Nutritional influence on epigenetics and effects on longevity
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\textbf{Purpose of review}
This review synthesizes recently published information regarding nutrition and its impact upon epigenetically mediated mechanisms involved in longevity and aging.

\textbf{Recent findings}
Recent studies enriched considerably our understanding of the relationship between aging and gene–nutrient interactions that continuously shape our phenotype. Epigenetic mechanisms play an important role in mediating between the nutrient inputs and the ensuing phenotypic changes throughout our entire life and seem to be responsible, in part, for the biological changes that occur during aging. Less is known about the epigenetic role that nutrients have in directly influencing longevity and aging. However, recent studies clearly indicated that because nutrition modulates epigenetic events associated with various diseases (e.g., cancer, obesity, and diabetes), there is at least an indirect epigenetic link between nutrition and longevity and, therefore, biologic plausibility to hypothesize the epigenetic role of nutrition in altering longevity. Apart from limited human studies, promising animal studies brought us much closer to understanding how nutrition could have such an impact upon longevity and aging.

\textbf{Summary}
Complex epigenetic mechanisms are involved in aging and longevity, directly or indirectly via disease mechanisms. Nutrition has a strong impact upon epigenetic processes and, therefore, holds promise in having important roles in regulating longevity and aging.

\textbf{Keywords}
aging, disease, epigenetics, longevity, nutrition

Introduction
Longevity (length of life) is dictated by complex and heterogeneous factors including genetic blueprint, aging, health state, and various interactions with the environment, including nutrition (reviewed in [1]). Gene–nutrient interactions are, in part, responsible for regulating metabolic processes that are involved in the initiation and development of pathological conditions such as obesity and the metabolic syndrome, cardiovascular diseases, cancer, and alterations of the immune response [2–6]. One of the best studied mechanisms of nutrient–gene interactions is the epigenetic involvement (heritable patterns of phenotypic changes, maintained by other mechanisms than changes in DNA sequence) (Fig. 1a) [7]. Such epigenetic mechanisms are increasingly considered today as playing important roles in shaping both physiological and pathological aging [8]. Two main mechanisms are coding epigenetic information (DNA methylation and histone modifications such as acetylation, methylation, phosphorylation, and ubiquitination), which is then used to dictate chromatin structure, allowing for either upregulation or repression of gene expression (Fig. 1b) [9]. In addition, such epigenetic modifications are also modulated by the action of specific noncoding RNA (ncRNA) that regulates the DNA methylation of specific genes [10].

The purpose of this review is to synthetically present the latest scientific discoveries which indicate that nutrition could influence longevity and aging via epigenetic mechanisms.

Nutrition alters the epigenome
During the last 2 years significant data has been added to the common knowledge of how and when nutrients can influence the epigenetic regulation of gene expression. Both human and animal studies continued to strengthen the case that fetal programming of epigenetic patterns is influenced by maternal nutrition (reviewed in [11]). Among the nutrients that alter the epigenetic status during fetal development, a central role is played by...
the physiological methyl group donors that contribute to the maintenance of s-adenosylmethionine pool (SAM, the universal donor for methylation reactions): folate, choline and betaine, and methionine [12,13].

In humans, folate supplementation during perinatal development increased the DNA methylation of imprinted loci within the IGF2 gene (differentially methylated region, DMR) and was associated with lower birth weight [14**]. This change is opposite to the one induced in the same gene by the perinatal food deprivation reported earlier for the Dutch famine cohort [15]. It is worth mentioning that IGF2 loss of imprinting is responsible for somatic overgrowth (Beckwith-Wiedemann syndrome, discussed in [14**]). In another recent human study, the epigenetic impact of folate availability was strengthened by the association between autistic children and the presence of mutations within the reduced folate carrier gene RFC1 and consequent DNA hypomethylation in their mothers [16]. Interestingly, autistic children failed to have an increased risk for inheriting the maternal mutation, suggesting that maternally induced functional folate deficiency was important especially during fetal development. Recent animal studies also indicated that folate plays important epigenetic roles during fetal and postnatal development. Folate supplementation during juvenile-prepuberal period in rats increased the methylation of Ppara and glucocorticoid receptor promoters and decreased the methylation of insulin receptor gene [17]. Beyond its action during early development, folate availability also improved the regeneration of the adult central nervous system after induced injury, possibly by an epigenetically mediated mechanism [18]. The role of folate in the epigenetic regulation of fetal development is also summarized in a recent review [19].

The importance of choline, betaine, and methionine in modulating epigenetic mechanisms continued to be reinforced by recent studies, which indicated that, similarly to folate, these methyl donors act in concert for establishing the pool of SAM that is required for methylation reaction. The epigenetic roles of choline and betaine are discussed in a recent review [20], in which most of the studies focused on their roles upon brain development and function, and liver function. Using animal models, researchers have shown that choline and betaine are inducing gene-specific epigenetic changes, which correlate with fetal brain development. Betaine supplementation induces both histone methylation and DNA methylation changes in FAT10-positive cells from mouse liver (discussed in [21]). A methyl-deficient diet induced CpG (cytosine–guanine) island

**Figure 1** Schematic diagram depicting the relationship between nutrition, epigenetics, and aging

(a) Nutrition interventions may alter the epigenetic status of an individual by either acting upon the parental epigenetic imprinting (which is then inherited by the offspring), by directly influencing the new somatic epigenetic pattern in the fetus, or by acting later in life during other periods that are susceptible to epigenetic changes (e.g., early postnatal development or the prepubertal period). Once established, the epigenetic pattern will dictate, in part, the phenotype which, in turn, will be partially responsible for aging and establishment of life span. (b) Epigenetic mechanisms (DNA methylation and histone modifications as methylation and acetylation) dictate the chromatin configuration, which can be either permissive or repressive for gene expression. Chromatin structure, although robust and stable, is not permanent and can be influenced by nutrition. $\text{Ac}_p$, histone acetylation; $\text{Me}_C$, histone methylation; $\text{Me}_C$, methyl groups attached to cytosine within CpG sites.
The epigenetic involvement of other nutrients, although less studied than the above-mentioned methyl donors, brings, nonetheless, new insights that stress, more and more, the importance of nutrition in epigenetic regulation of gene expression (Table 1).

The epigenetics of aging

During the last couple of years we witnessed a remarkable increase in the number of studies addressing the relationship between epigenetic alterations and aging. Still in its infancy, and still focusing mainly on brain aging, this research clearly indicated that epigenetic mechanisms are not only responsible, in part, for the aging process but they are also dynamically related with memory formation and maintenance (discussed in [37]). Building upon previous research that indicated the role of DNA methyltransferases (Dnmt) and the epigenetic modifications of the protein phosphatase 1 (PP1) [37], Lubin et al. [38] demonstrated recently that pharmacological disruption of DNA methylation prevents formation of fear memory. More specifically, Penner et al. [39] indicated that the gene expression of Arc (involved in memory consolidation and synaptic plasticity) is reduced within the aged hippocampus, and its promoter and intragenic methylation is different between resting and exploring rats. The manipulation of the epigenome to improve memory became possible also via changes in histone acetylation. Histone deacetylase 2 (Hdac2) overexpression in mice decreased dendritic spine density and synapse densities, interfering with long-term potentiation and memory formation in the hippocampus [40]. Restoration of physiological H4K12 acetylation level reinstated the expression levels of learning-induced genes and associated with the recovery of cognitive abilities in a mouse model [41]. Moreover, HDAC inhibitors partially ameliorated the symptoms in various models of Huntington’s, Parkinson’s, stroke, amyotrophic lateral sclerosis, spinal muscular atrophy, and Alzheimer’s diseases (discussed in [42]).

In a recent human study, Christensen et al. [43] reported extensive changes in the methylation of CpG loci, which are tissue and age specific. Similarly, Rakyan et al. [44] also reported extensive DNA methylation changes in aging-associated differentially methylated regions (aDMRs) in whole blood DNA. In Drosophila, Lorbeck et al. [45] reported that the loss of demethylase Dme]\Kdm4 activity downregulates Hsp22 that controls longevity. The epigenetic link between disease and cellular senescence continued to be reinforced by Chen et al. [46], reporting that, in the CD4+CD28− subset of cells (involved in atherosclerosis progression), ERK and JNK signaling regulated Dnmt1 and Dnmt3a expression which, in turn, caused demethylation and overexpression of the TNFSF7 (CD70) gene. Cellular senescence (in adult stem cells) was also linked with its HDAC control via regulation of polycomb genes and the jumonji domain containing 3 (JMD3) gene [47]. In human mesenchymal cells silencing of MECP2 triggered the inhibition of S-phase cells and an increase in G1 cells, changes which

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are consistent with a senescent cellular phenotype [48].

These changes were accompanied by a reduction of apoptosis, the triggering of senescence, a decrease in telomerase activity, and the downregulation of genes involved in maintaining stem cell properties. Using a more versatile model – *Caenorhabditis elegans* (but not yet established as an appropriate epigenetic model for human research) – Greer *et al.* [49] reported that H3K4 demethylase RBR-2 is required for normal life span, consistent with the idea that H3K4 trimethylation excess (associated with chromatin activation) is detrimental for longevity. Interesting, aging was recently implicated in the alteration of histone H4 acetylation in oocytes, with potential consequences on the reproductive potential in aging females [50].

Another emerging area of epigenetic research involves the role of immunity in the aging process (discussed in [6]) but the information available comes from studies older than the reviewed period.

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### The epigenetic link between nutrition and longevity

Somehow surprisingly, research aimed at fully unraveling the complete mechanistic chain (nutrition to epigenetic changes to aging) is still in its infancy, although as indicated above, full biological plausibility exists already. Probably the most powerful deterrent for such studies is the longer time period required between nutritional exposure and the assessment of both epigenetic and aging modifications. In addition, such extended studies would also require complex assessment at intermediary time-points, rendering them not only time-consuming, but also significantly more expensive.

Although the established diminution of micronutrient availability in aged people and its epigenetic consequences was recently reinforced by a study showing decreased DNMT1 activity in human T cells with decreased folate and methionine availability [51], other mechanistic studies linking nutrition, epigenetics, and longevity or aging are few and performed in inferior organisms. Building on previous work in honeybee workers and queens, which indicated a strong epigenetic-driven regulation of longevity in response to dietary changes (discussed in [52]), Amdam *et al.* [53] reported positive correlation between associative learning performance and metabolic stress resilience. In *C. elegans* nutrient-driven alterations of promoter O-GlcNAcylation in genes linked to insulin signaling caused decreased life span [54].

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### Conclusion

The present knowledge on the epigenetic roles of nutrition upon longevity and aging is structured on three components: nutrition-driven epigenetic modifications, age-related epigenetic changes, and a comprehensive relationship between nutrition, epigenetics, and aging, with consequences upon longevity. As discussed above, these components do not weight equally in terms of abundance of knowledge. The first two components continue to be developed at an accelerated pace but the third one, which is also the most demanding in terms of experiment design, time allocation, and costs, is less developed. In part, this situation is also due to the frequent inference made upon the largely (still) hypothesized link between nutrition, epigenetics, and aging. As a result of its high biological plausibility built by the first two elements, there is a justified temptation to consider as a fact that nutrition is actually modulating the epigenetic mechanisms of aging. Limited studies also support this hypothesis. However, plausible this hypothesis may be, animal and human studies continue to be very limited in numbers, and the critical mass allowing certainty has not been achieved yet.

It is clear that nutrition interventions, when applied during critical windows of opportunity (e.g., embryonic and fetal development, and prepubertal period) are having profound effects upon shaping the epigenome that, in turn, will establish a certain phenotype (Fig. 1). This is especially important when considering the early origins of chronic disease, to which perinatal epigenetic imprinting plays a clear role, albeit not completely defined. On the other hand, clearly described mechanisms allow us to definitely implicate epigenetic phenomena as part of the aging process. Sometimes, such epigenetic mechanisms are causal to the evolution of aging.

Not enough data are available to clearly ascertain however that, in humans, there is an epigenetic link between nutrition and aging, except for an indirect link via chronic diseases (a clear player for decreased longevity). Therefore, future studies should integrate a full design addressing the causality hypothesis between nutrition and aging via epigenetic mechanisms.

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### References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 102–104).


This is an overview of the current knowledge on the noncoding RNA-driven epigenetic regulation of gene expression.


Steegers-Theunissen RP, Obermann-Borst SA, Kremer D, et al. Periconceptual maternal folic acid use of 400 mg per day is related to increased methylation of the IGF2 gene in the very young child. PLoS One 2009; 4:e7645.

This is a very important reading about the impact that maternal nutrition has upon the epigenetic imprinting process in children.


Meheidint MG, Niculescu MD, Craciunescu CN, Zeisel SH. Choline deficiency alters global histone methylation and epigenetic marking at the Re1 site of the calbindin 1 gene. FASEB J 2010; 24:184–195.

This is a breakthrough study, first of its kind in the field of choline research, regarding the intimate epigenetic mechanisms by which choline alters neurogenesis and brain development.


This is a very interesting and thorough study about the role of folate in the maintenance of epigenetic markers.


This is the most recent study indicating that maternal folate supplementation can rescue the defective epigenetic programming induced by a maternal protein-deficient diet.


Gong L, Pan YX, Chen H. Gestational low protein diet in the rat mediates ifg2 gene expression in male offspring via altered hepatic DNA methylation. Epigenetics 2010. [Epub ahead of print]


Description of one of the molecular mechanisms responsible for the epigenetic dysregulation of molecular mechanisms responsible for the maintenance of neurons in the hippocampus, during aging.


This is one of the latest studies indicating the intimate link between histone modifications and memory function.


A thorough profiling of tissue-specific epigenetic changes in humans, indicating that complex DNA methylation alterations are associated with aging.


Squillaro T, Alessio N, Cipollaro M, et al. Partial silencing of methyl cytosine protein binding 2 (MECP2) in mesenchymal stem cells induces senescence with an increase in damaged DNA. FASEB J 2010; 24:1593–1603. This is a very interesting study linking epigenetic dysregulation in stem cells with DNA damage and cellular senescence.