Proceedings of the Nutrition Society (2012), **71**, 75–83 doi:10.1017/S0029665111003302
 First published online 4 November 2011

A meeting of the Nutrition Society hosted by the Irish Section jointly with the American Society for Nutrition was held at University College Cork, Republic of Ireland on 15–17 June 2011

70th Anniversary Conference on 'Vitamins in early development and healthy aging: impact on infectious and chronic disease'

Symposium 4: Vitamins, infectious and chronic disease during adulthood and aging
Nutritional influences on epigenetics and age-related disease

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Nutritional epigenetics has emerged as a novel mechanism underlying gene–diet interactions, further elucidating the modulatory role of nutrition in aging and age-related disease development. Epigenetics is defined as a heritable modification to the DNA that regulates chromosome architecture and modulates gene expression without changes in the underlying bp sequence, ultimately determining phenotype from genotype. DNA methylation and post-translational histone modifications are classical levels of epigenetic regulation. Epigenetic phenomena are critical from embryonic development through the aging process, with aberrations in epigenetic patterns emerging as aetiological mechanisms in many age-related diseases such as cancer, CVD and neurodegenerative disorders. Nutrients can act as the source of epigenetic modifications and can regulate the placement of these modifications. Nutrients involved in one-carbon metabolism, namely folate, vitamin B_{12}, vitamin B_6, riboflavin, methionine, choline and betaine, are involved in DNA methylation by regulating levels of the universal methyl donor S-adenosylmethionine and methyltransferase inhibitor S-adenosylhomocysteine. Other nutrients and bioactive food components such as retinoic acid, resveratrol, curcumin, sulforaphane and tea polyphenols can modulate epigenetic patterns by altering the levels of S-adenosylmethionine and S-adenosylhomocysteine or directing the enzymes that catalyse DNA methylation and histone modifications. Aging and age-related diseases are associated with profound changes in epigenetic patterns, though it is not yet known whether these changes are programmatic or stochastic in nature. Future work in this field seeks to characterise the epigenetic pattern of healthy aging to ultimately identify nutritional measures to achieve this pattern.

Nutrition: Aging: Epigenetics: DNA methylation: Histone modifications

In the advent of Genome Wide Association Studies, considerable progress has been made elucidating genetic susceptibilities to complex chronic diseases[1]. Despite this progress there is still a substantial proportion of phenotypic disparity that has not been explained by genetics, thus shifting the focus to environmental influences. Nutrition is a major environmental exposure that influences all aspects of health and lifespan[2]. Nutrients are known to alter gene expression and thereby affect phenotype[3]. Epigenetics is a recently highlighted molecular mechanism by which nutrients can alter gene expression[4]. Epigenetic phenomena are heritable and modifiable marks that regulate gene

Abbreviations: CpG, cytosine-guanine dinucleotides; DNMT, DNA methyltransferase; EGCG, epigallocatechin-3-gallate; HAT, histone acetyltransferase; HDAC, histone deacetylase; SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; SIRT1, Sirtuin 1.

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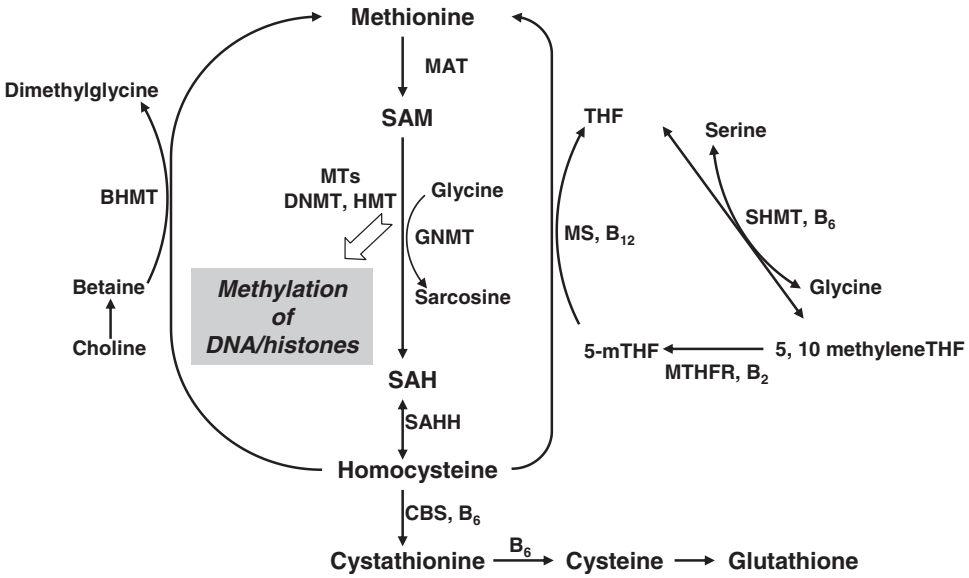

Fig. 1. One-carbon metabolism. S-adenosylmethionine (SAM) is the unique methyl donor for many biological methylation reactions including DNA and histone methylation. S-adenosylhomocysteine (SAH) is an inhibitor of methyltransferases such as DNA methyltransferases (DNMT) and histone methyltransferases. In one-carbon metabolism vitamins B_2, B_6, B_{12} and folate are coenzymes, while methionine, choline, betaine and serine are methyl donors. THF, tetrahydrofolate; 5-mTHF, 5-methyltetrahydrofolate; MT, methyltransferases; HMT, histone methyltransferases; MTHFR, methylenetetrahydrofolate reductase; MS, methionine synthase; SHMT, serine hydroxymethyltransferase; GNMT, glycine *N*-methyltransferase; CBS, cystathionine-β-synthase; MAT, methionine adenosyltransferase; SAHH, S-adenosylhomocysteine hydrolase; BHMT, Betaine homocysteine methyltransferase; B_2, vitamin B_2; B_6, vitamin B_6; B_{12}, vitamin B_{12}.

transcription without altering the underlying DNA sequence[4].

DNA methylation and histone modifications are classical epigenetic phenomena that alter localised DNA compaction to regulate expression[4]. DNA methylation is a biochemical modification of cytosine in DNA with a one-carbon unit (a methyl group) and is typically associated with gene repression[4]. Post-translation modifications of histone tails by methylation, acetylation, phosphorylation, biotinylation and ubiquitination modulate the compaction of the DNA around the core histones and serve as docking sites for transcriptional regulators[4]. Histone modifications can either activate or repress gene expression depending on the type of modification and the placement along the histone tail[4]. Extensive synergy exists between levels of epigenetic marks to determine accessibility of genes to transcriptional regulators[5].

Nutrition affects epigenetic phenomena at multiple levels[4]. First, nutrients act as a source of methyl groups or as co-enzymes for one-carbon metabolism that regulates methyl transfer[6]. B-vitamins including folate, vitamin B_{12}, vitamin B_6 and vitamin B_2 are involved as co-enzymes with methionine, choline, betaine and serine as methyl donors for DNA methylation and histone methylation[7]. Second, nutrients and bioactive food components can directly affect enzymes that catalyse DNA methylation and histone modifications[4]. Third, diet is the ultimate input determining systemic metabolism which modifies cellular milieu leading to alterations in epigenetic patterns[8].

Although it is known that these epigenetic phenomena can be modified by nutrients, their role in physiologic and pathological processes has not been extensively studied through these mechanisms[4]. In this overview, we will focus on the influences of nutrition on epigenetics and how these influences affect the age-related diseases.

Nutrition and DNA methylation

Nutrients, one-carbon metabolism and DNA methylation

DNA methylation is the most studied epigenetic mechanism which entails the addition of a methyl group at cytosine–guanine dinucleotides (CpG)[9]. The reactions involved in DNA methylation are a part of one-carbon metabolism, which regulates the transfer of the one-carbon moiety (methyl group) into biological methylation reactions[4]. B-vitamins are coenzymes in one-carbon metabolism (Fig. 1), supporting that nutrients regulate epigenetic reactions[10]. The amino acid methionine is converted to S-adenosylmethionine (SAM), the unique methyl donor for many biological methylation reactions including DNA methylation[4]. Folate-derived methyl groups are utilised for remethylation of homocysteine to produce methionine[10]. Choline also provides methyl groups for the folate-independent homocysteine remethylation reaction; together these demonstrate how nutrients can serve as the source of epigenetic modifications[11]. After transferring the methyl group, SAM is converted to S-adenosylhomocysteine (SAH), an inhibitor of methyltransferases[11].

https://doi.org/10.1017/S0029665111003302 Published online by Cambridge University Press

Deficiency of B-vitamins, methionine and/or choline can significantly affect DNA methylation by altering the levels of SAM and SAH[4,12,13].

Modifying the intake of these nutrients alters DNA methylation[14]. In animal models, folate deficiency along with aging[15] and multiple B-vitamins deficiency[16] induced genomic DNA hypomethylation in the colon. It is also reported that choline deficiency can change DNA methylation independently[17] or in conjunction with deficiency of other methyl donors[14]. Prolonged intake of diets deficient in sources of methyl groups such as methionine, choline, folate and vitamin B_{12} induce profound genomic hepatic DNA hypomethylation in a rodent model[18]. This model has also demonstrated that a methyl-deficient diet changes histone methylation[19] and microRNA production[20], which may potentiate the development of liver cancer.

Two previous human studies conducted in a metabolic unit demonstrated that marginal folate deficiency can change blood genomic DNA methylation[21,22]. Compared to animal studies, however, evidence demonstrating significant effects of folate supplementation on DNA methylation in free living human subjects is limited. Recently, Pizzolo *et al.*[23] reported that 8-week daily supplementation of 5 mg folic acid did not change DNA methylation in peripheral mononuclear cells despite increases in blood concentrations of folate and SAM and decreases in SAH. This observation suggests that changes in the levels of SAM and SAH may not always induce changes in DNA methylation. Consistently, two previous cystathionine β-synthase-deficient mouse studies demonstrated that increased levels of SAM and SAH are not always correlated with DNA methylation status in a tissue-specific manner[24,25]. It is important to note that different tissues have different susceptibilities to methyl deficiency and therefore this lack of response may not be consistent across all tissues[26].

Other specific nutrients can modify one-carbon metabolism to alter DNA methylation[4]. Retinoic acid is known to affect glycine N-methyltransferase which catalyses the reaction from SAM to SAH[27]. Genome-wide DNA methylation assays demonstrated 166 differentially methylated CpG sites between undifferentiated and retinoic acid-treated human embryonic stem cells[28]. Interestingly, a high-throughput DNA methylation array with neuroblastoma cells *in vitro* demonstrated that 402 gene promoters became demethylated and eighty-eight hypermethylated following retinoic acid treatment[29]. These studies indicate that nutrients can interact with the pathways regulating DNA methylation, though it remains to be determined how nutrients target specific genes for epigenetic modification or, alternatively, if these changes are stochastic in nature.

The trace element Se is an essential component of the antioxidant selenoproteins such as glutathione peroxidases[30]. Se has been known to influence the transsulfuration pathway in one-carbon metabolism which converts homocysteine to cysteine and ultimately glutathione[31]. In a rodent study, Uthus *et al.*[32] found that plasma total homocysteine and cysteine were significantly decreased and glutathione significantly increased by Se deficiency. They also found significantly decreased genomic DNA methylation by Se deficiency in the colon, with concomitant trend for decreased DNA methyltransferase (DNMT) activity ($P<0{\cdot}06$), suggesting a relationship between Se metabolism and DNMT function[33]. Most recently, Zeng *et al.*[34] reported that dietary Se supplementation increases exon-specific DNA methylation of the tumour suppressor p53 in the rat liver and colon thereby suggesting the over-supplementation with Se may increase cancer risk. These observations indicate that Se alters one-carbon metabolism leading to both genomic and gene-specific changes in DNA methylation.

Research into the chemopreventive effects of vitamin D has taken the forefront due to the role of the vitamin D receptor in cell-cycle regulation and differentiation[35]. Recent evidence demonstrates that incubation of MCF-7 breast cancer cells with vitamin D_3, which models oestrogen receptor+ non-invasive breast cancer, reduces the aberrant hypermethylation and restores gene expression of retinoic acid receptor β2[36] and phosphatase and tensin homologue[37]. Although this mechanism remains to be validated *in vivo*, this work indicates that vitamin D can modify gene-specific DNA methylation.

Bioactive food components and DNA methylation

Bioactive food components are compounds consumed in the diet that are not essential for life, though they may have beneficial health effects[4]. Numerous bioactive food components can alter epigenetic patterns through both direct and indirect interactions with the enzymes regulating the placement of epigenetic marks[4]. Research indicates that these interactions can be gene specific in nature, suggesting that the bioactive food compounds may target these enzymes to specific sites within the genome[38].

Genistein is an isoflavone belonging to the flavonoids group of compounds derived from legumes that has demonstrated great potential to regulate the epigenome[39,40]. In the *agouti* mouse model, it is well established that maternal dietary genistein increases the level of DNA methylation at the *agouti* locus and produces more pseudo-agouti black coat-coloured offspring[41]. In mouse embryonic stem cells, genistein does not affect *de novo* methylation occurring between day 0 and day 4, but interferes with subsequent regulatory processes leading to decreased methylation at the uncoupling protein 1 and synaptotagmin-like 1 promoters[42]. This indicates that genistein perturbed the methylation pattern of differentiated embryonic stem cells after *de novo* methylation in a time-dependent manner. Fang *et al.*[43,44] reported that genistein dose-dependently inhibited DNMT activity and partially reactivated genes repressed by hypermethylation such as retinoic acid receptor β, *p16* and *O*-6-methylguanine-DNA methyltransferase in oesophageal squamous cell carcinoma cell lines. Similar effects were observed from the cancer cell lines of colon[45], prostate[46] and cervix[47]. These observations indicate that genistein can modify DNA methylation tissue specifically, gene specifically and life cycle specifically.

Epigallocatechin-3-gallate (EGCG), the primary polyphenol in green tea, is known to have anti-cancer effects through many different mechanisms[48]. One candidate mechanism is the inhibition of DNMT1 leading to

https://doi.org/10.1017/S0029665111003302 Published online by Cambridge University Press

hypomethylation and de-repression of epigenetically silenced genes[49]. Nandakumar *et al.*[50] reported that EGCG reactivates silenced tumour suppressor genes *p21* and *p16* by reducing DNA methylation in human skin cancer cells, resulting in re-expression of mRNA and proteins of silenced tumour suppressors. Wong *et al.*[51] also reported that physiologically relevant concentrations of EGCG can induce the expression of forkhead box P3, a master switch that controls the development and function of regulatory T-cells and Jurkat T-cells *in vitro*. These cells play a critical role in the maintenance of tolerance and the control of autoimmunity. The expression of forkhead box P3 was associated with reduced DNMT expression and DNA demethylation in EGCG-treated cells, suggesting that EGCG may epigenetically modify forkhead box P3 methylation and promote regulatory T-cell induction and expansion to potentially support the immune response to cancer. The DNMT inhibitory effects of EGCG were not as potent as pharmacologic agents such as 5-aza-2′-deoxycytidine, though this is not unexpected as nutrients are not specifically designed as therapeutics. It appears that EGCG provides potentially sustained and longer-term exposure effects with lower toxicity compared with pharmacologic agents, demonstrating the potential benefits of natural substances as chemotherapeutics.

In addition to the direct inhibitory effects of DNMT1, it is also reported that consumption of polyphenols could increase the formation of SAH, which supports an additional mechanism inhibiting DNA methylation by EGCG[52]. Animal studies also demonstrated that EGCG consumption through drinking water can moderately decrease the level of SAM in the intestine[44]. Both observations indicate that the inhibitory effects of EGCG on DNMT1 could be conveyed indirectly by modifying one-carbon metabolism.

Apigenin from parsley[44], curcumin from turmeric[53], lycopene from tomato[54] and sulforaphane from cruciferous vegetables[55] are also known to have an inhibitory effect on DNMT, though their effects are weaker than that of tea polyphenols and genistein. Further studies are needed to determine the optimal nutrients intakes to effectively regulate the epigenome in health.

Nutrition and histone modifications

Bioactive food components and histone modifications

Histone proteins are essential for the packaging of DNA into chromosomes within the nucleus of a cell[56]. Post-translational modifications of histones have been highlighted due to their function to regulate gene expression, especially synergistic interactions with DNA methylation[5]. Further, dysregulated histone acetylation patterns have been associated with many diseases including cancer, cardiac hypertrophy and asthma[56–58]. Among many different types of histone tail modifications, histone acetylation has been the most frequent target to evaluate the epigenetic effects of nutrients, bioactive components and aging[38,59]. Histone acetylation is an epigenetic phenomenon that acetylates lysine residues at the histone tail to alter local DNA compaction, leading to site-specific changes in gene expression[60]. The histone acetylation status is regulated by a family histone acetyltransferases (HAT) and histone deacetylases (HDAC).

Butyrate is generated during the fermentation of dietary fibre in the large intestine[61]. Early in 1977, Riggs *et al.*[62] reported that addition of sodium n-butyrate to tissue culture media increases global histone acetylation in cancer cell lines. Thereafter, sulforaphane, an isothiocyanate from broccoli, broccoli sprouts and cabbage as well as allyl compounds from garlic such as diallyl disulfide and S-allyl mercaptocysteine have been demonstrated to have HDAC inhibitory effects[39]. In light of the development of chemotherapeutic HDAC inhibitors, this suggests potential functional significance of this family of bioactive food components as chemopreventive agents to regulate histone acetylation status[63].

Curcumin, a yellow pigment present in the spice turmeric (*Curcuma longa*), has been linked with multiple beneficial activities with anti-inflammatory, antioxidant and anti-cancer properties[64]. Curcumin is known to have inhibitory activity against HDAC and HAT, with a specifically strong inhibition of HAT in cancer models[64,65]. Kang *et al.*[66] demonstrated that curcumin-mediated HAT inhibitory activity is associated with decreased histone 3 and 4 acetylation in both glioblastoma cancer cells and adult neural-derived stem cells. Functionally, these epigenetic changes were associated with increased apoptosis in cancer cells and promoted neuronal differentiation in stem cells, suggesting possible therapeutic potential in cancer and neurodegenerative diseases.

Aging and nutritional epigenetics

There is a body of literature demonstrating changes in epigenetic patterns over the aging process. It is currently unknown whether these changes are programmatic or stochastic, and whether they are causal or resultant of the aging process in itself[67]. Aging is known to affect DNA methylation in a complex fashion[68]. Total methylcytosine content is prone to decrease by aging, leading to genomic hypomethylation in most vertebrate tissues[69,70], whereas promoter regions tend to undergo paradoxical hypermethylation in many genes[71]. The most plausible mechanism proposes that decreased expression of the maintenance DNMT1 underlies reduced genomic hypomethylation, while increased expression of *de novo* DNMT mediates promoter hypermethylation[72].

In previous studies, aging reduces genomic DNA methylation and increases promoter methylation of *p16* tumour suppressor gene in the mouse colon[15]. Dietary supplementation of the methyl donor folate increased both genomic and *p16* promoter DNA methylation in the aged mouse colon but not in the young, indicating that DNA methylation can be modified by diet in an age-dependent manner[15,73].

Wallace *et al.*[74] investigated the association of blood folate levels with promoter CpG island methylation in normal colorectal mucosa in a multicentre chemoprevention trial of aspirin or folic acid for the prevention of colonic adenoma. For each 10-year difference in age,

https://doi.org/10.1017/S0029665111003302 Published online by Cambridge University Press

they observed a 1·7% increase in methylation level for oestrogen receptor α and a 2·9% increase for secreted frizzled-related protein-1, both of which were statistically significant ($P<0·0001$). These genes are particularly relevant because secreted frizzled-related protein-1 acts as an inhibitor of the *Wnt* signalling, a pathway that is implicated in colorectal carcinogenesis[75]. Oestrogen receptor α activates a transcriptional programme regulating cellular proliferation, and this activity changes with aging due to reductions in sex hormones[76]. Erythrocyte folate levels were positively associated with methylation levels of both oestrogen receptor α ($P<0·03$) and secreted frizzled-related protein-1 ($P<0·01$)[74]. These results suggest that promoter CpG methylation in normal colorectal mucosa correlates with age and erythrocyte folate levels and that erythrocyte folate could be a clinical marker of colorectal DNA methylation.

Normal aging is accompanied by a profound loss of histone proteins from the genome that hypothetically would have a profound effect on genomic structural integrity and the regulation of transcriptional programmes[77]. Previous work in yeast models demonstrates increased overall histone expression promotes lifespan, underscoring the importance of histone-mediated regulation of DNA architecture in health[78].

Sirtuins, a group of conserved NAD+-dependent deacetylases, promote longevity in many organisms[79]. Sirtuin 1 (SIRT1) is known to deacetylate histones and non-histone proteins, thereby regulating metabolism, stress resistance, cellular survival, cellular senescence/aging, inflammation-immune function, endothelial functions and circadian rhythms[79]. Yeast silent information regulator 2, related to the mammalian homologue SIRT1, establishes and maintains chromatin silencing by removing acetylation at histone H4 at lysine 16 (H4K16)[80]. Dang *et al.*[81] reported an age-associated decrease in silent information regulator 2 protein accompanied by an increase in acetylation at H4K16, resulting in compromised transcriptional silencing.

Naturally occurring dietary polyphenols, such as resveratrol, curcumin, quercetin and catechins, have been shown to activate SIRT1 in a variety of models[82]. Since the activation of SIRT1 by polyphenols is beneficial in various cellular functions in response to environmental and pro-inflammatory stimuli, the regulation of SIRT1 activity by dietary polyphenols is a promising strategy against chronic inflammation, which plays an aetiological role in many age-related diseases.

Li *et al.*[83] found that histone H3 acetylation at lysine 9 and 14 sites, H3K9 and H3K14, respectively, which can be modulated by extrinsic signals, plays a key role in regulating mesenchymal stem cell aging and differentiation. Human mesenchymal cells in early and late passages were examined for their expression of osteogenic genes and genes involved in self-renewal and proliferation to determine their *in vitro* spontaneous differentiation towards the osteoblast lineage *v.* multi-potent potential, respectively. Altered expression of these genes were closely associated with epigenetic dysregulation of H3K9 and H3K14 acetylation but not with methylation of CpG islands in the promoter regions of most of these genes, suggesting that histone acetylation may be more sensitive to cellular senescence than DNA promoter methylation.

Nutritional influences on age-related diseases through epigenetics

Epigenetic patterns are heavily influenced by the environment; due to dietary requirements for sustenance, it follows that nutrition represents a substantial daily environmental input[84]. Nutrition influences our physiology over the course of the entire lifecycle, with particular phases representing times that are more sensitive to nutritional inputs[85]. Most recent studies indicate that the effects of nutrition in early life alters programmes leading to differential disease susceptibilities later in life which may be conveyed through epigenetic mechanisms[86]. Furthermore, the majority of age-related chronic diseases in the developed world are multi-factorial with substantial lifestyle components, indicating a significant role for nutritional epigenetics in their development[87].

Sie *et al.*[88] investigated the effect of maternal and post-weaning folic acid supplementation on colorectal cancer risk in the offspring. The data suggested for the first time that maternal folic acid supplementation at North American post-fortification levels recommended to women at reproductive age protects against the development of colorectal cancer in the offspring. This protective effect may be mediated in part by increased global DNA methylation, decreased epithelial proliferation and reduced DNA damage in the colorectum. However, the same group reported that high intrauterine and post-weaning dietary exposure to folic acid may increase the risk of mammary tumours in the offspring, mediated in part by altered DNA methylation and DNMT activity[89]. These results indicate that different tissues have variable responses to folic acid supplementation, again emphasising the tissue specificity of epigenetic regulation.

The disruption of the HAT and HDAC balance can also be a major mechanism underlying changing epigenetic patterns with functional disease output, including cancer and neurodegeneration[90]. In a rodent study, aged mice display specific deregulation of histone H4 at lysine 12 (H4K12) acetylation during learning and fail to initiate a hippocampal gene expression programme associated with memory consolidation. Restoration of deregulated histone acetylation reinstates the expression of learning-induced genes and recovers cognitive functions, purporting the importance of epigenetic histone regulation in neurological function[91]. Interestingly, Govindarajan *et al.*[92] reported that butyrate, which is known to have an HDAC inhibitory effect, improves memory function in an Alzheimer's disease mouse model when administered at an advanced stage of disease.

As aberrant histone deacetylation has been demonstrated to silence critical genes in carcinogenesis, HDAC inhibitors have great potential as new anti-cancer drugs due to their ability to modulate transcription[93]. HDAC inhibitors such as trichostatin-A induce apoptosis and suppress cancer cell growth by affecting the acetylation status of tumour suppressor genes in cancer cell lines, though their specificity to gene targets is not well understood[94,95].

https://doi.org/10.1017/S0029665111003302 Published online by Cambridge University Press

Sulforaphane and curcumin have similar effects on cancer cells by modifying histone acetylation[64,96]. Sulforaphane inhibits HDAC activity *in vivo* and suppresses tumorigenesis in APC^{min} mice[97]. *In vitro*, sulforaphane exerts differential effects on cell proliferation, HDAC activity and downstream targets in both normal and cancer cells[96]. Accompanied by reduced HDAC4 expression and activity, curcumin induces apoptosis and cell cycle arrest in medulloblastoma cells *in vitro* and reduced tumour growth in *in vivo* medulloblastoma xenografts[98]. These observations indicate that both sulforaphane and curcumin or any other bioactive components that have histone modification effects have the potential to be developed as cancer chemotherapeutic agents. Similar to trichostatin-A, it is important to determine the gene specificity of this nutrient-induced HDAC repression. Furthermore, studies need to determine whether the amounts of these nutrients can be consumed in the whole diet at physiological quantities or if supraphysiological supplements are required. The timing of nutrient exposure needs to be determined as well; are these nutrients effective at reducing carcinogenesis prior to cancer development, during early carcinogenesis or in late-stage disease?

Nutrition, systemic metabolism and epigenetics

In contrast to single-nutrient–single-gene interactions, systemic metabolism also plays a role in determining diet–gene interactions[8]. In light of the increasing prevalence of obesity and subsequent development of type II diabetes mellitus, a large proportion of the population is being exposed to chronic hyperglycaemia and impaired lipid homoeostasis leading to a substantially different cellular milieu[99]. Epigenetic mechanisms are currently being investigated within the scope of the metabolic profiles characteristic of obesity and its associated sequellae[100]. Exposure of macrophages to high glucose to model hyperglycaemia caused recruitment of lysine-specific demethylase 1H3 and a reduction in H3K9 methylation at the NF-κB-*p65* gene promoter leading to an increased expression of this transcription factor[100]. Similar results were observed in both endothelial cells and vascular smooth muscle cells[101]. These epigenetic marks were sustained following return to normoglycaemic conditions, lending support to the notion of metabolic memory that has been observed in clinical studies describing persistent vascular injury following previous poor metabolic control[102]. Furthermore, human vascular smooth muscle cells treated with high-glucose conditions demonstrated activating histone 3 at lysine 4 (H3K4) dimethylation marks and increased gene expression at the NF-κB targets, monocyte chemotactic protein-1 and *IL-6*, indicating epigenetic mechanisms underlying the hyperglycaemia-induced vascular inflammation[103].

Hypercholesterolaemia and circulating oxidised LDL are also systemic metabolic characteristics that potentiate the development of age- and obesity-related chronic diseases[104]. Consistent with the notion that chronic inflammation plays an aetiological role in atherogenesis, incubation of human umbilical-cord vein endothelial cells with oxidized LDL also led to altered epigenetic marks at inflammation-related genes[105]. Cells exposed to oxidized LDL demonstrated recruitment of cAMP-response-element-binding protein-binding protein/*p300* and reduced HDAC1 and HDAC2 binding leading to increased activating histone marks at the IL-8 and monocyte chemoattractant protein-1 promoters. *In utero* exposure to hypercholesterolemia from $ApoE^{-/-}$ mothers led to differential global histone methylation patterns in offspring vascular smooth muscle cells and endothelial cells[106]. These effects were further potentiated when offspring were fed a high-fat diet inducing hypercholesterolemia. Studies in primate models have demonstrated that maternal high-fat diet leads to altered hepatic histone modifications and epigenetic enzyme expression, with gene-specific changes localised to genes involved in circadian rhythms, lipid metabolism and heat shock responses[107]. Taken together, these studies demonstrate that both trans-generational and post-natal exposure to the metabolic characteristics of high-fat diet and hypercholesterolaemia lead to differential epigenetic patterns in various tissues which may potentiate chronic disease development later in life.

Conclusion and future perspectives

The field of nutritional epigenetics is further elucidating the nature of gene–diet interaction, thus providing support for the role of nutrition and lifestyle in determining phenotype from genotype[10]. Aging is associated with substantial changes in epigenetic patterns and recent work is implicating epigenetic mechanisms in the aetiology of many age-related diseases[108]. In some cases, evidence suggests that nutrients may slow down the age-related epigenetic changes and delay disease onset, though it is too soon to draw broad conclusions[86]. Future work seeks to characterise the epigenetic pattern of healthy aging and to identify nutritional measures to achieve this pattern.

Nutritional epigenetics is a field in its infancy; there is much research to be done that has great potential to yield findings with significant public health implications. Questions that remain to be answered include determining the tissue specificity of nutrient exposures, particularly as many studies have been performed *in vitro* with single-cell types. Specific timing of nutritional exposures and their concomitant efficacy of epigenetic regulations needs to be examined. Accumulating evidence supports the notion that maternal nutrition is critical in epigenetic programming of offspring[109], but other time periods of the lifecycle need to be investigated. This is particularly critical with respect to nutritional epigenetic interventions for diseases; should exposure be prior to disease development, implicating the importance of lifetime dietary patterns, or can there be effective therapeutic effects following disease diagnosis? Last, the question remains as to whether nutrition and aging modulate epigenetic patterns in a programmatic fashion or if the effects are more stochastic in nature. Genome Wide Association Studies technology that identified original gene–diet interactions is now being applied to nutritional epigenetics, embarking into the arena of Epigenome-Wide Association Studies which will support these endeavours[2].

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There is significant impetus to continue research within the field of nutritional epigenetics as the findings may support significant public health applications. While DNA sequences cannot be changed and aging cannot be avoided, individuals have the ability to change their diet. Nutrition has the potential to modulate the interactions between genes, aging and disease susceptibility through epigenetic mechanisms. Future work promises fruitful results underlying the role of nutrition guiding healthful aging phenotypes from genotype.

Acknowledgements

This material is based on work supported by the U.S. Department of Agriculture, under agreement no. 58-1950-7-707. Any opinions, findings, conclusion, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the U.S. Department of Agriculture. The authors declare no conflicts of interest. This project was supported in part by the National Institute of Health Grant R01 AG025834 (to S.W.C.). L.K.P., S.F. and S.W.C. participated in the conception, design and drafting of the manuscript.

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https://doi.org/10.1017/S0029665111003302 Published online by Cambridge University Press