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Epigenetic–Epitranscriptomic Regulation of Health span and Life Span

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Abstract

Aging is a complex, multifactorial process shaped by the interplay between genetic makeup and dynamic regulatory systems, with epigenetic and epitranscriptomic mechanisms playing a central role in integrating environmental, metabolic, and lifestyle influences across the lifespan. This review examines how these regulatory layers govern biological aging, lifespan, and health span, their modulation by environmental and nutritional factors, and their potential as therapeutic targets. With advancing age, alterations in DNA methylation, chromatin organization, histone post-translational modifications, and RNA chemical marks disrupt gene regulatory networks, driving genomic instability, chronic inflammation, and metabolic dysfunction that collectively impact lifespan and health span. Emerging evidence highlights the role of RNA modifications in fine-tuning cellular homeostasis and protein synthesis. Nutritional interventions and microbiota-derived metabolites, such as short-chain fatty acids, modulate these processes through nutrient-sensing pathways and metabolic cofactors, underscoring their dynamic and potentially reversible nature. Advances in high-throughput and multi-omics technologies reveal substantial inter-individual variability in biological aging trajectories and lifespan outcomes. Together, these findings position epigenetic and epitranscriptomic alterations as key mediators linking environmental exposures to disease risk and longevity. Integrating longitudinal human studies with multi-omics and computational approaches will be critical to refine biological age estimation and develop precision strategies to extend lifespan and health span.

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Introduction

Aging profoundly influences both lifespan and health span-the latter defined as the period of life free from disease-and is a major driver of chronic conditions, posing a significant global public health challenge. Central to this process are epigenetic mechanisms-heritable chemical and structural modifications that regulate gene expression without altering the DNA sequence. These mechanisms integrate environmental exposures, lifestyle factors, and cumulative cellular experiences to coordinate gene regulatory networks that maintain tissue homeostasis. Hallmarks of aging include widespread epigenetic alterations such as changes in DNA methylation, chromatin organization, histone post-translational modifications, RNA dynamics, and non-coding RNA regulation. Complementing these, epitranscriptomic modifications-including N6-methyladenosine (m6A), 5-methylcytidine (m5C), N1-methyladenosine (m1A), N4-acetylcytidine (ac4C), and N7-methylguanosine (m7G)-add an additional, dynamic layer of post-transcriptional control, influencing cellular function, stress responses, and potentially longevity [1-12].

Recent evidence suggests that approximately 50–55% of lifespan variability may be attributed to genetic factors after accounting for confounders; however, when lifestyle and social determinants of health are considered, epigenetic regulation emerges as a major modifiable contributor to both lifespan and health span. These observations underscore that longevity is not solely genetically predetermined but is strongly shaped by environmentally responsive regulatory systems. Consequently, targeting age-associated epigenetic dysregulation may offer opportunities to extend disease-free lifespan, positioning the epigenome as a critical interface between biology, environment, and healthy aging [13-17].

Among epigenetic mechanisms, DNA methylation is one of the most extensively characterized regulators of aging. Both site-specific and global changes in methylation patterns disrupt gene regulatory networks, impairing cellular and tissue function. For example, hypermethylation of the TP53 promoter is associated with reduced tumor suppressor activity and increased cancer risk, whereas methylation-mediated dysregulation of pro-inflammatory genes such as TNFα, IL1β, and IL6 contributes to vascular inflammation and atherosclerosis. Global hypomethylation, including reductions in 5-methylcytosine (5mC), is linked to downregulation of longevity-associated genes (e.g., ELOVL2) and increased expression of genes associated with senescence and genomic instability, including p15, p16, p21, LINE-1 elements, and endogenous retroviruses (ERVs). In contrast, elevated N6-methyladenine (6mA) levels may enhance stress-response pathways and proteostasis. Collectively, these methylation changes promote cellular senescence, cell-cycle arrest, and the senescence-associated secretory phenotype (SASP), highlighting DNA methylation as both a marker and mediator of aging [18- 29].

With advancing age, dysregulation of epigenetic and epitranscriptomic networks impairs immune function, tissue repair, and metabolic homeostasis, increasing susceptibility to chronic diseases such as diabetes, cardiovascular disorders, and neurodegeneration. Importantly, the inherent plasticity of these regulatory systems provides opportunities for intervention. Lifestyle factors-including nutrition, sleep, and circadian alignment-as well as pharmacological approaches can modulate these pathways and mitigate functional decline. Experimental evidence further supports the malleability of aging: caloric restriction extends lifespan across species via sirtuin-dependent and related pathways, while systemic interventions such as heterochronic parabiosis and circadian restoration highlight the role of circulating factors. In addition, cellular reprogramming and senolytic therapies demonstrate the potential to reverse aspects of age-related dysfunction at cellular and tissue levels. Together, these findings position the epigenome and epitranscriptome as active regulators-and promising therapeutic targets-of aging and health span [30-40].

Despite these advances, critical knowledge gaps remain. Much of the existing evidence derives from experimental models or cross-sectional human studies, limiting the ability to establish causality and capture temporal dynamics across tissues and populations. The interplay between DNA- and RNA-based regulatory layers, their tissue-specific variability, and their responsiveness to environmental, metabolic, and dietary factors are not yet fully understood. Moreover, the extent to which these pathways can be safely and effectively targeted to improve human health span remains uncertain. To address these gaps, this review first provides an overview of epigenetic and epitranscriptomic alterations associated with aging, followed by a detailed analysis of

their mechanistic roles and interactions with metabolic and environmental factors. I then examine emerging dietary and therapeutic interventions, evaluate current and prospective biomarkers of biological aging, and finally outline key challenges and future directions for translating these insights into strategies aimed at extending disease-free lifespan.

Epigenomic and Epitranscriptomic Drivers of Aging

Aging is increasingly recognized as a process shaped by epigenetic mechanisms, including DNA methylation, chromatin remodeling, histone modifications, and non-coding RNAs. Evidence from epigenetic clocks, twin studies, and longitudinal cohorts demonstrates that biological aging is highly responsive to environmental exposures and lifestyle factors, suggesting that a substantial component of lifespan variability-traditionally attributed to fixed genetic influence—may instead be mediated through dynamic, environmentally responsive epigenetic regulation. This view is reinforced by the observation that many genes governing longevity, stress resilience, and metabolic homeostasis are themselves epigenetically regulated, while emerging evidence indicates that epitranscriptomic modifications further fine-tune gene expression, adding an additional regulatory layer beyond the genome. Collectively, these findings support a model in which lifespan is determined not only by inherited genetic variation but also by adaptive regulatory systems that integrate internal and external signals across the lifespan [6, 41- 47].

Despite these advances, key questions remain regarding causality, reversibility, and mechanistic convergence. It is unclear whether age-associated epigenetic and RNA chemical changes act as primary drivers of aging or reflect downstream consequences of cumulative cellular stress, chronic inflammation, and metabolic dysfunction. Although interventions such as dietary restriction, circadian alignment, partial cellular reprogramming, and pharmacological targeting of chromatin regulators can slow or partially reverse epigenetic aging in model systems, their extent, durability, and tissue specificity in humans remain uncertain. Additional complexity arises from the interplay between metabolic dysfunction, inflammation, and epigenetic drift, as well as from unresolved questions about whether lifespan extension can occur without increasing cancer risk [48-49]. It also remains unclear whether diverse longevity-promoting interventions converge on shared regulatory pathways or act through distinct, context-dependent mechanisms. In this context, epitranscriptomic regulation-owing to its rapid responsiveness and reversibility-may represent a critical interface linking environmental and metabolic signals to gene expression. To address these challenges, this section provides a molecular overview of age-associated epigenetic and epitranscriptomic alterations across the lifespan, setting the stage for a focused discussion of their mechanistic roles and therapeutic potential in extending disease-free longevity.

Epigenetic Determinants of Aging

The epigenetic regulatory system-including DNA methylation, histone modifications, and non-coding RNA (ncRNA)-mediated control-maintains cellular identity, tissue organization, and tightly regulated gene expression throughout life by integrating environmental and metabolic signals without altering the DNA sequence [5-7, 16, 18, 19, 23, 24]. With aging, this system progressively loses fidelity, marked by global DNA hypomethylation alongside site-specific hypermethylation, weakening of heterochromatin, altered histone modification patterns, and disorganization of ncRNA networks. These changes destabilize chromatin, disrupt transcriptional programs, and promote genomic instability, aberrant activation of transposable elements, chronic inflammatory signaling, and impaired regulation of genes involved in DNA repair, immune function, metabolism, and mitochondrial maintenance [50-55].

Central to this remodeling are histone modification dynamics, which vary across tissues and species. Aging is consistently associated with loss of repressive marks such as H3K27me3, H3K9me3, and H4K20me3, alongside context-dependent changes in activating marks like H3K4me3. In hematopoietic stem cells, for example, aging increases H3K4me3 in mice but reduces H3K4me1, H3K4me3, and H3K27ac in humans. These alterations relax chromatin structure, enabling transcription of senescence-associated genes and repetitive elements, reinforcing cell-cycle arrest and the senescence-associated secretory phenotype (SASP), while promoting metabolic reprogramming toward pro-aging states [56-61].

Histone acetylation further links chromatin regulation to lifespan control through sirtuin deacetylases such as

SIRT1 and SIRT6, which maintain genome stability, suppress inflammation, and coordinate metabolism. Loss of SIRT6, for instance, increases H3K9 acetylation, enhances NF-κB-dependent transcription, promotes DNA damage, and accelerates senescence. Age-dependent changes in H4K16ac, along with additional modifications such as phosphorylation and ubiquitination, further destabilize chromatin; notably, accumulation of H2B monoubiquitination (H2Bub) in aging heterochromatin alters H3K4 and H3K79 methylation, disrupting transcriptional fidelity [64-68].

These epigenetic changes are driven by imbalances in chromatin-modifying enzymes and metabolic cofactors, including reduced EZH2 activity, increased histone demethylases, impaired sirtuin function, and declining S-adenosylmethionine (SAM), linking chromatin instability to metabolism and nutrient-sensing pathways such as mTOR. Consequently, longevity-associated regulators-including sirtuins, FOXO transcription factors, and signaling pathways such as AMPK, IGF, and mTOR-become dysregulated, while genome stability genes such as ATM, BRCA1, and WRN are compromised. Collectively, these processes support a model in which aging is driven less by fixed genetic mutations and more by cumulative epigenetic drift, where progressive chromatin disorganization undermines transcriptional coordination, cellular maintenance, and metabolic homeostasis, ultimately increasing susceptibility to age-associated diseases [69- 75].

Epitranscriptomic Drivers of Aging

Epitranscriptomics has transformed our understanding of RNA biology by revealing that RNA modifications are dynamic and reversible regulators of gene expression. A key milestone was the 2011 identification of fat mass and obesity-associated protein (FTO) as an N6-methyladenosine (m6A) demethylase, establishing RNA methylation as a reversible and biologically significant process. Advances in high-throughput, transcriptome-wide mapping have since uncovered widespread disruptions in RNA modifications across human diseases, particularly cancer, highlighting their functional importance and therapeutic potential. Beyond general gene regulation, RNA modifications are increasingly recognized as critical determinants of brain health and overall health span. The emergence of spatially and temporally resolved single-cell technologies has enabled precise profiling of RNA modifications in neural cells, uncovering cellular heterogeneity and refining neuronal subtypes. Studies in yeast and *C. elegans* demonstrate that RNA-modifying enzymes can directly influence lifespan, while in mammals, age-related alterations in these enzymes are linked to hallmarks of aging and neurodegenerative diseases. Together, these findings position the epitranscriptome as a dynamic regulator of longevity and a potential target for preserving brain function and mitigating disorders such as Alzheimer's disease [76-87].

Within this framework, epitranscriptomic marks regulate RNA stability, processing, and translation, thereby shaping cellular function and aging trajectories. Among these, m6A-the most abundant mRNA modification-plays a central role in RNA metabolism and exhibits age-dependent changes that contribute to cellular senescence, tissue dysfunction, and disease progression. Similarly, 5-methylcytosine (m5C) regulates RNA processing and stress responses, with context-dependent effects on aging. In contrast, N7-methylguanosine (m7G) supports translational efficiency and cellular homeostasis, and its decline has been associated with premature aging phenotypes. Other modifications contribute in distinct ways: 2′-O-methylation (Nm) stabilizes small RNAs and supports ribosomal function; N1-methyladenosine (m1A) is linked more to mitochondrial dysfunction and age-related pathologies than to primary aging mechanisms. One the other hand, adenosine-to-inosine (A-to-I) RNA editing enhances transcriptomic diversity, with age-dependent shifts influencing both longevity and neurodegeneration. Pseudouridylation (ψ) supports RNA stability and ribosome function, whereas N4-acetylcytidine (ac4C) is an emerging modification associated with RNA stability and disease, although its role in aging remains incompletely defined. Collectively, these modifications form a critical regulatory layer influencing RNA metabolism and contributing to cellular dysfunction during aging [88-100].

Taken together, epitranscriptomic modifications are dynamically regulated across the lifespan and influence key processes such as cellular senescence, stress responses, and translational control. Maintaining balanced epitranscriptomic regulation is therefore essential for preserving cellular function, enhancing resilience to age-related diseases, and supporting health span. Table 1 summarizes key RNA modifications,

their regulatory mechanisms, and their roles in aging biology [101-124].

Table 1: Key RNA Modifications and their Roles in Aging and Health Span

RNA Modification	Writers / Readers / Erasers	Molecular Effect	Aging / Health span Impact
m^6A	METTL3/14, WTAP; YTHDF/IGF2BP; FTO, ALKBH5	Regulates RNA splicing, stability, nuclear export, structure, and translation	Drops with age in blood and muscle; regulates cellular senescence via RNA stability; context-dependent roles in neurodegeneration and heart dysfunction; optimal levels required for tissue homeostasis 101-103
m^5C	NSUN1-7, DNMT2; ALYREF, YBX1; TET	Controls RNA stability, processing, localization, translation, and stress response	NSUN5 declines with age; context-dependent effects on lifespan and senescence; NSUN2 can promote or prevent senescence depending on cell state 104-106
A-to-I	ADAR1/2/3	Alters codon usage, RNA structure, splicing, and miRNA binding	Editing patterns shift with age; affects neural and immune transcripts 107-109
Ψ (pseudouridine)	PUS1-4	Enhances RNA stability, splicing, and translation fidelity	Levels change with age; affects ribosome function and RNA stability 110-112
m^1A	TRMT6/61A/B, TRMT10C; ALKBH1/3	Regulates RNA folding, stability, and translation efficiency	Dynamic with age; regulates protein synthesis and stress response 113-115
m^7G	METTL1/WDR4	Stabilizes tRNA, enhances translation, prevents ribosome stalling	Declines with age; loss induces premature aging phenotypes, senescence, and reduced lifespan 116-118
Nm (2'-O-methylation)	Fibrillarin & others methyltransferases	Stabilizes small RNAs (miRNA/piRNA), modulates ribosome structure and translation	Alters miRNA function and rRNA methylation during aging; linked to brain degeneration and neurodegeneration models 119-121
ac4C	NAT10	Enhances mRNA translation efficiency and tRNA stability	Levels shift with age; regulates mRNA stability & protein output. Direct role in aging unclear; implicated in cancer progression and neurodegeneration models 122-124

Abbreviations

m^6A: N^6-methyladenosine, m^5C: 5-methylcytosine, A-to-I: adenosine-to-inosine RNA editing, Ψ: pseudouridine, m^1A: N^1-methyladenosine, m^7G: N^7-methylguanosine, Nm: 2′-O-methylation, ac4C: N^4-acetylcytidine, mRNA: messenger RNA, tRNA: transfer RNA, rRNA: ribosomal RNA, METTL3/14: methyltransferase-like 3 and 14, WTAP: Wilms tumor 1-associating protein, YTHDF: YTH domain family proteins,

IGF2BP: insulin-like growth factor 2 mRNA-binding proteins, FTO: fat mass and obesity-associated protein, ALKBH5: alkB homolog 5, NSUN1-7: NOP2/Sun RNA methyltransferase 1–7, DNMT2: DNA methyltransferase 2, ALYREF: Aly/REF export factor, YBX1: Y-box binding protein 1, TET: ten-eleven translocation enzymes, ADAR1/2/3: adenosine deaminases acting on RNA 1, 2, 3, PUS1-4: pseudouridine synthases 1–4, TRMT6/61A/B: tRNA methyltransferases 6/61A/B, TRMT10C: tRNA methyltransferase 10C, ALKBH1/3: AlkB homolog 1/3, METTL1: methyltransferase-like 1, WDR4: WD repeat domain 4, Fibrillarin: rRNA 2′-O-methyltransferase, NAT10: N-acetyltransferase 10.

Diet–Epitranscriptome Interactions: Implications for Health span and Lifespan

Aging is characterized by a progressive decline in physiological and functional capacity, often culminating in frailty marked by the loss of bone and muscle mass. These changes reflect the cumulative impact of molecular and cellular alterations over time, yet their rate varies substantially among individuals of the same chronological age. This heterogeneity underscores that aging is not solely time-dependent but instead reflects differences in biological aging shaped by genetic, nutritional, lifestyle, and environmental factors [1-6]. Advances in defining the molecular hallmarks of aging have begun to explain this variability, with biological age–associated markers emerging as more accurate predictors of functional decline than chronological age, thereby providing a framework for personalized intervention strategies [8- 9].

Epigenetic and Epitranscriptomic Regulation of Biological Aging

Among the molecular determinants of aging, DNA methylation (DNAm) remains one of the most extensively characterized. DNAm involves the covalent addition of methyl groups to cytosine residues within CpG dinucleotides, modulating gene expression without altering the DNA sequence. Aging is associated with global hypomethylation of repetitive and intergenic regions-contributing to genomic instability-alongside localized hypermethylation of promoters of developmental and tumor suppressor genes, leading to dysregulation of critical pathways. These reproducible alterations form the basis of epigenetic clocks, which estimate biological age by integrating methylation patterns across CpG sites. While systemic clocks derived from blood or saliva provide global measures, tissue-specific clocks demonstrate that aging occurs at distinct rates across organs, a key consideration given that functional decline and disease often originate in specific tissues [125- 128].

Within this framework, biological aging acceleration (BAA)-defined as epigenetic age exceeding chronological age-has been consistently associated with increased risks of cardiovascular disease, neurodegeneration, metabolic disorders, and mortality. DNAm-based measures therefore provide a robust platform for understanding how genetic predisposition, environmental exposures, and interventions—including diet and pharmacological strategies-modulate aging trajectories. Extending beyond DNA-based regulation, epitranscriptomic modifications introduce a dynamic layer of control over gene expression. RNA modifications such as N6-methyladenosine (m6A) regulate mRNA stability, splicing, translation, and degradation, enabling rapid responses to metabolic and environmental cues. Age-related alterations in these processes are linked to disruptions in proteostasis, mitochondrial function, and stress-response pathways. Although RNA-based aging clocks are not yet fully established, emerging evidence suggests that epitranscriptomic signatures may complement DNAm-based measures by capturing more dynamic and tissue-specific dimensions of molecular aging [129-136].

Dietary Modulation of Epitranscriptomic Regulation

Dietary inputs represent a major modulator of epitranscriptomic regulation by influencing metabolic cofactors, enzyme activity, and nutrient-sensing pathways. Many RNA methylation marks, including m6A, depend on S-adenosylmethionine (SAM) as a methyl donor, whose synthesis relies on dietary methyl group sources such as methionine, folate, choline, and B-vitamins. Perturbations in these nutrients can disrupt methylation metabolism, directly altering RNA modification landscapes and downstream gene regulation. Experimental studies demonstrate that caloric restriction remodels global RNA methylation patterns

and modulates the expression of key epitranscriptomic regulators-including methyltransferase-like 3 (METTL3), methyltransferase-like 14 (METTL14), fat mass and obesity-associated protein (FTO), and alkB homolog 5 (ALKBH5)-across tissues, indicating that dietary inputs drive context-dependent regulatory adaptations [137- 142].

Similarly, supplementation with methyl donors such as betaine can counteract diet-induced alterations in m6A and associated metabolic pathways, reinforcing the link between nutrient availability and RNA-mediated regulation. Bioactive compounds, including polyphenols such as resveratrol and curcumin, further modulate RNA methylation and associated cellular processes, including intestinal integrity, metabolic regulation, and stress responses. Although direct human evidence remains limited, broader findings from nutritional epigenetics support a role for dietary patterns and bioactive molecules in shaping RNA biology. Other RNA modifications, such as adenosine-to-inosine (A-to-I) editing mediated by ADAR enzymes, contribute to transcriptomic diversity and gene regulation; however, their dietary modulation in humans remains an emerging area of investigation. Table 2 summarizes the relationships between key dietary components, their effects on RNA modifications, and their implications for health span, integrating evidence from experimental, preclinical, and emerging human studies [143-151].

Table 2: Dietary Components, RNA Modifications, and Effects on Health Span

Diet / Component	RNA Modification	Effect on Health span / Aging	Evidence
Caloric restriction	m^6A, m^1A	Remodels RNA methylation; enhances stress resistance, metabolic health	Animal [152]
Methionine restriction	m^6A, m^5C	Alters methylation via SAM; extends lifespan	Animal [153]
Methyl donors (Folate, B12, Choline, Betaine)	m^6A, m^5C	Maintains RNA methylation; supports RNA stability and translation	Animal / Human [154, 155]
Polyphenols (Resveratrol, Curcumin, EGCG)	m^6A	Modulates metabolism- and stress-related transcripts	Animal / Cell [156, 157]
Omega-3 fatty acids	m^6A	Influences lipid metabolism and insulin sensitivity	Animal / Emerging Human 158, 159
High-fiber / SCFA	m^6A, Nm	Modulates RNA methylation via gut microbiota interactions	Animal / Cell [160, 161]
Magnesium / Zinc	Ψ, Nm	Supports tRNA/rRNA stability and translation fidelity	Animal / Human [162, 163]
Antioxidants (Vitamin C, E)	A-to-I	Stabilizes RNA editing; protects transcriptome under oxidative stress	Animal / Human (emerging) [164, 165]

Abbreviations

m^6A, N^6-methyladenosine; m^5C, 5-methylcytosine; m^1A, N^1-methyladenosine; m^7G, N^7-methylguanosine; Nm, 2′-O-methylation; ac^4C, N^4-acetylcytidine; A-to-I, adenosine-to-inosine editing; ADAR, adenosine deaminases acting on RNA; SAM, S-adenosylmethionine; METTL3/14, methyltransferase-like 3/14; FTO, fat mass and obesity-associated protein; ALKBH5, alkB homolog 5; EGCG, Epigallocatechin-3-gallate; SCFA, Short-chain fatty acids.

Moreover, advances in high-throughput technologies-including methylated RNA immunoprecipitation sequencing (MeRIP-seq), pseudouridine sequencing (Pseudo-seq), and mass spectrometry-have enabled precise mapping and quantification of RNA modifications across biological systems. These approaches have revealed the dynamic responsiveness of the epitranscriptome to metabolic and environmental cues and have facilitated translational applications, including biomarker development and RNA-targeted therapeutic strategies. Collectively, these findings support a model in which diet shapes RNA modification landscapes in a tissue- and context-dependent manner, contributing to cellular homeostasis and influencing trajectories of biological aging [166-167].

Significance of the Review

Epigenetic and epitranscriptomic regulation lies at the core of aging, linking genetic predisposition with environmental, nutritional, and metabolic inputs; importantly, these modifications are reversible, making them compelling targets to enhance health span. Diet is a major modulator—through caloric restriction, nutrient composition, and bioactive compounds, it can reshape DNA and RNA modifications, strengthen cellular resilience, and delay age-related diseases-while microbiota-derived metabolites such as short-chain fatty acids (SCFAs) and RNA-modifying agents further highlight actionable intervention pathways. Adverse socioeconomic conditions can accelerate biological aging by disrupting these regulatory networks, underscoring the need for targeted strategies to reduce health disparities. These mechanistic insights carry significant public health implications: because aging is modifiable, population-level interventions focused on equitable access to healthy nutrition, physical activity, stress management, adequate sleep, and reduced environmental exposures could extend health span and lessen the burden of chronic disease. Moreover, the plasticity of epigenetic regulation emphasizes early-life and life-course interventions-including maternal health and childhood nutrition—to mitigate long-term risk, while emerging biomarkers such as epigenetic clocks may enable risk stratification, personalized prevention, earlier intervention, and reduced healthcare costs.

Limitations and Potential Biases of the Review

Despite substantial advances in understanding epigenetic and epitranscriptomic regulation in human aging, several limitations remain. A significant proportion of current evidence is derived from cell culture systems and animal models. While these provide critical mechanistic insights, they may not fully capture the complexity, heterogeneity, and environmental variability of human aging, limiting direct translation. Moreover, many studies in this field are observational or cross-sectional, enabling identification of associations with aging phenotypes but restricting causal inference. As a result, it often remains unclear whether specific epigenetic and RNA modifications actively drive aging or instead reflect downstream consequences of cellular stress, metabolic dysfunction, or disease processes.

Additional challenges stem from the rapidly evolving nature of epitranscriptomics. Although numerous RNA modifications have been identified, the functional roles, tissue specificity, and regulatory interactions of many remain incompletely characterized. At the same time, high-throughput technologies used to map epigenetic and RNA modifications-such as sequencing-based approaches and mass spectrometry-vary in sensitivity, resolution, and analytical pipelines, introducing technical variability and complicating cross-study comparisons. Furthermore, while lifestyle and nutritional interventions are increasingly linked to epigenetic and epitranscriptomic regulation, their effects must be interpreted cautiously due to substantial heterogeneity in human populations, including differences in genetics, diet, environmental exposures, and socioeconomic context. Addressing these limitations will require well-designed longitudinal human studies, integrative multi-omics approaches, and controlled intervention trials to better establish causality and enable reliable translation of these insights into strategies for extending health span.

Future Directions

Future research in aging biology should prioritize longitudinal human studies that track epigenetic and epitranscriptomic changes across the lifespan. Much of the current evidence is derived from cross-sectional studies and experimental models, which reveal associations but limit causal inference. Long-term population cohorts integrating environmental exposures, lifestyle factors, metabolic states, and molecular regulatory networks will be essential to clarify causality. In this context, epigenetic drift-characterized by global hypomethylation, locus-specific hypermethylation, and chromatin alterations-remains a key process linking

molecular dysregulation to increased susceptibility to chronic disease.

Advancing the field will also require the integration of multi-omics approaches with high-resolution technologies. Combining epigenomics, epitranscriptomics, transcriptomics, proteomics, metabolomics, and microbiome data-alongside single-cell and spatial profiling-can provide a systems-level understanding of aging. These approaches will enable identification of cell-type-specific regulatory signatures, improve biomarker discovery, and clarify how environmental and metabolic signals interact with gene regulatory networks. In parallel, greater attention to organ-specific aging and inter-organ communication is needed, as circulating factors such as cytokines, hormones, metabolites, and extracellular vesicles propagate senescence and inflammation across tissues, shaping organismal aging.

Finally, integrating epitranscriptomic biomarkers with established DNA methylation–based epigenetic clocks represents a promising direction. While epigenetic clocks are widely used to estimate biological age, their predictive value for health outcomes requires further validation. RNA-based signatures, owing to their dynamic nature, may capture short-term cellular responses not reflected in DNA methylation alone [170]. The development of integrated, multi-dimensional molecular clocks combining DNA, RNA, and other omics layers could enhance precision in biological age estimation, improve risk stratification, and support the development of personalized interventions to extend health span.

Conclusions

Aging results from a complex interaction between genetic inheritance and dynamic regulatory systems that control gene expression throughout life. Epigenetic and epitranscriptomic mechanisms are central to this process because they integrate environmental exposures, metabolic states, nutrition, and lifestyle factors that collectively shape biological aging. As individuals age, disruptions in chromatin organization, DNA and RNA chemical modifications, and gene regulatory networks can occur. These changes contribute to genomic instability, chronic inflammation, metabolic imbalance, and a gradual decline in physiological function, which helps explain why biological age may differ from chronological age. Importantly, many epigenetic and epitranscriptomic modifications are reversible, suggesting that environmental and metabolic interventions such as dietary patterns and microbiome-derived metabolites may influence aging trajectories. Continued advances in high-throughput sequencing, multi-omics approaches, and longitudinal human studies will be essential to clarify the underlying mechanisms and to develop precision strategies aimed at maintaining cellular resilience, delaying age-related diseases, and improving human health span together with lifespan.

Generative AI Statement

The author confirms that no content in this manuscript was generated using artificial intelligence (AI) tools. Limited AI-assisted technologies, if used, were restricted to non-substantive tasks such as language refinement or formatting, and did not contribute to the intellectual or scientific content of the work. All material has been written, reviewed, and verified by the authors, who take full responsibility for its accuracy, originality, and compliance with ethical standards.

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Conflict of Interest

The author declares no conflict of interest

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