Chapter 4
Nutritional and Lifestyle Impact on Epigenetics and Cancer

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Abstract Nutrition and lifestyle factors play an important role in human health as dietary imbalances are major determinants of several diseases including cancer. Emerging studies suggest that diet and nutrition can impact gene expression through epigenetic mechanisms. Epigenetic modifications are heritable and cause potentially reversible changes in gene expression that do not require alteration in DNA sequence. Epigenetic marks include changes in DNA methylation, histone modifications, and small noncoding miRNA. Aberrant epigenetic modifications probably occur at an early stage in neoplastic development and are widely described as essential players in cancer progression. Epigenetic modifications also mediate environmental signals and provide links between susceptibility genes and environmental factors in the etiology of cancer. The present chapter initially highlights the role of various epigenetic mechanisms in the regulation and maintenance of mammalian genome. Focusing on the effect of various endogenous factors that include environmental, lifestyle, nutritional, and social-economic/racial aspects; this chapter discusses their impact on the process of carcinogenesis through various epigenetic modifications. Elucidating the impact of nutrition and lifestyle factors on epigenetic mechanisms may serve as a personalized prediction tool assessing cancer susceptibility and in providing recommendation and guide for prevention and therapeutic options against cancer.

Keywords DNA methylation • Histone modification • Noncoding RNA • Dietary agents • Gene–environment interaction • Carcinogens • Chemoprevention

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Abbreviations

AA	African American
BPDE	Benzo(a)pyrene diol epoxide
CA	Caucasian American
DNA	Deoxyribonucleic acid
DNMT	DNA methyltransferases
EGCG	Epigallocatechin-3-gallate
ER	Estrogen receptor
EZH2	Enhancer of zeste homolog 2
GSTP1	Glutathione S-transferase pi
GTP	Green tea polyphenols
HAT	Histone acetyltransferase
HDAC	Histone deacetylases
HDM	Histone demethylases
hMLH1	Human mutL homolog 1
HMT	Histone methyltransferases
HPV	Human papillomavirus
IGF	Insulin-like growth factor
LINE	Long interspersed nuclear element
lncRNA	Long noncoding RNA
LSD1	Lysine specific demethylase 1
MBD	Methyl-binding domain proteins
MGMT	$O(6)$-methylguanine methyltransferase
miRNA	MicroRNA
ncRNA	Noncoding RNA
PAH	Polycyclic aromatic hydrocarbons
PcG	Polycomb-group proteins
piRNA	Piwi-interacting RNA
RARbeta	Retinoic acid receptor beta
RepA	Short repeat RNA
SAH	S-adenosyl-L-homocysteine
SAM	S-adenosyl methionine
SFN	Sulforaphane
siRNA	Small interfering RNA
TIMP-3	Tissue inhibitor of metalloproteinases-3

Introduction

Cancer is widely recognized as a heterogeneous disease resulting from genetic and epigenetic alterations inherited by a series of transformations in clonally selected cells exhibiting selective growth advantage, sustaining proliferative signaling,

evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. Although genetic lesions drive tumor progression, however it is becoming clear that epigenetic perturbations are equally important in cancer development. Epigenetics is referred to as the study of stable inheritance of gene expression that occurs without changes in the DNA sequence. A majority of cancers result from changes that accumulate throughout the lifespan as a result of exposure to various endogenous factors that include environmental, lifestyle, nutritional, and social-economic/racial aspects. Epigenetic disruption of gene expression by these endogenous factors plays a critical role in cancer progression. A number of epigenetic mechanisms have now been identified in mammals. There are three major epigenetic mechanisms which are known to regulate gene expression. These include DNA methylation, modulation of chromatin structure by posttranslational modification of histone or nonhistone proteins, and small noncoding microRNAs (miRNAs) that alter gene expression by either inhibiting translation or causing targeted degradation of specific mRNAs. These mechanisms are critical components in the normal development and growth of cells and their modifications contribute to neoplastic phenotype.

Mechanisms Underlying Epigenetics

DNA Methylation

Methylation of cytosine residues within the dinucleotide sequence-CpG is one of the most widely studied epigenetic modifications in mammals [1]. Forming an essential component of the cellular epigenetic machinery, DNA methylation in collaboration with histone modification regulates gene expression by modulating DNA packaging and chromatin architecture [2]. DNA methylation is a chemical modification that involves transfer of a methyl (CH_3) moiety from the donor *S*-adenosyl methionine (SAM) to the 5′ position of cytosine residue that precedes guanine in the CpG dinucleotide sequence, forming 5-methyl cytosine and *S*-adenosyl-L-homocysteine (SAH) [1, 3–6]. The mammalian genome has been reported to harbor 3×10^7 methylated cytosine residues mostly within CpG dinucleotide sequences [4]. Although CpG sequences are unevenly distributed throughout the human genome, they are frequently enriched in gene promoters (often referred as CpG islands) and large repetitive sequences such as Long interspersed nuclear element (LINE) and ALU retrotransposon elements [7]. DNA methylation is catalyzed by a group of enzymes known as DNA methyltransferases (DNMTs) [1, 4]. There are three major DNA methyltransferases (Dnmt1, Dnmt3a, and Dnmt3b) identified in mammals. Evidence from phenotypic analyses of mice with mutant DNMT genes have provided useful mechanistic insights into the role and establishment of DNA methylation patterns during development [4, 8]. Dnmt1 enzyme has been demonstrated to have a 5–30-fold more preference for hemimethylated substrates and therefore popularly designated as maintenance methyltransferase. It preserves the existing

methylation patterns in the daughter DNA strands by adding methyl groups to hemimethylated CpG sequences following replication. However Dnmt1 has also been demonstrated to be involved in de novo methylation activity in embryo lysates and its sequence specificity was shown to be confined to 5′-CpG-3′ dinucleotide sequence with little dependence on sequence context or density [9]. Dnmt3a and Dnmt3b enzymes are essential for global de novo methylation as they preferentially target unmethylated CpG sequences [10]. They have been shown to be highly expressed in developing mouse embryos and establish methylation patterns postimplantation [10]. Although Dnmt3L, the fourth family member, lacks intrinsic DNMT activity by itself, it colocalizes with Dnmt3a and Dnmt3b to establish genomic imprints in maternal germ line [11] and facilitate methylation of retroposons. Dnmt2, another member of DNMT family, was found to lack biochemical detectable DNMT activity and its deletion in mice had no obvious phenotypic effects on genomic methylation pattern or methylation of retroviral DNA [10].

Hypermethylation of CpG islands is usually associated with gene silencing. There are multiple routes through which DNA methylation can suppress transcription. A general mechanism is to exclude binding of proteins that modulate transcription through their DNA binding domains [12]. For example, binding of chromatin boundary element binding protein CTCF to DNA is blocked by CpG methylation, which allows the enhancer to activate transcription [13, 14]. This mechanism has been demonstrated to be essential for imprinting of *Igf2* gene [15]. Beside this, CpG methylation has been shown to block the binding of several other transcription factors; however, their biological consequences remain unknown [16]. Another mechanism for DNA methylation mediated gene repression involves binding of specialized DNA binding proteins to the methylated CpG stretches, which form repressor complexes with histone deacetylases (HDACs) and cause chromatin compaction [17–19]. In mammals six methyl-CpG-binding proteins have been characterized to date, which include MeCp2, MBD1-4, and Kaiso. Studies demonstrate that all (except mammalian MBD3) possess a domain that specifically targets them to methylated CpG regions in vitro and in vivo [20, 21].

Histone Modifications

In addition to DNA methylation, posttranslational modification of N-terminal histone tails play a significant role in epigenetic regulation of gene expression [22, 23]. A typical nucleosome unit consists of ~146 bp of DNA wrapped around an octamer of histones (H2A, H2B, H3, and H4) representing the fundamental building unit of eukaryotic chromatin. A diverse array of covalent chemical modification of less structured, protruding N-terminal tails of core histones by methylation, acetylation, ubiquitination, phosphorylation, sumoylation, and ADP-ribosylation dictate the dynamics of chromatin state [24]. Euchromatin is lightly packed form of chromatin where DNA is accessible for transcription, whereas heterochromatin represents

tightly packed chromatin state inaccessible to cellular transcriptional machinery. Most of the chemical modifications occur at Lysine (K), Arginine (R), and Serine (S) residues within the histone tails. These distinct histone modifications on one or more histone tails (often referred to as 'Histone code') which may act sequentially or in combination are recognized by other proteins that signal further downstream events. A number of enzymes have been implicated in catalyzing (addition or removal) various histone modifications. Examples include histone acetyltransferases (HATs), histone deacetylases (HDACs), histone methyltransferases (HMTs), histone demethylases (HDMs), histone kinases, etc. In brief, HATs catalyze the addition of acetyl group on the ε-amino group of lysine residues in the N-terminal tail of histones, which neutralize the positive charge, relax the chromatin and facilitate the binding of transcriptional machinery to the DNA [25]. Till date 25 HATs have been characterized which are divided into four families. Examples include GNAT (*hGCN5*, *PCAF*), MYST (*MYST*, *Tip60*), p300/CBP (*p300/CBP*, SRC (*SRC-1*), and TAFII250 families (TAFII250) [3, 6, 26]. In contrast, HDACs catalyze the removal of acetyl groups from lysine residues resulting in the compaction of chromatin configuration which repress transcription [27]. HDACs are classified into four groups. HDAC-1, -2, -3, and -8 are members of Class I HDAC family while HDAC-4, -5, -6, -7, -9, and -10 belong to class II HDAC family. HDAC-11 belongs to Class IV HDAC group. Sirtuins, which require NAD⁺ as cofactor for their activity, are structurally unrelated to other HDAC classes, constitute Class III HDAC family [28, 29]. HMTs catalyze the addition of methyl groups to lysine or arginine residues while HDMs act to remove them [30–32]. Examples of histone lysine methyltransferase include EZH2 (Enhancer of zeste homolog 2) and that of histone lysine demethylase include LSD1 (Lysine specific demethylase 1) [33, 34]. Depending on the site of lysine methylation (K4, K9, K27, etc. in Histone H3) and methylation status (mono, di, or tri methylation), histone methylation may have activating or repressive effect on gene expression [26, 34]. H3K4, H3K36, and H3K79 methylation have activating effects on gene transcription, whereas methylation of H3K9, H3K27, and H4K20 is generally associated with gene silencing or transcriptional repression [26, 32, 35]. A plethora of literature is available on each group of histone modifying enzymes, their mechanism of action and various histone modifications, which is beyond the scope of this chapter.

Noncoding RNAs

Recent evidence indicates that noncoding RNA (ncRNA) transcripts play a fundamental role in epigenetic regulation of gene expression and have been implicated in various epigenetic mechanisms such as transposon silencing, X-chromosome inactivation, DNA imprinting, and paramutation [36–38]. In humans, ncRNAs include microRNA (miRNA), small interfering RNA (siRNA), and piwi-interacting RNA (piRNA) which account for majority of transcripts, representing

approximately 98 % of all human transcriptional output [39, 40]. Based on the size, ncRNA can be classified into small ncRNA which are generally less than 200 nucleotides in length and long ncRNA (lncRNA) transcripts that are more than 200 nucleotides in length. They can be divided into further subtypes based on their genomic origin and biogenic processes [37]. Both types of ncRNAs have been shown to be essential '*epigenetic modifiers*' constituting a hidden layer of complex internal signals controlling multiple levels of gene expression associated with development and physiology of an organism [38, 41–43]. lncRNAs have been demonstrated to be involved in gene silencing via mechanisms involving both histone modifications and DNA methylation. For example, the antisense lncRNA located in the *p14/p15/INK4* locus, *ANRIL*, was reported to cause gene silencing via recruitment of polycomb proteins (PcG) [44, 45]. Another well studied example includes the involvement of a 17 kb lncRNA, *XIST*, in X-chromosome inactivation which ensures X-linked gene dosage compensation in mammalian females [46–49]. This process involves the recruitment of mammalian PRC2 complex containing the histone methyltransferase EZH2 to the locus by a short repeat RNA (RepA) within XIST and deposition and spreading of repressive H3K27me3 marks throughout the X-chromosome. In addition to histone modifications, lncRNAs were also reported to mediate gene silencing through DNA methylation. One such example includes *Kcnq1ot1*, which in addition to interacting with PRC2 complex and G9a, has been implicated in the recruitment of Dnmt1 through a critical 890 bp region to the CpG island of the imprinted genes [50].

Small ncRNAs particularly miRNAs regulate key epigenetic mechanisms. Short RNAs (50–200 nucleotides) were reported to be transcribed from H3K27me3-enriched PRC2 target genes and cause cell-type specific gene silencing in *cis* by stabilizing the PRC2 complex near the transcription site through interactions via formation of stem-loop structures [51]. MiRNAs are known to regulate various components of cellular epigenetic machinery particularly polycomb complexes and thus affect multiple downstream effects [33, 52–54]. One such example include miR-214 which downregulates Ezh2 expression by targeting its 3′-UTR region and accelerates skeletal muscle differentiation and transcription of developmental regulators in embryonic stem cells [55]. There are other miRNAs which have been implicated in the repression of Bmi1, a component of PRC1 complex [56–58]. DNA methylation has also shown to be modulated by miRNAs. Dnmt1 and 3 have been reported to be targeted by the miR-29 family in lung cancer and leukemia cells [59, 60]. In addition to the role of small ncRNAs as regulators of various epigenetic mechanisms, in many instances they are themselves targets of the same epigenetic processes which may lead to further downstream alterations. For example, in human breast tumorigenesis and metastasis decreased expression of a set of miRNAs was attributed to gene hypermethylation [61–63]. In summary, recent evidences suggest that ncRNAs have emerged has key regulators of epigenetic mechanisms and also, that the modulation of these RNA transcripts by the same epigenetic processes may lead to major consequences.

Factors Affecting the Epigenome

Effect of Environmental Factors on the Epigenome

Environmental factors including chemical carcinogens, environmental pollutants, dietary contaminants, and physical carcinogens play important role in the etiology of human cancer. In general, the degree to which environmental factors influence carcinogenesis depends on the presence of specific hazardous entity and duration of exposure. However, the degree to which hazardous exposures affect cancer largely reflects variation in susceptibility to a given environmental exposure. Generally environmental factors that are capable of initiating tumor development by altering the epigenome include agents which are capable of inducing changes either directly or indirectly in the genomic DNA, and agents that affect critical cellular regulatory processes of gene transcription such as DNA damage and repair, cell cycle control, and cell death process.

Studies demonstrate that the mismatch repair gene *MHL1* is frequently hypermethylated in sporadic tumors exhibiting microsatellite instability [64]. Similarly, silencing of *MGMT*, the DNA repair gene encoding the protein responsible for the removal of carcinogen-induced O^6-methylguanine adducts from DNA (which if left unrepaired results in G to A transition mutation), appears to increase the mutation rate in critical cellular regulators, including tumor suppressors and oncogenes [65]. These studies provide cues that environmental exposures alter either the expression or the activity of enzymes involved in de novo DNA methylation (Dnmt3A and Dnmt3B) and/or the maintenance of DNA methylation (Dnmt1) may predispose to mutational events [64, 65]. Additionally, different agents in the environment may also induce mutational events through preferential binding to hypermethylated DNA. Studies on benzo(a)pyrene diol epoxide (BPDE), a carcinogen from tobacco smoke that exhibits preference for methylated CpG sites, resulting in formation of DNA adducts and G to T transfersions, often found in cancers of the aero-digestive tract in tobacco smokers. It has been shown that certain infectious agents such as human papillomavirus (HPV) induce gene silencing via DNA hypermethylation of the promoters of host genes including *CDH1*, *RB1*, *INK4a/p16*, *CDNK2A*, *MTHFR*, *PEG3,* and others listed in Table 4.1.

The agents in the second group may alter the pattern of chromatin modifications (histone code) in a transient manner and are likely to induce changes in key cellular processes including gene transcription, DNA damage response, and DNA repair. Primary epigenetic targets for environmental factors in this group may be the proteins and protein complexes responsible for histone modifications such as HATs and HDACs, whose activities are often found deregulated in cancer. Recent studies showed that HATs are involved in the process of DNA repair, suggesting that even moderate and transient inhibition of HAT activity induced by environmental exposures may compromise DNA repair, leading to mutation fixation and genomic instability [110]. Similarly, HDAC was shown to be required for efficient DNA repair, suggesting that the removal of histone acetylation is required for restoration of

Table 4.1 Targeted genes and epigenetic mechanisms affected by environmental, dietary, and lifestyle factors

Targeted genes	Epigenetic mechanisms	Agents/exposure	References
Environmental factors			
CDKN2A, MGMT	Binding of PAHs to methylated CpGs	Tobacco smoke	[66–69]
CDKN2A, CDKN2B (p15 gene), MLH1	Inhibition of histone acetylation; damage of core histone	Nickel	[70–73]
RASSF1A, MGMT CDKN2A, SNSG	Preferential binding to methylated lysine or modified histone proteins causing DNA damage	AFB1	[74–76]
DNMTs	Inhibition of DNMTs (acute exposure), increased DNMT activity (chronic exposure)	Cadmium	[77]
c-myc	Decrease of SAM leading to global hypomethylation and activation of oncogenes	Arsenic	[71, 78, 79]
p16/INK4A	DNA methylation-mediated silencing of key cellular regulators	Ionizing radiation	[69]
Genes not identified	Global hypomethylation	UV radiation	[80, 81]
Genes not identified	De novo methylation associated with chronic inflammation and cell proliferation	Bacteria (H. pylori)	[82–84]
Genes not identified	Methylation of viral genome; binding of viral proteins to host gene promoters; hypermethylation of host gene promoter; changes in chromatin modification; patterns and recruitment of HDACs	HPV, EBV, HBV HPV, EB	[85–94]
Dietary and lifestyle factors			
APC-1A, CDKN2D (p14 gene)	Alcohol metabolites such as acetaldehyde acts as co-carcinogens with HBV and HCV viruses depleting SAM, aflatoxin, and obesity	Alcohol	[95–98]
CDKN2A, hMLH1, MGMT, RASSF1A, SFRP	Disruption of heterochromatic silencing; inhibition of SIRT1	Dihydrocoumarin	[99, 100]
Genes not identified	Posttranslational modification of histone and DNA methylation	Folate deficiency	[101]
Genes not identified	Modifications in DNA methylation and histone modifications; increased binding of methyl-CpG-binding proteins	Low methionine-intake	[96, 101, 102]
Genes not identified	Re-activation of inactive X-chromosome and silent alleles LOI	Unknown	[103–106]
IGF2, transposable elements	Histone-based germ line inheritance	Transgenerational epigenetic inheritance	[107–109]

normal (default) chromatin structure following the completion of DNA repair. A tight regulation of HAT and HDAC activity is thus essential for proper regulation of gene transcription and DNA repair. Reduced levels of histone acetylation or enhanced histone deacetylation may result in the compaction of chromatin, blocking access of transcription factors to DNA and/or impeded progression of RNA polymerase. Therefore, different environmental factors may transiently alter chromatin-modifying/remodeling activities and alter patterns of histone modifications impeding DNA repair and other chromatin-based processes.

Another possible epigenetic 'target' of adverse environmental exposure may be general methyl-C-binding proteins, a group of proteins (including MBD1, MBD2, MBD3, MeCP2, and KAISO) that bind to methylated CpG sites [111]. Some members of this family, exemplified by MeCP2, were found to bind and recruit HDAC to chromatin. Changes in MeCP2 protein stability and function elicited by the hazardous agents in diet and environment may thus affect normal gene transcription, leading to aberrant cell proliferation and cancer [112]. Given that histone modifications and DNA methylation appear to work together to establish a permissive or repressive chromatin state, agents in the environment and diet that affect one of these intimately linked and self-reinforcing mechanisms would inevitably affect the other. Although poorly understood, the molecular mechanisms by which epigenetic carcinogens in environment and diet may exhibit adverse effects on histone modifications are beginning to emerge. Several recent studies have examined the effect of specific environmental carcinogens on histone modifications and suggest that these agents may affect the pattern of histone modifications through different mechanisms (Table 4.1).

Another prospective mechanism by which environmental exposure including ingestion affect the epigenome involve transposable elements. Transposons when activated may cause genetic mutations and transcriptional noise [112]. For example, the Alu family alone consists of several hundred thousand elements and is shown to be heavily methylated and transcriptionally silent in somatic cells. It is well documented that the activation of transposable element-derived promoters may be a consequence of perturbed DNA methylation, transposable elements were shown to be activated by various kinds of cellular stress. Therefore, stress induced by environmental agents may activate transposable elements, leading to altered establishment and maintenance of epigenetic states.

Epigenetic Modifications by Nutritional Factors

Studies have demonstrated that maternal nutrition imbalance and metabolic disturbances during embryonic development have a persistent effect on the health of the offspring and may be passed down to the next generation [113]. The potential effect of nutritional factors on phenotype has best demonstrated by studies on the risk of cancer for pregnant women and fetuses. When mother is exposed to adverse conditions, the fetal nutrition may cause alterations in structure, physiology, and metabolism that predispose individuals to several diseases including cancer.

Selected dietary components consumed during early pregnancy may influence post-natal risk of cancer development, although all dietary components are not harmful. In those cases where adverse effects on fetal development were observed, a proposed mechanism includes methylation of genes due to dietary food components in the mother's diet. Both hypermethylation and hypomethylation of selected genes were observed. Genes that were overexpressed included *Klf6*, *Klf9*, *Nid2*, *Ntn4*, *Per1*, and *Txnip*, and genes that were repressed included *Bcar3*, *Cldn12*, *Csf1*, *Jag1*, *Lgals3*, *Lypd3*, *Nme1*, *Ptges2*, *Ptgs1*, and *Smarcb1* [113, 114]. In animal models, deficiencies of macronutrients during placental growth have been shown to affect fetal growth. Most of the genes that contribute to reduced fetal growth are regulated by imprinting, and the maternal allele is affected in these cases. Functionally, the nutrient transport from mother to fetus via the placenta is affected dramatically by the hypomethylation of genes in the embryonic trophectoderm [115].

Direct effects of nutritional factors on epigenetic changes are most studied and among the best understood is the relationship between dietary methionine and DNA methylation [115]. Methionine, an essential amino acid, plays a central role in the epigenetic regulation by serving as methyl donor for methylation reactions. In the process of cytosine methylation, DNMT enzyme converts SAM to *S*-adenosylhomocysteine (SAH); therefore, an optimal supply of SAM or removal of SAH is essential for the normal establishment of genome-wide DNA methylation patterns [116]. CpG methylation patterns are largely erased in the early embryos and then re-established in a tissue-specific manner. Therefore, early embryonic development may represent a sensitive stage, and dietary and environmental factors that affect DNA methylation reaction and the activity of DNMTs may result in permanent fixation of aberrant methylation patterns [110, 116]. In postnatal development and adulthood, established patterns of DNA methylation and histone modifications must be maintained through multiple mitotic divisions; therefore, inappropriate quantities of methionine, other food components, and environmental agents may affect normal patterns of DNA methylation and histone modifications. In this respect, it is interesting to note that in adult men with hyperhomocysteinemia, a disorder occurring in several genetically determined and acquired diseases with uremia, treatment with high doses of folate increases methylation levels at specific genes and restores normal expression [110]. In addition to methylation of DNA, methylation of histones, a distinct epigenetic mechanism dependent on 1-carbon groups, may be affected by consuming excessive levels of specific nutritional factors. Therefore, nutrition factors are likely to directly or indirectly (through changes in DNA methylation) affect histone modifications such as histone methylation.

Lifestyle Factors Affecting the Epigenome

Lifestyle factors including exercise and diet plays an important role in regulating the epigenome and altering gene expression. Exercise can modify the epigenome in order to preserve and prolong life. Exercise has been shown to induce positive changes in DNA methylation within adipose tissue and regulate metabolism in both

healthy and diseased individuals [117]. Increased DNA methylation of genes *Hdac4* and *Ncor2* has also shown to increase lipogenesis following exercise [117]. Exercise also leads to beneficial changes in DNA methylation patterns in skeletal muscle [118]. Not only is obesity an indicator for diseases such as type 2 diabetes and cardiovascular disease, but also puts additional stress on the system which can itself negatively impact health [119]. Acute exercise is associated with DNA hypomethylation of the entire genome in skeletal muscle cells of sedentary individuals and high intensity exercise tends to cause reduction in promoter methylation of certain genes [120]. Exercise is also known to positively influence the expression patterns of miRNAs in leukocyte cells [121]. The health benefits of physical exercise, especially on a long-term and strenuous basis, have a positive effect on epigenetic mechanisms and ultimately may reduce incidence and severity of cancer [122].

Studies in genomic imprinting have revealed how DNA methylation patterns are influenced by diet, and how epigenomic sensitivity to specific diet influences cancer susceptibility. Dietary fat comprises a large part of the Westernized diet, which results in increased adipose tissue via adipocyte hypertrophy and hyperplasia [123]. Dietary fat influences adipokine release through their influence on the epigenome affecting DNA methylation and posttranslation modification of the histone proteins. This represents one of the methods by which dietary fat may influence cancer progression. Overconsumption of well-done meats or saturated fats causes increase in somatic *GSTP1* inactivation by CpG island methylation in the promoter region increasing susceptibility to prostate cancer [124].

Several studies have provided evidence that alcohol consumption is associated with different epigenetic changes in human cancer [125]. In a large epidemiological study (the Netherlands Cohort Study on diet and cancer), analysis of DNA methylation showed that the prevalence of promoter hypermethylation of several genes including *APC-1A*, *CDKN2D*, *CDKN2A*, *hMLH1*, *MGMT,* and *RASSF1A* was higher in colorectal cancer patients with high alcohol (and low folate) intake than among colorectal cancer patients with high folate/low alcohol intake. In addition, the study of human head and neck squamous cell carcinoma showed that the promoter hypermethylation of *MGMT* gene and the genes known to regulate the WNT pathway occurs more frequently in both heavy and light drinkers compared to nondrinkers. The mechanism underlying the epigenetic changes caused by alcohol abuse may also involve SAM. This small metabolite is regenerated from demethylated SAM via the methionine cycle, which involves folate. Therefore, imbalance of this cycle through alcohol consumption may result in depletion of SAM and aberrant epigenetic patterns. In addition, it was shown that the human class I alcohol dehydrogenase (ADH) genes may be regulated by epigenetic mechanism. The class I ADH genes were found to be repressed in human hepatoma through epigenetic modification suggests that changes associated with alcohol-metabolizing genes may also enhance other toxic effects of alcohol on different organs, most notably the liver, including hepatic tumorigenesis [110].

Tobacco smoke is a complex aerosol that contains polycyclic aromatic hydrocarbons (PAHs), mostly benzo[a]pyrene, which is considered the most carcinogenic. Epigenetic targets of the PAHs from tobacco smoke induce DNA damage through

preferential binding to methylated CpG sites, a phenomenon already demonstrated for BPDE, a carcinogen found in tobacco smoke. Several studies have demonstrated hypermethylation and silencing of several genes in lung cancer associated with smoking [126]. The genes frequently altered by promoter hypermethylation in lung cancers of smokers are *p53*, *p16* and *MGMT*. In addition, different components in tobacco smoke induce histone changes and alter histone code. Some potentially novel histone marks, including acetylation, monomethylation, and dimethylation, in specific lysine and arginine residues of histones H3 and H4 in mouse lungs.

Nutrients extracted from the diet enter metabolic pathways and are transformed into useful molecules. These nutrients are known to have epigenetic targets in cells such that they can be used to modify the epigenome in order to correct abnormally activated or silenced genes and can be combined into an "epigenetic diet" useful as a therapeutic and/or chemopreventive measure. During this transitory phase methyl groups are formed from key nutrients including folic acid, B vitamins and s-adenosyl methionine (SAMe), and these methyl groups comprise important epigenetic marks for gene silencing. Diets high in such methyl rich nutrients may significantly alter gene expression and offer protective health benefits [123]. Deficiencies in folate and methionine, both of which are involved in cellular processes that supply methyl groups needed for DNA methylation, can change the expression (imprinting) of growth factor genes such as (IGF1) influencing cancer progression [127]. In addition, several natural nutrients products have interesting biological properties and structural diversity. These include polyphenols present in fruits, vegetables, and other dietary botanicals. Phenolic acids, flavonoids, stilbenes, and lignans are the most abundantly occurring polyphenols that are also an integral part of everyday nutrition in populations worldwide. Certain food components epigenetically increase the levels of DNA repair enzymes such as MGMT and MLH1, others such as blueberry anthocyanins actively decrease DNA damage. Anthocyanin is an effective antioxidant for humans that is found in plants and are easily identified by its potent red or purple pigment. It is found in plants such as eggplant, plums, pomegranate, red onion, cranberries, blueberries, kidney beans, and cherries which all possess anthocyanins. This flavonoid serves as a powerful antioxidant that contributes to scavenging of DNA-damaging free radicals. While the direct fate of anthocyanins in vivo following digestion may be less than 5 % (the majority being rapidly excreted), the potent residual antioxidant property remains in blood following consumption of anthocyanin-rich foods due to metabolic breakdown of the flavonoids and resultant increase in uric acid levels. Some of the common examples of the most studied and promising cancer preventive polyphenols include EGCG (from green tea), curcumin (from curry plant), genistein (from soy), resveratrol (from grapes and berries), and sulforaphane (from broccoli). A large number of dietary agents on DNA methylation, histone modifications, and regulation of expression of noncoding miRNAs in various human cancers are shown in Tables 4.2 and 4.3. Significant gains have been made in understanding the molecular mechanisms underpinning the chemopreventive effects of polyphenols, and consequently, a wide range of mechanisms and gene targets have been identified for individual compounds.

Table 4.2 Effects of dietary agents on epigenetic modifications

Source	Dietary agents	Molecular mechanisms	Molecular targets	Cancer type	References
Soy	Equol	HDAC inhibitor	H2A/H2B/H3/H4	Breast	[128]
			Acetylation		
	Genistein	HAT inhibitor	H2A/H2B/H3/H4	Esophageal; prostate; breast; renal	[128–136]
		HADC inhibitor	Acetylation		
			p21, p16, PTEN,p53		
			FOXA3, SIRT1, hTERT		
	Daidzein	HDAC inhibitor	Histone acetylation	Esophageal; prostate	[128, 129, 136]
	Biochanin A	DNMT inhibitor		Esophageal	[129, 136, 137]
	Daidzein	DNMT inhibitor	RARβ,MGMT,CDKN2A,GS TP1,HMGNS,BTG3	Breast	[129, 136, 137]
	Genistein	DNMT inhibitor	RXRα,CDX2,GSTP1, W1F1	Prostate	[129, 131, 132, 136, 137]
				Esophageal	
Poison ivy	Fisetin	Unknown		Cervix; breast	[138, 139]
		DNMT inhibitor		Breast, esophageal	[137, 140]
Garlic	Allyl mercaptan	SIRT1 inhibitor	H3/H4 acetylation p21/ WAF1	Erythroleukemia liver, colon	[141–144]
	S-allylmercapto cysteine	HAT inhibitor	H3/H4 acetylation	Erythroleukemia	[144–146]
Cashew nuts	Anacardic acid	HDAC inhibitor	H3K9 and H3K14 deacetylation	Leukemia; cervix breast; prostate	[147–152]

(continued)

Table 4.2 (continued)

Source	Dietary agents	Molecular mechanisms	Molecular targets	Cancer type	References
Turmeric	Curcumin	HAT and HDAC inhibitor	Histone acetylation	Cervix; HIV; hepatoma; leukemia; prostate brain, lymphoma	[153–164].
		DNMT inhibitor	GATA4, EOMES,GZMB	Leukemia, esophageal	[137, 165, 166]
Green tea	Catechin	HAT and DNMT Inhibitor	H3/H4 acetylation	Lymphocytes, breast	[140, 167]
	Epicatechin	HAT and DNMT inhibitor		Lymphocytes, esophageal	[140, 167, 168]
	Epicatechin gallate	HAT and DNMT inhibitor		Colon, prostate, esophageal	[167–169]
	Epigalocatechin-3-gallate	HAT inhibitor	H3K27 trimethylation	Colon, prostate	[137, 167–173]
		HMT inhibitor	EZH2,SUZI2	Prostate cancer	
		DNMT inhibitor	RARβ, MGMT,MLH1 CDKN2A, RECK,TERT RXRα,CDX2,GSTP1, W1F1		
Green and black tea	Polyphenon B	Increase HDAC1 expression		Liver cancer	[174]
Broccoli	Isothiocyanates	HDAC inhibitor	H3/H4 acetylation	Prostate, leukemia, erythroleukemia	[142, 175–179]
	Sulforaphane	HDAC inhibitor	p21,GSTP1	Colon, Esophageal	[175, 180]
		Decreases DNMT expression	H3/H4 acetylation RARβ, HBD-2, p21, Bax	Prostate, breast, colon, kidney, colon, esophageal	[129, 136, 169, 181–183]

			TNFα, IL-8,RBP		
Parsley and celery	Luteolin	SIRTI activator and DNMT inhibitor		Cervix, esophageal	[137, 138]
	Apigenin	DNMT inhibitor		Esophageal	[137]
Grapes, wine and eucalyptus	Resveratrol	SIRTI activator and DNMT inhibitor		Colon, lungs, breast	[182, 184–186]
Indian trumpet	Baicalein	DNMT inhibitor		Breast cancer	[182]
Beat root	Beatnik	DNMT inhibitor		Breast cancer	[182]
Tomatoes	Lycopene	Unknown		Breast	[187]
Citrus	Hesperidin	DNMT inhibitor		Esophageal	[137]
	Quercetin	DNMT inhibitor		Breast; colon; esophageal	[137, 140, 182, 186, 188]

Table 4.3 Dietary agents and changes in mRNA

Source	Dietary agent	Cancer type	miRNA	Reference
Green Tea	EGCG	Neuroblastoma	miR-92, miR-93,miR 106b, miR-34a, miR-99a	[189]
		Hepatocellular carcinoma	miR-467b, miR-487b, miR-197, miR-805, miR-374, let-7f, miR-350, miR-24-1, miR-137, miR-335-3p, let-7a, miR-222, miR-26b, miR-30c-1, let-7d, miR-98, miR-30c, miR-30b, miR-32, miR-674, miR-532-5p, let-7 g,miR-18a, miR-192, miR-302d, miR-30b, miR-802, let-7e, miR-322, miR-720, miR-146b, miR-340-3p, miR-185, miR-425, miR-10a, miR-126-5p, miR-101a, miR-30e, let-7c, miR-141, miR-33, miR-29a,miR-199b,miR-450a-5p,miR-21,miR-23a,miR-101b,miR-148a, miR-193, miR-23b, miR-107, miR-140, miR-551b, miR-466c-5p, miR-106a, miR-590-3p, miR-875-3p, miR-224, miR-292-5p, miR-678, miR-469, let-7b, miR-463, miR-574-3p, miR-201, miR-290-3p, miR-181a, miR-302a, miR-429, miR-133a, miR-190b, miR-710, miR-135b, miR-296-5p, miR-191, miR-188-5p, miR-298, miR-181a-1,miR-466 g, miR-26b,miR-466f-3p,miR-29b, miR-1224,miR-291b-5p, miR-324-5p, miR-486, miR-128, miR-450b-3p, miR-135a, miR-294, miR-671-5p, miR-878-3p, miR-801, miR-370, miR-1, miR-494, miR-133b	[190]
		Lung carcinoma	let-7c, miR-210	[190]
		Pancreatic cancer	let-7c	[190]
		Colon cancer	miR-27a, miR-20A, miR-17-5P, miR-21	[191]
		Bladder cancer	miR-203	[192]
Turmeric	Curcumin	Lung cancer	miR-320, miR-26a, let-7i, miR-130a, mir-16, miR-125b,miR-23a, miR-27b, miR-155, miR-625, miR-576-3p, miR-186, miR-9	[193]
		Leukemia cells	miR-15a, miR-16-1	[194]
		Pancreatic cancer cells	miR-103, miR-140, miR-146b, miR-148, miR-15b, miR-181a, miR-181b, miR-181d, miR-195, miR-196a, miR-199a, miR-19a, miR-204, miR-20a, miR-21, miR-22 miR-23a,b, miR-24, miR-25, miR-26a, miR-27a, miR-34a, miR-374, miR-510, miR-7, miR-92, miR-93, miR-98	[195]
		Prostate cancer cells	miR-151a, miR-151-5p, miR-221, miR222	[196]

Source	Compound	Cancer cell type	miRNAs	
Soy	Genistein	Ovarian cancer cells	miR-100, miR-122a, miR-125b, miR-126, miR-135, miR-135b, miR-136, miR-137, miR-141, miR-152, miR-190, miR-196a, miR-196b, miR-204, miR-205, miR-206, miR-217, miR-22, miR-296, miR-30a-3p, miR-30a-5p, miR-331, miR-335, miR-342, miR-362, miR-449b, miR-454, miR-497, miR-500, miR-501, miR-503, miR-515, miR-517c, miR-532, miR-565, miR-578, miR-584, miR-585, miR-590, miR-595, miR-625, miR-647, miR-7, miR-765, miR-766	[197, 198]
		Pancreatic cancer cells	miR-200	[130, 135]
		Prostate cancer cells from lymph node	miR-106b, miR-1224-5p, miR-1228, miR-1231, miR-1246, miR-1260, miR-1267, miR-1268, miR-129, miR-1290, miR-1308, miR-1469, miR-149, miR-150, miR-152, miR-15a, miR-17, miR-1825, miR-185, miR-18b, miR-1908, miR-1915, miR-197, miR-1972, miR-1973, miR-1974, miR-1975, miR-1977, miR-20a, miR-20b, miR-24, miR-296-5p, miR-483-5p, miR-513a-5p, miR-548q, miR-572, miR-575, miR-612, miR-638, miR-654-5p, miR-659, miR-671-5p, miR-7, miR-762, miR-764, miR-874, miR-92b, miR-939	[199]
Grapes, wine and eucalyptus	Resveratrol	Prostate cancer cells	miR-101, miR-106a, miR-106b, miR-1274b, miR-136, miR-141, miR-145, miR-17, miR-182, miR-1826, miR-200b, miR-200c, miR-20a, miR-20b, miR-21, miR-214, miR-221, miR-222, miR-302c, miR-375, miR-378, miR-720, miR-768-3, miR-93	[200]
		Colorectal cancer cells	miR-1, miR-100-1/2, miR-102, miR-103-1, miR-103-2, miR-146a, miR-146b-5p, miR-16-0, miR-17, miR-181a2, miR-194-2, miR-196a1, miR-205, miR-206, miR-21, miR-23a,miR-23b, miR-25, miR-26a, miR-29c, miR-30a-3p, miR-30c-1,miR-30d, miR-30e-5p, miR-323, miR-340, miR-363-5p, miR-424, miR-494, miR-497, miR-560, miR-565, miR-572, miR-574, miR-594, miR-615, miR-622, miR-629, miR-631, miR-638, miR-639, miR-657, miR-659, miR-663, miR-801, miR-92a-2	[201]
Parsley and celery	Apigenin	Lung cancer cells	miR138, miR-125a-5p	[202]
		Neuroblastoma cells	miR-138	[203]
	Luteolin	Prostate cancer cells	miR-630	[203]
		Gastric cancer cells	miR-34a	[203]
Berries	Ellagitannins	Hepatocellular carcinoma	miR-let-7e, miR-370, let-7a, let-7c, let-7d, let-7a, let-7c, let-7d	[204]

Several studies have demonstrated that green tea polyphenol (GTP) constituent, EGCG is a potent demethylating agent which inhibits enzymes involved in DNA methylation as well as an effective histone modifying agent [33, 173, 205, 206]. It is well known that CpG island hypermethylation at the promoter region leads to epigenetic repression of several critical tumor suppressor genes during tumorigenesis. A study suggests that EGCG acts as a competitive inhibitor of DNMT (Ki = 6.89 μM), which binds to the catalytic pocket and inhibit DNMT activity in a dose-dependent manner [168]. Furthermore, EGCG treatment (5–50 μM for 12–144 h) was found to effectively reactivate methylation-silenced genes—$p16^{INK4a}$, retinoic acid receptor beta *RARbeta*, *O*(6)-methylguanine methyltransferase *MGMT*, and human mutL homolog 1, *hMLH1* in human esophageal cancer KYSE 510 cells. EGCG was also reported to inhibit HDACs and increase permissive or active histone modifications such as histone acetylation at the target gene promoters. Studies from our laboratory showed that exposure of prostate cancer cells to GTP caused re-expression of epigenetically silenced glutathione S-transferase pi, *GSTP1* gene which correlated with the promoter demethylation due to DNMT1 inhibition and histone modifications at the promoter region [173]. However, GTP treatment did not show any global hypomethylation effect which could result in genomic instability as the methylation status of LINE-1 promoter remained unaffected as demonstrated by methylation-specific PCR. GTP treatment decreased mRNA and protein levels of MBD1, MBD4, MeCP2, and HDAC 1-3, whereas acetylated histone H3 (LysH9/18) and H4 were found to be elevated. In another study, we demonstrated that GTP treatment caused cell cycle arrest and apoptosis by inducing proteasomal degradation of class I HDACs in human prostate cancer cells [207]. Studies by Li et al. [206] demonstrated that EGCG in combination with trichostatin A (TSA) could synergistically reactivate ERα expression in ERα negative MDA-MB-231 breast cancer cells by modulating histone methylation and acetylation patter at the gene promoter. In addition, they also reported that treatment with EGCG and/or TSA contributes to transcriptional activation of estrogen receptor (ER)-α by causing a decreased binding of transcription repressor complex, Rb/p130-E2F4/5-HDAC1-SUV39H1-DNMT1 to the regulatory region of the gene.

EGCG has been reported to modulate polycomb proteins such as Bmi-1 and EZH2 [33, 172, 208]. EGCG alone or in combination with DZNep was shown to decrease PcG proteins including EZH2, EED, SUZ12, MEL18, and BMI-1 via a mechanism involving proteasome-associated degradation. The reduction in PcG protein levels correlated with a decrease in repressive chromatin marks—H3K27me3 and H2AK119ub and HDAC-1 levels, whereas accumulation of acetylated H3 levels was found to be elevated. In a recent study, we reported that in breast cancer cells, EGCG or GTP treatment induced expression of epigenetically repressed *TIMP-3* gene is mediated by modulating epigenetic mechanisms involving EZH2 and class I HDACs independent of the promoter DNA methylation [33]. After EGCG or GTP treatment, the protein levels of class I HDACs and EZH2 were significantly reduced. Interestingly, transcriptional activation of TIMP-3 was associated with decreased EZH2 localization and H3K27me3 at the promoter with a concomitant elevation in H3K9/18 acetylation levels.

Numerous epidemiological and experimental studies have demonstrated the chemopreventive effects of genistein and other isoflavones on various cancer types [209]. The role of genistein and other soy isoflavones as epigenetic modulators regulating gene expression has been widely reported by several studies. Genistein has been shown to be more potent DNMT inhibitor as compared to biochanin A or daidzein. A study reported that genistein (2–20 μM/L) could reactivate methylation-silenced genes such as *RARbeta*, *p16INK4a*, and *MGMT* in esophageal squamous carcinoma cells KYSE 510 and prostate cancer LNCaP and PC3 cells [129, 136]. Another study demonstrated that genistein treatment in breast MCF10AT benign cells and MCF-7 cancer cells depletes telomerase (hTERT) activity through epigenetic modulation which involves genistein mediated decrease in Dnmt1, Dnmt3a, and Dnmt3b levels [130, 135]. Furthermore, genistein was shown to repress hTERT promoter by chromatin remodeling which involved increase in trimethyl-H3K9 enrichment with a concomitant decrease in dimetyl-H3K4 chromatin marks. A study by King-Batoon et al. [187] showed that a low, nontoxic dose of genistein (3.125 μM, re-supplemented every 48 h for 1 week) could partially demethylate *GSTP1*, a tumor suppressor gene, in MCF-7, MDA-MB-468, and MCF10A breast cells. Similar in vitro studies in other cancer types provide evidence that genistein is a potent demethylating as well as histone modifying agent, which could reverse the silenced state of critical tumor suppressor genes [131, 132, 210, 211]. A study by Basak et al. [212] demonstrated that AR downregulation in prostate cancer cell line LNCaP by genistein was attributed to the inhibition of HDAC6-Hsp90 co-chaperone function, which is required for AR protein stabilization. Genistein and other soy isoflavones are known to modulate miRNAs as well [135, 197, 198, 213, 214]. Parker et al. [197, 198] performed miRNA profiling of genistein treated and untreated UL-3A and UL-3B cell lines and found 53 miRNAs which were differentially expressed. Upregulation of miR-200 and let-7 by isoflavones was shown to downregulate ZEB1, slug, and vimentin and therefore cause reversal of epithelial to mesenchymal transition (EMT) in gemcitabine resistant pancreatic cancer cells [135]. In human uveal melanoma cells, genistein treatment was demonstrated to cause significant growth inhibition by targeting miR-27a and its target ZBTB10 [214]. However, in vivo clinical studies were inconclusive and did not fall in line with the studies performed in cell line models.

Curcumin has been shown to modulate multiple intracellular pathways associated with proliferation, survival, invasion, apoptosis, and inflammation [215]. In the context of epigenetic pathways, several studies have reported curcumin to be a potent modulator of DNMTs, histone modifying enzymes such as HDACs and HATs as well as miRNAs [216]. In silico molecular docking studies of curcumin with Dnmt1 revealed that it can block or inhibit the catalytic thiol group of C1226 binding site in the enzyme resulting in decreased DNMT activity [216, 217]. This study was further validated by in vitro experimental studies which showed curcumin to be a potent DNA hypomethylating agent [165]. Curcumin was reported to be an effective HDAC inhibitor. Docking studies performed for curcumin binding to HDAC-8 revealed curcumin to be a more potent HDAC inhibitor than known pharmacological inhibitors such as sodium butyrate and valproic acid [164]. Another

study reported that curcumin treatment of B-NHL cell line, Raji cells could reduce HDAC-1,-3. and -8 protein levels in a dose-dependent manner and increase H4 acetylation levels [162]. In agreement with earlier findings, studies by Chen et al. [163] reported significant reduction in p300/CREB binding protein (CBP), HDAC-1, and HDAC-3 levels after exposure of Raji cells to curcumin. Studies revealed curcumin to be a specific inhibitor of p300/CBP HAT, which has emerged a novel target for cancer treatment [149, 154, 218]. Curcumin treatment caused proteasomal degradation of p300 and other closely related CBP proteins with no such effect on HATs such as GCN5 and PCAF [154]. Curcumin has also been closely linked to its ability to modulate miRNAs in cancer cells. A microarray based study of the effect of curcumin (10 μM) on the miRNA profile in pancreatic cancer cells PxBC-3 showed significant changes in the expression of 29 miRNAs (11 upregulated and 18 downregulated) after 72 h treatment [195]. Further studies confirmed that MiRNA-22, which has tumor suppressive function, was upregulated after exposure to cur-cumin and its downstream target genes SP1 and ESR1 were suppressed in these pancreatic cells. Ali et al. [219] demonstrated that treatment of pancreatic cancer cells with curcumin and its analog CDF could induce gemcitabine sensitivity via induction of miR-200 and inactivation of miR-21 expression.

Epigenetic studies on resveratrol have been previously focused on SIRT1 and acetyl transferase p300 [138, 139, 177, 220]. Resveratrol was identified as a potent dietary activator of SIRT1, which lowers the K_m (Michaelis constant) for both acety-lated substrate and NAD$^+$. It was reported to stimulate SIRT1-dependent p53 deacetylation which ultimately contributes to increased cell survival [138]. In another study by Wood et al. [139], resveratrol was shown to activate sirtuins from metazoans—*Caenorhabditis elegans* and *Drosophila melanogaster* and delay aging without any effect on fecundity. The antitumor effect of resveratrol was reported to be mediated partly by SIRT1 [221]. In addition, resveratrol was shown to have a negative effect on *Survivin* gene expression through histone deacetylation at the gene promoter and display a more profound inhibitory effect on BRCA-1 mutant cells both in vitro and in vivo [178]. In prostate cancer cells, resveratrol was reported to cause downregulation of MTA1 (metastasis associated protein) and destabilize the NuRD (Nucleosome remodeling deacetylase) complex thus allowing p53 acety-lation. Furthermore, activation of p53 was shown to induce proapoptotic pathways causing apoptosis in prostate cancer cells [222].

Sulforaphane (SFN) at physiological concentrations has been shown to down-regulate Dnmt1 gene expression in human colon Caco-2 cells [223]. Studies by Meeran et al. [224] demonstrated that in MCF-7 and MDA-MB-231 breast cancer cells, SFN treatment cause dose and time-dependent inhibition of hTERT (Human telomerase reverse transcriptase) via an epigenetic mechanism involving DNA methylation and histone modifications. SFN treatment was shown to cause down-regulation of Dnmt1 and Dnmt3a, which induced site-specific demethylation at hTERT gene first exon facilitating the binding of CTCF associated with hTERT repression. Furthermore, ChIP analysis of hTERT promoter revealed that active his-tone chromatin marks such as acetyl-H3, acetyl-H3K9, and acetyl-H4 were increased, whereas repressive chromatin marks which include trimethyl-H3K9 and trimethyl-H3K27 were reduced after SFN treatment in a dose-dependent manner.

The SFN-induced hyperacetylation was reported to promote the binding of repressor proteins such as MAD1 and CTCF to the hTERT regulatory region. In another study, Myzak et al. [183] reported that SFN metabolites—SFN–cysteine and SFN-N-acetylcysteine—were more potent HDAC inhibitors in vitro as compared to SFN or its glutathione conjugate. Furthermore, SFN treatment in HCT116 human colorectal cancer cells increased β-catenin-responsive reporter (TOPflash) activity in a dose-dependent manner and inhibited HDAC activity. Consequently, there was an induction in acetylated histone levels bound to p21 (Cip1/Waf1) promoter. In human prostate epithelial cells BPH-1, LNCaP, and PC3, SFN treatment was shown to inhibit HDAC activity, which was accompanied by an increase in acetylated histone levels by 50–100 % and a corresponding induction of p21 and Bax expression which lead to downstream events such as cell cycle arrest and apoptosis [225]. SFN treatment was shown to inhibit HDAC activity in breast cancer cells, but no change in H3 or H4 acetylation was observed [226]. Studies by Myzak et al. [225] provided first evidence for inhibition of in vivo HDAC activity and suppression of tumorigenesis in APC-min mice.

The effect of apigenin on epigenetic related enzymes and their mechanisms was not recognized until recently. Apigenin treatment has been shown to cause a marked decrease in DNMT activity in vitro [137]. Studies from our laboratory demonstrated that apigenin mediated growth arrest and apoptosis in prostate cancer cells was due to the inhibition of class I HDACs [227]. In vivo studies using PC-3 xenografts in athymic nude mice further confirmed that oral intake of apigenin (20 and 50 μg/mouse/d over an 8-week period) reduces tumor burden, HDAC activity, and HDAC -1/-3 protein levels. HDAC-1 and HDAC-3 mRNA and protein levels were found to be significantly decreased in apigenin treated (20–40 μM) PC-3 and 22Rv1 prostate cancer cell lines, which resulted in a global decline in histone H3 and H4 acetylation levels. A corresponding elevation in p21/waf1 and bax levels was observed in both in vitro and in vivo studies, which resulted in the induction of downstream events, that is, apoptosis and cell cycle arrest. In a recent study by Paredes-Gonzalez et al. [228], apigenin was shown to reactive Nrf2 gene which encodes a key transcription factor known for regulating antioxidative defense system and skin homeostasis, in mouse skin epidermal JB6 P+ cells via epigenetic mechanisms. Hypermethylation of 15 CpG sites in Nrf2 promoter was demonstrated to be reversed by apigenin treatment in a dose-dependent manner. Furthermore, apigenin treatment resulted in decreased expression of Dnmt1, Dnmt3A, Dnmt3B, and HDAC (1–8) levels. However, the nuclear localization of Nrf2 was shown to be enhanced and there was increased expression of Nrf2 as well as its target gene NQO1 after apigenin treatment.

Social-Economic and Racial Factors Affecting the Epigenome

Few studies have reported significant epigenetic differences in socio-economic/racial status that account for the differences in cancer and their outcomes [229]. Certain populations are prone to specific types of cancer such as African Americans

(AA) who have 14 % higher incidence and 34 % higher death rates than Caucasian Americans (CA) men. Although access to quality healthcare, socioeconomic status, and genetic make-up is implicated in this disparity, the fundamental causes of such cancer disparity seem to be a complex phenomenon. Many investigators are trying to address various sociocultural determinants as a major cause of cancer disparity and in understanding and underpinning mechanisms for designing better community specific interventions for different populations. For example, AA have been found to have statistically significant lower plasma concentrations of certain antioxidants such as vitamin E, alpha-carotene, beta-carotene, lutein, and zeaxanthin than CA [230]. This report indicates that low levels of antioxidants may affect the epigenome and gene expression leading to higher susceptibility and differential cancer outcomes. More research is needed to fully understand how these epigenetic modifications occur and subsequently affecting cancer outcome in diverse population.

Summary and Conclusions

From the studies described herein, it is clear that nutritional and lifestyle factors hold great promise in cancer prevention and in therapy by causing epigenetic modifications. As the importance of epigenetic modifications in cancer is well recognized, precise contribution of epigenetic mechanisms and cellular targets of epigenetic alterations by various endogenous factors in human cancer needs further investigation. Although recent advances in the field of cancer epigenetics has enhanced our understanding of epigenetic changes in normal cellular processes and abnormal events leading to tumorigenesis, however deeper understanding of the global patterns of epigenetic modifications by dietary compounds and lifestyle factors in cancer will lead to the design of better strategies to prevent and cure cancer. Moreover, sufficient preclinical and clinical data is required on the epigenetic changes induced by dietary phytochemicals which will lead to better understanding of the epigenetic targets and pathways altered by these agents to elicit their efficacy in cancer. Additional preclinical and clinical studies are required to analyze the safety profile of doses, route of administration, organ bioavailability alone, and in combination in order to obtain maximum beneficial effects. At last, systematic well-designed randomized placebo-controlled trials with adequate power and relevant clinical epigenetic endpoints are needed. Despite these challenges, research on diet and nutrition continues to emerge and will offer new epigenetic targets and promising agents with more opportunities for prevention, and perhaps therapy of cancer in the near future.

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