

Review

Dietary Interventions for Healthy Aging: An Epigenetic Perspective

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ABSTRACT: Aging is closely associated with epigenetic alterations, including changes in DNA methylation, acetylation, and shifts in histone modification patterns, which drive cellular decline and increase susceptibility to diseases. This review examines the connection between aging-related diseases and epigenetic mechanisms and explores how dietary interventions can influence this process. We discuss the Mediterranean diet (MD), caloric restriction (CR), and the ketogenic diet (KD) as key nutritional strategies. These interventions supply essential substrates and regulate enzymes central to epigenetic remodeling, thereby affecting gene expression networks involved in inflammation, metabolism, and cellular stress responses. By correcting age related epigenetic dysregulation, such dietary patterns can slow attenuate cellular senescence and reduce the risk of chronic diseases. Current evidence supports the association between diet quality and decelerated epigenetic aging. Future research is needed to establish causality and to develop personalized nutritional approaches for promoting longevity and healthspan.

Keywords: Epigenetics, Cellular senescence, Age-related diseases, Diet, Nutritional intervention

1. Introduction

By 2050, one in five individuals globally will be over 65, presenting unprecedented challenges for public health systems worldwide [1]. The global demographic shift toward an older population is accompanied by a substantial increase in the prevalence of age-associated diseases [2]. Among the established hallmarks of aging, epigenetic alterations encompassing DNA methylation, histone modifications, chromatin remodeling, and non-coding RNA networks, collectively regulate gene expression patterns that influence longevity and disease susceptibility [3]. Such patterns form the basis of highly accurate “epigenetic clocks,” which not only track biological age but also underscore the central role of epigenetics in aging and its potential as a modifiable target [4]. Epigenetic clocks are statistical models that estimate biological age (as opposed to chronological age) by analyzing DNA methylation levels at specific CpG sites across the genome. The early Horvath and Hannum clocks

were primarily trained to predict chronological age, using elastic net regression to select features from high-dimensional CpG sites, and exhibit high stability and generalizability. Subsequently developed clocks, such as PhenoAge and GrimAge, incorporated phenotypic information related to mortality and disease, thereby extending the utility of epigenetic clocks from mere age prediction to health risk assessment [5, 6]. Importantly, diverse age-related pathologies, from Alzheimer’s disease (AD) and cardiovascular disease (CVD) to metabolic disease and cancer, may share a common foundation in epigenetic dysregulation, wherein altered methylation and histone landscapes disrupt transcriptional programs, leading to neurodegeneration, vascular dysfunction, and malignant progression (Fig. 1).

The epigenome’s plasticity offers a compelling interface through which environmental factors, particularly nutrition, can influence aging trajectories. Long-term dietary habits are now recognized as major determinants of individual aging rates and vulnerability to

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age-related diseases [7, 8]. This raises a pivotal question: how can transient nutritional signals be converted into persistent cellular memory to systemically modulate aging? Emerging evidence points to metabolism as the critical link. Key metabolic cofactors such as S-adenosylmethionine (SAM), nicotinamide adenine dinucleotide (NAD⁺), α -ketoglutaric acid (α -KG) and

acetyl-CoA that drive epigenetic modifications are themselves derived from nutrients and cellular metabolic pathways [9]. Thus, diet can remodel the epigenetic landscape by modulating the availability of these substrates and the activity of chromatin-modifying enzymes, thereby translating nutritional input into durable gene expression programs [10, 11].

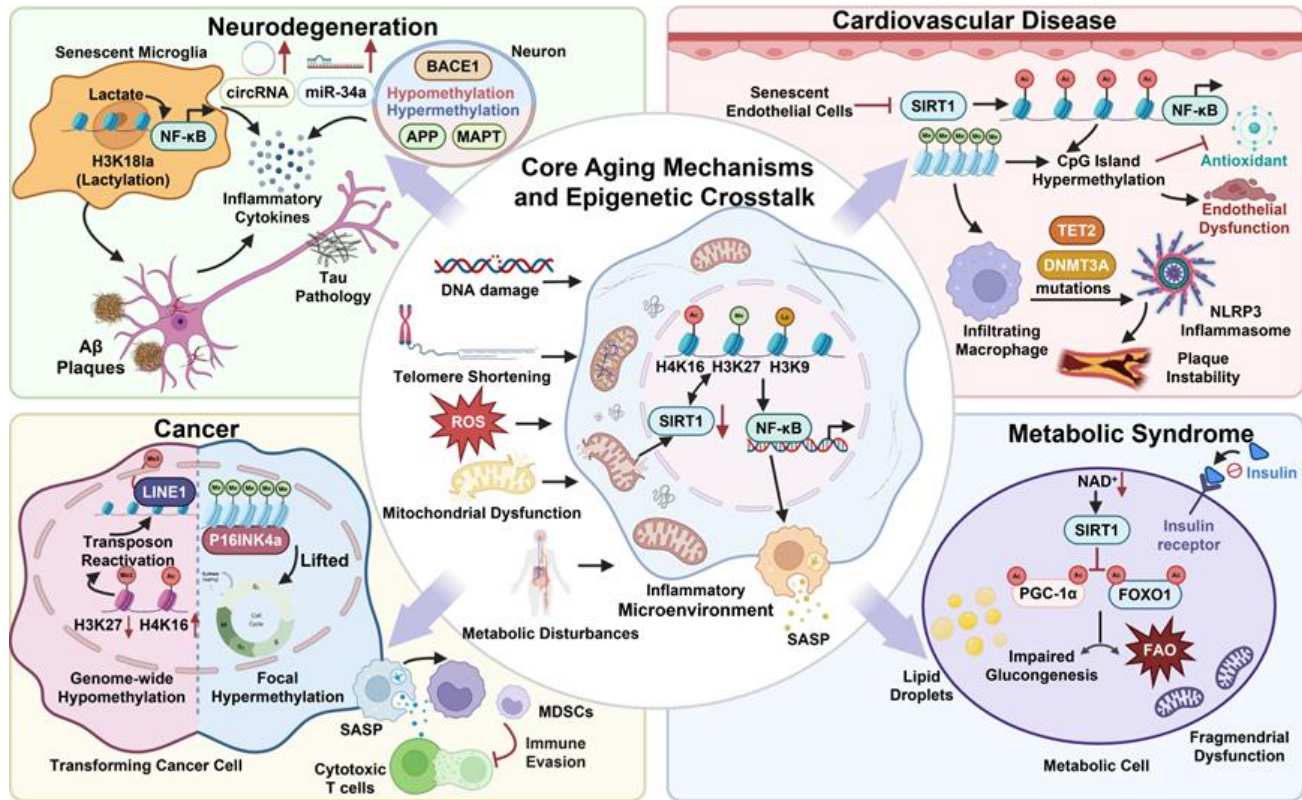


Figure 1. Epigenetic crosstalk and core aging mechanisms driving the progression of various age-related diseases. The diagram highlights a central regulatory hub radiating into four major pathological axes: (I) Neurodegeneration, characterized by microglial lactylation (H3K18la) and epigenetic dysregulation in neurons leading to A β plaques and Tau pathology; (II) Cardiovascular disease, involving endothelial SIRT1 downregulation and NLRP3-driven plaque instability through macrophage mutations; (III) Metabolic syndrome, marked by NAD⁺ depletion and impaired energy homeostasis through the PGC-1 α and FOXO1 pathways; (IV) Cancer, driven by genomic instability, LINE1 reactivation, and SASP-mediated immune evasion. Abbreviations: beta-secretase 1 (BACE1), fatty acid oxidation (FAO), long interspersed nuclear element-1 (LINE1), microtubule associated protein Tau (MAPT), myeloid-derived suppressor cells (MDSCs).

This review systematically maps the molecular connections within the diet–metabolite–epigenetics–aging axis, with a focused analysis on how defined nutritional patterns, particularly the Mediterranean diet (MD), caloric restriction (CR), and ketogenic diet (KD), reprogram epigenetic landscapes to delay aging and combat age-related pathologies. We detail the mechanisms by which specific diets and their derived metabolites regulate these epigenetic marks and discuss the translational potential and future directions of nutrition-based epigenetic interventions for healthy aging.

2. Core metabolic regulators of the aging epigenome

The dynamic regulation of epigenetic modifications in cells is not only intricately modulated by specific enzymes but also directly influenced by the intracellular metabolic network. At the same time, the dietary components involved in various eating patterns also play an important role in the synthesis and degradation of metabolic products (Table 1). The key metabolic cofactors mentioned above, their biosynthesis, consumption, and balanced interplay govern the establishment of key epigenetic modifications. Furthermore, these processes

play significant roles in aging and the pathological mechanisms underlying various diseases [12].

Table 1. Key bioactive components and their corresponding mechanisms

Dietary Component	Common foods	Mechanism of Action	References
Choline	Eggs, beef, liver, chicken breast, fish	Acts as a direct precursor to SAM, thereby facilitating DNA methylation.	[110, 111]
Folic Acid	Spinach, kale, broccoli, legumes, citrus fruits	Serves as a participant in one-carbon metabolism via tetrahydrofolate, thereby promoting the synthesis of SAM.	[112, 113]
Methionine	Meat, fish, eggs, dairy products, beans, nuts	Acts as the essential precursor for SAM, regulating methyl donor availability.	[114, 115]
Betaine	Beetroot, spinach, quinoa, shrimp	Supplies methyl groups via the BHMT pathway and modulates DNMT activity.	[116]
Vitamin B12	Animal liver, fish, shellfish, meat, eggs, dairy products, fortified cereals	Serves to catalyze the remethylation of homocysteine, thereby sustaining SAM levels.	[117, 118]
Vitamin B6	Fish, potatoes, bananas, fortified cereals, beef liver	Functions as a cofactor within serine hydroxymethyl-transferase, facilitating one-carbon metabolism.	[119]
SCFAs	Whole grains, legumes, resistant starch, fermented foods	Are converted to acetyl-CoA to facilitate histone acetylation and activates GPCR signaling to regulate non-coding RNA genes.	[120]
EGCG	Green tea, matcha	Inhibits DNMT1, depletes SAM, reverses CpG island hypermethylation, and restores gene expression.	[121]
Quercetin	Apples, onions, berries, capers, dark chocolate	Orchestrates one-carbon metabolism and modulates DNA methyltransferase activity, thereby reversing hypermethylation of tumor suppressor genes.	[122, 123]
Vitamins A and C	Liver, cod liver oil, egg yolk, carrot, strawberries, kiwifruit, bell peppers, broccoli	Serve as essential cofactors for TET enzymes, thereby facilitating active DNA demethylation through the oxidation of 5-methylcytosine.	[124, 125]
Polyphenols	Berries, green tea, turmeric, rosemary, garlic	Orchestrate the activity of HATs and sirtuins, while governing the expression of miRNAs and lncRNAs implicated in aging and oncogenesis.	[126–129]
Lactic Acid	Yogurt, fermented vegetables, sourdough bread	Serves as a direct donor for histone lactylation, thereby linking glycolytic metabolism to the regulation of epigenetic processes.	[130–132]
BHB	Ketogenic diet, fasting state, coconut oil, medium-chain triglycerides (MCT)	Functions to inhibit HDACs while also serving as a precursor for histone β -hydroxybutyrylation.	[133]
Succinyl-CoA	Meat, fish, whole grains, legumes, tricarboxylic acid cycle metabolites	Acts as the sole donor for histone succinylation, thus establishing a direct link between the tricarboxylic acid cycle and epigenetic regulation.	[134]

Abbreviations: betaine-homocysteine methyltransferase (BHMT).

2.1. SAM

SAM serves as the universal methyl donor for the methylation of nucleotides, proteins, phospholipids, and key epigenetic marks within the cell [13]. Its biosynthesis depends on the methionine cycle and folate metabolism, while its metabolic product, S-adenosylhomocysteine (SAH), acts as a competitive inhibitor of methyltransferases. Consequently, the SAM/SAH ratio dynamically regulates the activity of DNA methyltransferases (DNMTs) and histone methyltransferases (HMTs) [14]. Research indicates that aging is often accompanied by genome wide DNA hypomethylation alongside localized hypermethylation at

specific gene promoter regions [15]. Additionally, nutrient-sensing pathways directly influence SAM production. In models of hepatocellular carcinoma, upregulation of enzymes like DNMT3B can lead to relatively increased SAM availability, driving hypermethylation of specific loci like the suppressor of cytokine signaling1 (SOCS1) promoter [16]. Conversely, during overall aging, diminished SAM synthesis capacity may result in widespread hypomethylation. Additionally, nutrient-sensing pathways directly influence SAM production [17]. For instance, mechanistic target of rapamycin complex 1 (mTORC1) signaling upregulates the expression of methionine adenosyltransferase 2 α (MAT2A), enhancing SAM synthesis, which in turn

supplies methyl groups for RNA modifications such as N(6)-methyladenosine (m⁶A) [18, 19].

2.2. NAD⁺

NAD⁺ functions not only as a central coenzyme in redox reactions but also as an essential substrate for NAD⁺ consuming enzymes such as poly(ADP-ribose) polymerases (PARPs) and sirtuins [20]. Sirtuins catalyze the deacetylation of histone proteins like histone H3 lysine 9 (H3K9) and numerous non-histone substrates including the peroxisome proliferator-activated receptor- γ coactivator-1 α (PGC-1 α), forkhead box proteins O1 (FOXO1), and the nod-like receptor protein 3 (NLRP3), playing broad roles in metabolic regulation, stress resistance, and DNA repair [21, 22]. Progressive decline in NAD⁺ levels is associated with histone hyperacetylation, mitochondrial dysfunction, and chronic inflammation, accelerating the progression of neurodegenerative disorders, metabolic syndrome, and cardiovascular diseases [23]. Studies in macrophages have shown that the serine synthesis pathway mediated by phosphoglycerate dehydrogenase (PHGDH) consumes NAD⁺, thereby maintaining low NAD⁺ availability and limiting the activity of SIRT1 and SIRT3. Inhibiting PHGDH leads to NAD⁺ accumulation, activating SIRT1 and SIRT3, which triggers histone deacetylation and promotes acetylated dependent degradation of NLRP3 protein, ultimately suppressing inflammatory responses [24]. This illustrates how metabolic pathways can locally modulate NAD⁺ levels. Accordingly, supplementation with NAD⁺ precursors such as nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR) has been shown in multiple aging and disease models to restore sirtuin activity, improve mitochondrial function, and extend lifespan [25].

2.3. α -KG

As a key intermediate in the tricarboxylic acid cycle, α -KG serves as an essential cofactor for various α -KG dependent dioxygenases, including the ten-eleven translocation (TET) family enzymes that catalyze active DNA demethylation and Jumonji C domain containing histone demethylases [26]. Thus, α -KG levels directly regulate DNA demethylation dynamics and histone methylation states [27, 28]. Under normal physiological conditions, α -KG sustains TET enzyme activity, promoting the conversion of 5-methylcytosine to oxidized derivatives such as 5-hydroxymethylcytosine, which is generally associated with open chromatin and gene activation, playing vital roles in maintaining stem cell pluripotency, cellular differentiation, and immune cell function [29]. In conditions like hyperglycemia or aging,

reduced α -KG levels in tissues such as the heart impair TET activity, leading to abnormal accumulation of 5mC/5hmC at specific genomic regions like transforming growth factor beta receptor II (TGFB β 2), thereby activating fibrotic pathways [30, 31]. Furthermore, mutations in isocitrate dehydrogenase 1 (IDH1) or IDH2 produce 2-hydroxyglutarate (2-HG), which structurally mimics α -KG and competitively inhibits TET and JmJc enzymes, causing genome wide DNA and histone hypermethylation and driving malignancies such as glioma [32]. Building on these findings, recent studies demonstrate that tumor suppressors like p53 can elevate α -KG levels by upregulating pyruvate carboxylase and Isocitrate dehydrogenase 1 (IDH1), thereby counteracting tumor progression [33].

2.4. Acetyl-CoA

Acetyl-CoA is the direct and obligatory acetyl group donor for histone acetylation catalyzed by histone acetyltransferases (HATs) [20]. Its nuclear concentration is tightly regulated by multiple metabolic pathways. In cells with high glycolytic or glutaminolytic flux, such as proliferating cancer cells or those exposed to high glucose or lipid levels, mitochondrial and nuclear acetyl-CoA pools increase, driving histone hyperacetylation. This contributes to metabolic dysregulation, senescence-associated secretory phenotype (SASP), and oncogenesis [34]. Notably, acetyl-CoA also participates in a dynamic equilibrium with sirtuin-mediated deacetylation and can modulate key metabolic enzymes, including SAM synthetase, via acetylation. Moreover, diet-derived metabolites can directly influence acetylation states. β -hydroxybutyrate (BHB) generated during ketogenic diets not only acts as an inhibitor of class I histone deacetylases (HDACs) to elevate global acetylation but also serves as a substrate for p300 (KAT3B), inducing β -hydroxybutyrylation [35].

2.5. Other Metabolites

Short-chain fatty acids (SCFAs), particularly butyrate and propionate, are primary metabolites generated by the gut microbiota through the fermentation of dietary fiber. These compounds act as potent inhibitors of class I and IIa HDACs, thereby elevating histone acetylation levels in intestinal epithelial cells and local immune populations [36]. This epigenetic modulation contributes to the regulation of intestinal barrier integrity, the preservation of immune homeostasis, and the fine-tuning of inflammatory responses [37]. Beyond SCFAs, the metabolic derivatives of polyphenols and specific amino acids also participate in shaping gut health through analogous epigenetic pathways. For instance, resveratrol

can indirectly elevate NAD⁺ levels via AMP-activated protein kinase (AMPK) activation, thereby enhancing SIRT1 activity [38, 39]. Amino acids such as serine and glycine influence the production and consumption of SAM through one-carbon metabolism, modulating methylation equilibrium [40]. Collectively, these mechanisms illustrate how dietary components shape the endogenous metabolome, either by directly supplying metabolite precursors or by modulating gut microbiome-derived metabolites, thereby influencing the epigenetic landscape [41].

3. Different patterns of diet

The aging process is profoundly shaped by dynamic interactions between genes and the environment. Among all environmental factors, nutrition stands out as a modifiable lever capable of directing epigenetic activity. Multiple clinical studies have confirmed that diet influences biological aging through epigenetic modifications (Table 2). Common dietary patterns influence systemic metabolic states that regulate the activity of epigenetic enzymes (Fig. 2). This positions nutritional intervention deliberately remodels the epigenetic landscape, thereby decelerating molecular and cellular hallmarks of aging and shifting the trajectory toward an extended healthspan.

Table 2. Key clinical studies of dietary interventions targeting epigenetic aging.

Source	Population	Duration	Intervention	Epigenetic mechanism	Outcomes
Meir et al. [46]	256 participants with abdominal obesity or dyslipidemia	18 months	MD, polyphenol-rich Green-MD diet	DNA methylation based epigenetic clock (Horvath2013, Hannum2013, Li2018, Horvath skin and blood2018, PhenoAge2018, PCGrimAge2022)	Changes in biological age
Meir et al. [135]	120 participants with abdominal obesity or dyslipidemia	18 months	Low fat diet, Mediterranean, low carbohydrate	DNA methylation, chronological age and mAge (calculated by a 240-CpG-based prediction formula)	Changes in biological age and cardiometabolic diseases
Corella et al. [136]	7187 participants	3 years	MD	MiR-410	Changes in triglycerides and stroke
Giraldo et al. [137]	1002 patients with coronary heart disease	7 years	MD	MiR-1, miR-150, and miR-145	Changes in coronary heart disease
Kou et al. [138]	144 obese participants	12 months	Low-carbohydrate diet, low-fat diet	DNA methylation based epigenetic clock (DunedinPACE, PCPhenoAge, PCGrimAge)	Changes in weight loss-induced health outcomes and cardiometabolic health
Ryan et al. [139]	220 healthy adult participants	24 months	CR	DNA methylation based epigenetic clock (Horvath, PCHorvath, Hannum, PCHannum, PhenoAge, PCPhenoAge, GrimAge, PCGrimAge, DunedinPACE)	Changes in biological age
Li et al. [140]	958 healthy adult participants	2 years	Daily multivitamin-multimineral supplement, cocoa extract	DNA methylation based epigenetic clock (PCHannum, PCHorvath, PCPhenoAge, PCGrimAge, DunedinPACE)	Changes in biological aging and aging-related chronic conditions
Ferrari et al. [141]	777 participants aged 70 years and older	3 years	Vitamin D, omega-3, home exercise program	DNA methylation based epigenetic clock (PhenoAge, GrimAge, GrimAge2, DunedinPACE)	Changes in biological aging
Robinson et al. [142]	21 participants aged 50-65 years with BMI > 30 kg/m ²	1 month	Daily greens-based supplement	DNA methylation based epigenetic clock (Horvath, PCGrimAge, AdaptAge, DamAge)	Changes in epigenetic aging markers and individual gut microbial taxa
Villanueva et al. [129]	43 healthy adult participants	8 weeks	Multi-modal intervention	Baseline epigenetic age acceleration	Changes in biological aging
Perlmutter et al. [143]	50 healthy adult participants	90 days	Polyphenols	DNA methylation based epigenetic clock (OMICmAge, DunedinPACE, PhenoAge)	Changes in markers of epigenetic aging

Ferreri et al. [144]	97 women aged 40 to 75 years	/	Nutritarian diet, standard American diet	EAA, Horvath Pan Tissue, Horvath skin and blood, and Hannum	Changes in biological aging
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Abbreviations: body mass index (BMI), epigenetic age acceleration (EAA)

3.1. Mediterranean diet

The traditional MD is characterized by abundant plant-based foods such as fruits, vegetables, bread, other cereals, potatoes, legumes, nuts, and seeds; fresh fruit as a daily dessert; olive oil as the principal source of fat; dairy products (mainly cheese and yogurt); fish and poultry consumed in low to moderate amounts; minimal

red meat; and low to moderate wine intake, typically with meals [42]. In current analyses, the MD stands as one of the most consistent dietary patterns associated with favorable CVD and other health outcomes, including reduced all-cause mortality and an increased likelihood of healthy aging [43]. It is proposed that the MD may delay biological aging by modulating the epigenetic state.

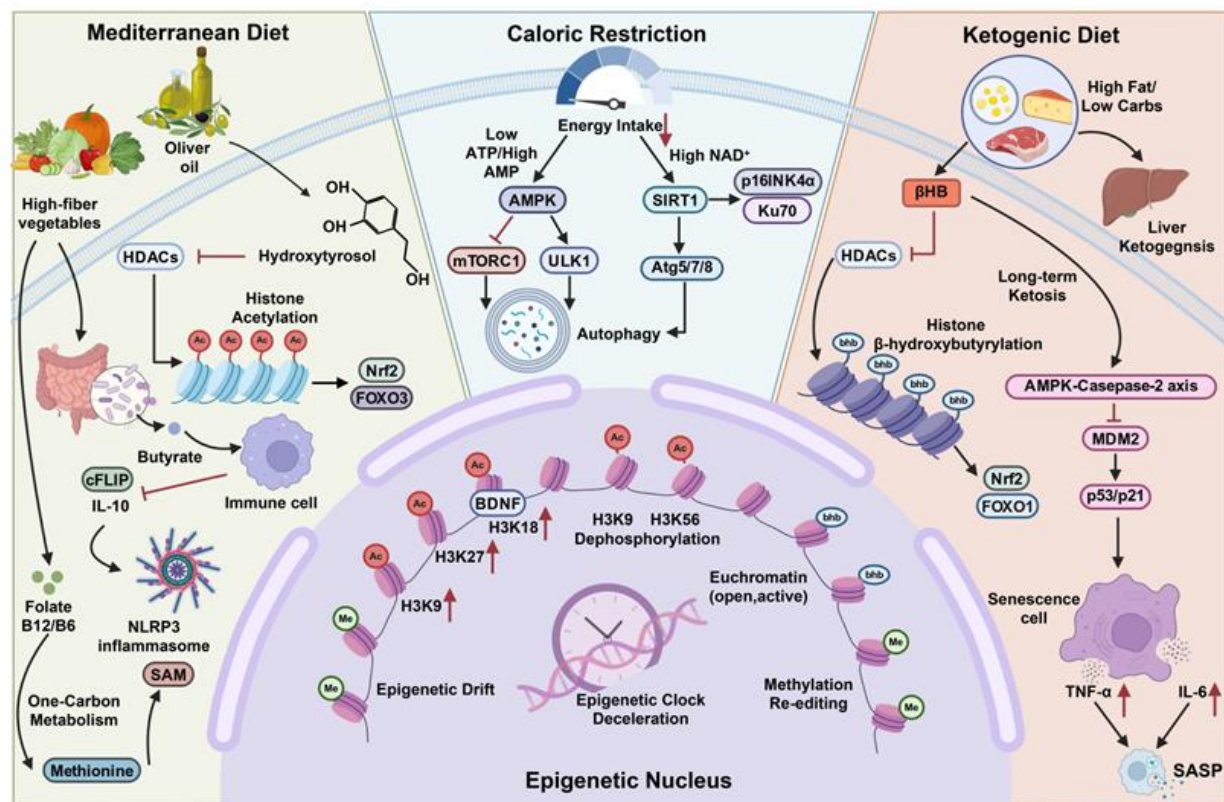


Figure 2. Diverse dietary interventions targeting the epigenetic landscape to decelerate the biological aging clock and promote healthy longevity. The diagram highlights three major nutritional strategies and their molecular impacts on the cell: (I) Mediterranean Diet, which utilizes bioactive compounds like hydroxytyrosol from olive oil and fiber-derived butyrate to inhibit HDACs, alongside folate-driven one-carbon metabolism to modulate DNA methyltransferases and suppress the NLRP3 inflammasome; (II) Caloric Restriction, which acts through nutrient-sensing pathways by activating AMPK and SIRT1 to promote autophagy and cellular proteostasis while downregulating senescence markers like p16INK4a; (III) Ketogenic Diet, which induces liver ketogenesis to produce BHB, leading to β -hydroxybutyrylation and the inhibition of the AMPK-Caspase-2-p53 axis to reduce the Senescence-Associated Secretory Phenotype. These interventions collectively converge within the Epigenetic Nucleus to counteract epigenetic drift, promote methylation re-editing, and maintain active euchromatin, ultimately resulting in the deceleration of the Epigenetic Clock.

Various food components within the MD can influence aging through epigenetic pathways. Polyphenols, owing to their potent antioxidant and anti-inflammatory properties, differentially modulate epigenetic processes and metabolic regulation. Olive oil, rich in polyphenols such as hydroxytyrosol and

oleuropein, serves as a source of potent epigenetic modulators. By inhibiting histone deacetylase (HDAC) activity, hydroxytyrosol increases the acetylation levels of histones H3K9ac and H3K27ac at the promoter regions of genes involved in anti-inflammatory and antioxidant responses, including Nrf2 and FOXO3 [44]. This

promotes a more open chromatin structure and activates the transcription of these protective genes. The resulting optimization of histone acetylation patterns enhances cellular resistance to oxidative stress and mitigates chronic inflammation, thereby directly counteracting inflammaging [45]. Similarly, resveratrol from red wine activates SIRT1 and can also elevate H3K9ac and H3K27ac levels to exert anti-aging effects [15]. Moreover, higher intake of green tea, Mankai, and other foods rich in polyamines and polyphenols has been associated with decelerated epigenetic aging [46]. Beyond polyphenols, the MD is abundant in leafy greens and legumes, providing essential micronutrients such as folate, vitamin B6, and vitamin B12, which are core components of the one-carbon metabolism pathway responsible for generating S-adenosylmethionine (SAM) [48].

In addition, cocoa flavanols lower blood pressure through epigenetic processes involving the downregulation of functional genes such as DNMTs and methylenetetrahydrofolate reductase (MTHFR) [47]. Curcumin, a major curcuminoid, leads to a marked reduction in HDAC1 expression by inhibiting the inflammatory marker matrix metalloproteinase-2 (MMP-2), while concurrently increasing tissue inhibitor of metalloproteinase-1 (TIMP1) through histone H3 acetylation [48]. Recently, omega-3 polyunsaturated fatty acids (n-3 PUFAs) found in fish, hazelnuts, and olive oil, contribute to the prevention of age-related cognitive decline by influencing DNA methylation in various cell types [49]. Additionally, the abundant dietary fiber in the MD serves as the primary fermentation substrate for beneficial gut microbiota. The microbial fermentation of fiber produces SCFAs, notably butyrate, which is a known potent HDAC inhibitor. By inhibiting HDAC activity, butyrate can suppress the transcription of FLICE-like inhibitory protein (cFLIP) and IL-10, thereby inhibiting caspase-8-dependent NLRP3 inflammasome activation [50, 51]. Both in vivo and in vitro studies have demonstrated that butyrate can ameliorate cognitive impairment, neuronal damage, and reduced levels of brain-derived neurotrophic factor (BDNF) induced by quinolinic acid. This effect is achieved through a specific increase in H3K18ac at the BDNF gene promoter. [52].

The evidence discussed thus far establishes that MD exerts its anti-aging effects through epigenetic mechanisms, namely by mitigating age-related epigenetic drift and stabilizing transcriptional programs. Translating these mechanistic insights into a disease-specific context reveals how MD components modulate major age-related pathologies. Polyphenols serve as key dietary epigenetic regulators. Resveratrol activates the PGC-1 α /SIRT1/AMPK axis and influences DNMT activity in cancer prevention and therapy [53]. In addition, the green tea polyphenol epigallocatechin gallate (EGCG) inhibits

DNMTs across multiple cancer cell models, leading to reactivation of methylation-silenced genes, and also interferes with HDACs and HATs, underscoring its potential against both cancer and neurodegenerative disorders [54, 55]. In AD, a direct causal link has been established: a diet deficient in folate and vitamins B6/B12 induces global DNA methylation dysregulation and specific hypomethylation of the PSEN1 (presenilin 1) promoter, increasing amyloid- β production and cognitive impairment. Crucially, SAM supplementation restores PSEN1 methylation and reverses these AD-like features [56–58]. Polyphenols from extra virgin olive oil further activate the SIRT1 pathway, suggesting a role in AD management [59]. Regarding cardiovascular health, extra virgin olive oil modulates circulating microRNAs, reducing let-7e-5p and increasing miR-17-5p, miR-20a-5p, and miR-192-5p, thereby conferring benefits, and MD-associated elevation of miR-188 inhibits cyclin-dependent kinase 5 (CDK5), a negative regulator of SIRT1, reducing endothelial cell senescence and potentially delaying atherosclerosis [60, 61]. Other diet-derived metabolites also show promise: short-chain fatty acids such as butyrate act as HDAC inhibitors and G protein-coupled receptor (GPCR) ligands, slowing type 2 diabetes mellitus (T2DM) progression, a finding particularly relevant given the reduced abundance of butyrate-producing gut microbiota in T2DM patients [62]. Finally, the MD may influence the insulin/insulin-like growth factor 1 (IGF-1) signaling axis, a conserved longevity pathway; reduced Ins/IGF-1 activity extends lifespan across species and upregulates FOXO transcription factors, which coordinate metabolism, apoptosis, and oxidative stress resistance, and have been shown to attenuate proteotoxicity in AD models [63]. Collectively, these findings provide a theoretical framework for developing precise, nutrition-based anti-aging interventions.

3.2. Caloric restriction

CR is characterized by a moderate reduction in daily caloric intake while ensuring adequate provision of essential nutrients (amino acids, vitamins, minerals), resulting in energy consumption lower than expenditure. CR is known to delay the onset of numerous aging-associated diseases in mammals, including cancer, diabetes, atherosclerosis, cardiovascular diseases, and neurodegenerative disorders [64]. As a gold-standard intervention for delaying aging, a core mechanism of CR is the systemic remodeling of the epigenome. Even short-term CR has been shown to alter age-dependent gene expression, leading to phenotypic changes. Jung et al. found that very short-term (10-day) CR attenuated age-related inflammatory processes mediated by oxidative

stress-associated proteins NF- κ B and activating protein-1 (AP-1) in the kidneys of old rats [65]. Extensive research from rodents to primates confirms that reducing energy intake without malnutrition promotes healthy longevity, with benefits extending beyond lifespan extension to the modulation of core biological processes of aging, key among which are epigenetic modifications that dynamically respond to nutritional signals.

The metabolic effects of CR are mediated through cellular energy sensing. Reduced ATP and altered redox status during CR elevate NAD⁺ and AMP levels, activating two key nutrient sensors: SIRT family and AMPK [66, 67]. NAD⁺ activates SIRT1 while AMP activates AMPK, which subsequently inhibits mechanistic target of rapamycin kinase (mTOR) and PGC-1 α [68]. CR also upregulates SIRT expression; these NAD⁺-dependent deacetylases inhibit NF- κ B signaling, enhance genomic stability, and maintain homeostasis through histone deacetylation. In CR rats, acetylation levels at H3K9, H3K27, H3K56, and H4K16 are approximately 30% higher than in ad libitum-fed controls, linking CR-induced lifespan extension to histone acetylation status [69]. SIRT1 activation by NAD⁺ enhances stress resistance and genomic stability through deacetylation of histones (H3K9, H3K56) and non-histone proteins including p53, FOXO transcription factors, p16INK4a, and Ku70, all implicated in CR-mediated longevity [69–72]. Concurrently, AMPK activation by elevated AMP accelerates catabolic pathways while inhibiting anabolic processes. Lithocholic acid (LCA), which accumulates during CR, slows aging through the TULP3-sirtuin-v-ATPase-AMPK axis [73]. AMPK phosphorylates and activates p53, inducing cell cycle arrest and apoptosis, while SIRT1 modulates apoptosis through FOXO and caspase regulation [74, 75]. The balance between these pathways determines cell fate in response to CR [76]. CR-induced AMPK activation inhibits mTORC1 signaling and stimulates unc-51 like autophagy activating kinase 1 (ULK1), promoting autophagy [77]. Additionally, AMPK and SIRT1 coordinately induce autophagy-related proteins via FOXO transcription factors, with SIRT1 directly deacetylating autophagy effectors including autophagy-related protein 5/7/8 (Atg5/7/8) [78].

CR also alters miRNA expression profiles. In mouse mammary tissue, six months of 30% CR increased the expression of miR-203, which targets caveolin-1 and p63, reducing breast cancer incidence, progression, and metastasis, thereby promoting longevity [79]. Margolis et al. found that in overweight men undergoing short-term energy restriction, whole-body protein synthesis was inversely correlated with circulating concentrations of muscle-specific miRNAs (miR-1-3p, miR-133a-3p, miR-133b, and miR-206), suggesting that CR-based therapies

may target muscle miRs and immune-metabolic pathways to prevent age-related comorbidities [80]. This synergistic multi-pathway regulation constitutes the molecular foundation for CR's ability to decelerate the overall aging process.

Evidence from clinical studies has established that caloric restriction can modulate the onset and progression of age-related diseases. CR confers specific protection to the nervous system, in part through epigenetic mechanisms. CR attenuates age-related methylation changes in the hippocampus, both at CG and CH sites, while also inducing CR-specific methylation patterns, which may collectively contribute to its neuroprotective effects, including improved memory function and the prevention of age-related degenerative changes [81]. At the central level, CR remodels the epigenome in key metabolic regulatory centers like the hypothalamus, altering DNA methylation and histone modifications. This remodeling improves energy homeostasis and hormonal signaling, thereby counteracting obesity-related brain dysfunction [70]. The benefits of energy restriction extend to metabolic health. Dogan et al. found that long-term CR alters methylation at specific CpG sites of genes such as IGF-1R and FOXO1 in the aging mouse brain [82]. CR's influence on the epigenome is closely linked to core nutrient-sensing pathways. Analysis of these nutritionally responsive pathways revealed that methylation changes at key CpG sites are significantly correlated with metabolic parameters such as insulin levels and glucose tolerance. This underscores the pivotal role of the insulin/IGF-1 signalling (IIS) pathway in mediating the anti-aging effects of CR [83]. CR also exerts direct protective effects on the heart. In rodent models, CR significantly increases cardiac telomerase activity and upregulates the expression of proteins including IGF-1, SIRT1, and phosphorylated FOXO1 [84]. Furthermore, CR enhances autophagic capacity and improves left ventricular diastolic function in diabetic rat models, which are crucial for maintaining normal cardiac performance and retarding the progression to heart failure. These cardioprotective effects may involve CR-mediated increases in SIRT1 and FOXO1 protein expression, coupled with decreased levels of phosphorylated protein kinase B (p-Akt) and the tumor suppressor p53, collectively resisting diabetic cardiomyopathy and myocardial aging [85].

3.3. The ketogenic diet

KD is a dietary strategy characterized by low carbohydrate, normal protein, and high, normal, or reduced fat intake, with or without a concurrent reduction in caloric intake as in the very low-calorie ketogenic diet (VLCKD). The KD has demonstrated efficacy in

managing obesity, metabolic disorders and related conditions, neurological diseases, and various pathological states including cancer, non-alcoholic fatty liver disease, and chronic pain [86]. As a potential intervention for delaying aging, the core mechanism of the KD lies in inducing physiological ketosis, which converts the primary ketone body into a potent class of epigenetic signaling molecules. As a signaling molecule, BHB can serve as a substrate for histone modifications and regulate a spectrum of epigenetic phenomena, including histone acetylation, β -hydroxybutyrylation, histone methylation, DNA methylation, and microRNA expression [87].

Through direct mechanisms, BHB acts not only as an energy substrate but also as a covalent donor for histone modifications. It directly induces β -hydroxybutyrylation while simultaneously inhibiting HDAC activity. These actions collectively promote chromatin opening and enhance the transcription of genes related to antioxidant defense and metabolic adaptation, such as Nrf2 and FOXO1 [88, 89]. At a systemic level, studies have detected significant DNA methylation changes at 786 genes in obese patients following VLCKD intervention. These genes are involved in critical biological processes including adipose tissue function, neurological function, muscle development, and metabolism, indicating a reprogramming of biological pathways related to obesity, metabolism, and aging at the gene regulatory level [90]. For instance, adult epilepsy patients undergoing a 12-week modified ketogenic diet exhibited a genome-wide decrease in DNA methylation in whole blood cells, which was associated with pathways like lipid metabolism, revealing the diet's extensive capacity to remodel the epigenome [91]. Concurrently, KD or exogenous ketone supplementation may promote anti-aging effects. These effects are likely mediated by modulating DNA methylation in genes associated with changes in brain adenosine levels, including KLF14, ELOVL2, FHL2, OTUD7A, SLC12A5, ZYG11A, and CCDC102B [92].

Furthermore, the KD can directly promote healthy aging through ketone body-mediated epigenetic regulation and proteostasis. BHB serves not only as a fuel source but also as a direct donor of histone modifications. Wang et al. found that β -hydroxybutyrylation is a key mechanism for reversing muscle atrophy in aged mice, exerting protective effects by enhancing the expression of genes involved in mitochondrial function [93]. This provides a unifying molecular clue for the benefits of interventions like caloric restriction and exercise. Furthermore, BHB can directly interact with misfolded proteins, altering their conformation and facilitating their clearance via autophagy. In the cognitive domain, short-term KD feeding in aged mice was shown to rapidly remodel the synaptic proteome through BHB-mediated

activation of the Protein Kinase A (PKA) signaling pathway, thereby improving memory function [94].

However, prolonged adherence to a ketogenic diet may trigger entirely opposite, pro-aging consequences. Wei et al. found that a continuous KD activates the AMPK-caspase-2 signaling axis, inhibits MDM2 function, leading to sustained activation of the p53-p21 pathway. This ultimately induces widespread cellular senescence in multiple organs, including the heart, kidneys, and liver. These senescent cells secrete large quantities of pro-inflammatory factors such as IL-6 and TNF- α , forming a SASP that disrupts the tissue microenvironment and can even lead to cardiac fibrosis in mice [95]. Notably, a similar trend of elevated pro-inflammatory factors was observed in the plasma of obese patients after six months on a KD. This suggests that long-term ketosis may, through the reprogramming of epigenetic and cellular signaling pathways, shift the metabolic benefits toward chronic inflammation and tissue damage.

The epigenetic modulation induced by KD may offer a strategy to promote longevity and prevent age-related disorders [96]. The neuroprotective effects of KD are largely mediated by its principal ketone body-BHB. Li et al. demonstrated that BHB protects cholinergic neurons in AD models. In SH-SY5Y cells, BHB ameliorated amyloid- β (A β)-induced reductions in cell viability and tropomyosin receptor kinase A (TrkA) expression. This was achieved by inhibiting the upregulation of HDAC1/2/3 and counteracting the decrease in histone acetylation levels specifically H3K9ac and H4K12ac [97]. KD also impacts metabolic parameters. In a rat model of metabolic syndrome, supplementation with a BHB precursor enhanced the novel histone modification H3K9bhb (β -hydroxybutyrylation) across multiple tissues. This epigenetic change upregulated lipolytic genes like Hmgcs2 and was associated with reductions in body weight, blood glucose, and blood pressure [98]. The diet's potential extends to oncology. KD has been investigated as an adjuvant therapy for glioblastoma and for the prevention of prostate, colon, pancreatic, and lung cancers. Evidence suggests that KD may influence tumor biology by modulating the expression of genes critical for cancer cell survival and proliferation, in part through effects on DNA methylation. BHB and acetoacetate act as epigenetic modulators by inhibiting HDAC activity and by serving as donors for β -hydroxybutyrylation, a post-translational modification that influences histone and non-histone protein function, thereby affecting gene expression programs in cancer cells [99, 100].

3.4. Others

The Alternative Healthy Eating Index (AHEI) was developed as a standardized measure of dietary quality, emphasizing increased consumption of fruits, vegetables, whole grains, nuts, and legumes while restricting red meat, processed foods, refined grains, and sugar-sweetened beverages. Although the AHEI was originally validated for its capacity to reduce chronic disease risk, accumulating evidence suggests that adherence to this dietary pattern may also modulate the rate of biological aging through epigenetic mechanisms, particularly DNA methylation. Evidence from epidemiological studies establishes a clear association between AHEI adherence and decelerated epigenetic aging. At the molecular level, individuals with higher AHEI scores exhibit lower levels of DNA methylation-based aging biomarkers, positioning diet quality as a modifiable determinant of biological age [101]. Component analysis further reveals that specific dietary elements drive these effects: carbohydrate quality, dietary fiber, and the intake of whole grains and fruits show significant associations with decelerated epigenetic aging, whereas the intake of vegetables, nuts, and legumes does not exhibit statistically significant associations in this context [102]. This dissociation highlights the importance of moving beyond generalized dietary recommendations toward component-specific epigenetic insights, positioning AHEI not merely as a chronic disease prevention tool but as a precision nutrition strategy for slowing biological aging.

4. Conclusions

This review delineates the intricate interplay between diet, epigenetic regulation, and the biology of aging. We have established that aging is intimately linked to epigenetic dysregulation, primarily through alterations in DNA methylation, histone modifications, and non-histone protein modifications. These changes destabilize transcriptional programs, thereby driving cellular decline and serving as a pivotal mechanistic nexus connecting fundamental aging processes to the pathogenesis of major age-related diseases. Accumulating evidence underscores that long-term dietary patterns are a critical determinant of individual aging rates and disease susceptibility. Diet exerts its influence by modulating the availability of key metabolic intermediates such as SAM, NAD⁺, acetyl-CoA, and α -KG, which in turn regulate the activity of epigenetic modifying enzymes. This mechanism converts transient nutritional signals into persistent gene expression patterns, thereby systemically influencing the trajectory of aging. Dietary interventions, including the Mediterranean diet, caloric restriction, and the ketogenic diet, can counteract age-related epigenetic drift. Functioning as tools for complex epigenetic reprogramming, they collectively act upon the "diet–

metabolite–epigenetics–aging" axis, ultimately remodeling the epigenome to attenuate hallmarks of aging such as cellular senescence and chronic inflammation.

In summary, the convergence of genomics, nutritional genetics, and multi-omics integration is establishing a new paradigm in which personalized nutrition shifts toward actively modulating the aging process through epigenetic mechanisms [103]. Leveraging multi-omics data, including clinical tests, immune repertoire, targeted metabolomics, gut microbiomes, and assessments of physical fitness and facial skin, now enables the estimation of biological age for distinct organs and systems, providing a granular view of individual aging trajectories [5, 104, 105]. This is complemented by longitudinal host-microbiome multi-omics analyses, which unravel the complex interactions shaping host physiology and identify precise targets for intervention [106]. Notably, machine learning models that integrate microbiome, metabolomic, and clinical data have demonstrated the capacity to predict postprandial glycemic responses, guiding personalized dietary strategies that mitigate the glycation-induced epigenetic damage associated with aging [103]. Programs like ZOE PREDICT exemplify this approach, using multi-omics to generate personalized dietary scores that improve cardiometabolic health [107]. Concurrently, microbial community-scale metabolic models have emerged as powerful tools for designing personalized prebiotic, probiotic, or dietary interventions aimed at optimizing specific metabolic outputs, such as short-chain fatty acid production. The success of these models in predicting individual-specific responses, which correlate with cardiometabolic and immune health markers, underscores the shift toward precision probiotics [108]. These tailored interventions are designed to restore specific microbial functions, such as lactate or butyrate production, based on an individual's baseline microbiota and metabolic profile. This progression, highlighted by the growing recognition of responder versus non-responder phenotypes in probiotic supplementation, emphasizes the necessity of integrating microbiome-based selection criteria with multi-omics tools and predictive algorithms. Collectively, these advancements are forging a cohesive framework in which nutrition is used to reprogram the gut microbiota's functional output, thereby precisely targeting epigenetic marks to slow, or potentially reverse, the trajectory of biological aging [109].

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Author contributions

Xinyu Zhang: conceptualization, writing. Ziyue Xie: conceptualization, writing. Huimin Bian: editing, funding. Yu Li: editing. Ruigong Zhu: conceptualization, editing, funding. Jia Sun: conceptualization, editing. All authors read and approved the final version of the manuscript.

Competing interests

The authors declare no competing interests

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