Impact on DNA methylation in cancer prevention and therapy by bioactive dietary components.

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Source
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Abstract
It is well established that aberrant gene regulation by epigenetic mechanisms can develop as a result of pathological processes such as cancer. Methylation of CpG islands is an important component of the epigenetic code and a number of genes become abnormally methylated during tumorigenesis. Some bioactive food components have been shown to have cancer inhibition activities by reducing DNA hypermethylation of key cancer-causing genes through their DNA methyltransferase (DNMT) inhibition properties. The dietary polyphenols, (−)-epigallocatechin-3-gallate (EGCG) from green tea, genistein from soybean and possibly isothiocyanates from plant foods, are some examples of these bioactive food components modulated by epigenetic factors. The activity of cancer inhibition generated from dietary polyphenols is associated with gene reactivation through demethylation in the promoters of methylation-silenced genes such as p16INK4a and retinoic acid receptor β. The effects of dietary polyphenols such as EGCG on DNMTs appear to have their direct inhibition by interaction with the catalytic site of the DNMT1 molecule, and may also influence methylation status indirectly through metabolic effects associated with energy metabolism. Therefore, reversal of hypermethylation-induced inactivation of key tumor suppression genes by dietary DNMT inhibitors could be an effective approach to cancer prevention and therapy. In this analysis, we focus on advances in understanding the effects of dietary polyphenols on DNA methylation modulation during the process of cancer development, which will offer exciting new opportunities to explore the role of diet in influencing the biology of cancer and to understand the susceptibility of the human epigenome to dietary effects.

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Impact on DNA methylation in cancer prevention and therapy by bioactive dietary components
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Other Sections▼
Abstract
Introduction
DNA methylation and cancer
DNA methyltransferases (DNMTs)
DNMT1
DNMT3
The effects of dietary components on DNA methylation
1. Methyl-donor related diet
2. Dietary polyphenols
3. Selenium
4. Isothiocyanates

dm
Future research direction
Summary
References

Impact on DNA methylation in cancer prevention and therapy by bioactive dietary components
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Keywords: Diet, Cancer prevention, DNMT, DNA methylation, EGCG, Genistein

Other Sections▼
Abstract
Introduction
DNA methylation and cancer
DNA methyltransferases (DNMTs)

DNMT1
DNMT3

The effects of dietary components on DNA methylation
1. Methyl-donor related diet
2. Dietary polyphenols
3. Selenium
4. Isothiocyanates

Future research direction
Summary
References
Introduction

There has been considerable interest in the use of botanicals for various cancer prevention and therapy approaches. Some bioactive food components with DNA methyltransferase (DNMTs) inhibition properties may influence DNA methylation processes and apply their cancer inhibition activities through reactivating key tumor suppressor genes. These dietary compounds including (−)-epigallocatechin 3-gallate (EGCG) and genistein are widely found in green tea, soybean products and some fruits. This review will introduce current advances for the use of these compounds in cancer chemoprevention including modulating epigenetic mechanisms as applied to in vitro cell cultures as well as in vivo animal and human studies.
The DNMT3 family includes two major members, DNMT3a and DNMT3b, which play an important role in mediating de novo methylation processes (Table 1) [13, 14]. Both DNMT3a and DNMT3b have a similar C-terminal catalytic domain as DNMT1 has, and variable N-terminal domains [17]. These specific domains allow DNMT3 to directly interact with various transcriptional regulators such as DNA methyltransferase 1 associated protein 1 (DMAP1), histone deacetylases (HDACs), suppressor of variegation 3–9 homolog 1 (SUVR39H1) and Rb, thereby influencing gene regulation through epigenetic signaling [18].

### Table 1

Summary of DNA methyltransferases (DNMTs)

<table>
<thead>
<tr>
<th>DNMT</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA methyltransferase (DNMTs)</td>
<td>The C-terminal domain of DNMT1 contains all the conserved motifs characteristic of cytosine-5-methyltransferase and shares a set of 10 conserved amino acid motifs, where the motifs I (DxFGxGXG), IV (GFCQ), and VI (ENV) are most conserved and harbor the active center of the enzyme [19]. The catalysis process involves a conserved mechanism that has been studied best in the bacterial cytosine-5-methylation (SmC) methyltransferase (Mtase), M.HhaI [20–22]. Briefly, this mechanism involves Mtase binding to the DNA, eversion of the target nucleotide so that it projects out of the double helix (“base flipping”) into the catalytic pocket of the enzyme, covalent attack of a conserved cysteine nucleophile on cytosine C6, transfer of the methyl group from S-adenosylmethionine to the activated cytosine C5, and the various release steps. The key residue of DNMT1 is cysteine in a PCQ motif conserved in the active site of all DNMTs. M.HhaI performs a nucleophilic attack on the conserved cysteine of the target cytosine. Moreover, base flipping plays an important role in the enzymatic reaction by providing high accessibility of the target base to the enzyme, thereby allowing for intricate chemical reactions to occur and for accurate recognition of the flipped base. It has been verified in M.HhaI that Gin 237, the amino acid residue of motif ENV (motif VI), is in a stable situation of the flipped cytosine of the DNA protein complex [23]. Homozygous knockout of DNMT1 is lethal to the embryo in mammals, suggesting a crucial role of DNMT1 in embryonic development. However, studies on DNMT1-overexpression in embryonic stem cells also resulted in lethality of the embryo suggesting accurate expression of DNMT1 is a key factor in maintaining embryonic development [24]. As expected for a maintenance methyltransferase, DNMT1 has a 30- to 40-fold preference for hemimethylated sites [25]. Further investigations proved that DNMT1 activity is required for de novo methylation at non-CpG cytosines [26]. However, increased DNMT1 expression of DNMT1 is a key factor in maintaining embryonic development [24].</td>
</tr>
</tbody>
</table>
chemotherapy and prevention.

Currently the best evidence to show that nutritional components can modulate epigenetic status of mammal cells comes from studies with mice carrying the agouti viable yellow gene (Fig. 2) [35, 36]. The normal function of the agouti gene is to confer a wild-type coat color but dominant mutations at the agouti locus cause a pleotropic syndrome which results in excessive amounts of yellow pigment on the coat, together with systemic effects including obesity and a vulnerability to various types of cancer. Various agouti viable yellow alleles (AIAP and Ahvy) have been identified by inserting an intracisternal A particle (IAP), a retroviral element, into the gene. The coat color of mice carrying such an allele varies from yellow to mottle to wild type agouti, which is dependent on the methylation status of IAP in the alleles. When methylated the gene behaves like a wild type allele and is expressed only in the hair follicle. When the unmethylated gene is expressed ubiquitously, the result is the phenotype of the full agouti syndrome, but intermediate levels of methylation cause a mottled appearance. Therefore, the coat color and other aspects of the agouti phenotype provide a direct readout of the methylation status of the allele. The AIAP model system has been successfully used for detecting epigenetic control in mammals through dietary supplementation with methyl donors such as folate, which will be discussed later in this review.

Numerous studies have demonstrated that certain dietary components inhibit cancer proliferation by affecting epigenetic signaling pathways both in vitro and in vivo [37, 38]. The green tea polyphenol, EGCG, is believed to be a key active ingredient for cancer inhibition through epigenetic control. It has been found that EGCG can reverse CpG island hypermethylation of various methylation-silenced genes and reactivate these gene expressions through inhibition of DNMT1 enzymatic activity [39]. Moreover, EGCG has been proposed to regulate gene expression through the mechanism of chromatin remodeling suggesting that EGCG could exert its anticancer ability through both epigenetic mechanisms. Another well-known bioactive dietary compound is the soybean isoflavone, genistein, which has also been found to inhibit tumorigenesis through epigenetic control in several cancer cell lines [40, 41].

Cellular DNA methylation processes involve a series of catalytic reactions including one-carbon metabolism, creation of the principal methyl donor, S-adenosylmethionine (SAM), and methyl transfer reactions [42] (Fig. 3). As a consequence of methyl group transfer, SAM is converted to S-adenosylhomocysteine (SAH), which binds with high affinity to methyltransferases and induces product inhibition. The ratio of SAM:SAH is therefore an important determinant of the methylation capacity. Disturbances in this system may be caused by dietary imbalances by affecting the major regulatory enzymes, thereby altering DNA methylation [43]. Therefore, in a pathological condition such as precancer or even cancer, appropriate intake of a methylation-regulatory bioactive diet may interfere with tumorigenesis leading to cancer prevention and anticancer therapy.

Other Sections

Abstract

Introduction

DNA methylation and cancer

DNA methyltransferases (DNMTs)

DNMT1

DNMT3

The effects of dietary components on DNA methylation

1. Methyl-donor related diet

2. Dietary polyphenols

3. Selenium

4. Isothiocyanates

Future research direction

Summary

References

1. Methyl-donor related diet

A methyl donor diet, referring to a series of dietary components including folate, vitamin B12 and many other compounds, can be used for synthesis of SAM [44]. Folate, a water-soluble B vitamin, which must be obtained from dietary sources or supplements, is of fundamental importance for normal DNA synthesis and repair (Table 2) [45]. S-Methyltetrahydrofolate (S-MTHF), the predominant form of folate in plasma, provides the methyl group for synthesis of methionine and SAM, the universal methyl donor of biological methylation (Fig. 3).

Table 2

Summary of dietary components for cancer inhibition

Extensive evidence has accumulated suggesting that folate deficiency plays a significant role in developing several tumors, including cancers of the colorectum, lung, pancreas, esophagus, stomach, cervix, and breast, as well as neuroblastoma and leukemia [46]. This may be due to the abnormal process of DNA synthesis and methylation caused by low folate status and numerous studies have explored the relationship between folate status and the human epigenome, both in vitro and in vivo. The AIAP model system, which has been introduced previously, has been successfully used to detect the methylation status in mammals when administering folate-deficient dietary supplementation [35, 36, 47]. Wolff et al. found that when pregnant female mice were fed a diet supplemented with methyl-donors (folate, methionine, choline and vitamin B12), a large proportion of offspring have a wide-type coat color due to increased IAP methylation as compared with the maternal mice fed with a standard diet [48]. In addition, a methyl group- rich diet has been shown to significantly reduce the proportion of progeny with a kinked tail in AxinFused mice by one-half via increased CpG methylation in the promoter of the AxinFused gene [49]. However, studies in rats with diets deficient in folate showed that significant genome-wide DNA hypomethylation, as well as gene-specific DNA hypermethylation occurs in the liver, suggesting that the effects of folate deficiency on DNA methylation are gene- and site-specific depending on cell type, target organ, and stage of transformation [50, 51].

The most common cause for impairment of folate uptake is chronic ethanol ingestion, which can reduce the intestinal and renal uptake of folate by altering the binding and transport kinetics of folate transport systems [52]. There have been several intervention studies of human populations that investigated the effects of folate deficiency and/or supplementation on DNA methylation status [53, 54]. Generally, folate deficiency was associated with genome-wide DNA hypomethylation. However, the supplementation studies have either no effect or minor effects on DNA methylation [55, 56] suggesting that the timing and duration of folate intervention is important to carcinogenesis. Moreover, a high dose of folate supplementation may promote tumorigenesis if the administration is given after the preancerous lesions have been established [57]. Therefore, an appropriate exposure time of folate supplementation plays an important role in its protective roles on human health.

Other Sections

Abstract

Introduction

DNA methylation and cancer
DNA methyltransferases (DNMTs)

DNMT1

DNMT3

The effects of dietary components on DNA methylation

1. Methyl- donor related diet

2. Dietary polyphenols

3. Selenium

4. Isothiocyanates

Future research direction

Summary

References

2. Dietary polyphenols

Phenolic compounds are among the largest and most ubiquitous groups of plant metabolites. Recently, interest has been focused on the effects of dietary polyphenolic compounds on their anti-oxidative, anti-inflammatory, and anti-carcinogenic activities [54–60]. All plant polyphenolic compounds arise from the common intermediate, phenylalanine, or its close precursor, shikimic acid. They can be divided into at least ten different classes based on their general chemical structures, such as phenolic acids and derivatives, flavonoids, stilbenes, lignans and others [60]. In this review, we have chosen a select group of polyphenols with the properties of DNMT inhibition to further understand the bioavailabilities of dietary polyphenolic compounds on cancer prevention.

2.1 Tea polyphenols

Green tea, a popular beverage consumed worldwide, has been extensively demonstrated to improve human health by prevention of cancer, heart disease, and cataracts. The most abundant chemical compound in green tea beverages is catechins, which include (-)-epicatechin (EC), (-)-epicatechin-3-gallate (ECG), (-)-epigallocatechin (EGC) and (-)-epigallocatechin-3-gallate (EGCG) (Fig. 4) [61]. Many studies in recent years have demonstrated the chemopreventive and anticancer potential of green tea polyphenols. These investigations have suggested a positive association between green tea and a lower incidence of gastric, esophageal, breast, ovarian, pancreatic, colorectal and skin cancers [60, 62, 63]. Many authors have considered EGCG to be the key active ingredient of green tea because this compound is the most abundant catechin, and the cancer inhibitory activity of EGCG has been extensively demonstrated (Table 2). Moreover, various studies have shown that EGCG can effectively inhibit carcinogenesis in various animal organs [64–66]. Possible mechanisms for the anticancer property of EGCG include: inhibition of cellular oxidative stress, reduction in cancer cell proliferation, inhibition of angiogenesis, and regulation of signal transduction [67].

Fig. (4)

Representative structures of selected dietary polyphenols: EC, EGC, EGCG, genistein and quercetin.

Recently, several studies have suggested that EGCG can inhibit DNMT activity through a direct interaction with the enzymes, thereby leading to demethylation and reactivation of methylation-silenced genes (Fig. 3) [37, 39, 68–69]. Treatment of human esophageal cancer cells with EGCG has been shown to lower DNMT1 activity leading to hypomethylation and re-expression of genes including the tumor suppressor p16INK4a, RAR β, MGMT, and the DNA mismatch repair gene, hMLH1 [39]. Similar effects were observed in prostate, colon, lung and breast cancer cell lines [37, 69–74]. Our previous studies also show that EGCG treatment can down-regulate expression of a tumor promoting gene, hTERT (human telomerase reverse transcriptase), which leads to inhibition of telomerase activity through decreasing methylation of the hTERT promoter [37]. Although hypermethylation of gene promoters is generally associated with gene silencing, the hTERT promoter, paradoxically, is highly methylated in most tumor cell types, rendering hTERT active [75]. Our studies indicated that EGCG can also inhibit oncogene expression through influencing DNA methylation status of these genes. Moreover, Mittal et al. found that EGCG treatment results in significant inhibition of UVB-induced global DNA hypomethylation patterns in the SKH-1 hairless mouse model [36]. In a study investigating past lifestyle factors in gastric cancer patients, a decreased intake of green tea was found to correlate with methylation of the CDX2 gene [76]. Taken together, these findings provide solid evidence that EGCG can exert its anticancer effects through modulation of DNA methylation. Currently, green tea extracts have been applied in clinical trials including oral cancer prevention indicating tea polyphenols could be used in multiple human cancer preventive and therapeutic purposes due to their bioactivities such as regulating epigenetic factors [77].

Various findings indicate that EGCG is the most potent DNMT inhibitor in tea catechins through direct and indirect mechanisms. In normal metabolic processes, EGCG is methylated by catechol-O-methyltransferase (COMT) through the transfer of a methyl group from S-adenosylmethionine (SAM) to form MeEGCG and DiMeEGCG both in vitro and in vivo [78, 79]. Given the evidence that EGCG is also a potent inhibitor of COMT, it is thought that EGCG may act as an inhibitor of the DNMTs because both COMT and DNMT belong to the same superfamily of SAM-dependent methyltransferases and share a common core structure at the catalytic site [19, 39]. In a previous study, it was shown that EGCG is a competitive inhibitor of DNMT in a dose-dependent manner [39]. They also investigated the inhibitory activities of structural analogues of EGCG including EGC, ECG, and methylated EGCG and found a rank order of potency: EGCG > EGC, MeEGCG > ECG, and DiMeEGCG > EC. Molecular modeling of the interaction between EGCG and DNMT1 indicated that docking of EGCG (D ring) into the putative cysteine pocket formed potential hydrogen bonds with two catalytically important residues, Glu1265 and Pro1223, which were the same residues that appear to stabilize the flipped cytosine through hydrogen bonding [19, 23]. The potential inhibition of DNMT3a and DNMT3b by tea polyphenols has also been determined by using the prokaryotic SssI DNA methyltransferase, which is functionally similar to the human DNMT3a and DNMT3b and methylates both unmethylated and hemimethylated DNA substrates with almost equal efficiency [80, 82]. It was found that EGCG shows a more potent direct inhibition on SssI DNA methyltransferase than the other tea polyphenols suggesting an overall inhibition of DNMT1, DNMT3a and DNMT3b by EGCG.

2.2 Soy isoflavone genistein

The soybean product, genistein, belongs to flavonoids, the largest class of phenolic compounds (Fig. 4) [60]. Genistein has been shown to be associated with a lower incidence and mortality rate of breast cancer in Asian women who consume soybean products as their daily diet [83, 84]. Genistein is believed to be a chemopreventive agent against various types of cancer cells, including cancers of...
was synergistically enhanced in combination with 5-aza-2′-deoxycytidine [40, 92]. However, the anti-cancer properties of genistein in reactivation of gene expression including p16INK4a, RAR β, MGMT, phosphatase and tensin homolog (PTEN) and CYLD and the effect on breast cancer have raised concerns because its estrogen-like effect may be contraindicated for women at high risk of breast cancer or breast cancer patients with estrogen-sensitive tumors. Studies both in epidemiology and animals have confirmed that exposure to soy diet is one common way to prevent breast cancer and other cancers by maintaining a protective DNA methylation profile [91].

It has been shown that genistein supplementation of maternal mice during gestation could shift the coat color of heterozygous viable yellow agouti (Avy/a) offspring, indicating that genistein acts during early embryonic development [90]. Day et al. also reported that genistein may be involved in regulating the development of cells by modulating epigenetic events such as DNA methylation and/or chromatin modification (Table 2 and Fig. 3) [40, 41, 89].

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In addition to the aforementioned EGCG and genistein, the inhibition of DNMT activity of other common dietary phenolic compounds, which are abundant in many fruits, vegetables, and beverages, was also determined [68, 80]. These compounds include myricetin and quercetin (flavanols), hesperetin and naringenin (flavanols), apigenin and luteolin (flavanoids), garcinol, curcumin, and hydroxycinnamic acid. All these compounds are weaker direct inhibitors of the DNMTs compared with EGCG because these polyphenols, lacking a gallic/pyrogallic acid moiety, cannot form a similarly strong coordination with the DNMT catalytic center, which, in turn, interferes with the activities of DNMTs inhibition. However, polyphenols with catechol structures could still exert a considerably strong indirect inhibition of DNA methylation through converting SAM: SAH ratio during their metabolic methylation by COMT.

3. Selenium

Selenium is an essential trace element with both anti-oxidant and pro-apoptotic properties (Table 2) [94, 95]. Interventional trials provide the strongest evidence for protective effects of selenium against various cancers. Davis et al. have demonstrated that in the colon and liver, selenium deficiency causes global hypomethylation and in addition, promoter methylation of p53 and p16 genes, suggesting that impacting DNA methylation may be a crucial mechanism of selenium for cancer prevention [96]. Selenium has been shown to inhibit DNMT through direct interaction and indirect action by influencing plasma homocysteine concentrations and the SAM: SAH ratio [97, 98].

4. Isothiocyanates

Isothiocyanates, metabolites of glucosinolates, are found naturally in cruciferous vegetables, such as broccoli, cabbages, and watercress and have been reported to reduce the incidence of prostate cancer (Table 2) [99]. Phenethyl isothiocyanate (PEITC), a hydrolytic product of glucosinolate gluconasturtin, has been shown to reduce cell growth of prostate cancer both in vivo and in vitro [100, 101]. Current studies have found that PEITC could reactivating the expression of glutathione S-transferase gene (GSTP1), a cellular detoxifying factor, through inducing demethylation of the promoter of GSTP1 in prostate cancer cells [102]. A synergistic effect on reactivating GSTP1 was also observed when PEITC was combined with 5-aza-2′-deoxycytidine. However, the precise mechanism of the effect of the isothiocyanates on DNA methylation is still unknown and requires further investigation.

Dietary supplement approaches have been amply demonstrated in cancer prevention by influencing epigenetic pathways both in vitro and in vivo. Future investigations on dietary intervention that combine these dietary components with epigenetic modulators such as the DNMT inhibitor, 5-aza-2′-deoxycytidine (5-aza-dCyd), could be applied in clinical trials. Moreover, future exploration for new drugs using dietary compounds with more biological activity will be beneficial for new cancer therapeutical approaches.

Future research direction

Interest in the role of bioactive botanic ingredients on epigenetics in human health and disease has expanded rapidly in recent years. In this review, we have discussed some bioactive dietary compounds which could exert their anticancer properties through epigenetic mechanisms. These dietary components including folate, EGCG, genistein, selenium and isothiocyanates can influence DNA methylation processes, thereby leading to altered gene expression profiles and ultimately, cancer inhibition. This study will offer exciting new opportunities to explore the role of diet in influencing the biology of cancer and to understand the susceptibility of the human
epigenome to dietary effects. More importantly, better understanding the precise mechanisms of the impact of the human diet on cancer development will certainly facilitate the field of new drug discovery and novel approaches to cancer therapeutic strategies.

Acknowledgments

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Abbreviations

COMT catechol-O-methyltransferase  
DNMT DNA methyltransferase  
EGCG (−)-epigallocatechin 3-gallate  
GSTP1 glutathione S-transferase gene  
hMLH1 human mutL homolog 1  
hTERT human telomerase reverse transcriptase  
IAP intracisternal A particle  
MGMT O6-methylguanine methyltransferase  
5mC MTase cytosine-C5-methylation methyltransferase  
PEITC phenethyl isothiocyanate  
RARβ retinoic acid receptor β  
SAH S-adenosylhomocysteine  
SAM S-adenosylmethionine

Other Sections▼

Abstract

Introduction

DNA methylation and cancer  
DNA methyltransferases (DNMTs)  
DNMT1  
DNMT3

The effects of dietary components on DNA methylation

1. Methyl- donor related diet  
2. Dietary polyphenols  
3. Selenium  
4. Isothiocyanates

Future research direction

Summary

References

References


Summary of DNA methyltransferases (DNMTs)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene location</th>
<th>Molecular weight (kDa)</th>
<th>Expressional distribution</th>
<th>Methylation preference</th>
<th>Activity on DNA</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNMT1</td>
<td>19p13.2</td>
<td>183</td>
<td>Ubiquitous expression</td>
<td>Hemimethylated CpG sites</td>
<td>+++</td>
<td>Primary maintenance methyltransferase in cell division and embryonic development; high expression in tumors</td>
</tr>
<tr>
<td>DNMT3a</td>
<td>2p23</td>
<td>102</td>
<td>Ubiquitous expression</td>
<td>CpG dinucleotides</td>
<td>+</td>
<td>De novo methyltransferase; modestly increased in certain tumors</td>
</tr>
<tr>
<td>DNMT3b</td>
<td>20q11.2</td>
<td>98</td>
<td>Localized expression in testis, thyroid and bone marrow</td>
<td>CpG dinucleotides</td>
<td>+</td>
<td>De novo methyltransferase; mutated expression leads to ICF syndrome; high expression in tumors</td>
</tr>
<tr>
<td>DNMT3L</td>
<td>21q22.3</td>
<td>48</td>
<td>Restricted to gonocytes</td>
<td>No catalytic activity</td>
<td>−</td>
<td>Regulatory factor for de novo DNA methylation and histone modification</td>
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Fig. (2) Epigenetic effects of the agouti gene on mouse coat color. The agouti viable yellow alleles (AIAP and Ahvy) are formed by inserting an intracisternal A particle (IAP) into the agouti locus. When IAP is methylated, the gene is expressed only in the skin, similar to expression of the wild type allele. Hypomethylation of the IAP gene will generate a ubiquitous expression leading to a yellow coat color, obesity and tumors.

Click on image to enlarge

Unmetilated CpG
Metilated CpG

Table 2 Summary of dietary components for cancer inhibition

| Dietary components | Food source | Classification Functions in DNA methylation Roles in cancer prevention Target gene References |
|--------------------|-------------|------------------------------------------|---------------------------------|-----------------|-----------------|----------|
| Folate | Many beans and vegetables and some fruits | Water-soluble B vitamin | Providing methyl group for SAM synthesis (Methyl-donor) | Deficiency causes genome-wide DNA hypomethylation and genomic instability | N/A | 44–46 |
| EGCG | Green tea Botanic polyphenol (Flavonol); tea catechins | Potent DNMT1 inhibitor; SAM/SAH | Reactivation of tumor suppressor genes by promoter hypomethylation p16INK4a; RAR β; MGMT; hMLH1; GSTP1; WIF-1; RECK 39, 68, 72–74 |
| Genistein | Soybean Botanic polyphenol (isoflavone) | DNMT1 inhibitor | Reactivation of tumor suppressor genes by promoter hypomethylation p16INK4a; RAR β; MGMT; PTEN; CYLD 40, 92 |
| Isothiocyanates | Cruciferous vegetables | Metabolites of glucosinolates | N/A | Reactivation of GSTP1gene by promoter hypomethylation GSTP1 102 |

Click on image to enlarge

Fig. (4) Representative structures of selected dietary polyphenols: EC, EGC, ECG, EGCG, genistein and quercetin.

Fig. (5) Molecular mechanisms of EGCG on DNMT1 inhibition. A, Molecular structure of hydrogen-binding network of interaction between EGCG and DNMT1 [36]. Hydrogen bonds that form between EGCG and DNMT1 are represented with dotted lines. The numbers of amino acid residues of DNMT1 contacting with the atoms of EGCG are indicated. B, Schematic drawing of EGCG affecting DNA methylation through inhibiting DNMT1. EGCG shows competitive inhibition of DNMT1 by effectively forming at least four hydrogen bonds within the DNMT1 catalytic binding center, thus blocking entry of the DNA nucleotide cytosine into its active site and preventing methylation process. The gallic acid moiety (D ring) of EGCG plays a crucial role in its high-affinity interaction with the catalytic site of DNMT1.