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Diet and nutritional intervention in cancer epigenetics

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Abstract: **For long, it was believed that we are at the mercy of our genes, that our genetic makeup is beyond our influence. However, in recent years, the developing field of epigenetics have proven otherwise. The epigenome is highly susceptible to changes in environmental factors. Altered epigenetic marks are responsible for altered gene expression. Numerous studies suggest that deregulated epigenetic modifications are present ubiquitously in virtually all types of malignancies including cancer. In fact, epigenetic changes appear to be present in nearly every stage of cancer development. Thus, epigenetic therapy for medicinal or chemopreventive purposes has grown to become a subject of huge importance. A number of bioactive dietary components are of particular interest in the field of epigenetics (Nutriepigenomics). Many of these compounds display anticancer properties and may play a role in cancer prevention. Numerous studies suggest that a number of nutritional compounds have epigenetic targets in cancer cells. Importantly, emerging evidence strongly suggests that consumption of dietary agents can alter normal epigenetic states as well as reverse abnormal gene activation or silencing. Epigenetic modifications induced by bioactive food compounds are thought to be beneficial in cancer prevention and therapy. This article will primarily focus on dietary factors that have been demonstrated to influence the epigenome and that may be used in conjunction with other cancer prevention and chemotherapeutic therapies. Another focus shall include how different stages of life affect the influence of these factors on the epigenome.**

Keywords: Epigenetics; Epigenetic therapy; Nutriepigenomics; Bioactive food compounds

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1. Introduction

Epigenetics refers to heritable changes not encoded in the DNA sequence but play an important role in the control of gene expression. Epigenetic modifications are of particular interest in the field of cancer research since their impact on the epigenome is involved in cell proliferation, differentiation and survival. Furthermore, epigenetic modifications are often involved in transcriptional regulation and have been implicated both in tumour development and progression. Epigenetic modifications causing transcriptional deregulation may result in the inappropriate expression or activation of transcription factors associated with oncogenes and/or the failure to express genes responsible for tumour suppression. In fact, cancer cells have genome-wide aberrations in a number of epigenetic markers, including global hypomethylation, global downregulation of miRNAs, promoter-specific hypermethylation, histone deacetylation and upregulation of epigenetic machinery. In addition, the impact of epigenomic processes in cancer is apparent by the finding that at least half of all tumour suppressor genes are inactivated through epigenetic mechanisms in tumorigenesis. However, the potential reversibility of epigenetic changes suggest that they could be modulated by nutrition and bioactive food compounds. Bioactive dietary components consumed by ingesting natural products including fruits and vegetables can act as sources of vitamins and minerals. While this is an invaluable role, these agents have high potential for application to oncogenesis owing to in part to their anticarcinogenic properties. A growing body of evidence suggests that dietary agents as well as non-nutrient components of fruits and vegetables can affect epigenetic processes and are involved in processes, including the reactivation of tumour suppressor genes, the initiation of apoptosis, the repression of cancer-related genes and the activation of cell survival proteins in different cancers. Dietary phytochemicals such as tea polyphenols, genistein, sulforaphane (SFN), resveratrol, curcumin and others have demonstrated to be effective agents against cancer since they affect the epigenome through influences on various epigenetic mechanisms[1]. Different stages of life have shown to be of value in understanding the influence of dietary components on the epigenome. Studies have shown that the epigenome can be strongly shaped by nutrition in prenatal period through transgenerational mechanisms and in early postnatal life when critical development processes are taking place. Although more stable, the epigenetic marks in adulthood are also dynamic and modifiable by environmental factors such as diet. The field of epigenetics is of tremendous relevance in determining health outcome. It provides evidence that we could positively impact our genes just by simply making changes in our diet regimen. This concept is really empowering because it always assumed that our genes are beyond our influence.

2. The epigenetics of cancer

Epigenetics is the study of heritable changes in gene

expression without alteration to the DNA sequence -A change in phenotype without change in genotype-These changes simply affect how a cell shall read the gene. In simple terms epigenetic modifications change the likelihood of gene expression but don't change the sequence; and these modifications can be passed on from parent to offspring. Epigenetics show how different lifestyle choices and environmental exposures alter marks on top of DNA and play a role in determining health outcome. At least 3 systems including DNA methylation, histone modification and non-coding RNA (ncRNA)-associated gene silencing are currently considered to initiate and sustain epigenetic change.

DNA methylation: It refers to the addition of a methyl group to the cytosine ring of those cytosines that precede a guanosine (CpG dinucleotide) to form methyl cytosine (5-methylcytosine). CpG dinucleotides are found at increased frequency in the promoter region of many genes and methylation in the promoter region is frequently associated with gene silencing.

Histone modifications: epigenetic histone modifications occur on the tails of histone proteins to which different chemicals are added (Acetyl, Phosphate, Methyl, etc.)

It is known that epigenetic mechanisms play critical roles in regulating many cellular functions and that their deregulation may disrupt the control of fundamental processes leading to a diseased state. In fact, epigenetic disruption is a near universal feature of human malignancy and a key driver of many cancers.

Cancer has been heavily linked to epigenetics for a long time. A study conducted by Feiburg and Vogelstein in 1983, clearly demonstrated that genes of colorectal cancer cells (from primary human tumour tissues) were substantially hypomethylated when compared with the normal tissue genome. This suggests that genome-wide hypomethylation could activate oncogenes that lead to chromosome instability, whereas DNA hypermethylation at specific sites on the genome could initiate silencing of tumour suppressor genes[2]. This coexistence of both genome wide hypomethylation and local hypermethylation is the hallmark of tumorigenesis.

Scientists have once thought that mutations were the most important factor causing cancer, now the prevailing opinion is that epigenetic modifications cause cancer more often than mutations do. Two important features that distinguish epigenetic changes from genetic alterations are the gradual appearance and reversibility of epigenetic events (since epigenetic modifications change the likelihood of gene expression but not the sequence). These features make epigenetic alterations an attractive target for therapeutic intervention and the development of preventive strategies. After all, it is much easier to turn genes on or off than to change the genetic sequence.

Epigenetic therapy is fast gaining popularity in the treatment of many chronic diseases, especially cancer. Traditional cancer therapy focused on killing cancer cells. However, this approach aims to restore cancer cells to their original nature[3]. Recent evidence has highlighted the key role of epigenetic mechanisms in mediating gene-environment interactions and translating exposures into tumorigenesis. Global DNA hypomethylation, gene promoter hypermethylation and aberrant histone post-translational modifications are hallmarks of neoplastic cells. Epi-drugs targeting methylation and demethylation pathways are now being considered for their reversal of epigenetic abnormalities in cancer cells.

3. Nutriepigenomics

Promising evidence in humans suggest that diet along with other environmental factors directly influence epigenetic mechanisms. Putting it simply, nutriepigenomics deals with the diet-epigenome interaction. It is the study of nutrients and bioactive dietary components and their influences on mechanisms influencing the epigenome. Diet has shown to have one of the strongest impacts on epigenetic tags. For example, just by simply switching to a high-fat and low-carbohydrate diet regimen could influence activity of HDAC inhibitors and open up the chromatin, leading to improvement in mental abilities[4].

Another example would be the queen bee diet. Throughout its life, the queen bee is fed royal jelly. In a series of experiments, scientists determined that royal jelly silences a key gene (DNMT3), which codes for an enzyme that silences a group of queen genes. When DNMT3 is turned "on", the queen genes are epigenetically silenced, and the larvae develop into the default "worker" variety. But when royal jelly turns DNMT3 "off", the queen gene jumps into action, turning the larvae into queens[5].

The landmark 1981 report on a diet and cancer submitted to the office of technology assessment of the US congress concluded that 35% of total cancer was attributed to diet with estimates by some authorities surveyed for that report being as high as 70%. The 35% estimate of diet-attributed cancer has been widely cited by many authorities ever since 1981[6].

Even today, mounting evidence continues to point to dietary habits as a modifier of cancer risk and tumour behaviour. The fact that nutrients and bioactive dietary components interact so strongly with the epigenome, it is only natural that these factors may be involved in the epigenetics of cancer both in positive and negative perspectives.

Why epigenetic alterations occur in cancer isn't well understood although theories include this response being induced from sustained cellular stress.

One of the reasons for cellular stress is an imbalance in the oxidant-antioxidant system. Prolonged tissue

excess of highly reactive molecules such as ROS (Reactive Oxygen Species) leads to chronic inflammation. Chronic inflammation is known to spur on ageing and associated chronic diseases such as cancer, cardiovascular diseases, diabetes, etc.[7,8].

Food choices play a vital role in keeping the oxidant-antioxidant system in balance. Whole plant-based foods are rich in antioxidants while foods that are highly processed and/or of animal origin are often rich in promoting the production of ROS. Laboratory animal studies suggest that experimental tumour formation initiated by chemical carcinogens was increased by consumption of nutrients like fat, animal protein and/or calories, which generally represented the effects of diets rich in animal-based food [9,10].

An example of a potential anti-cancer preventive agent is lycopene- a red carotenoid pigment in tomatoes. In a study for preventive agents of prostate cancer, lycopene, as an antioxidant induced several mechanisms that favour cancer inhibition including anti-proliferative, anti-oxidative and anti-inflammatory responses while down-regulating genes contributing to androgen receptor signalling pathway[11,12].

In the present article, we will review in depth, the effects of nutrition and bioactive dietary compounds on the epigenome for potential cancer prevention and therapy.

4. Bioactive Food Components (BFC's) and their influence on methylation

DNA methylation is the main epigenetic modification in humans. Today, DNA methylation analysis is one of the most valuable sources for cancer biomarkers as it is one of the most common molecular alterations in human neoplasia. DNA methylation is carried out by a group of enzymes known as DNA methyltransferase (DNMT). There are 3 major types:

DNMT 1, DNMT3a, DNMT3b

DNMT3a and DNMT3b are responsible for De Novo methylation allowing embryonic cells to differentiate into a cell type. DNMT1 is responsible for maintenance of DNA methylation after differentiation, and is active during cell division[13-16].

Aberrant DNA methylation of CpG sites is among the earliest and most frequent alterations in cancer. In contrast to specific hypermethylation of tumour suppressor genes, an overall hypomethylation of DNA can be observed in tumour cells. This decrease in global methylation can be detected early, well before the development of frank tumour formation.

From genome wide studies it has become clear that dynamic regulation of DNA methylation is critical epigenetic mechanism of cancer initiation, maintenance and progression. Epi-drugs targeting methylation and demethylation pathways are now being considered for the reversal of epigenetic abnormalities in cancer cells. However, one of the challenges as we go forward is figuring out how to target epi-drugs towards toxic epigenetic marks while leaving alone the beneficial ones that help maintain our health.

A number of bioactive dietary components are of particular interest in the field of epigenetics. Numerous studies suggest that a number of nutritional compounds have epigenetic targets in cancer cells, especially methylation and demethylation pathways.

Dietary variables have been found to be significantly associated with methylation status. In the Lovelace Smokers Cohort of current and former smokers, Stidley and colleagues evaluated whether diet and multivitamin use influenced the prevalence of gene promoter methylation of 8 genes commonly silenced in lung cancer. Methylation was categorized as low (fewer than 2 genes methylated) or high (2 or more genes methylated). Significant protection against methylation was found for green leafy vegetables and folate and with current use of multivitamins[17].

Restoring proper methylation may represent a fundamental process by which some nutrients function to influence the gene expressing patterns. Epigallocatechin-3-gallate (ECGC) from green tea can reactivate methylation-silenced genes by inhibiting the enzymatic activity of DNA methyltransferase[18]. Further, the annurca polyphenol from annurca apples reversed methylation and reactivation of DNA repair gene hMLH1 in invitro models of colorectal cancer[19,20].

All of these studies suggest just how huge a role diet and nutrition play in modulating epigenetic modifications. Recent evidence mainly from in vitro studies indicates that the cancer prevention activity of Bioactive Food Compounds (BFC's) involves modulation of epigenetic processes. By interfering with epigenetic processes deregulated during tumour development, BFC's could influence transcriptional programmes and affect DNA repair, oxidative stress, inflammation, cell growth, differentiation and apoptosis, among other processes.

Interference at the DNA methylation level represents a promising mechanism of dietary modulation of gene expression for cancer prevention[21]. BFCs can affect DNA methylation through at least four mechanisms:

(1) Dietary factors are important sources of methyl group necessary for AdoMet synthesis. Familiar nutrients like folic acid, B vitamins and SAM-e (S-Adenosyl methionine, a popular over the counter supplement are key components of methyl-making pathways). Diets high in methyl donating nutrients can rapidly alter gene expression, especially during early development when the epigenome is first being established.

(2) Dietary factors can affect methyl group utilization by processes including shifts in DNMT activity. Researchers showed that plant flavones could

reduce the levels of DNMT and reverse an excess of methylation or DNA hypermethylation. This only suggests that eating foods containing flavones such as parsley, peppers and celery might be able to genetically reduce cancer risk although their potential as anticancer therapeutics still require further exploration. Thus, eating more plant flavones could reduce cancer risk[22,23]. The results make you wonder: could parsley be much more than just a garnish?

(3) BFC's are related to DNA demethylation, although direct evidence is still lacking.

(4) DNA methylation patterns leading to activation or suppression of genes related to cancer development could be influenced in response to dietary interventions.

4.1. Methyl donor nutrients

Labile methyl groups for DNA methylation reactions are supplied mainly by choline and methionine, and are regenerated endogenously by folate and vitamin B12 in the 1-carbon metabolism pathway. Nutrition has shown to have a strong connection with breast cancer-risk. In a study by Park CS and colleagues, Lipotrope (dietary methyl donors and cofactors) supplementation resulted in a 25% decrease in Bcl-2 protein expression. Cancer treatment failure is often correlated with Bcl-2 protein upregulation [24].

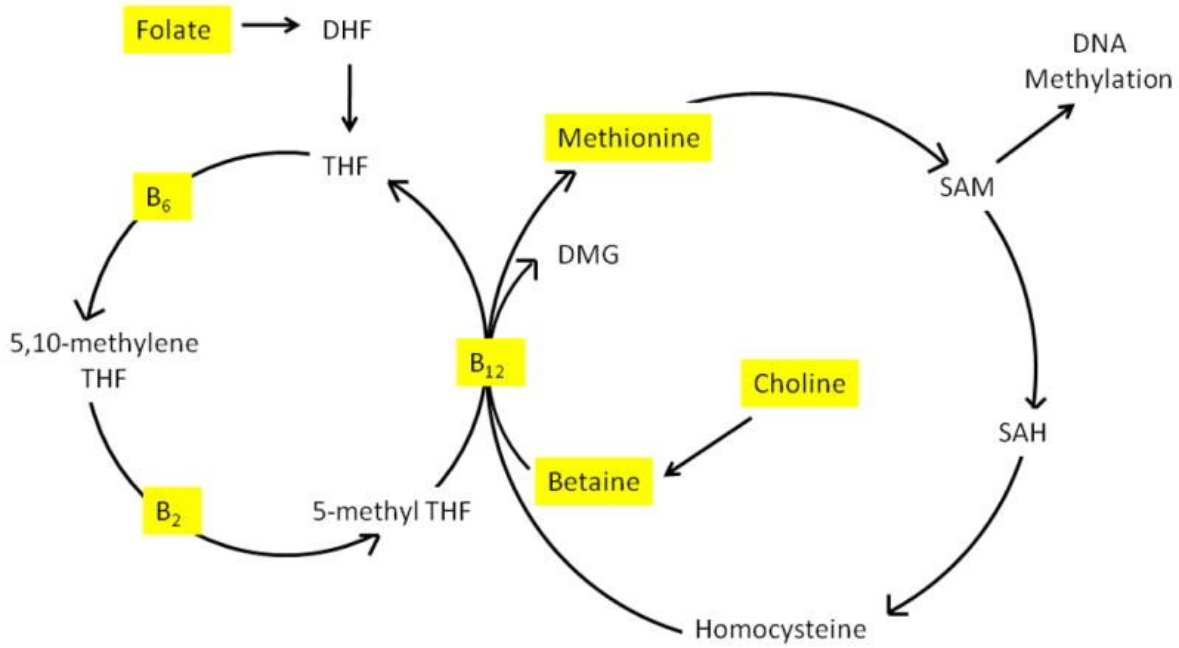

Figure 1. Involvement of dietary micronutrients in one-carbon metabolism Substrates obtained via diet are highlighted in yellow. (1) Vitamin B6 is a cofactor to serine hydroxy methyltransferase in the conversion of tetrahydrofolate (THF) to 5,10-methylene THF. (2) Vitamin B2is a precursor to FAD, which is a cofactor to methylenetetrahydrofolate reductase (MTHFR) in the conversion of 5,10-methylene THF to 5-methyl THF. (3) Vitamin B12 is a precursor to methionine synthase, involved in the production of methionine from homocysteine and betaine. Acronyms: dihydrofolate (DHF), flavin adenine dinucleotide (FAD), dimethylglycine (DMG), methylenetetrahydrofolate reductase (MTHFR), S-adenosylhomocysteine (SAH), tetrahydrofolate (THF)[25].

4.2. Polyphenols

Epigallocatechin-3-gallate (EGCG; 20 μ*M*), the main catechin (a polyphenol class) from green tea, has been shown to inhibit DNMT in human oesophageal (KYSE 150), colon (HT29), prostate (PC3), and mammary (MCF-7 and MDA-MB-231) cancer cell lines[26].

Genistein, an anticancer estrogen-like isoflavone of soy products has also been shown to inhibit DNMT activity in different cancer cell lines. Genistein engages a large number of mechanisms to produce its effects. It modulates genes that regulates cell-cycling and programmed cell death (apoptosis), inhibits the nuclear protein complex (nuclear factor-kappa-B) that activates DNA transcription responsible for stress-factor induced cancer, inhibits transcription and expression of prostate-specific antigen that promotes prostate cancer and blocks estrogen receptors thus minimizing the promotion of breast cancer by endogenous estrogen[27-29].

4.3. Selenium

Evidence from animal and cell culture experiments shows that the anticancer effects of selenium may involve interference with DNA methylation. Deficiency in dietary selenium (0 mg/kg diet) caused global DNA hypomethylation in rat liver and colon tissues and in human colon cancer cells Caco-2 (0 μM added selenium) in which methylation of the p53 promoter region was also influenced by selenium status. Selenium also inhibited the expression of DNMT1 in a human adenocarcinoma cell line (HT29) [30,31].

4.4. Retinoids

Retinoids may alter the DNA methylation process by enhancing 1-carbon metabolism. Cellular retinol-binding protein 1 (CRBP1) and RARβ play a central role in retinoid signalling by functioning as an intracellular retinol transporter and as a nuclear receptor for retinoic acid, respectively. In several cancer cell lines and primary tumours, both genes were shown to be epigenetically silenced by promoter region hypermethylation. Colorectal cancer patients in the highest quartile of dietary vitamin A intake (mean daily consumption 155μg; interquartile range 102–239μg) were more likely to present with unmethylated CRBP1 and RARβ[32]. Retinoic acid reversal of the transformed phenotype in NB4 acute promyelocytic leukaemia cells involved the demethylation of RARβ2 promoter with re-expression of this gene. Inhibition of DNMT expression and activity was shown to mediate these epigenetic effects via the retinoid[33]. Similarly, in MCF-7 breast cancer cells, inhibition of DNMT1expression by retinoic acid (0.35μM) led to promoter demethylation and re-expression of RARβ2[34].

5. Window of Vulnerability

Cancer may have a developmental origin and perturbations in the fetal environment have been hypothesized to programme disease risk in later life. Critical period for establishing and maintaining epigenetic marks is early development.

Embryogenesis is characterized by extensive epigenetic reprogramming and improper modulation of the epigenome during this highly sensitive period may have short and long-term effects on the new born and his/her progeny. Thus, epigenetic marks could represent the mechanisms whereby an adult organs genome would retain the memory of early life environmental exposure, including nutrition, by long term alterations in gene expression programming.

Breast cancer has also been reported to fetal exposure to maternal hormones and nutrients. The hypothesis that breast cancer is initiated in utero as a result of increased fetal exposure to maternal estrogen levels was proposed by Trichopoulos based on population studies showing an association with high birth-weight and increased risk of breast cancer in adult life [35].

Increased risk of vaginal cancer among daughters of mothers who had consumed diethylstilbestrol during pregnancy for prevention of miscarriage has also been reported [36,37].

In addition to embryonic period, environmental and epigenetic influences may alter developmental stages such as childhood and puberty, especially in females. In males, spermatogenesis starts at puberty and continues throughout life; whereas in females, oogenesis begins from birth and is arrested in the prophase of meiosis until puberty. Hence, in girls, oocytes remain until puberty in a haploid demethylated state, which is more susceptible to environmental stressors than the diploid demethylated state of the male germline. Later during adulthood, women may exhibit other susceptible windows of exposure during the menstrual cycle, pregnancy or menopause. These timings/windows of exposure must be considered when analysing the interaction between the environment, epigenetics and cancer.

6. Conclusion

The reversible nature of epigenetic processes and the observation that aberrations in DNA methylation and histone modification are early events in carcinogenesis emphasize the relevance of the epigenome as a promising target for BFC's for cancer prevention strategies.

Because diet-epigenome interactions are likely to occur in-utero, the impact of early-life nutrition on cancer-risk programming should be investigated further.

However, we are only at the early stages of understanding the epigenetic effects of dietary compounds. Many variables like individual responsiveness to the food consumed, timing of exposure, quantity, composition of Bioactive food component, etc have rendered epidemiological and clinical intervention studies inconsistent.

So far, most studies have focused on single candidate genes or mechanisms. With the emergence of novel technologies such as next-generation sequencing, future research has the potential to explore nutriepigenomics at a genome-wide level to understand better the importance of epigenetic mechanisms for gene regulation in cancer chemoprevention.

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