Journal of Nutrition & Intermediary Metabolism 16 (2019) 100098

Contents lists available at ScienceDirect

Journal of Nutrition & Intermediary Metabolism

journal homepage: www.elsevier.com/locate/jnim

Relationship of nutrigenomics and aging: Involvement of DNA methylation

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HIGHLIGHTS

- To improve understanding of how dietary factors influence global DNAm in healthy and diseased populations.
- Quantification of global DNAm is necessary to facilitate comparability across epigenetic studies.
- Epigenetic modifications during aging or CR are unknown, this is an area with great potential, because epigenetic-driven changes in gene expression as a result of diet or lifestyle are thought to contribute to lifelong health.

ARTICLE INFO

Keywords:
Epigenetics
Nutrition
Aging
DNA methylation

ABSTRACT

Complex epigenetic mechanisms are involved in aging and longevity. Nutrition has a strong impact upon epigenetic processes and, therefore, holds promising roles in regulation of longevity and aging. In this review, we combine recently published information regarding nutrition and its impact on epigenetically mediated mechanisms involved in metabolic responses that lead to aging in a narrative way with questions and future directions at the end of each section. The paper strictly focuses on modulation of DNA methylation (DNAm) by nutrients, and its role in regulation of aging process. Understanding the mechanisms by which nutrition influences epigenome is crucial for the development of preventive and interventional strategies to increase well-being and health for a sustainable longevity.

1. Introduction

Nutrient inputs play an important role in mediation of epigenetic mechanisms and hence resulting in phenotypic changes throughout our entire life and seem to be responsible, in part, for the biological changes that occur during aging. Recent studies considerably enriched our understanding of the relationship between nutrition, aging and gene-nutrient interactions that continuously shape our phenotype [1]. Research trials clearly indicate that nutrition modulates epigenetic events associated with various diseases (e.g., cancer, obesity, and diabetes). However, there is an indirect epigenetic link between nutrition and longevity and, therefore, biologic plausibility should hypothesize the epigenetic role of nutrition in altering longevity [2].

Nutrigenomics is "*the study of bidirectional interactions between genes and diet*". The study of epigenetics encompasses all those processes that induce heritable changes in gene expression without a change in the DNA nucleotide sequence [3]. The major epigenetic mechanisms are DNA methylation (DNAm), histone modification and non-coding RNA [4,5]. Such processes are involved in the regulation of tissue-specific gene expression, cell differentiation and genomic imprinting. However, epigenetic dysregulation is frequently seen with ageing [4,6]. Relatively little is known about the factors that initiate such changes. However, there is emerging evidence that the early life environment in general and nutrition in particular, can induce long-term changes in DNAm resulting in an altered susceptibility to a range of ageing associated diseases [7].

The long standing significance and consequences of nutrition affect the individuals themselves as well as the subsequent generations. Malnutrition is a detrimental factor for progression and development of long-lasting diseases that may adversely affect the life-span. As an example, it is quite clear since 1930s that the life-span of rodents in laboratory can be increased by balancing food consumption in terms of

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https://doi.org/10.1016/j.jnim.2019.100098
Received 7 October 2018; Received in revised form 7 April 2019; Accepted 14 May 2019

controlled energy intake [8]. Since then, scientists have been studying the impact of food, overfeeding and underfeeding in different and broad spectrum forms of life from yeast to primates [9,10]. In particular, caloric restriction (CR), within the range of physiological requirements, has been one of the nutrition research areas with regards to longevity which holds prime interest [11,12]. CR is known to increase the healthy life-span in a wide spectrum of organisms i.e., yeast, mice and non-human primates [13,14]. All the health effects of CR are linked to reprogramming of major metabolic pathways causing it to utilize the fuel efficiently, and it also reduce the oxidative damage to macromolecules [15,16].

While studies of the function and characterization of genomic modification in diet-associated longevity are just emerging, there is a need of better understanding this complex linkage of nutrition, genome and aging to provide favourable clinical prospects for prevention of human aging and related disorders. We have tried to present an overview of the previous published research on nutrigenomics and its impact on aging related mechanisms. As DNAm is the basis of nutrigenomics, been given more emphasis in this paper. We have also provided some definitions to the basic concepts such as ‘nutrigenomics’ and ‘epigenetics’ with detailed description of their scope and current trends. At the end of each section, we have provided some research questions and/or potential hints for future directions based on the published literature.

2. Nutrigenomics and nutrigenetics: two sides of a coin

The gene-nutrient interaction has been a subject of interest for a very long time. New insights about the influence of nutrients on the genes and vice versa were introduced. There are few major questions that provided a basis for further research studies. These questions include: 1) will gene expression at cellular level in response to metabolic process, influence the health of an individual? 2) Are gene expression and metabolic response inducing by the interaction between genotype and environment/nutrient? 3) How does this interaction process occur between gene and nutrient and how it leads to the prescription of specific diets or nutrition therapy for each individual?

Much of the research works done so far and has been surrounding these questions. In order to answer these questions, ‘nutrigenomics’ was introduced. The studies on ‘nutrigenomics’ are focused on the effects of the nutrients over the genome, proteome, and metabolome [17]. It has been found during numerous studies that humans have 99.9% identity between their genomes. A distinct difference between their weight, height, eye colour/hair, and other features is only 0.1% of the gene sequence and this difference, among other factors, also determines the nutritional requirements and the risk of developing diseases [17].

More explicitly, ‘nutrigenomics’ may be defined as “*the study of the genome-wide influences of nutrition or dietary components on the transcriptome, proteome and metabolome, of cells, tissues or organisms, at a given time*” [18–24]. Nevertheless, this definition needs to be broadened in order to encompass nutritional factors that protect the genome from damage because, ultimately, nutrigenomics has also to be accounted as concerned with the impact of dietary components on the genome, the ‘proteome’ (the sum total of all proteins), and the ‘metabolome’ (the sum of all metabolites). As in pharmacogenomics, where a drug will have diverse impacts on different segments of the population, researchers recognize that only a portion of the population will respond positively to specific nutritional interventions, while others will be unresponsive, and still other could even be adversely affected.

Equally important another area of such studies is ‘epigenomics’, which may be defined as “*the study of the complete set of epigenetic modifications in a cell or in a tissue at a given time”* [25]. The ‘epigenome’ consists of chemical compounds that modify or mark the genome in such a way that it can indicate, what a cell can do and where and when to do it. These marks are called ‘epigenetic marks’. These ‘epigenetic marks’ are passed from one cell to another when they divide themselves and thus will be passed from generation to generation. These signatures are influenced by genotype in the surrounding media, e.g. (environment, diet, and drugs) and will determine the phenotype.

There is still another term used i.e., ‘nutrigenetics’, which on the other hand, aims to understand “*how the genetic makeup of an individual coordinates their response to diet*” [18–27]. In this way ‘nutrigenetics’ considers underlying genetic polymorphisms or in other words, ‘nutrigenetics’ embodies the science of identifying and characterizing gene variants associated with differential responses to nutrients, and relating this variation to disease states [23]. Therefore, both disciplines (nutrigenomics and nutrigenetics) aim to unravel diet/genome interactions; however, their approaches and immediate goals are distinct. ‘Nutrigenomics’ and ‘nutrigenetics’, as often quoted, “two sides of a coin”. Nutrigenomics' looks at the target goal of ‘personalized nutrition’ to be realized, the effects of diet on whole-body metabolism (i.e., genes, proteins, and metabolites), while ‘nutrigenetics’ looks at the influence of genotype on nutritionally related disease [24]. It is important to understand the relationship between ‘nutrigenomics’, ‘nutrigenetics’ and other sciences particularly those with an “-omics” suffix (e.g., ‘transcriptomic’, ‘proteomics’, ‘metabollmics’, etc [28].

3. DNA methylation and post-translational histone modification

DNAm, a characteristic feature of many eukaryotic genomes, consists of the addition of a methyl group at the carbon 5′ position of the cytosine within the cytosine-guanine (CpG) dinucleotide in a complex reaction that probably involves the flipping of the cytosine base out of the intact double helix. Typically, DNAm occurs in CpG-di-nucleotide rich regions (CpG Island) [29]. DNAm is the fundamental mechanism for the epigenetic control of gene expression and the maintenance of genomic integrity [30]. Therefore, an evaluation of DNAm status is important for the study of cell growth regulation, tissue specific differentiation [29] carcinogenesis [31] and ageing. As shown, human DNA methylation has an important role in regulation of genes expression, maintaining DNA stability and integrity in most of the biological processes, i.e. cell-proliferation, genomic imprinting, normal development and aging [11,32].

Modification of histone basically includes histone-acetylation and methylation. Caloric restriction activates SIRT1 and HDAC1 genes affected by deacetylation, changes the expression of key genes i.e. Foxo, p53, Ku70, p16^{INK4a} and PGC-1a. In regulating of key genes i.e. hTERT and p16^{INK4a}, histone modification also plays an important role. Consequently, during caloric restriction (CR) for example, epigenetic regulation actively reverses aberrant gene expression, which adds to CR associated aging delay and longevity.

4. Regulation of ageing associated epigenetic mechanisms by nutrition

Diet plays a central role in DNAm (Fig. 1), which is common throughout the human life. Although, energy is the main driving force for all such biochemical processes while micronutrients are the major players in DNAm. Most of the previous studies in elucidating the role of energy intake have used the caloric restriction (CR) and its effects on DNAm, For example, in pancreatic acinar cell's DNAm was compared in between caloric restricted rats and control rats (nourished *ad-libitum*) recommended that caloric restriction increased methylation level of proto-oncogenes such as Ras [33]. Similarly, in human cells an aging-associated and tumor suppressor gene, p16INK4a, DNA hyper-methylation was observed on its binding site E2F-1. This hyper-methylation stops the E2F-1 factor from binding to p16INK4a promoter, causing down-regulation in p16INK4a, contributing to CR induced longevity. In response to caloric restriction, DNMT1 activity increases and it corrects the decreased methylation level during aging [13].

Several nutrients are the source of epigenetic alterations and they can regulate the placement of these alterations (Table-1). Fenech and

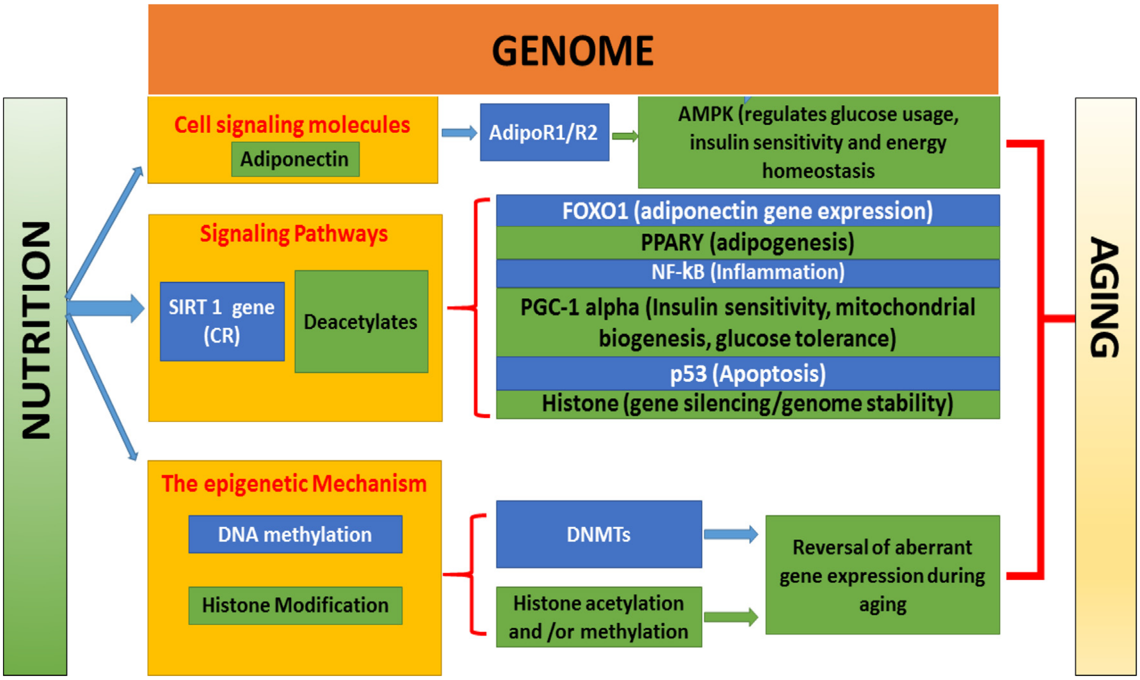

Fig. 1. Adaptive responses of genomes to nutrition that are linked with aging.

colleagues identified nine key nutrients that may affect genomic integrity in various ways [34]. When consumed in high amount in food, six of these nutrients (folate, vitamin B_{12}, niacin, vitamin E, retinol, and calcium) are associated with a reduction in DNA damage, whereas three others (riboflavin, pantothenic acid, and biotin) are associated with an increase in DNA damage to the same extent observed with occupational exposure to genotoxic and carcinogenic chemicals. The authors concluded that the observations indicate that nutritional deficiency or excess can cause DNA damage on its own and that effects are of the same magnitude as that of many common environmental toxicants.

In one carbon metabolism, nutrients like folate, vitamin B6, vitamin B12, methionine, riboflavin, betaine and choline are involved in DNA-methylation by regulating levels of the universal methyl donor S-adenosylmethionine (SAM) and methyltransferase inhibitor S-adenosyl homocysteine. The folate and choline-mediated methylation pathways intersect at the formation of methionine, the precursor of SAM, from homocysteine. Successful recycling of methionine from homocysteine is essential for the procurement of SAM to subsequent methylation reactions. Because methyl-donors and methylation cofactors are obtained from the diet, and an imbalance or deficiency can lead to elevated plasma homocysteine [35,36], which is a cause of oxidative stress and an established marker of cardiovascular disease risks [37]. Additionally, high homocysteine concentrations could adversely influence kinetics of the methylation reaction [38,39]. Other nutrients and bioactive food components such as retinoic acid, resveratrol, curcumin, sulforaphane and tea polyphenols can modify epigenetic patterns by altering the levels of S-adenosylmethionine and S-adenosylhomocysteine or leading the enzyme that catalyse DNAm and modification of histone.

Folate is among the nutrients most often cited as critical to genomic stability. Some controlled intervention studies showed [40,41] that folate intake greater than 200 µg/day is required for chromosomal stability. It was argued that reducing plasma folate concentration from 120 to 12 nmol/L *in vitro*, which is considered to be within the equivalent adequate range *in vivo*, causes as much genome damage as that induced by an acute exposure to 0.2 Gy of ionizing radiation. It was concluded that even moderate folate deficiency within the physiological range causes as much DNA damage in cultured lymphocytes as ten times the annual allowed limit of exposure to X-rays and other forms of low linear energy transfer ionizing radiation for the general population. The typical plasma folate concentration for most populations is only 10–30 nmol/L, a level adequate to prevent anaemia “but apparently insufficient to minimize chromosomal damage.”

5. Body composition and DNA methylation

So far, most studies in ‘epigenetics’ and ‘nutrigenetics’ have been conducted using animal models which provide evidence that changes in DNAm patterns can influence risk of obesity and related diseases [77–80]. As an example, in the yellow Agouti mouse, the protective effect of methyl-donor micronutrient intake against obesity was specifically due to increased methylation of the *Avy* metastable epiallele [77,79]. Almost similar results have been achieved in humans, where researchers have identified alterations in gene-specific methylation that were related to weight change [81,82] and weight status [83,84] in obese patients. While gene-specific changes provide insight into regulatory pathways, changes at the global level are also important to consider because global DNAm is responsive to environmental modifications [85], and genomic stability has health implications beyond the function of a specific gene. Despite findings that global DNAm is related to several obesity-related diseases including cardiovascular disease [86–88], metabolic syndrome [89], and diabetes [42]. Little is known regarding the direct relation between global DNAm and body size. Current knowledge consists mostly of mixed findings from cross-sectional studies in adult populations [87–91].

Some studies from maternal-infant dyads have been conducted to investigate relations of perinatal characteristics, including birth weight, with cord blood DNAm [92–94]. One study reported that high and low birth weight, as well as premature birth was associated with significantly lower cord blood DNAm [94]. However, inference from perinatal studies is limited, as it is not known whether functional consequences of these associations contribute to obesity in later life. To date, the largest gap in literature is the lack of longitudinal studies to assess the temporal relation between global DNAm and subsequent changes in anthropometry. While cross-sectional studies provide a preliminary idea of how global DNAm and body size are related, they cannot overcome the potential for reverse causation bias. Furthermore, little is known regarding global DNAm and weight status in children.

Table 1
Macro and micro-nutrients as DNA methylation agents.

Micronutrient	Reference (Author/year)	Results
High fat diet	Zhao et al., 2014 [42]	Maternal high fat feeding increased fetal liver triglyceride accumulation. Likewise, hepatic histology correlated with non-alcoholic liver disease induced by DNA methylation in MAPK.
Protein Methionine (essential amino acid)	Peterson and Laniel, 2004 [43]	Play a unique role in epigenetic processes by serving as the penultimate methyl donor for mammalian methylation reactions. High intakes of dietary MET influences CpG methylation in DNA.
Folate	Choi and Mason, 2002; Miller et al., 1994; De Cabo et al., 1995; Kim, 2004; Harnack et al., 2002; La Vecchia et al., 2002; Konings et al., 2002; Fuchs et al., 2002; Song et al., 2000; Kim et al., 1996; Fang and Xiao, 2003; Jacob et al., 1998; Trasler et al., 2003; Rampersaud et al., 2000; van England et al., 2003; Jhaveri et al., 2001; Bhave et al., 1988; Zapisek et al., 1992; Sohn et al., 2003; Davis and Uthus, 2003; Cooney et al., 2002; Pufulete et al., 2003 [44–65]	Plays a central role in one carbon metabolism
	Price RJ et al., 2015 [66]	Folic acid induced increased BRCA1 protein expression in Hs578T.
	Li W et al., 2015 [67]	Folic acid increases methylation potential and DNMT activity, modifies DNA methylation and ultimately decreases APP, PS1 and Aβ protein levels.
Selenium	Davis et al., 2000 [68]	Modulates DNA methylation in both CRC cell lines and in colon tissue of rats by inhibition of DNMT expression; deficiency decreased DNA methylation in Caco-2 cells and in rat liver and colon
	Davis and Uthus, 2003 [63]	The adverse effects of folate deficiency, including alterations in one-carbon metabolism
	Lin W et al., 2015 [69]	Associated with a decreased risk of breast cancer and this beneficial effect was limited to women with CC genotype of MTHFR rs1801133.
	de Miranda JX et al., 2014 [70]	Epigenetic mechanisms represent relevant molecular targets involved in selenium inhibitory effects in breast cancer cells.
Phytochemicals & Polyphenolics (Gensing)	Zhang Y et al., 2013 [71]	They studied a potential epigenetic mechanism by which dietary GEN controls the responses of WNT genes during carcinogen induction, which involves DNA methylation, histone modifications and their interactions at the regulatory region of gene.
Flavonoid glycosides	Lewinska A et al., 2015 [72]	They observed that flavonoid glycosides can cause DNA hypomethylation with capability to modulate cancer cell epigenome leading to changes in the gene expression patterns.
Curcumin	Shu L et al., 2011 [73]	Their study provides data on the CpG demethylation ability of CUR on Neurog1 by activating its expression. This suggests a probable epigenetic modifying role for this phyto-chemical compound in human prostate cancer cells.
Quercetin Diosmin	Ma L et al., 2004 [74]	Their study suggests that quercetin prevents the formation of colony, growth and hypermethylation of bladder cancer cell lines. Quercetin-induced apoptosis may be linked with a decrease in mutant p53 and Survivin proteins.
	Lewinska A et al., 2015 [72]	They found that diosmin is the most intoxicating genotoxic agent in DU145 cells, sequentially results in its pro-apoptotic activity.
Food contaminants such as arsenic	Rager JE et al., 2015 [75]	Both the arsenic and cancer-associated genes are enriched for the binding sites of common transcription factors known to play roles in carcinogenesis, demonstrating a novel potential mechanistic link between iAs exposure and bladder cancer.
	Pelch KE et al., 2015 [76]	Altered gene expression observed in Cd and iAs transformed cells may result from altered DNA methylation status.

Paediatric populations are an ideal setting to examine this relation, as the childhood 'epigenome' has endured fewer environmental exposures that could obscure the associations of interest. However, animal models indicate that DNAm profiles are sensitive to external stimuli, such as dietary intake, during specific postnatal periods, and that the epigenetic changes can influence body composition [78], because adipocyte quantity is not set until early adolescence [95]. The childhood years represent a particularly important time frame to elucidate molecular mechanisms involved in adipogenesis for obesity intervention efforts.

6. Research questions and future directions

Being relatively new emerging nutritional sciences, 'nutrigenomics' and 'nutrigenetics' have a long way to go to answer yet many questions. It is not unique with these sciences as all other sciences have also been developed in this fashion. The main challenges these sciences are having ahead include a clear and well-defined relationship between our genome and nutrition in an abstract and quantifiable manner. The following goals of 'nutrigenomics' and 'nutrigenetics' research can be defined:

1. Identification of transcription factors that function as nutrient sensors and the genes they target; the elucidation of the signalling pathways involved, and characterization of the main dietary signals;
2. Measurement and validation of cell and organ specific gene expression signatures of the metabolic consequences of specific micronutrients and macronutrients;
3. Elucidation of the interactions between nutrient related regulatory pathways and pro-inflammatory stress pathways, to understand the process of metabolic dysregulation that leads to diet-related diseases;
4. The identification of genotypes that are risk-factors for the development of diet related human diseases (such as diabetes, hypertension or atherosclerosis) and quantification of their impact; and the use of nutritional systems biology to develop biomarkers of early metabolic dysregulation and susceptibility (stress signatures) that are influenced by diet.

In light of evidences that DNAm is reversible via dietary changes [96], pointing towards opportunities for public health intervention. Elucidating the role of DNAm in linear growth would improve understanding of regulatory mechanisms involved in human development, and may also provide insight on disease aetiology. The positive association between height and Alu methylation in the MESA population is noteworthy, since short adult stature is associated with risk of some chronic diseases, such as cardiovascular disease [77,79]. Additionally, the fact that children of underweight mothers exhibited lower global DNAm than their counterparts suggests that the documented relation between gestational nutrient restriction and risk of adult chronic diseases [97] may be mediated by 'epigenetic' mechanisms.

Primary healthcare settings are a practical venue to target underweight reproductive-aged women for nutrition education. Such interventions aimed at modifiable 'epigenetic' mechanisms are relatively inexpensive, readily available, and could become a public health priority. Evaluating the influence of dietary interventions on DNAm profiles and subsequent changes in body composition will improve knowledge of biological pathways that underlie excess weight gain. Findings will have important implications for the development of effective intervention programs, as well as clinical recommendations aimed at improving cardio-metabolic health and preventing adult chronic diseases.

7. Conclusion

Although DNAm occurs mainly during intrauterine development, it is responsive to environmental modifications and can change sporadically throughout lifespan [98], although the changes or modulation in later age maybe challenging if not impossible. The limited and discordant findings gathered so far point towards the need to improve understanding of how dietary factors influence global DNAm in healthy populations. This will certainly pave the way to understand it in the diseased individuals. Additionally, use of reliable and reproducible laboratory techniques to quantify global DNAm is necessary to facilitate comparability across epigenetic studies in order to further refine the existing techniques. Epigenetic modifications can be the result of aging, stress and diet [99–101]. Although precise targets for epigenetic modifications during aging or CR are unknown, this is an area with great potential, because epigenetic-driven changes in gene expression as a result of diet or lifestyle are thought to contribute to lifelong health [99]. In fact, histone deacetylases, like sirtuins, modify epigenetic patterns [100]. DNA methylation age measures the cumulative effect of an epigenetic maintenance system. This novel epigenetic clock can be used to address a host of questions in developmental biology, cancer and aging research [102].

Conflicts of interest

All authors declare no conflict of interest regarding this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jnim.2019.100098.

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