression of Insulin-like growth factor II (Igf2) and H19 in the liver is modified by maternal exposure to a low protein diet and folic acid during gestation. This alteration is achieved through the regulation of DNA methylation of these genes by DNA methyltransferase, as reported in their research. Zhu et al[96] have demonstrated that parental environmental exposures have an impact on the epigenetics of gametes and the early embryo, and have provided evidence for transgenerational inheritance in livestock. According to the findings of Sosa-Larios et al, insufficient protein availability during gestation leads to the increased expression of MafA (MAF BZIP Transcription Factor A) gene in pancreatic β-cells of male juvenile offspring.[97] This effect is attributed, at least partially, to DNA hypomethylation. The aforementioned process has the potential to induce developmental dysregulation of β-cell function, thereby exerting an impact on the offspring's long-term health.[97]

Diabetic Risk Factors

Diabetes mellitus is a persistent metabolic ailment that has a global prevalence affecting a significant number of individuals. The association between diabetes and various health complications, such as cancer, has been established through scientific research.[98] Contemporary research has demonstrated that diabetes and cancer exhibit overlapping risk factors, such as adiposity, insulin resistance, and persistent inflammation. The epigenetic modification of DNA methylation plays a pivotal role in the regulation of gene expression and is implicated in various cellular processes, including the advancement of cancer. Recent research indicates that the process of DNA methylation is a crucial factor in the association between diabetes and cancer.[99] The pathogenesis of cancer can be influenced by alterations in DNA methylation that are triggered by diabetes and its related comorbidities. The pathophysiology of diabetes involves the dysregulation of blood glucose levels, insulin resistance, and chronic inflammation.[100] These metabolic disturbances have been shown to impact the enzymatic activity of DNA methyltransferases and the availability of methyl donors, ultimately leading to changes in DNA methylation patterns throughout the genome. The anomalous methylation patterns observed in individuals with diabetes may lead to the activation of oncogenes and the suppression of tumor suppressor genes, thereby augmenting the susceptibility to cancer.

Empirical evidence has demonstrated that distinct diabetic factors exert an influence on the process of DNA methylation and epigenetic modifications in the context of cancer. The condition of elevated blood glucose levels, known as hyperglycemia, has been observed to cause a reduction in methylation levels both globally and in specific regions of the genome.[101] This effect is believed to be mediated by the production of methylglyoxal and the presence of oxidative stress. This process alters the methylation patterns of genes that control cellular proliferation, programed cell death, and the formation of new blood vessels. The activation of PI3K/Akt and MAPK signaling pathways by insulin resistance and hyperinsulinemia is known to regulate the activity of epigenetic modifiers such as HDACs and DNMTs.[102,103] The presence of persistent inflammation in individuals with diabetes mellitus results in the secretion of cytokines that modify the activity and gene expression of enzymes involved in one-carbon metabolism, which is crucial for epigenetic reprograming.[104]

Elucidating the mechanisms by which diabetic factors modulate DNA methylation and epigenetic regulation may unveil novel therapeutic targets for the prevention and management of diabetes-related malignancies. Interventions aimed at modifying lifestyle and pharmaceutical agents that target dysregulated pathways may have the potential to restore abnormal methylation patterns and alleviate the risk of cancer in individuals with diabetes.

Microbiota

Recent research has proposed that epigenetic mechanisms function at the interface of the microbiota and the intestinal epithelium. The study conducted by Ansari et al[105] highlights the significance of examining dysbiosis at the molecular level, particularly in relation to DNA methylation, as a potential causal factor in the development of colorectal cancer. The gut microbiota has been shown to exert an influence on epigenetic modifications, specifically through the processes of DNA methylation

and histone modification, which in turn affect the functioning of the immune system.[106] The study conducted a comparative analysis of DNA methylation patterns in conventionally raised and germ-free mice. The findings indicate that the existence of a commensal microbiota triggers alterations in methylation at regulatory elements in a specific set of genes that play a crucial role in maintaining intestinal homeostasis.[107] The study conducted by Sun et al. demonstrated that the presence of microbial dysbiosis is a characteristic feature of colorectal cancer.[108] Additionally, there exists a correlation between infections and anomalous DNA methylation in gastrointestinal tract cancers, as reported in previous studies.[109] In a study conducted by Ansari et al, it was observed that exposure to microbiota during dextran sodium sulfate-induced acute inflammation caused significant modifications in DNA methylation and chromatin accessibility at regulatory elements.[105] These modifications led to changes in gene expression programs that were enriched in functions associated with colitis and colon cancer. The study conducted by Ansari et al demonstrated the indispensability of microbiota-induced epigenetic programing in maintaining optimal intestinal homeostasis in vivo. This was achieved through the utilization of genetic interventions.[105] The existence of epigenetic mechanisms that are responsive to microbiota has been documented in both intestinal cells and peripheral tissues. However, additional investigation is necessary to comprehensively elucidate the intricate interplay between the host and microbiota. The aforementioned interactions are observed to materialize in various biological processes such as signaling relay, metabolism, immunity, tumor development, genetic instability, sensitivity to cancer chemotherapy and immunotherapy, as reported in literature.

Pharmaceuticals Consumption

The investigation of changes in DNA methylation patterns at specific gene promoter sites and throughout the entire genome is an increasingly promising area of research in the study of epigenetic modifications resulting from drug abuse.[110] The available literature indicates an increasing amount of evidence pointing toward the importance of DNA methylation in the development and maintenance of drug dependence. The consumption of drugs of abuse has been observed to be correlated with modifications in methylation patterns.[111] However, it remains unclear whether these changes are indicative of predisposition or a direct effect.

The study conducted by Wang et al[111] proposed that the methylation of the BRCA1 and PR promoters in tumor cells may have a correlation with the use of aspirin, thereby affecting the mortality rate in patients diagnosed with breast cancer. In their study, Li et al[112] observed that hypomethylation of ABCB1 is correlated with decreased drug absorption, elevated platelet reactivity, and a heightened likelihood of ischemic events in patients with symptomatic intracranial artery stenosis who are undergoing antiplatelet therapy. The authors also noted that this hypomethylation plays a significant role in the development of aspirin resistance. Michigami's research demonstrated that alterations in molecular mechanisms within atrophic mucosa (AM) among individuals with prolonged aspirin usage may significantly contribute to the decrease in cancer occurrence.[113] Furthermore, the methylation process of the CDH1 gene in Adenomatous Metaplasia (AM) could potentially serve as an indicator for the presence of gastric cancer. The study conducted by Hogarth et al[114] demonstrated that the use of demethylating agents has exhibited potential in the treatment of leukemia. It was observed that the cytotoxic effects of thiopurine drugs may be attributed to their ability to inhibit DNA methylation.[114] According to Webb et al.'s[115] research, it is suggested that antidepressants have the potential to modify DNA methylation in humans, thereby facilitating the remission of mood symptoms. In their study, Mahna et al[110] provided a comprehensive overview of the methylation modifications observed in several genes due to the administration of diverse drugs such as cocaine, opioids, cannabinoids, amphetamine, phenobarbital, and alcohol, in both human and animal models.

Conclusions

Numerous studies have recently looked into the relationship between epigenetic markers and lifestyle elements like diet, behavior, stress, physical exercise, work practices, smoking, and alcohol use. DNA methylation is a sophisticated epigenetic mechanism that is essential for controlling gene expression in both healthy and malignant cells. DNA methylation can change signaling pathways that influence biological activities like cell cycle, DNA repair, cell development, and proliferation via regulating gene expression. Therefore, abnormal DNA methylation can result in the incorrect production of oncogenes or the silencing of tumor suppressors, which can contribute to the emergence of disease states like cancer. Contrary to genetic changes, however, DNA methylation modifications may be reversible with the aid of methylation inhibitors. Epigenetics is anticipated to contribute to the understanding of how environmental factors affect gene expression and to a deeper comprehension of how each person reacts to environmental cues and acquired risk factors.

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Informed Consent

For this type of study, informed consent is not required.

Research Involving Human Participants and/or Animals

This article does not contain any studies with human participants or animals performed by any of the authors.

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