Review

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Longevity: epigenetic and biomolecular aspects

Abstract: Many aging theories and their related molecular mechanisms have been proposed. Simple model organisms such as yeasts, worms, fruit flies and others have massively contributed to their clarification, and many genes and pathways have been associated with longevity regulation. Among them, insulin/IGF-1 plays a key and evolutionary conserved role. Interestingly, dietary interventions can modulate this pathway. Calorie restriction (CR), intermittent fasting, and protein and amino acid restriction prolong the lifespan of mammals by IGF-1 regulation. However, some recent findings support the hypothesis that the long-term effects of diet also involve epigenetic mechanisms. In this review, we describe the best characterized aging pathways and highlight the role of epigenetics in diet-mediated longevity.

Keywords: caloric restriction; epigenetics; longevity.

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Introduction: general features of epigenetics

Twin studies have limited the genetic contribution to longevity at only 25% at birth; it has therefore been proposed that epigenetic factors and lifestyle might also contribute to aging. Epigenetic regulation of gene expression can be elicited by three distinct principal mechanisms: (i) DNA methylation, (ii) post-translational histone modifications and (iii) non-coding RNA interference (1, 2).

(i) DNA methyl transferases (DNMTs) are the key enzymes responsible for DNA methylation. They transfer a methyl group from *S*-adenosyl-L-methionine to produce 5-methylcytosine (3). DNMTs can be subdivided into two groups: (a) DNMT3a, DNMT3b and cofactor DNMT3L (DNA methyltransferase-like protein), which are capable of *de novo* DNA methylation during embryogenesis (4); and (b) DNMT1, which, during replication, maintains the methylation pattern of the parental strain on the newly synthesized DNA strand. Methylated DNA can be recognized and bound by specific proteins, collectively referred to as methylated DNA-binding proteins, which can, in turn, recruit transcription regulatory factors and other chromatin remodeling proteins (5). In addition, DNA methylation and histone methylation synergistically ensure *de novo* DNA methylation (6). Hypermethylated DNA occurs mainly on CpG islands, whereas non-CpG DNA methylation has been limited to embryonic stem cell and neural development. In addition, methylated DNA has been observed in intron/exon junction and associated with alternative splicing (7), whereas the modified 5-methylcytosine (5mC) 5-hydroxymethylcytosine (5hmC) marks active chromatin regions. Methylated DNA is characteristic of heterochromatin and is traditionally believed to be associated with gene silencing. However, more recent data challenge the link between DNA methylation and genome silencing, suggesting a wider role of DNA methylation including a number of biological processes such as genomic imprinting, X-chromosome inactivation, suppression of repetitive elements, alternative splicing, transcriptional activation (5hmC) and carcinogenesis (8, 9).

(ii) Histones, the basic proteins responsible for chromatin assembly and remodeling can undergo many reversible posttranslational modifications at both their amino- and their carboxy-terminal tails. Since the discovery of this mechanism, more than 100 distinct histone modifications have been identified. Acetylation on lysine residues, methylation on lysine and arginine residues, ubiquitylation, biotinylation at specific lysine residues as well as phosphorylation or ADP-ribosylation at specific sites normally occur. The best studied modifications are acetylation/deacetylation and methylation/demethylation, whose function

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is involved in chromatin remodeling. Two enzyme families lead to acetylation/deacetylation: histone acethyltransferases (HACs) and histone deacetylases (HDACs). HACs transfer the acetyl group from acetyl-CoA to the lysine residues of H3 and H4 histones; the insertion of negative charges neutralizes the positive charge on lysine residues and weakens the charge-dependent affinity between histones and DNA, driving chromatin relaxation (euchromatin), which helps in transcription factor binding. On the contrary, HDACs remove the acetyl groups, DNA sticks to histones and nucleosomes and becomes more packed (heterochromatin) and inaccessible to transcription factors (10). A crosstalk between DNA methylation and histone posttranslational modification can occur in two different ways: methylated DNA can recruit histone posttranslational modifying proteins or histone-modifying proteins can directly or indirectly induce a DNA methyl writer, such as DNMTs, to establish the DNA methylation pattern (11).

Methylation can also occur on histones; however, mono-, di- or tri-methylation of lysine residues does not affect its positive charge and, therefore, the effect on nucleosome dynamics appears to be less direct than the acetylation/deacetylation of histones. In fact, lysine methylation can be associated with both activation (H3K4me and H3K36me) and repression (H3K9 and H3K27) of transcription. Very few data exist on arginine methylation, and thus its role on nucleosome dynamics appears to be even more crucial (12).

(iii) miRNAs (micro RNA) and siRNAs (small interfering RNAs) determine the epigenetic regulation at the post-transcriptional level. They target different transcripts, avoiding their translation. miRNAs are the most well-known small non-coding RNA, which influence aging and lifespan. Notably, miRNAs, such as lin-4, miR-1, miR-145 and miR-140, modulate the insulin/IGF-1 pathway, as well as lipid metabolism. Moreover, miR-34a, members of the miR-106b family and miR-449a modulate the p53-p21-pRb and p16-pRb pathways in order to regulate apoptosis and cell proliferation, and class I HDAC and SIRT1 activity.

Biomolecular mechanisms of aging

Thanks to simple model organisms and genetic and molecular biology studies, many genes and pathways involved in longevity have been identified, helping to depict the molecular scenario of aging. The genes and pathways involved in the aging process were previously catalogued as metabolism, proliferation and growth, and cell protection system. However, it is now clear that these three processes are strictly interconnected and such distinction is useless. It is now clear that upstream signals transduced by metabolic pathways modulate stress response converging on the activation/inhibition of transcription factors [mainly belonging to the forkhead transcription factors family (FoxO)], thus linking the regulation of gene expression to nutrients availability and stress inputs (see Figure 1 for a scheme).

High metabolic rates are unfavorable for survival. This is consistent with the observation that the conserved mitochondrial protein CLK-1 inhibits metabolism and prolongs *Caenorhabditis elegans* lifespan from 15% to 30% (13). Proliferation and growth control, which respond to IGF-1-like and GH signals, are very relevant to aging in most species including humans (14–57).

In *C. elegans,* inactivation of DAF-2 (an ortholog of insulin receptor), IGF-1 and AGE-1 (an ortholog of phosphatidylinositol-3-kinase) prolongs its lifespan (16, 17), whereas loss of function of insulin receptor and CHICO extends survival in *Drosophila* (18, 19). Mutation of GH receptor and deletion of *mTOR* or *S6 kinase* prolong the lifespan of mice and reduce the incidence of age-related disease in them (20–22). Moreover, GH deficiency in humans reduces IGF-1 and insulin levels, resulting in reduction of cancer and diabetes mortality (23).

Many evidences associate the overexpression of stress response genes to increased longevity. *Hsp70*, *MnSOD* and catalase in *Drosophila* (24) and *SOD2* (25), *HSF1* and *YAP-1* in yeast (26, 27) are some consistent examples. Furthermore, the main ability to detoxify xenobiotics (28) or repair DNA damages [e.g., *mei-41* in *Drosophila* or *DDR-2* in yeast (29)] has a major role in survival.

Consistent with this scenario, homeostatic genes, such as p53, inhibit the IGF-1 pathway (30) and play a key role in DNA damage repair as well as in the clearance of injured cells, resulting in increased longevity. p53 cooperates with the *Ink4/ARF* gene product and regulates telomeres length, thus contributing to the prevention of cancer, whereas hypermethylation of this locus, observed in gastric mucosa, has been associated with aging (31).

Similarly, deletion of the two major aging and nutrient-sensing pathways in yeast, the PKA- and TOR-dependent pathways, increase chronological lifespan, inhibiting pro-aging signals with the involvement of key factors of stress response and damage repair (32–38). That confirms how nutrient-sensing pathways are conserved from yeast to humans (15) and their role in the aging process.

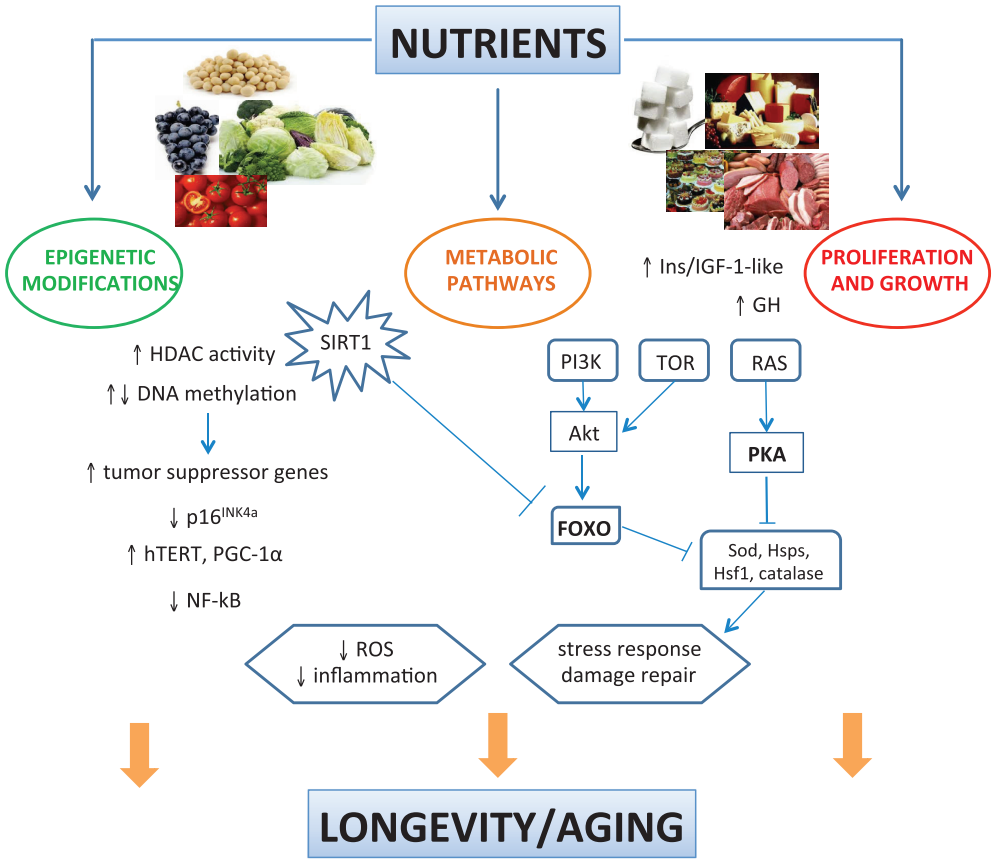

Figure 1: Signal transduction, nutrient sensing as well as epigenetic profile are nutrient dependent and converge on longevity regulation.

The best characterized intervention to prolong lifespan or to delay the onset of age-related diseases in eukaryotes is the reduction of nutrient intake without malnutrition (dietary restriction) (39). Its effects could be due either to a general reduction of metabolic rate and IGF-like signals or to the absence of specific nutrients that would affect survival responses acting as signals (39, 40).

The FOXO transcription factors, conserved in many organisms, regulate several cell functions such as gluconeogenesis, stress resistance, autophagy and apoptosis, and are upstream regulated by insulin, growth signals, nutrients and stress (41). It is therefore believed that these transcription factors play a central role in the regulation of longevity by nutrient intake.

Calorie restriction changes the gene methylation profile, suggesting that one of the mechanisms through which CR exerts its anti-aging effect is epigenetic mechanism. In particular, *HRAS* in the pancreas and *MYC* in the liver are hypomethylated in aging mice but are more methylated in animals under CR (42, 43). In addition, CR seems to affect the expression of DNMTs *in vivo* (44) and *in vitro* (45), wherein glucose restriction represses p16 and activates human telomerase reverse transcriptase (hTERT) through an epigenetic mechanism (46). In addition, protein restriction as well as mTOR pharmacological inhibition is associated with modulation of specific histone markers (47).

Another link between CR and epigenetic modification is represented by sirtuin deacetylases (48, 49). Increased level of the Sir2 ortholog, which was originally discovered in yeast, where some inconsistencies between the two adopted aging models exist on their role in aging (50–52), and in worms and flies, prolongs lifespan with an insulin/IGF-1-dependent pathway (52), regulated by the histone demethylase UTX-1 (53). These results are confirmed by the lack of CR-induced lifespan extension observed in the absence of *Sir2* (48, 54, 55). Loss of SIRTs provokes several developmental and metabolic defects, including genomic instability, in knockout mice (55, 56). Two of the major SIRT1 targets are PGC1α [peroxisome proliferator-activated receptor (PPAR)-γ co-activator 1 α] and FOXO proteins (57, 58). When higher energy is required, such as during exercise or caloric restriction, SIRT1 activation increases mitochondrial respiration and lipid oxidation

(59). Furthermore, FoxO3a deacetylation allows the up-regulation of catalase and MnSOD (60). The existence of a PPAR responsive element within the *Sirt1* promoter region (61) is consistent with the observation that PPARα-null mice live shorter than their wild-type counterpart (62). However, this observation has two critical limitations: (i) PPARα has many targets involved in ketogenesis and in response to fasting; therefore the association with SIRT1 is purely speculative; (ii) the impairment of many genes results in the reduction of lifespan without being necessarily involved in the regulation of aging. SIRT-1 regulates the lipid profile, inhibits PPAR-γ and decreases the activity of retinoid as well as that of thyroid hormone receptors, thus lowering adipogenesis and increasing adipolysis as well as adiponectin transcription (63, 64). In addition, it inhibits SREBP1 (sterol regulatory element binding protein 1), thus influencing the lipid profile also through the regulation of lipogenic genes (65).

In primates, the role of sirtuins is controversial. It has, in fact, been demonstrated that sirtuins prolong their lifespan, but only of obese animals or those under a high-fat diet (66, 67). Thus, SIRT1 regulates some age-related pathways and its deficiency has been associated with increased replicative senescence in human fibroblasts (68), since it decreases during senescence (59).

Epigenetic variations during development and aging

Different epigenetic patterns (69) contribute to the establishment and maintenance of the differentiated state in cells and tissues (70). It is well known that during gametogenesis and embryogenesis a huge number of epigenetic changes occur. Environmental factors, such as diet, significantly influence the methylation patterns of the fetus, determining its individual epigenetic pattern since intrauterine life. As an example, exposure *in utero* to a high-fat diet provokes the age-related hypomethylation of the estrogen receptor promoter in rats (71). Likewise, a low-protein diet during pregnancy induces hypomethylation of PPARα and the glucocorticoid receptor loci in the liver tissue of the offspring (72). Histone modifications and altered expression of epigenetic enzymes are observed in primate liver after the consumption of a maternal high-fat diet; these alterations influence the genes involved in lipid metabolism and heat shock response (73). Accordingly, mice under a methyl-donor-rich diet exhibit variations in coat color, body weight and health (74). Lastly, the offspring of sheep under a diet lacking folate, vitamin B_{12} and methionine, during the conception period, became obese and showed an impaired immune response (75). For these reasons, some authors talk about the 'fetal basis of adult disease' (76).

Notably, epigenetic alterations induced during embryogenesis can be reversed by interventions in neonates. Leptin reverses the hypermethylation of the PPARα promoter induced by reduction of food intake in pregnant women (77), an effect similar to that observed after folic acid supplementation in juvenile rats (75).

Observations in humans are consistent with model organisms. Children of pregnant women suffering from nutrient scarcity during the Second World War in Holland between 1944 and 1945 (Dutch hunger winter) were more susceptible to chronic degenerative disease in aging (78) and showed increased mean level of methylation compared with same-sex siblings born in other periods (79). More in-depth studies revealed hypomethylation of the imprinted *IGF-2* gene (80). In addition, IL-10, leptin, ATP-binding cassette A1 and guanine nucleotide-binding protein genes are hypermethylated in the offspring of mothers exposed to famine during the conception period (81).

Loss of imprinting has been linked to pediatric diseases and cancer in adulthood (82). It is interesting to note that monozygotic twins display different genome-wide methylation profiles (83), confirming that the ability to preserve epigenetic patterns might be individually determined (84).

Epigenetic modifications accumulate over time, but environmental factors such as visceral adiposity may influence the methylation status of CpG within the *RXRA* gene promoter at an early age (85). On the contrary, genomic regions that show heritable DNA methylation patterns, such as the IGF2/H19 region and other functionally important regions, show more stable DNA methylation state during life (86).

The DNA epigenetic pattern continues to change during life. Aging DNA becomes hypomethylated (87–89), especially in repetitive sequences such as Alu elements (90), even if some authors report that DNA methyltransferases do not change significantly (87); on the contrary, other researchers showed that Dnmt1 and Dnmt3a levels decrease during aging, whereas *Dnmt3b* expression increases (91). In contrast, some of the CpG islands are hypermethylated and silenced in a tissue-specific fashion; these regions include transcription factor-binding sites (92) or promoters of genes involved in the regulation of gene expression, senescence, apoptosis and tumorigenesis (93–96). An example is the CR-induced down-regulation of the $p16^{INK4a}$ gene (97), which is a tumor suppressor as well

as an aging-associated gene, whose silencing is obtained through hypermethylation of the transcription factor E2F-1 binding site within the gene promoter (42, 98).

A recent study compared the DNA methylation profiles of leukocytes in centenarians, youngsters and their respective offspring. Researchers found that, in the centenarians' offspring, the characteristic hypomethylation of the elderly was delayed and, interestingly, the genes involved in metabolism, nucleotide biosynthesis and control of signal transduction are differently methylated between the centenarians' offspring and the controls, suggesting a possible role in human longevity (99). Furthermore, different epigenetic profiles, in particular the methylation pattern, could be associated with the functional, cognitive and physiological status in the elderly and thus with their quality of aging (100).

A previous study compared the genome of centenarians and newborns showing a lower methylation content in the centenarians, whereas newborns had a more homogeneous methylation pattern (101). It has been postulated that aging could be associated with a loss of epigenetic control rather than with an increase or decrease in methylation activity; however, the majority of epigenetic changes do not determine a known age-related phenotype (102). In contrast, Thompson et al. (103) suggested that the epigenomic dysregulation during aging is non-random and tissue specific. Other authors are trying to use methyloma as a biomarker of chronological aging in humans (104, 105). One of the possible epigenetic biomarkers of aging could be *ELOVL2* (fatty acid elongase 2), which is unmethylated in newborns, whereas its methylation levels significantly increase with age in different tissues (106). At the same time, several other genes show methylation alteration during aging, including tumor suppressors (*COX7A1, LOX, RUNX3, TIG1, p16INK4A, RASSF1, DUSP22*) and genes involved in growth and development (*IGF2, cFos*), cell-cell adhesion (*CDH1*), metabolism (*ELOVL2, SLC38A4, SLC22A18, MGC3207, ECRG4, ATP13A4, AGPAT2, LEP*), DNA repair (*MLH1*) and the control of signal transmission (*FZD1, FZD7*) (107).

Also, histone modifications and chromatin structure are fundamental for gene expression and during lifespan change in response to environmental conditions. According to Narita et al. (108), aging cells tend to form regions of heterochromatin called senescence-associated heterochromatin foci, which may be involved in gene silencing to stop proliferation (108). In addition, during aging, histone proteins appear reduced, probably leading to an unstable genome structure (109); according to this observation in yeast, histone expression increases its lifespan (110), whereas during normal aging histone deacetylase Sir2 expression decreases (111).

A recent study describes in detail the changes occurring in circulating miRNA during life (112, 113). Differences in circulating miRNAs have been described in many age-associated diseases (112). Some miRNAs, such as miR-93, miR-669c, miR-214, mir-29 and miR-709, are up-regulated during aging (113); the related target genes are linked to proliferation, mitochondrial function and thus oxidative stress (114, 115). In contrast, expression of other senescence-related miRNAs (miR-23a, miR26a, miR-30a and let-7 family miRNAs) could be regulated by HDAC activity (116).

Nutrient modulation of epigenetic patterns

Nutrient deprivation/replenishment has been shown to induce epigenetic rearrangements in several ways (32, 117–119). Glucose availability and epigenetic patterns have been linked to cultured macrophages. High glucose results in increased expression of *NF-κB* and inflammation mediators (120–122). Dietary restriction increases the lifespan of human cultured cells with a contemporary increase in SIRT1 expression (42, 123, 124). SIRT1 is a NAD-dependent deacetylase whose expression is related to the down-regulation of p53 (125–127), FoxO (128, 129) and Ku70 (130, 131), a protein required during non-homologous end-joining DNA repair, and to the up-regulation of PGC-1α, a regulator of glucose metabolism (132, 133).

Analogously, during dietary restriction, as previously mentioned, *H-RAS* locus is silenced through DNA methylation (37), whereas the transcription factor RUNX3 as well as TIG1, a tumor suppressor frequently silenced in cancer cells, is up-regulated (134). Furthermore, a change in the methylation status of *TNF-α* locus occurs during dietary-restricted regimens.

Since the expression/silencing of these loci is associated with nutrient deprivation, they have been proposed as predictive biomarkers of diet-induced obesity/weight loss (135–137).

As mentioned before, caloric restriction is not the only dietary regimen capable of affecting epigenetics, but many other bioactive food components interfere with the epigenetic mechanism that influences, either directly or indirectly, the activity of epigenetic modification enzymes (Table 1).

The molecules involved in such regulation may be subdivided into four different subclasses: (a) co-enzymes necessary for methyl-donor metabolism; (b) substances affecting histone modification; (c) molecules acting directly on the methylation/acetylation processes; and

Table 1: Bioactive food components and their epigenetic functions.

Bioactive food component	Food source	Epigenetic functions
Catechins	Tea	SIRT1 activation, DNMT1 inhibition, ↓ DNMT1, DNMT3a/b, HDAC expression, ↑ H3-H4 acetylation at specific sites
Curcurmin	*Curcuma longa*	SIRT1 activation, H3 and H4 acetylation, DNMT1 inhibition, HAT and HDAC inhibition
Genistein	Soybeans	DNMT inhibition, DNA methylation
Lycopene	Tomatoes	DNA methylation
Quercitin	Citrus fruits, buckwheat	SIRT1 activation
Resveratrol	Berries, peanuts, grapes, wine	SIRT1 regulation, alteration of histone acetylation, FOXO deacetylation
Spermidine	Aged cheese, mushrooms, legumes, corn, whole grains	HAT inhibition
Sulforaphane	Cruciferous vegetables	↓ DNMT1/3 expression, ↓ HDAC, hTERT inhibition

(d) factors affecting the epigenetic pattern through modification of the extracellular environment (138). Spermidine, a naturally occurring polyamine, directly inhibits histone acetyltransferases (HATs), thus maintaining the hypoacetylated state of histone H3 (139). This results in higher heat and oxidative stress resistance with contemporary reduced rates of cell necrosis during aging both in human and in yeast cells. Interestingly, this mechanism is evolutionarily conserved across many species, including flies, nematodes and human cells. In addition, age-related histone acetylation may be modified by dietary strategies that deplete cellular acetyl CoA, the sole donor for acetylation reactions. Depletion of acetyl CoA has been recently shown to be sufficient for the induction of autophagy and lifespan extension. Whether these effects are dependent on epigenetic changes is not yet known (140, 141). Spermidine has the potential to be safe for testing its epigenetic-dependent and -independent effects on human health span. In one human study, an enhancement of the blood polyamine concentration due to a polyamine-rich traditional Japanese food showed no obvious adverse effects (142).

Some food seems to be able to inhibit DNMT, such as green tea and soybeans through polyphenols (epigallocatechin gallate) and genistein bioactive molecules, respectively (143–145), or HDAC, such as broccoli sprouts, which contain sulforaphane (146, 147).

Great importance is widely attached to folate in the regulation of epigenome, especially during embryogenesis. In adults, folic acid deficiency is linked to the development of several cancers such as lung, brain, breast, cervix, ovary and colorectal cancer (148, 149). Folate, choline and methionine deficiency cause DNA hypomethylation (150). Blood folate levels have been associated with methylation in CpG islands in colorectal mucosa at the promoter of the estrogen receptor α gene and frizzled-related protein-1, which are both involved in cellular proliferation (151). Piyathilake et al. (152) associated a healthy dietary pattern (rich in folate; vitamins B_{12}, B_2, and B_6; and other 'cancer protective' micronutrients) with decreased risk of developing cervical intraepithelial neoplasia and the methylation level of the long interspersed nucleotide elements (L1s) of peripheral blood mononuclear cells (152).

Many polyphenols, which not only have antioxidant properties, but also regulate gene expression and chromatin structure, have the ability to interfere with epigenetic patterning.

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is the most studied bioactive compound related to aging. It increases longevity in simple model organisms as well as in mammals (153, 154), mimicking the effects of caloric restriction. It is contained in berries, peanuts, grapes and wine. It has been linked to histone modification and DNA methylation, principally through SIRT1 regulation (155, 156). Resveratrol reduces NF-κB activation and has a role in inhibiting the development of breast as well as prostate cancer (157), by regulating cell survival through FOXO deacetylation (158). Resveratrol supplementation reduces inflammation and increases insulin sensitivity (159, 160). Similarly, quercetins, curcumins and catechins activate SIRT1 in different model systems (161). Many other polyphenols influence the SIRT1 activation state (162), and thus they could be of benefit against some chronic diseases (163). Likewise, it has been reported that resveratrol, as well as quercetins, curcumins and catechins, inhibits COX-2, iNOS and adhesion molecules through the suppression of NF-κB and AP-1 (164–166), which determines

the anti-inflammatory effect of these polyphenols. Additionally, another flavonoid present in lemons, naringerin, shows an anti-diabetic effect by the promotion of glucose uptake in skeletal muscle cells (167).

Curcumin is known as a natural anti-inflammatory agent; it is a polyphenol extracted from the spice *Curcuma longa*. It is involved in different epigenetic modifications and regulates H3 and H4 acetylation, DNMT1 and, with a mechanism that involves miRNA, SP1 and PTEN. The most relevant effect is NF-κB inhibition (163). Morimoto et al. (168) linked the effect of curcumins in heart-failure prevention in mice to the inhibition of HATs, HDACs and p300 degradation induction (169).

Many epigenetic targets have been identified for tea polyphenols and catechins: H3 and H4, *NF-κB, IL-6, SUZ12/HAT, HDAC, HMT, P16INK4a*, *RNRβ, RECK1, hTERT, WIF-1, RXRα, RXRβ, CDX2/DNMTI* and *Bcl-2*. Their role in cancer prevention is fundamentally linked to apoptosis and cell-cycle arrest in tumor cells (170). Epigallocatechin binds to the catalytic region of DNMT1 and inhibits its activity (171). Furthermore, it has been shown to decrease DNMT1, DNMT3a, DNMT3b and HDAC levels, whereas it increases the acetylation of particular regions of histones H3 and H4 (172). Epigallocatechin prevents UV-induced carcinogenesis of the skin in mice (173), whereas epicatechins and catechins have shown anti-aging effects in *C. elegans* (174).

Vegetables such as broccoli, cabbage and cauliflower contain sulforaphane, phenethyl isothiocyanate, indole-3-carbinol and diindolymethane that induce cell-cycle arrest and apoptosis in cancer cells through epigenetic mechanisms (153, 175–177). A similar effect has been detected for quercetin in citrus fruits and buckwheat (178), lycopene in tomato (179) and ellagic acid (pomegranate, walnuts, almonds) (180). Moreover, low doses of sulforaphane inhibit hTERT, allowing the binding of transcriptional repressors to the regulatory region and the reduction of DNMT1 and DNMT3a expression levels (153), whereas it inhibits *in vitro* melanoma cell growth and proliferation by down-regulating deacetylases (181). In addition, lycopene protects against UV-induced carcinogenesis by inhibition of epidermal ornithine decarboxylase and reduction of inflammation (182). Moreover, as reported by Jones and Hughes (183), black currant juice (which contains flavonoids and quercetin) prolongs the lifespan of female mice, which live longer than male mice, probably through SIRT1 inhibition (184).

Genistein, contained in soybeans, participates in the modulation of chromatin structure and DNA methylation; among its epigenetic targets are histones, *SIRT1, p21, p16, PTEN, p53, FOXO3A* and *hTERT* (185, 186), which, in turn, are key regulators of cell-cycle regulation and cell survival. In contrast, studies on mice CD-1 reveal that exposure to genistein during the neonatal period can promote uterine adenocarcinoma, probably due to the atypical hypomethylation of CpG islands in Nsbp1 (nucleosomal binding protein) (187). Organosulfur compounds of onions and garlic inhibit DNA adduct formation through the up-regulation of antioxidant defenses and DNA repair systems (188).

Conclusion

It is becoming evident that not only calorie restriction but also the restriction of selected nutrients increases the lifespan in a wide array of organisms including humans. Recent data suggest that these restrictions not only have a direct effect on metabolism but also are capable of regulating gene expression. Regulation of key transcription factors by nutrient availability through direct interaction of these factors with nutrient-sensing factors occurs. In addition, many data suggest that the amount and quality of nutrients in the diet influence longevity by modifying the epigenetic pattern. A large number of clinical trials are testing the efficacy of phytochemicals and drugs to inhibit HDAC or DNMT (124) on some tumors and degenerative aging-related diseases. In humans, safety concerns and the possibility of off-target effects suggest the use of only natural substances such as spermidine or resveratrol for clinical trials (189).

Finally, it is interesting to note that epigenetic patterns may be heritable in some cases. The combination of heritability and lifestyle-dependent modification of epigenetics makes this mechanism of gene expression regulation a proof of principle of Lamarckian theories.

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