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Effects of Dietary Nutrients on DNA Methylation and Imprinting

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1. Introduction

DNA methylation is an enzymatic modification carried out by DNA methyltransferases. Alterations in DNA methylation patterns are the best understood epigenetic cause of disease and were first discovered in studies during the 1980s that focused on X chromosome inactivation (Avner and Heard 2001), genomic imprinting (Verona et al. 2006) and cancer (Feinberg and Tycko 2004). DNA methylation involves the addition of a methyl group to cytosines in CpG (cytosine/guanine) pairs (Ehrlich and Wang 1981, Laird and Jaenisch 1994). The added methyl group does not affect the base pairing itself, but the protrusion of methyl groups into the DNA major groove can affect DNA–protein interactions. Methylated CpGs are usually associated with silenced DNA, can block methylation sensitive proteins from binding to the DNA and are subject to high mutation rates. DNA methylation patterns are established and maintained by DNMTs, enzymes that are essential for proper gene expression patterns (Robertson 2002) (Figure 1). DNA methylation is an essential epigenetic

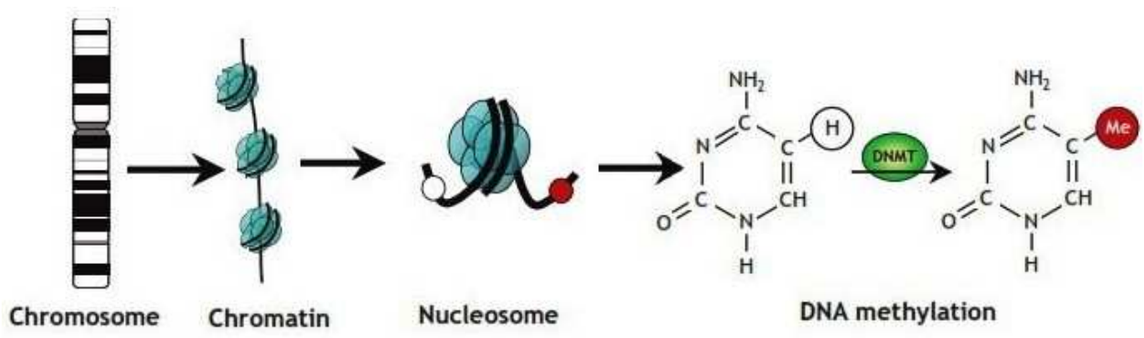


Fig. 1. Schematic representation of DNA methylation. Strands of DNA envelop histone octamers, forming nucleosomes. These nucleosomes are bundled together into chromatin, the building blocks of chromosomes. DNA methylation occurs at the 5′-position of cytosine residues in a reaction catalyzed by DNA methyltransferases (DNMTs). Together, these modifications create a unique epigenetic signature that regulates chromatin organization and gene expression.

mechanism of transcriptional control. This methylation plays a crucial role in maintaining cellular function, and alterations in methylation patterns may contribute to the development of cancer. Abnormal DNA methylation (global hypomethylation accompanied by region-specific hypermethylation) is frequently found in tumor cells. Global hypomethylation can result in chromosome instability, and hypermethylation has been linked with the silencing of tumor suppressor genes. DNA methylation predominantly involves the covalent addition of a methyl group (CH_3) to the 5′ position of a cytosine that precedes a guanine in the DNA sequence. This is referred to as an epigenetic modification, as it does not alter the coding sequence of the DNA. The distribution of methylated CpG dinucleotides in the genome is asymmetric. In contrast to the relative paucity of CpGs in the genome as a whole, these dinucleotides can be found at high frequency in small stretches of DNA termed CpG islands.

2. DNA methylation in carcinogenesis

Differential patterns of DNA methylation in cancer have been recognized for more than two decades (Brown and Strathdee 2002). The situation has been confusing because virtually all types of cancer examined have both global hypomethylation and gene-specific hypermethylation in promoter regions (Baylin et al. 1998). Hypermethylation of promoter regions, which is associated with transcriptional silencing, is at least as common as actual DNA mutation as a mechanism for the inactivation of classical tumor suppressor genes in human cancers (Jones and Baylin 2002, Tsou et al. 2002). Additionally, a number of candidate tumor suppressor genes that are not commonly inactivated by mutation are transcriptionally silenced by this mechanism (Jones and Baylin 2002). The aberrant methylation of genes that suppress tumorigenesis appears to occur early in tumor development and increases gradually, ultimately leading to a malignant phenotype (Fearon and Vogelstein 1990, Kim and Mason 1995). Genes associated with tumorigenesis can be silenced by this epigenetic mechanism. In an excellent review on tumorigenesis, Hanahan and Weinberg (Hanahan and Weinberg 2000) have noted the major hallmarks of cancer. The crucial properties required to generate the characteristic malignant attributes associated with cancer are the ability to replicate without limitation, indifference to positive growth signals, disregard for growth inhibitory factors, evasion of programmed cell death, sustained angiogenesis, and the ability to invade and metastasize (Hanahan and Weinberg 2000). Each of these traits is influenced by a gene or set of genes. Failure to express the gene correctly and produce functional regulatory proteins leads to the uncontrolled pattern of cell behavior observed in a typical neoplasm. Hypermethylation is associated with the inactivation of virtually all pathways involved in the cancer process, including DNA repair, cell cycle regulation, apoptosis, carcinogen metabolism, hormonal response, and cell adherence (Momparler 2003, Esteller 2002, Costello and Plass 2001). Moreover, CpG island hypermethylation in human cancer is specific enough to enable the use of these aberrantly hypermethylated loci as biomarkers of malignant disease (Esteller 2003).

Although both global hypomethylation and regional DNA hypermethylation are well documented in cancer (Figure 2), the mechanisms behind these events remain unclear, particularly the paradox of why some DNA remains hypomethylated in the presence of increased DNA methyltransferase activity and expression. It has been suggested that the deregulation of DNA methyltransferases might lead to genome-wide hypomethylation in

cancers (Pogribny et al. 2004). A significant correlation between overexpression of DNMT3b4, an inactive splice variant of DNMT3b, and DNA hypomethylation on peri-centromeric satellite regions of pre-neoplastic and neoplastic tissue provides support for this hypothesis (Saito et al. 2002). DNA methyl-transferases have also been found to bind with higher affinity to DNA strand breaks, abasic sites, and uracils than to similar hemimethylated CpG sites, consistent with their ancestral function as DNA repair enzymes (James et al. 2003). These same DNA lesions are often present in human pre-neoplastic cells, raising the possibility that DNA lesions may be a necessary prerequisite for the disruption of normal DNA methylation patterns in pre-neoplastic and neoplastic cells (James et al. 2003).

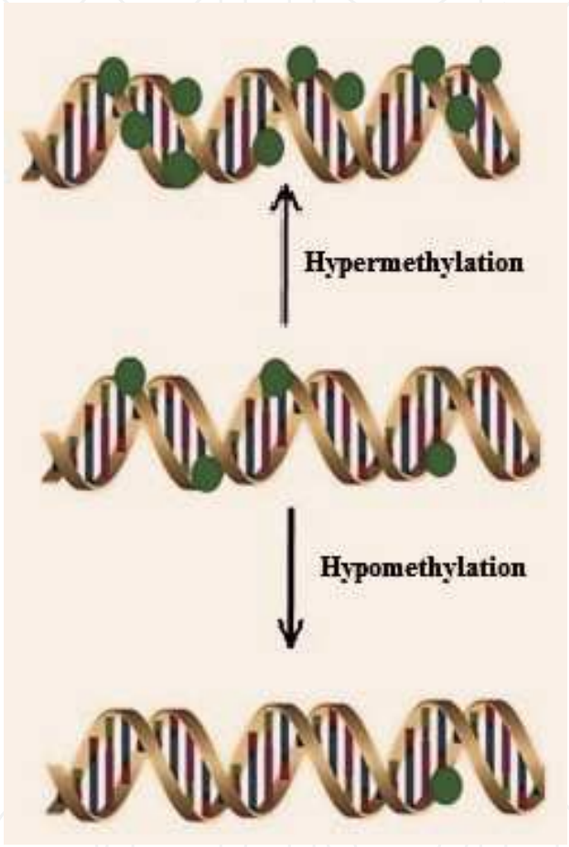


Fig. 2. Abnormal DNA methylation leads to the activation of oncogenes, genome instability and retrotransposon activation, and to the inactivation of genes such as tumor suppressor genes.

3. Diet and DNA methylation

Several bioactive food components can modulate DNA methylation and cancer susceptibility. Studies on dietary factors that are involved in one-carbon metabolism provide the most compelling data for an interaction between nutrients and DNA methylation. The one-carbon metabolism pathway influences the supply of donor methyl groups and consequently the biochemical pathways of methylation processes (Figure 3). These nutrients include vitamin B12, vitamin B6, folate, methionine, and choline. Folate plays the central

role in one-carbon metabolism. In this pathway, a carbon unit from serine or glycine is transferred to tetrahydrofolate to form 5,10-methylenetetrahydrofolate (Scott and Weir 1998). Vitamin B6 is a necessary co-factor for glycine hydroxymethyltransferase in the synthesis of 5,10-methylenetetrahydrofolate (Ross 2003). This folate can be used for the synthesis of thymidine, can be oxidized to formyltetrahydrofolate for the synthesis of purines or can be reduced to 5-methyltetrahydrofolate and used to methylate homocysteine to form methionine (Ross 2003). The vitamin B_{12}–dependent enzyme methionine synthase (MS) catalyzes the synthesis of methionine from homocysteine. Methionine is subsequently converted to S-adenosylmethionine (SAM) by an ATP-dependent transfer of adenosine to methionine via methionine adenosyltransferase (Ross 2003). S-adenosylmethionine can then donate its labile methyl groups to more than 80 biological methylation reactions, including the methylation of DNA, RNA, and proteins (Choi and Mason 2001). When the folate source is inadequate, plasma and cellular levels of homocysteine increase. Although an alternative zinc-requiring enzyme in methionine synthesis, betaine-homocysteine methyltransferase, may partly compensate for the reduced MS activity, it is well known that dietary folate depletion alone is a perturbing force sufficient to diminish cellular SAM pools (Miller et al. 1994). This leads to a rise in cellular levels of S-adenosylhomocysteine (SAH), as the equilibrium of the SAH-homocysteine interconversion actually favors SAH synthesis. Hence, when homocysteine metabolism is inhibited (as in folate deficiency), cellular SAH will be increased. Increased SAH inhibits methyltransferase activity and, subsequently, DNA methylation reactions (De Cabo et al. 1995). The inhibition of DNA methylation resulting from insufficient dietary folate has also been associated with increased cancer susceptibility.

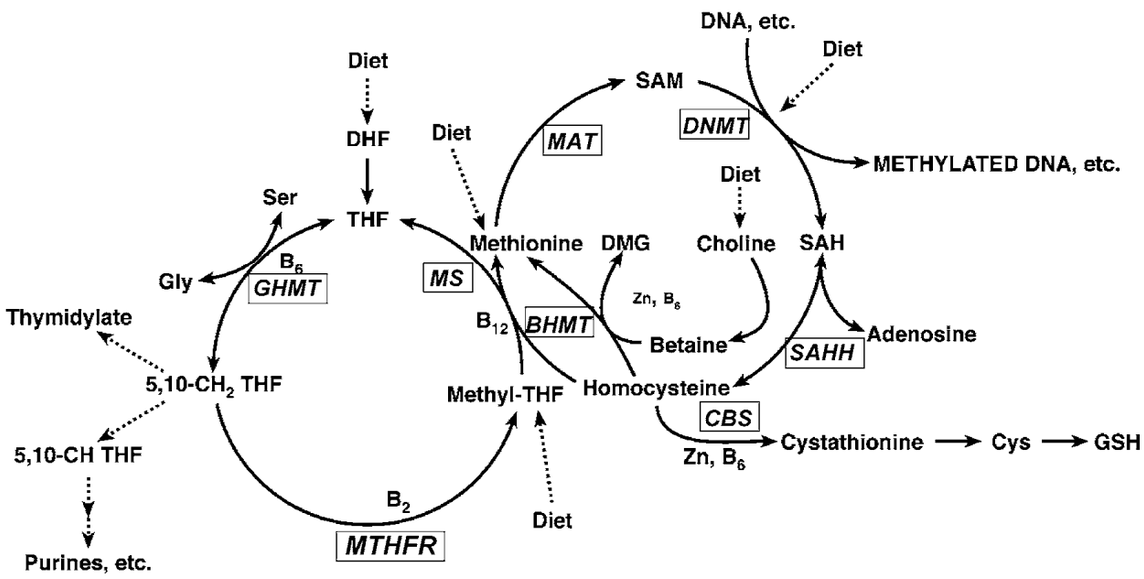


Fig. 3. Dietary factors, enzymes, and substrates involved in DNA methyl metabolism. Enzymes are shown in italics with a box around them.

A large number of epidemiologic and clinical studies suggest that dietary folate intake and blood folate concentrations are inversely associated with colorectal cancer risk (Kim 2004). Animal studies using chemical and genetically predisposed rodent models have provided considerable support for a causal relationship between folate depletion and colorectal carcinogenesis, as well as a dose-dependent protective effect of folate supplementation (Song et al. 2000). However, animal studies have also shown that the dose and timing of folate intervention are critical in providing safe and effective chemoprevention; exceptionally high supplemental folate concentrations as well as folate intervention after microscopic neoplastic foci are established in the colorectal mucosa promote rather than suppress carcinogenesis (Kim 2004). Animal studies have shown that folate deficiency causes DNA hypomethylation prior to the development of tumors (Jacob et al. 1998). DNA hypomethylation has also been found in the lymphocytes of humans on low dietary folate and can be reversed by folate repletion (Trasler et al. 2003). In contrast, folate deficiency with or without reductions in Dnmt1 did not affect either overall genomic DNA methylation levels or the methylation levels of two candidate genes, E-cadherin or p53, in normal and neoplastic intestinal tissue (Song et al. 2000). These studies suggest that the effects of folate deficiency on DNA methylation are highly complex, appear to depend on cell type, target organ, and stage of transformation and are gene- and site-specific.

Gene polymorphisms may modulate the effect of dietary folate on DNA methylation and cancer susceptibility. A single nucleotide substitution at position 677 of the methylenetetrahydrofolate reductase (MTHFR) gene (C677T) has been associated with a reduced risk of colon cancer (Curtin et al. 2004) but an increased risk of breast cancer (Alshatwi 2010, Beilby et al. 2004). When cellular folate is low, the presence of this TT genotype is associated with an increase in homocysteine concentration and DNA hypomethylation. These studies highlight the importance of taking into consideration interactions between folate status and key genes in the folate and one-carbon metabolic pathways when investigating the effect of folate on DNA methylation.

Several bioactive components in food have also been shown to affect DNA methylation. Many of these nutrients, including genistein, zinc, selenium and vitamin A have also been associated with cancer susceptibility. Although deficiencies of some food components induce global DNA hypomethylation, deficiencies of other food components induce global hypermethylation. For example, zinc deficiency (Wallwork and Duerre 1985) and retinoic acid excess (Rowling et al. 2002) has been shown to reduce the use of methyl groups from SAM in rat liver and to result in global DNA hypomethylation. Selenium deficiency decreased DNA methylation in Caco-2 cells and in rat liver and colon (Davis et al. 2000). In contrast, vitamin C deficiency has been linked with DNA hypermethylation in lung cancer (Haliwell 2001). There may be optimum amounts of certain dietary components that enable normal DNA methylation. For example, both absences and excesses of dietary arsenic have been shown to cause global hypomethylation in rat liver (Uthus 1993).

Phytoestrogens, such as genistein, are thought to be involved in preventing the development of certain prostate and mammary cancers by supporting the retention of a protective DNA methylation pattern (Beilby et al. 2004). The intake of genistein was positively correlated with changes in prostate DNA methylation at the CpG islands of

specific mouse genes, as evaluated using mouse differential hybridization arrays (Day et al. 2002). Other phytoestrogens have also been shown to alter DNA methylation. Neonatal exposures to the phytoestrogens coumestrol and equol have been found to lead to specific hypermethylation of the c-Ha-ras proto-oncogene in pancreatic cancer (Lyn-Cook et al. 1995).

The effect of bioactive food components on gene-specific DNA methylation is less clearly understood than the effect of bioactive food components on global DNA methylation. In a rat model of hepatocellular carcinoma, a choline-deficient diet induced hypomethylation of CpG sites in the c-myc gene as well as the overexpression of this gene (Tsujiuchi et al. 1999). Methylation of the promoter region of p53 in Caco-2 cells decreased when cells were cultured in the absence of selenium (Davis et al. 2000). Arsenic has been shown to induce hypo-methylation of the 5′ regulatory region of Ha-ras in animals (Okoji et al. 2002). Interestingly, dietary factors that modify global DNA methylation can simultaneously cause opposite effects on gene-specific methylation. For example, folate deficiency causes global DNA hypomethylation but hypermethylation of the 5′ regulatory sequence of the H-cadherin gene (Jhaveri et al. 2001). Moreover, retinoic acid leads to global hypomethylation but region-specific hypermethylation. Thus, the pattern of gene-specific methylation may not be in concert with the track of overall alterations in genomic DNA methylation.

Nutrients have also been shown to affect gene transcription by altering exon-specific DNA methylation. For example, in animals fed methyl-deficient diets, increased levels of mRNA for c-fos, c-Ha-ras, and c-myc were correlated with hypomethylation at specific sites within the exons of these genes (Zapisek et al. 1992). In a hepatocarcinogenesis study with chronic dietary methyl deficiency, methylation in the p53 gene coding region decreased and then increased, which corresponded to high p53 mRNA levels in pre-neoplastic liver tissue and then lower p53 mRNA levels after tumor formation (Sohn et al. 2003). This suggests that methylation changes in the coding region of genes can affect gene transcription and that gene-specific methylation can vary during the carcinogenic process.

Bioactive food components can also modulate DNA methylation by interfering with DNMT activity. Green tea has been shown to inhibit carcinogenesis in many animal models (Fang et al. 2003). Recently, epigallocatechin-3-gallate, the major polyphenol from green tea, was found to inhibit DNMT activity by binding to the enzyme, which resulted in the reactivation of methylation-silenced genes in cancer cells (Fang et al. 2003). Rats fed selenium- or folate-deficient diets had significantly reduced liver and colon DNMT activity; however, the mechanism for this inhibitory effect is not known (Davis and Uthus 2003). Studies on cultured rat liver cells and in animals have shown that cadmium is another active inhibitor of DNMT (Takiguchi et al. 2003). Moreover, both cadmium and zinc inhibited DNMT activity in nuclear extracts from rats fed either a control or a methyl-deficient diet (Poirier and Vlasova 2002). The inhibitory effects of cadmium and zinc may be caused by the binding of these metals to a cysteine residue in the active site of DNMT (Poirier and Vlasova 2002).

4. Diet and gene interaction

Although many bioactive food components have been shown to modify epigenetic events and cancer susceptibility, looking at individual nutrients may be too simplistic.

Combinations of dietary deficiencies in methyl-related compounds such as folate, choline, and methionine cause decreased tissue SAM, global DNA hypomethylation and ultimately hepatic tumorigenesis in the absence of treatment with carcinogens (Steinmetz et al. 1998). The percentage of CpG sites that lose methyl groups on both DNA strands gradually increases in the liver after either folate or methyl deficiency, in spite of the presence of elevated DNA methyltransferase activity (Pogribny et al. 2004). Hence, it appears that DNA methyltransferase is incapable of methylating double-stranded unmethylated DNA present in the pre-neoplastic liver, and this may result in the establishment of a cancer-specific DNA methylation profile. Alterations in the DNA methylation profile may explain why these animals develop cancer in the absence of treatment with carcinogens. However, it is also possible that the increased mitogenesis leads to mutations, and it is a combination of mutagenesis and altered DNA methylation that leads to cancer. Moreover, other tissues, such as pancreas, spleen, kidney, and thymus, displayed no changes in the DNA methylation level or DNA methyltransferase activity after folate/methyl deficiency (Pogribny et al. 2004). These findings suggest that a folate/methyl-deficient diet causes specific DNA hypomethylation in the liver as well as hepatic tumorigenesis. These findings further support the hypothesis that alterations in the DNA methylation profile can cause cancer and that it is important to look at interactions between nutrients.

Diets that are deficient in choline or in both choline and methionine have also been shown to cause hepatocellular carcinoma in animals after 12–24 months of consumption (Brunaud et al. 2003). However, the carcinogenicity of a methyl-deficient diet is much higher when combined with vitamin B12 deficiency (Brunaud et al. 2003). Dietary arsenic has also been shown to interact with a methyl-deficient diet. The administration of arsenic alongside a methyl-deficient diet in mice resulted in genome-wide hypomethylation, as well as reduced methylation of the promoter region of the oncogene Ha-ras (Okoji et al. 2002). This process would be expected to induce expression of the oncogene and contribute to tumor development.

Another important dietary interaction that affects DNA methylation and cancer susceptibility occurs between alcohol and folate. Alcohol has been shown to cleave folate, impair folate absorption, increase folate excretion, and interfere with methionine synthase activity (Pufulete et al. 2003). A high alcohol intake may lead to localized folate deficiency and DNA hypomethylation, even when dietary folate intake and blood folate concentrations are normal (Pufulete et al. 2003).

Dietary selenium has been shown to modulate many of the adverse effects of folate deficiency, including alterations in one-carbon metabolism and aberrant crypt formation, a pre-neoplastic lesion (Davis and Uthus 2003). In contrast, SAM, SAH, and genomic methylation were not affected by any dietary interaction between selenium and folate. These results suggest that selenium alters some of the effects of folate deficiency, probably by shunting the buildup of homocysteine through the trans-sulfuration pathway.

5. Imprinting and DNA methylation

Several genes that are involved in mammalian developmental processes do not follow Mendelian genetics and are expressed in a mono-allelic fashion. DNA methylation is a critical element in this imprinting process. Methylation can mark specific alleles and

establish a mono-allelic expression pattern of the imprinted genes. Much has been learned about the importance of DNA methylation in imprinting from the Dnmt1-deficient mouse. Loss of methylation on the imprinted Xist gene in Dnmt1-deficient cells does not activate Xist. This is surprising in light of the fact that the RNA product of the Xist gene is thought to spread an inactive state along one of the X-chromosomes in eutherian females. In contrast, the mono-allelic expression of the imprinted genes H19, Igf2 and Igf2r has been shown to be disrupted in Dnmt1 mutant cells. This observation established for the first time a causal link between DNA methylation and gene activity (Ramchandani et al. 1999). Differentially methylated regions (DMRs) in imprinted genes have been shown to serve as imprinting boxes that control the imprinting of the Igf2r gene (Cervoni et al. 1999) and the Prader Willi/Angelman syndrome domain (Bhattacharya et al. 1999). DMRs are also crucial elements in regulating reciprocal monoallelic expression of the maternal regulation of the imprinted H19 and Igf2 genes (Hendrich and Bird 1999). Experiments with Dnmt1 deficient mice have shown that the establishment of DMRs in imprinted genes requires methylation transmission through the germ line. Dnmt1 rescue in knockout ES cell lines did not restore imprinted methylation of the above-mentioned genes, even though Dnmt1 restoration was able to reestablish imprinting in the whole animal (Zhang et al. 1999). This is in accord with the fact that methylation of the Snrpn gene on the maternal allele is established during oogenesis and maintained thereafter (Ng et al. 1999).

6. MicroRNA and DNA methylation

MicroRNAs are a new class of noncoding, endogenous, small RNAs that regulate gene expression by translational repression, representing a new essential class of regulatory molecules. MicroRNAs can play essential roles in regulating DNA methylation and histone modifications, creating a highly organized feedback mechanism. Epigenetic mechanisms such as promoter methylation and histone acetylation can also alter microRNA expression. A connection between epigenetic phenomena and microRNA has been described in numerous physiological processes, and an altered balance between them represents one of the mechanisms leading to pathological conditions such as cancer. An abnormal expression of microRNA has been associated with the development or progression of human cancers through the alteration of cell proliferation and apoptosis processes (Iorio et al). A methyl-deficient diet, which induces tumors in rats, also induced prominent early changes in the expression of microRNA genes, including miR-34a, miR-127, miR-200b, and miR-16a, which are involved in the regulation of apoptosis, cell proliferation, cell-to-cell connection, and epithelial-mesenchymal transition in the rat (Tryndyak et al. 2009). Mice fed a methyl-deficient diet contracted nonalcoholic steatohepatitis, which was accompanied by alterations in the expression of several microRNAs including miR-29c, miR-34a, miR-155, and miR-200b. Interestingly, alterations in the expression of these microRNAs are paralleled by changes in the protein levels of their targets. These studies suggest that alterations in the expression of microRNAs are a prominent event during the development of cancer and nonalcoholic steatohepatitis caused by dietary methyl deficiency (Pogribny et al. 2010).

Similar to the methyl-deficient diet, folate deficiency induced a marked global increase in microRNA expression in human lymphoblastoid cells. miR-222 was significantly overexpressed under folate-deficient conditions in vitro. This finding was confirmed in vivo

in human peripheral blood from individuals with low folate intake, suggesting that microRNA expression might be a potential biomarker of nutritional status in humans (Marsit et al. 2006). The Göttingen minipig, an animal model of obesity, was fed either a high cholesterol or a standard diet. Body weight, total cholesterol, and HDL were higher, and miR-122 was lower (1.4-fold; $P < 0.0015$) in pigs fed the high-cholesterol diet compared with those fed the standard diet, implicating this microRNA in obesity as well (Cirera et al. 2010).

A few reports have suggested that bioactive food components may reduce carcinogenesis through microRNA action [reviewed in (Saini et al. 2010)]. Genistein represses human uveal melanoma cells and murine chronic lymphocytic leukemia cells by altering miR-16 levels (Salerno et al. 2009). Curcumin represses human pancreatic cancer cells by upregulating miR-22 and downregulating miR-199a (Sun et al. 2008). Curcumin also upregulates miR-15a and miR-16 expression, which could inhibit the expression of B-cell lymphoma 2 (Bcl-2) and thereby induce apoptosis in MCF-7 breast cancer cells (Yang et al. 2009). Furthermore, miR-10a, a key mediator of metastatic behavior in pancreatic cancer, is a retinoic acid target. Retinoic acid receptor antagonists effectively repress miR-10a expression and block metastasis (Weiss et al. 2009). In neuroblastoma cells, miR-34a functions as a potential tumor suppressor, and retinoic acid-induced differentiation of the neuroblastoma cell line enhanced miR-34a expression and decreased expression of its target, E2F transcriptional factor 3 (Weiss et al. 2009).

7. Conclusion

Given that DNA methylation is at the heart of many phenotypic variations in health and disease, it seems likely that understanding and manipulating the epigenome holds enormous promise for preventing and treating common human illness. DNA methylation also offers an important window into understanding the role of interactions between the environment and the genome in causing disease, and in modulating these interactions to improve human health. Within the past two decades, scientists have discovered many details about the process of DNA methylation. Scientists now know that methylation plays a critical role in the regulation of gene expression, and they have also determined that this process tends to occur at certain locations within the genomes of different species. Moreover, DNA methylation has been shown to play a vital role in numerous cellular processes, and abnormal patterns of methylation have been implicated in several human diseases. However, as with other topics in the field of epigenetics, gaps remain in our knowledge of DNA methylation. As new laboratory techniques are developed and additional genomes are mapped, scientists will undoubtedly continue to uncover many of the unknowns of how, when, and where DNA is methylated, and for what purposes.

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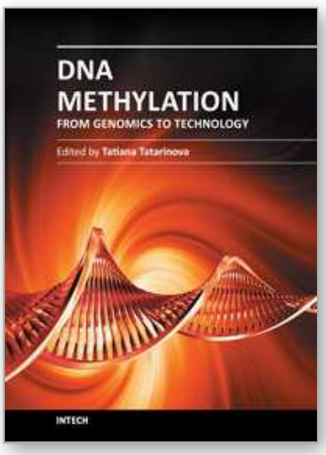
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Epigenetics is one of the most exciting and rapidly developing areas of modern genetics with applications in many disciplines from medicine to agriculture. The most common form of epigenetic modification is DNA methylation, which plays a key role in fundamental developmental processes such as embryogenesis and also in the response of organisms to a wide range of environmental stimuli. Indeed, epigenetics is increasing regarded as one of the major mechanisms used by animals and plants to modulate their genome and its expression to adapt to a wide range of environmental factors. This book brings together a group of experts at the cutting edge of research into DNA methylation and highlights recent advances in methodology and knowledge of underlying mechanisms of this most important of genetic processes. The reader will gain an understanding of the impact, significance and recent advances within the field of epigenetics with a focus on DNA methylation.

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