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Nutrition, Histone Epigenetic Marks, and Disease

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Abstract
The dietary intake of essential nutrients and bioactive food compounds is a process that occurs on a daily basis for the entire life span. Therefore, your diet has a great potential to cause changes in the epigenome. Known histone modifications include acetylation, methylation, biotinylation, poly(ADP-ribosylation), ubiquitination, and sumoylation. Some of these modifications depend directly on dietary nutrients. For other modifications, bioactive dietary compounds may alter the activities of enzymes that establish or remove histone marks, thereby altering the epigenome. This chapter provides an overview of diet-dependent epigenomic marks in histones and their links with human health.

Keywords: Bioactive food compounds, diet, epigenome, minerals, nutrition, vitamins

Abbreviations:

A^{vy}	Viable yellow agouti
CoA	Coenzyme A
DNMT1	DNA methyltransferase 1
FAD	Flavin adenine dinucleotide
H3K4me3	K4-trimethylated histone H3
H3K9ac	K9-acetylated histone H3
H3K9me2	K9-dimethylated histone H3
H3K9me3	K9-trimethylated histone H3

H4K5ac	K5-acetylated histone H4
H4K8ac	K8-acetylated histone K12
H4K12ac	K12-acetylated histone H4
H4K12bio	K12-biotinylated histone
H4H4K16ac	K16-acetylated histone H4
H4K20me3	K20-trimethylated histone H4
HAT	Histone acetyl transferase
HDAC	Histone deacetylase
HLCS	Holocarboxylase synthetase
HMT	Histone methyl transferase
JmjC	Jumonji C
K	Lysine
LSD1	Lysine-specific demethylase 1
SET	Suppressor of variegation enhancer of zeste trithorax
Sir2	Silent information regulator 2

1 Introduction

The human epigenome is constantly exposed to a variety of environmental factors that may alter chromatin structure, gene regulation, genome stability, and an individual's predisposition to disease. Frequently, individuals are exposed to these factors in a controlled environment over a short period of time in subsets of the general population. The treatment of cancer patients with the histone deacetylase inhibitor, belinostat (Ma et al. *2010*), and lifestyle choices such as smoking are examples (Launay et al. *2009*). This is not the case for human nutrition.

The dietary intake of essential nutrients and bioactive food compounds is a process that occurs on a daily basis for the entire life span. Therefore, it has great potential for causing changes in both the epigenome and disease risk. A well-documented example is the feeding of defined diets to agouti mice, where dietary supplementation with methyl donors and genistein resulted in increased DNA methylation of a long terminal repeat in the viable yellow agouti (A^{vy}) locus and an alteration in offspring coat color and disease susceptibility in adulthood (Cooney et al. *2002*; Dolinoy et al. *2006*; Waterland and Jirtle *2003*; Wolff et al. *1998*). Epidemiologic studies also indicate that adult disease risk is associated with poor nutritional status early in development. Individuals exposed to the famine during the Dutch Hunger Winter of 1944 and 1945 is the most widely recognized example (Heijmans et al. *2008*). Put simply, dietary choices during pregnancy can alter the disease risk of the unborn child later in life. It remains to be seen whether such scenarios hold true under conditions that are more moderate than the Dutch Hunger Winter.

A large number of covalent modifications have been identified in the N-termini of histones, while some modifications also exist in the hinge regions and the C-termini. Known modifications include acetylation, methylation, biotinylation, poly(ADP-ribosylation), ubiquitination, and sumoylation (Boulikas *1988*; Boulikas et al. *1990*; Camporeale et al. *2004*; Chambon et al. *1966*; Kouzarides and Berger *2007*; Shiio and Eisenman *2003*; Stanley et al. *2001*; Wolffe *1998*). For many of these modifications, unambiguous links have been established with human disease and nutrition.

One might consider classifying diet-dependent histone modifications according to the following scheme. In one group of histone marks, nutrient supply is a limiting factor only under exceptional circumstances, but bioactive compounds and essential nutrients in food may modulate the abundance of the modification by altering enzyme activities. This group of histone marks would include iron-, calcium-, and riboflavin-dependent demethylation of histones and the inhibition of histone deacetylases by sulforaphane. In a second group of histone marks, essential nutrients or functional groups thereof are attached to histones, and dietary nutrient availability can be a limiting factor for creating these marks. Histone methylation, biotinylation, and poly(ADP-ribosylation) belong in this group. In a third group of histone marks, specific nutrients are attached to histones, but the availability of these nutrients is not a limiting factor under normal circumstances. Sumoylation and ubiquitination belong in this group.

2 Acetylation of Histones

Histone acetylation marks are associated with transcriptionally active chromatin (Kouzarides and Berger *2007*). Lysine (K)-9 acetylated histone H3 (H3K9ac), H4K5ac, H4K8ac, H4K12ac, and H4K16ac are the most frequently studied markers for acetylation-mediated gene activation. There are two dietary compounds directly involved in acetylation events. The first is acetate, which can be derived from the metabolism of glucose, amino acids, fatty acids, and other compounds in intermediary metabolism (Garrett and Grisham *1995*). Except for circumstances of prolonged total starvation, it is nearly impossible to deplete the body pool of acetate. The second is coenzyme A (CoA), which is required for generation of the energy-rich acetyl-CoA for subsequent acetylation reactions. The vitamin pantothenic acid is an integral part of the CoA molecule (Garrett and Grisham *1995*). In the most recent edition of the Dietary Reference Intakes, the Food and Nutrition Board acknowledges that human pantothenic acid requirements are unknown (National *1998*). Thus, only recommendations for Adequate Intake are available for pantothenic acid. These recommendations are based solely on the intake of pantothenic acid in the general, apparently healthy, population (National *1998*). There is currently no compelling evidence to suggest that the prevalence of pantothenic acid deficiency is quantitatively meaningful in Western societies; the prevalence of deficiency in

Table 1. Histone deacetylases

Class	Member
I	HDAC1, HDAC2, HDAC3, HDAC8
II	HDAC4, HDAC5, HDAC6, HDAC7A, HDAC9, HDAC10
III	SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, SIRT7
IV	HDAC11

developing countries or in unique, small subgroups within the general population is unknown.

Acetylation of histones is catalyzed by histone acetyl transferases (HATs) such as PCAF, STAGA, and TFTC, which are grouped on the basis of their catalytic domains such as GCN5 and PCAF {see (Lee and Workman *2007*) for an excellent review}. Little is known about dietary modulation of HAT activity; however, the dietary polyphenol curcumin is an inhibitor of the acetyl transferase p300 (Morimoto et al. *2008*).

Histone deacetylases (HDACs) catalyze the enzymatic removal of acetyl mark from the ε-amino group of lysines in histones during gene repression (Minucci and Pelicci *2006*). The family of HDACs comprises 18 isoforms, which are categorized into four classes, depending on sequence identity and domain organization (Table 1) (Dokmanovic et al. *2007*). Histone deacetylation by class III HDACs (sirtuins) is coupled to NAD+ hydrolysis, which is a niacin-dependent event; the dietary supply of niacin and niacin precursors is discussed below. Sir2 (silent information regulator 2) in simple eukaryotes and its mammalian ortholog SIRT1 play important roles in life span extension in response to caloric restriction (Boily et al. *2008*). The efficacy of SIRT1 in enhancing the life span in mammals appears to depend on salvaging NAD in the nicotinamide phosphoribosyl transferase pathway (Ho et al. *2009*a). The phenolic compound resveratrol activates sirtuins and increases the life span in Saccharomyces cerevisiae, Caenorhabditis elegans, Drosophila melanogaster, and the fish Nothobranchius furzeri, but its efficacy in mammals is uncertain (Evason et al. *2005*; Howitz et al. *2003*; Kang et al. *2002*; Valenzano et al. *2006*). Resveratrol is present in grapes and red wine at relatively high concentration (Celotti et al. *1996*).

Hypoacetylation of histones is a hallmark of human cancer. HDAC inhibitors may induce cell cycle arrest, differentiation, and apoptosis in cancer cells. Thus, HDAC inhibitors are considered promising tools in the prevention and treatment of the disease (Liu et al. *2006*), and synthetic inhibitors such as belinostat are already being tested in clinical trials (Ma et al. *2010*). Importantly, HDAC activity may be modulated by a number of dietary compounds. Sodium butyrate is an HDAC inhibitor that can be produced by gastrointestinal fermentation of fermentable fiber, particularly resistant starch (Cummings et al. *2001*; Davie *2003*). Nicotinamide is a competitive inhibitor of the class III sirtuins, and it may restore some of the cognitive deficits in Alzheimer's disease (Green et al. *2008*). Sulforaphane is an isothiocyanate found in relatively high concentrations in cruciferous vegetables such as broccoli and brussel sprouts.

Although it inhibits HDACs (Ho et al. *2009*b; Myzak et al. *2006*), it is uncertain whether pharmacologically effective concentrations can be achieved through a normal diet. Synthetic selenium-containing analogs of suberoyl hydroxamic acid also show promise as HDAC inhibitors (Desai et al. *2010*). The extent to which dietary selenium compounds affect HDAC activity is unknown.

Diseases other than cancer are also linked with acetylation events in the epigenome, although unambiguous cause-and-effect relationships still remain to be demonstrated for many of these diseases. A link to diabetes is proposed because of the physical interactions of the HATs p300, CBP, and PCAF with hepatocyte nuclear factor and glucokinase (Gray and De Meyts *2005*). These interactions do not constitute a classical epigenetic mechanism but rather a change in transcription factor and enzyme activity. The abundance of histone H4 acetylation marks is abnormally increased in the promoters of NFκB-dependent proinflammatory genes in lung diseases such as asthma and cystic fibrosis (Selvi and Kundu *2009*). Nevertheless, the roles of HATs and HDACs and the possible modulation by dietary intervention in these diseases are far from being understood. Roles for histone acetylation are also proposed for neurodegenerative disorders, cardiac hypertrophy, and malaria; however, the underlying mechanisms and environmental perturbations remain to be elucidated (Freitas-Junior et al. *2005*; McKinsey and Olson *2004*; Saha and Pahan *2006*).

It is difficult to establish causal links between changes in acetylation marks in the epigenome and roles for HDACs in human health because HDACs also target nonhistone proteins such as transcription factors (Drummond et al. *2005*; Selvi and Kundu *2009*). It also appears that both drugs and dietary compounds that affect HDACs elicit off-target effects by modifying the transcriptional activity of genes not related to disease. For example, evidence suggests that HDAC inhibitors increase the acetylation of histones in transposable elements. This is associated with their transcriptional activation (Brunmeir et al. *2010a*, *b*; Montoya-Durango et al. *2009*), and transcriptional activation of transposable elements impairs genome stability (Fan *2007*; Gasior et al. *2006*). More studies are needed to investigate aberrant gene regulation caused by these off-target effects.

3 Methylation of Histones

Methylation events in the epigenome depend on the dietary supply of methyl donors and other essential cofactors. Both cytosines in DNA and histones are targets for methylation (Kouzarides and Berger *2007*; Li and Bird *2007*). This chapter focuses exclusively on histone epigenetic marks, whereas cytosine methylation is covered in other chapters in this book. The reader should note, however, that the histone methyl transferase (HMT) G9a is known to interact with DNA methyltransferase 1 (DNMT1) (Esteve et al. *2006*). When DNMT1 is knocked down by using siRNA, both cytosine and H3K9 methylation on chromatin are impaired, confirming DNMT1 as the primary loading factor. Consistent with this notion, aberrant cytosine

methylation impairs both histone methylation and histone biotinylation (Chew et al. *2008*).

Both arginine and lysine residues in histones are potential targets for methylation (Bedford and Clarke *2009*; Martin and Zhang *2005*). HMT activity toward lysine and arginine residues is found in a family of enzymes with a conserved catalytic domain called SET (suppressor of variegation, enhancer of zeste, trithorax) (Albert and Helin *2010*). The human genome encodes 48 SET domain-containing proteins and DOT1L, which does not contain a SET domain but has lysine methyltransferase activity. The domain structures, phylogenetic tree, and histone targets of HMTs are covered in depth in an excellent recent review (Albert and Helin *2010*).

Histone methylation is a dynamic and reversible process. As of today, three classes of histone demethylases have been identified (Klose et al. *2006*). The largest class of demethylase enzymes contains a Jumonji C (JmjC) domain. The JmjC domain-containing enzymes can demethylate mono-, di-, and trimethylated histones by an oxidative mechanism that requires Fe(II) and alpha-ketoglutarate as cofactors (Tsukada et al. *2006*). The following subgroups in the general population are at risk for developing iron deficiency: infants (particularly premature and low-birth-weight babies), young children, menstruating and pregnant women, vegetarians, and people who have internal bleeding or who get kidney dialysis treatment (National *2011*). Nevertheless, it is unclear to what extent iron deficiency affects histone demethylation events. Lysine-specific demethylase 1 (LSD1) is the founding member of the second class of histone demethylases. Enzymes in this class demethylate only mono- or dimethylated H3K4me and H3K9me and depend on flavin adenine dinucleotide (FAD) as a coenzyme for oxidative demethylation. FAD is one of the two coenzyme forms of the vitamin riboflavin (Rivlin *2007*). Dietary riboflavin deficiency is uncommon in developed countries, but deficiency may be precipitated by adrenal and thyroid hormone deficiency, psychotropic agents such as chlorpromazine, antidepressants such as imipramine and amitriptyline, chemotherapeutic drugs such as Adriamycin, and antimalarial agents such as quinacrine (Rivlin *2007*). It is unknown whether riboflavin deficiency affects histone demethylation to a meaningful extent. Peptidylarginine deiminase 4 is the third class of histone demethylases, and it was the first to be identified. It converts methylated arginine to citrulline (as opposed to producing unmethylated arginine) in a Ca^{2+}-dependent reaction (Wang et al. *2004*). It is unknown whether calcium deficiency affects histone demethylation to a meaningful extent. Please note that vitamin D and biotin play important roles in calcium homeostasis and cellular compartmentalization, respectively (Griffin et al. *2006*; Norman and Henry *2007*).

Histone methylation depends on a sufficient supply of S-adenosylmethionine (SAM) as a methyl donor (Figure 1). In this reaction, a methyl group is transferred from SAM to histones (or other methyl acceptors) and SAM is converted to S-adenosylhomocysteine (SAH). In addition to SAM, numerous other nutrients and metabolites also play key roles in one-carbon metabolism and, hence, methylation reactions {see (Bailey *2007*) for an elaborate review}. Briefly, L-homocysteine can be remethylated to produce L-methionine in a reaction that depends on both 5-methyltetrahydrofolate and vitamin B_{12}. Deficiency of

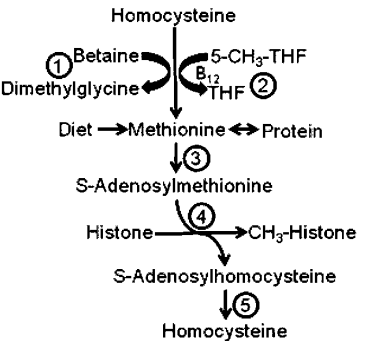

Figure 1. One-carbon flux. Abbreviations: CH_3 methyl, THF tetrahydrofolate. 1. betaine: homocystein methyltransferase, 2. methionine synthase, 3. methionine adenosyltransferase, 4. histone methyltransferase(s), 5. S-adenosylhomocysteine hydrolase.

vitamin B_{12} is frequently seen in vegans, the elderly, and after surgical removal of the ileum. Furthermore, it leads to folate depletion by trapping the latter as 5-methyltetrahydrofolate (Green and Miller *2007*). Dietary compounds such as betaine and choline also play important roles in replenishing the one-carbon pool (Bailey *2007*). Finally, zinc is a cofactor for DNMT1 (Wolff et al. *1998*); impaired methylation of cytosines may precipitate aberrant patterns of histones marks, as described above.

Folate deficiency used to be relatively common in the general population and was blamed for being a factor contributing toward birth defects, particularly neural tube defects and congenital heart defects (Bailey *2007*). Many countries have adopted a policy mandating folate fortification of staple foods. These policies have proven effective with regard to decreasing the incidence of neural tube defects and, perhaps, congenital heart defects (Botto et al. *2003*; Honein et al. *2001*). Most studies of folate and birth defects have focused on abnormalities in cytosine methylation and impaired thymidine synthesis, with the latter leading to uracil misincorporation into DNA.

It is difficult to unambiguously attribute adverse effects of methyl deficiency to distinct patterns of histone methylation for the following reasons. Firstly, the great number of histone methyltransferases (48 SET domain-containing proteins and DOT1L) requires a combination of sound enzyme kinetics data with regard to substrate affinity and fairly advanced computer algorithms to predict effects of altered methyl supply on the biological activity of individual enzymes. This information is not yet available. It is also important to consider possible effects of single nucleotide polymorphisms on substrate affinity and enzyme activity. Secondly, it is currently unclear to what extent betaine and choline can substitute for folate in one-carbon metabolism, although some mathematic models are emerging (Reed et al. *2006*). Thirdly, histone methylation marks can have opposing effects in gene regulation. Classical examples include H3K4me3 and H3K9me, which are transcriptional activation and repression marks, respectively (Kouzarides and Berger *2007*). Thus, methyl deficiency might affect both gene activation and repression. Finally, the flow of information among marks in the epigenome is immense and goes far beyond a cross talk among methylation marks. Epigenomic synergies have been documented for H3K4acme3

and H3K9ac in gene activation (Kouzarides and Berger *2007*) and for cytosine methylation, H3K9me2, and H4K12bio in the repression of retrotransposons (Chew et al. *2008*). Despite these limitations, the following themes have emerged in the field of diet-dependent changes in the histone methylome and their consequences for human health.

Loss of H4K16ac and H4K20me3 is a hallmark of human cancer (Fraga et al. *2005*), and there is now consensus that aberrant methylation marks in the epigenome play a significant role in cancer development and progression (Poke et al. *2010*). Evidence suggests that HATs, HDACs, and HMTs can act as tumor suppressor genes or oncogenes. Occasionally, these effects also depend on chromosomal rearrangements and the expression of fusion proteins (Albert and Helin *2010*; Fraga and Esteller *2005*; Huang *2002*). Clearly, the abundance of histone methylation marks depends on the dietary methyl supply. For example, when mice are fed a choline- and methionine-deficient diet, the enrichment of the repression mark H3K9me2 decreases in the promoters of imprinted genes Igf2 and H19 in the prostate; however, the changes in H3K9me2 enrichment do not affect the imprinting of these two genes (Dobosy et al. *2008*). In contrast, feeding a methyl-deficient diet increases the abundance of H3K9me3 and the expression of the Suv39h1 methyltransferase in preneoplastic nodules and liver tumors in rats compared with controls on a normal diet (Pogribny et al. *2006*). It is possible that these apparently contradictory observations are caused by locus-specific effects, by epigenomic synergies with other epigenetic marks, or by a combination of both mechanisms.

Distinct H3K9, H3K27, and H4K20 methylation marks are enriched across tandem repeats (e.g., major and minor satellites), DNA transposons, retrotransposons, long interspersed nucleotide elements, and short interspersed nucleotide elements in the mouse genome (Martens et al. *2005*). Evidence that epigenetic mechanisms are important in retroelement control and cancer prevention are as follows (Chen et al. *1997*; Chen and Townes *2000*; Chew et al. *2008*; Jahner et al. *1982*; Slotkin and Martienssen *2007*; Walsh et al. *1998*; Yoder et al. *1997*): Firstly, the human genome contains at least 54 transcriptionally active LTRs (Buzdin et al. *2006*). Retrotransposons and any integrating virus produces DNA breaks during integration (Gasior et al. *2006*) that may directly or indirectly lead to tumorigenesis (Fan *2007*). Secondly, retrotransposition events account for ~10 % of known spontaneous mutations in mice (Kazazian and Moran *1998*; Smit *1999*). Thirdly, retroelements are associated with break-prone segmental duplications in tumors (Darai-Ramqvist et al. *2008*). Finally, chromosomal instability caused by aberrant epigenetic marks and the insertion of retrotransposons lead to oncogene activation, tumor suppressor gene inactivation, and the disruption of essential genes (Check *2003*; Eden et al. *2003*; Feinberg and Tycko *2004*).

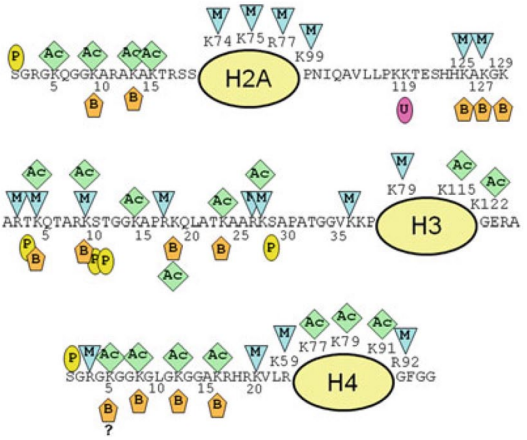

Figure 2. Modifications in histones H2A, H3, and H4. Biotinylation sites in histone H2B are unknown. Abbreviations: Ac acetate, B biotin, M methyl, P phosphate, U ubiquitin. "?" = awaits confirmation.

4 Biotinylation of Histones

Biotinylation of histones is a novel epigenetic mark that was discovered in the Zempleni laboratory (Bao et al. *2011*a; Camporeale et al. *2004*; Chew et al. *2006*; Kobza et al. *2005*; Kobza et al. *2008*; Stanley et al. *2001*) and subsequently confirmed by two independent laboratories (Bailey et al. *2008*; Ghosh *2009*). To date, 12 distinct biotinylation sites have been identified in histones (Figure 2), and all known species of biotinylated histones are gene repression marks (Camporeale et al. *2007*a; Chew et al. *2008*; Gralla et al. *2008*; Pestinger et al. *2011*). Biotinylation marks appear to be more abundant in histones H3 and H4 than in other histones. Evidence suggests that nucleosomal condensation increases in response to biotinylation of K12 and possibly other target sites in histone H4 (Filenko et al. *2011*).

Holocarboxylase synthetase (HLCS) plays a pivotal role in covalently linking biotin to histones (Bao et al. *2011*a; Camporeale et al. *2006*, 2007; Kobza et al. *2008*). Consistent with the important roles of HLCS in epigenomics, no living HLCS null individual has ever been reported, indicating this condition may cause embryonic lethality. HLCS knockdown studies (~30 % residual activity) produced phenotypes such as decreased life span and heat resistance in Drosophila melanogaster (Camporeale et al. *2006*), and aberrant gene regulation in human cell lines (Chew et al. *2008*; Gralla et al. *2008*; Pestinger et al. *2011*). Mutations have been identified and characterized in the human HLCS gene. These mutations cause a substantial decrease in HLCS activity and metabolic abnormalities (National *2008*; Suzuki et al. *2005*). Unless diagnosed and treated early, HLCS deficiency appears to be uniformly fatal (Thuy et al. *1999*).

HLCS is present in both nuclear and extranuclear structures (Chew et al. *2006*; Narang et al. *2004*). Nuclear HLCS is a chromatin protein (Camporeale et al. *2006*); its binding to chromatin is mediated by physical interactions with histones H3 and H4 (Bao et al. *2011*a). Our knowledge of HLCS regulation consists

of the following: (a) Both the abundance of HLCS mRNA and the nuclear translocation of HLCS depend on biotin (Gralla et al. *2008*). (b) The human HLCS promoter has been tentatively identified (Warnatz et al. *2010*) but not yet characterized in great detail. (c) The expression of HLCS is repressed by miR-539 (Bao et al. *2010*). (d) HLCS-dependent histone biotinylation cross talks with cytosine methylation in gene regulation. When cytosine methylation marks are erased by treatment with 5-aza-2′-deoxycytidine, the expression of HLCS decreases compared with untreated controls. The effects of 5-aza-2′-deoxycytidine on HLCS expression are partly mediated by cytosine demethylation of the promoters in the two human miR-153 genes, leading to high levels of miR-153 and, subsequently, miR-153-dependent degradation of HLCS mRNA (Bao et al. *2011*b).

The binding of biotin to histones is a reversible process, but the identity of the histone debiotinylase is uncertain. Circumstantial evidence indicates that biotinidase has histone debiotinidase activity (Ballard et al. *2002*; Chew et al. *2007*). Biotinidase has histone biotinyl transferase activity in vitro (Camporeale et al. *2004*; Hymes et al. *1995*), but HLCS appears to be more important than biotinidase for catalyzing histone biotinylation in vivo (Camporeale et al. *2006*). Presumably, the histone transferase activity of biotinidase is an artifact caused by artificially high concentrations of the biotin donor biotin-ε-lysine in vitro, thereby shifting the reaction equilibrium toward biotinylation of histones.

Histone biotinylation is a comparably rare event in human tissues (i.e., <0.001 % of histones are biotinylated) (Bailey et al. *2008*; Kuroishi et al. *2011*; Stanley et al. *2001*); however, the abundance of an epigenetic mark is not an indicator of biological importance. For example, serine-14 phosphorylation in histone H2B and histone poly(ADP-ribosylation) are detectable only after induction of apoptosis and major DNA damage, respectively, but the role of these epigenetic marks in cell death is unambiguous (Boulikas *1988*, *1989*; Cheung et al. *2003*). The abundance of histone biotinylation marks is much greater in confined genomic loci compared with bulk histones. For example, about one out of three molecules of histone H4 is biotinylated at K12 (Wijeratne et al. *2010*). Please note that about 50 % of the histones are biotinylated in Candida albicans chromatin (Ghosh *2009*).

While the abundance of biotinylated proteins depends on biotin supply in adults (Chew et al. *2008*; Stratton et al. *2006*) and human cell cultures (Camporeale et al. *2007*a; Chew et al. *2008*; Gralla et al. *2008*; Pestinger et al. *2011*), human biotin requirements are still unknown (National *1998*). Depletion of histone biotinylation causes deregulation of genes (Camporeale et al. *2007*b; Gralla et al. *2008*; Pestinger et al. *2011*). The production of viral particles, the frequency of retrotransposition events, and the number of chromosomal abnormalities increase when long terminal repeats are derepressed by biotin depletion or HLCS knockdown in cell cultures, humans, and Drosophila (Chew et al. *2008*). Retrotransposition events can also cause cancer (Check *2003*; Darai-Ramqvist et al. *2008*; Eden et al. *2003*; Fan *2007*; Feinberg and Tycko *2004*; Kazazian and Moran *1998*; Smit *1999*). Thus, biotin deficiency may be a risk factor for cancer formation. Recently, we have proposed an alternative model to explain the roles of biotin in epigenetic mechanisms of gene regulation

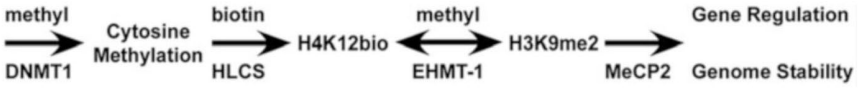

Figure 3. Epigenomic synergies between diet-dependent methylation and biotinylation events. Abbreviations: DNMT1 DNA methyltransferase 1, EHMT-1 euchromatic histone methyltransferase, H3K9me2 K9-dimethylated histone H3, H4K12bio K12-biotinylated histone H4, HLCS holocarboxylase synthetase, MeCP2 methyl-CpG-binding domain protein 2.

(Kuroishi et al. *2011*). According to that model, biotin regulates the assembly of a HLCS-containing multiprotein gene repression complex. This protein complex mediates gene repression through histone methylation and histone deacetylation events, whereas histone biotinylation is a mere side product created by this complex with no meaningful biological functions.

It is now widely appreciated that nutrients may have synergistic effects in gene regulation by epigenomic mechanisms. For example, while folate deficiency alone is typically insufficient to impair gene regulation, a combined deficiency of folate and other methyl donors can have detrimental effects for health (Christman *2003*; Cooney *2008, 2009*; Kirkland et al. *2007*; Wolff et al. *1998*). Evidence also demonstrates the existence of cross talk among biotinylation and methylation marks in maintaining genome stability (Camporeale et al. *2007*a; Chew et al. *2008*; Gralla et al. *2008*; Pestinger et al. *2011*). Specifically, we reported that histone biotinylation is substantially impaired when cytosine methylation marks are erased by treating cells with 5-aza-2′-deoxycytidine but that the depletion of histone biotinylation marks does not affect cytosine methylation (Chew et al. *2008*). These previous studies suggest that biotinylation of histones depends on prior methylation of cytosines and that H3K9me2 marks cross talk with K12-biotinylated histone H4 (H4K12bio) in the repression of long terminal repeats (Figure 3).

Derepression of retroelements by biotin depletion and HLCS deficiency unambiguously links biotin status with cancer risk; however, the causal links between histone biotinylation and the teratogenic effects of biotin deficiency remain to be demonstrated (Mock *2009*; Watanabe *1983*). The human requirement for biotin is unknown (National *1998*). Thus, only recommendations for Adequate Intake are available for biotin. These recommendations are based solely on the intake of biotin in the general, apparently healthy, population (National *1998*). This approach is flawed in the case of biotin where dietary intake data are only crude estimates. Currently, no studies are available that quantified biotin in foods by using chemically specific assays (Zempleni and Mock *2000*), and it is unclear whether intake estimates exceed or underestimate the true biotin intake. Also, the "normal state" is defined by using biotin-dependent carboxylases or urinary metabolites as markers while ignoring the apparently subtle changes occurring at the chromatin level.

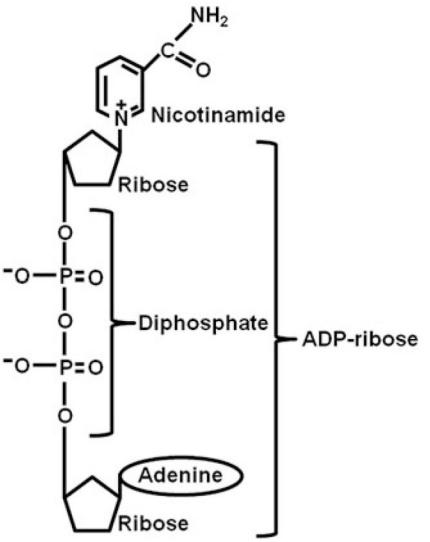

Figure 4. Chemical structure of nicotinamide adenine dinucleotide.

5 Poly(ADP-ribosylation) of Histones

All five major classes of histones are targets for poly(ADP-ribosylation), but the mark is more abundant in histones H1 and H2B than in other classes (Boulikas et al. *1990*; Kim et al. *2005*). Lysine residues in histones are among the prime poly(ADP-ribosylation) sites (Messner et al. *2010*). Poly(ADP-ribosylation) of histones is catalyzed by poly(ADP-ribose) polymerase and depends on nicotinamide adenine dinucleotide (NAD+) as ADP-ribose donor; nicotinamide is released in this reaction (Figure 4). Poly(ADP-ribosylation) is characterized by the binding of multiple subunits of ADP-ribose. Branching of the poly(ADP-ribose) chains may occur every 30–50 residues and involves ribose-ribose 1″ →2′ bonds (Kim et al. *2005*; Miwa et al. *1981*). The abundance of poly(ADP-ribosylation) marks is low in normal cells but can increase substantially in response to treatment with mitogens and DNA damaging agents (Boulikas *1988*; Boulikas et al. *1990*). It has been suggested that poly(ADP-ribosylated) histones are intermediates in nuclear processes that involve DNA strand breaks including repair, replication, and recombination (Boulikas *1990*; Boulikas et al. *1990*; Kim et al. *2005*; Malanga and Althaus *2005*). It is speculated that poly(ADP-ribose) can induce free DNA domains by removing histones from specific nucleosomes whose DNA has been damaged (Boulikas *1993*). The massive negative charge introduced by poly(ADP-ribosylation) might play a role in histone removal. Poly(ADP-ribosylation) of histones is a reversible process; ADP-ribose residues are removed by poly(ADP-ribose) glycohydrolase (Miwa et al. *1981*).

The water-soluble vitamin niacin (as nicotinamide) is an essential building block of NAD+, and poly(ADP-ribosylation) of histones depends on niacin supply. Please note that NAD+ can also be derived from dietary sources other than

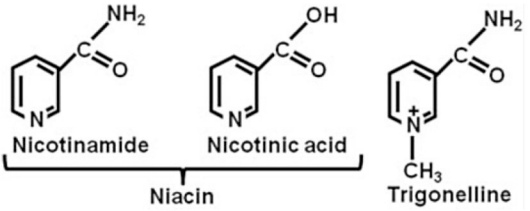

Figure 5. Chemical structures of nicotinamide, nicotinic acid, and trigonelline.

niacin. Humans can convert the essential amino acid L-tryptophan to niacin (National *1998*), and trigonelline can be demethylated to produce nicotinic acid, which is a bioactive niacin derivative (Figure 5). Coffee is a good source of trigonelline, and it can contribute meaningful quantities of niacin to the daily intake (Casal et al. *2000*). Niacin deficiency is rare in Western societies, but might be observed in societies where most of the dietary niacin comes from plant-based foods. In plants, most of the niacin is present as nicotinic acid esters with various macromolecules, which have a low bioavailability (Mason et al. *1973*). Nicotinic acid can be released by alkaline treatment during cooking such as during preparation of corn-based tortillas. There are no published reports linking dietary niacin with the cellular response of DNA strand breaks in humans.

6 Ubiquitination and Sumoylation of Histones

Ubiquitin is a 76-amino acid protein that is covalently attached to K119 in histone H2A and K120 in histone H2B via an isopeptide bond with G76 in ubiquitin (Zhang *2003*). About 5–15 % and 1–2 % of histones H2A and H2B, respectively, are ubiquitinated (Robzyk et al. *2000*; West and Bonner *1980*). Histones H3 and H1 are also targets for ubiquitination, but the abundance of ubiquitination marks in these histones is low (Chen et al. *1998*; Pham and Sauer *2000*). Ubiquitination of histone H2B is catalyzed by Rad6 (or its mammalian orthologs HR6A and HR6B) and Bre1 (or its human orthologs) (Hwang et al. *2003*; Koken et al. *1991*; Pickart *2001*). The enzymes responsible for the ubiquitination of histone H2A have not yet been identified. Apparently, $TAF_{II}250$ plays a role in the ubiquitination of histone H1 (Pham and Sauer *2000*). At least four lysine residues in ubiquitin (i.e., K11, K29, K48, and K63) can serve as attachment sites for additional ubiquitin molecules, thereby creating polyubiquitin chains (Pickart *2001*). The majority of ubiquitinated histone H2A is monoubiquitinated, but polyubiquitinated H2A has also been detected (Nickel et al. *1989*). In contrast, no polyubiquitinated histone H2B has been reported to date. Deubiquitination of histones is catalyzed by isopeptidases such as Ubp8 (Henry et al. *2003*; Wilkinson *2000*); at least 19 histone deubiquitinases have been identified in yeast (DAndrea and Pellman *1998*). Sequential ubiquitination and deubiquitination are both involved in transcriptional activation in a process that is mediated by methylation of K4, K36, and K79 in histone H3 (Briggs et al. *2002*).

Histones are also modified by covalent binding of small ubiquitin-like modifier (SUMO) proteins. SUMO shares 18 % identity with ubiquitin and has a similar 3D structure (Melchior *2000*). Sumoylation of lysine residues in histones is mediated by the ubiquitin-like protein SUMO-1 conjugating enzyme, UBC9, and it plays a role in gene repression. Sumoylation marks can be removed enzymatically by ULP-related proteases (Nathan et al. *2003*).

As of today, there are no published reports linking nutrient intake to aberrant patterns of histone ubiquitination and sumoylation. Theoretically, one can envision scenarios where impaired protein synthesis in cells might affect ubiquitination and sumoylation, but this is pure speculation.

7 Conclusions

While the link between diet and epigenetic mechanisms is most apparent for dietary methyl donors (e.g., folate, choline, and betaine) (Kouzarides and Berger *2007*; Li and Bird *2007*), it is now widely appreciated that other dietary molecules also modify the epigenome. Examples include the biotin-dependent assembly of gene repression complexes (Kuroishi et al. *2011*), the pantothenic acid-dependent generation of acetyl-CoA (Garrett and Grisham *1995*) as a substrate for acetylation of histones, the curcumin-dependent inhibition of histone acetyl transferases (Morimoto et al. *2008*), the niacin-dependent deacetylation of histones by class III histone deacetylases (HDACs) (Boily et al. *2008*; Dokmanovic et al. *2007*), the butyrate- and sulforaphane-dependent inhibition of HDACs (Cummings et al. *2001*; Davie *2003*; Ho et al. 2009; Myzak et al. *2006*), the iron-, riboflavin-, and calcium-dependent demethylation of histones (Tsukada et al. *2006*; Wang et al. *2004*, *2009*), and the niacin-dependent poly(ADP phosphorylation) of histones (Boulikas et al. *1990*; Kim et al. *2005*; Messner et al. *2010*). Nutrient-dependent modification of the epigenome is an exciting field of research, because diet is the one environmental factor that the entire population is exposed to on a daily basis during all stages of life, and where exposure can be modified by lifestyle choices.

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