

The central dogma of aging

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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- The Central Dogma of Aging extends the canonical DNA→RNA→protein information flow to metabolites.
- Layer-specific imbalances in anabolism, modification and catabolism propagate across levels to drive aging.
- The exposome acts hierarchically on the four layers and thereby sets the aging trajectory.
- This framework offers a rationale for aging interventions at any layer, and the exposome.

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Aging is driven by interconnected molecular and cellular changes that lead to functional decline and increased disease susceptibility. Here, we propose a novel "Central Dogma of Aging" hypothesis that extends the classical central dogma of molecular biology (DNA > RNA > protein) to encompass DNA, RNA, protein, and metabolite. The four layers are interconnected and mutually regulated by a 4C (Coding, Catalysis, Constitution and Catabolism) rule, referred to as the Central Dogma; each is further modulated by anabolism (synthesis), modification (post-synthesis alterations), and catabolism (degradation) process. Aging arises from imbalances in anabolism, modification, and catabolism across DNA, RNA, proteins, and metabolites, and is dynamically challenged by the exposome—cumulative environmental stimuli. The Central Dogma of Aging offers a comprehensive model for aging mechanisms, with implications for targeted therapies to promote healthiness and longevity.

INTRODUCTION

Current understanding of aging mechanisms

Aging represents the progressive deterioration of physiological functions, increasing vulnerability to diseases like cardiovascular, neurodegenerative disorders, and cancer.^{1,2} Despite extensive studies, the underlying mechanisms remain incompletely understood, with environmental factors playing a pivotal role alongside genetic predispositions.^{3,4} The current "Hallmarks of Aging", provide valuable frameworks for understanding age-related changes, further categorized to primary, antagonistic, and integrative hallmarks. Genomic instability (DNA and chromatin abnormalities), telomere attrition (uncapping and shortening), epigenetic alterations (altered DNA and histone modifications), loss of proteostasis (defective proteome homeostasis), and disabled macroautophagy (impaired turnover of subcellular compartments, including DNA, RNA, proteins, and metabolites) are categorized as primary causes of aging. Mitochondrial dysfunction (DNA instability and metabolic disturbance), deregulated nutrient sensing (metabolism fluctuation), and cellular senescence constitute the antagonistic mechanisms. The integrative hallmarks include extracellular matrix (ECM) changes, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis.^{5,6}

The primary hallmarks reflect a progressive collapse of the central dogma of molecular biology,^{7,8} and disturbed metabolic homeostasis, although RNA and metabolites are not explicitly highlighted. The transcriptome is not merely an intermediary, but serves as a critical regulatory hub: deficits in transcription efficacy, splicing, editing, modification, decay, and localization are not fully a reflection of upstream genomic abnormality, but also independently drive downstream proteostasis collapse and metabolic imbalances, inducing aging. Metabolic perturbations are also prominent during aging, e.g., declines in energy metabolite NAD⁺, accumulations of pro-inflammatory lipids, and imbalances in amino acid pools. The changes are not merely manifestations of other hallmarks but actively drive aging, extending beyond the DNA, RNA, and protein layers of the central dogma of molecular biology. The boosting, scavenging, restriction or supplementation of certain metabolites directly modulate epigenetics, epitranscriptomics, proteostasis, and extends lifespan. Recent integrated multi-omics enhance our comprehension of the mechanisms underlying aging. The epigenomic and/or epitranscriptomic changes affect the proteome, which in turn influence the metabolome.⁹ Nonlinear and interconnected pathways were revealed across the aging process and

outperform single-omics models to estimate biological age.⁹⁻¹¹ Yet, a conceptual framework unifying all these layers is lacking.

The central dogma of aging hypothesis

Current aging models sometimes feel fragmented, with overlapping categories that do not always emphasize the sequential and interconnected flow of biological information and processes. DNA acts as the genetic blueprint, wherein aging manifests as genomic instability (DNA damage accumulation),¹²⁻¹⁴ arising from DNA replication errors,^{15,16} telomere attrition,¹⁷⁻²¹ and epigenetic drift,²²⁻²⁴ particularly loss of heterochromatin,²⁵ and leading to cell cycle arrest and senescence. At RNA level, altered transcriptional elongation,^{26,27} editing capacity,²⁸ and modifications (e.g., N6-methyladenosine (m⁶A), N7-methylguanosine (m⁷G)) compromise precise gene regulation.²⁹⁻³¹ The impairments in the flow from DNA to RNA, including transcriptional stalling due to DNA damage (transcriptional stress) and reduced RNA adaptability,³² with increased transcriptional noise,³³ contribute to decoupling of transcription and translation during aging across species.³⁴ At protein level, the impaired post-translational modifications (PTMs),³⁵ and accumulation of misfolded proteins,^{36,37} leading to proteostatic collapse.^{38,39} Unlike the sequence-based fidelity of DNA, RNA, and protein, metabolic information is encoded not in linear sequences but in the concentration gradients, substrate–enzyme specificity, and dynamic equilibrium of anabolic and catabolic process.⁴⁰ Loss of metabolic fidelity during aging manifests as disrupted nicotinamide adenine dinucleotide (NAD⁺)/NADH ratios,⁴¹ accumulation of oncometabolites,⁴² or failure of allosteric regulation,⁴³ without involving template-directed errors.

Building on the flow of biological information and the hallmarks of aging,^{5,6,44} here, we propose a unifying model: The Central Dogma of Aging. This framework is organized into four layers: DNA, RNA, protein, and metabolite, each governed by anabolism (synthesis), (post-synthetic) modification, catabolism (degradation); interconnected by C^{oding} (DNA coding RNA and vice versa; RNA coding protein), C^{atalysis} (protein catalyzing replication, repair, telomere lengthening, transcription, translation, folding [conformation], modification, and metabolism); and ribosomal RNA (rRNA) catalyzing protein synthesis), C^{onstitution} (nucleotides, amino acids, lipids, carbohydrates, and derivatives constituting (modifying) DNA, RNA, and protein) and C^{atabolism} (recycling DNA, RNA, and protein). Aging is a progressive loss of stoichiometric and thermodynamic balance across the biosynthesis, modification, and degradation of the four layers, culminating in systemic function decline (Figure 1).^{45,46} These intracellular layers form a tightly interconnected and dynamic network; the dysfunction in any layer propagates bidirectionally, generating vicious cycles that accelerate aging; e.g., metabolites influence epigenetics, PTMs and protein functions,^{47,48} and genomic instability can trigger transcriptomic and proteostasis loss.^{32,38,49} The recursive crosstalk underscores aging as a failure of integrated communication. On top of the four layers, exposome encompasses environmental factors, including microenvironment, systemic factors, microbiota, diet, lifestyle, mental stressors, and space elements, and modulates the Central Dogma, thereby influencing aging.

The Central Dogma of Aging model extends the classical central dogma of molecular biology, incorporating metabolites, and emphasizing feedback loops and influence of exposome.^{50,51} The Central Dogma of Aging incorporates the major primary hallmarks of aging: DNA layer consists of genomic instability, telomere attrition, and epigenetic alterations; protein layer includes

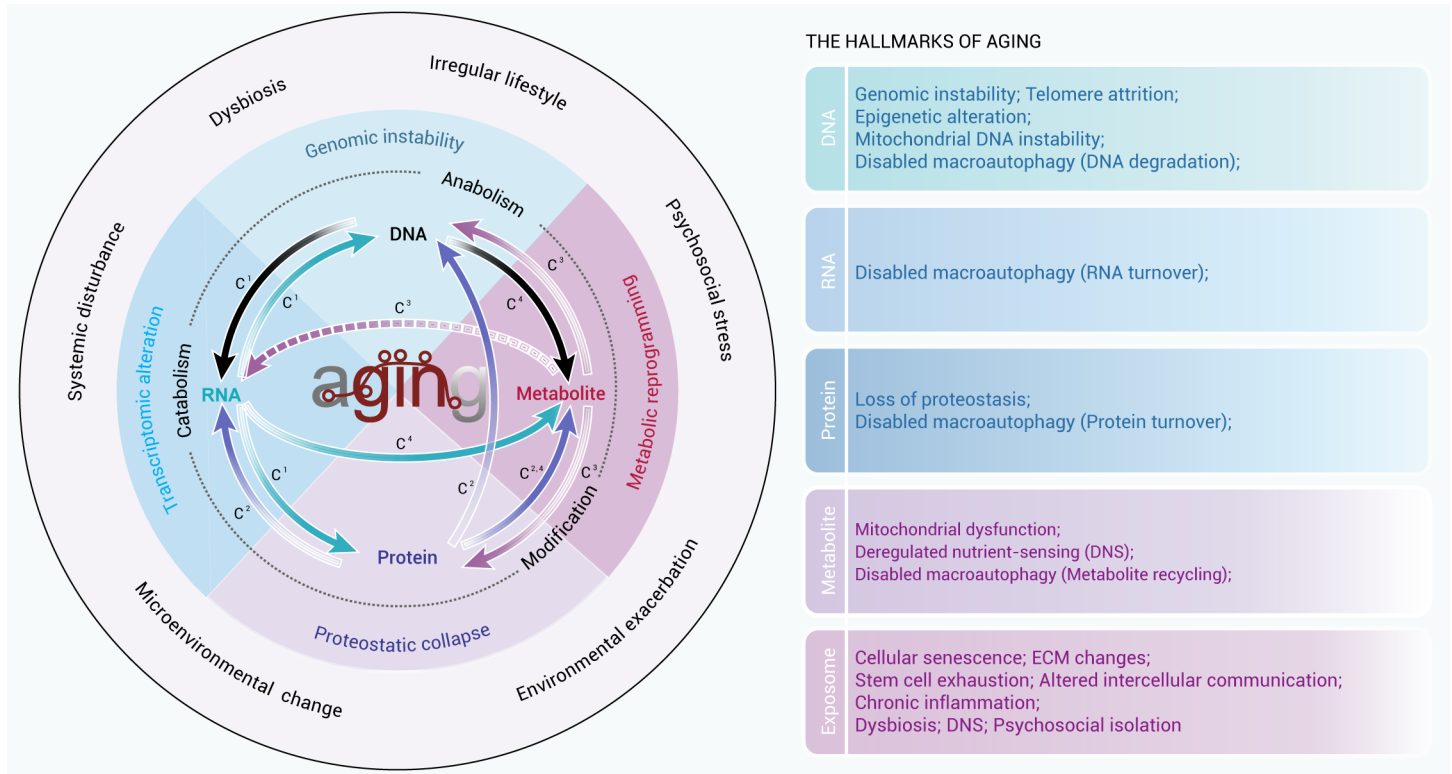


Figure 1. The central dogma of aging The Central Dogma is organized into four layers, i.e., DNA, RNA, protein, metabolite, interconnected by C'oding (DNA encodes RNA; in certain substances, RNA encodes DNA; RNA encodes protein), C²atylis (protein catalyzes DNA replication, repair, and telomere lengthening; RNA transcription, processing, translation and decay; folding, modification, activity, and stability; metabolism; some RNA catalyze RNA and protein synthesis), C³onstitution (nucleotides, amino acids, carbohydrates and lipids constitutes (modifies) DNA, RNA, protein and metabolite) and C⁴atabolism (recycling of DNA, RNA, protein, and metabolite). The Central Dogma of Aging posits that aging arises from imbalances in anabolism, modification, and catabolism across the four layers of the Central Dogma: the disturbance of DNA layer corresponds to genomic instability, including replication and repair impairment, chromatin modifications and remodeling deficits, telomere attrition and DNA fragmentation; the impairment of RNA layer refers to transcriptomic alteration, including efficiency and accuracy decline, abnormal post-transcriptional processing (e.g., splicing/editing/modification), and impaired decay and RNA aggregation; the deficiency of protein layer leads to proteostatic collapse, including defective biosynthesis, unfolded protein response (UPR), altered PTMs, dysfunctional changes, mis-localization, aggregation, defective turnover (e.g., caused by defects in ubiquitin-proteasome and autophagy-lysosome system); the disrupted metabolite layer dictates metabolic reprogramming causing signaling disturbance, energy deficits, epi-modification changes, and structural abnormality. Bridging to the Hallmarks of Aging: the DNA layer includes genomic instability, telomere attrition, epigenetic alterations, mitochondrial DNA instability and disabled macroautophagy (DNA degradation); the RNA layer covers disabled macroautophagy (RNA turnover); the protein layer consists of loss of proteostasis, and disabled macroautophagy (protein turnover); the Metabolite layer covers mitochondrial dysfunction (energetic), deregulated nutrient sensing, and disabled macroautophagy (metabolite recycling); the Exposome comprises cellular senescence, ECM changes, stem cell exhaustion, altered intercellular communication, chronic inflammation, dysbiosis, and psychological isolation. The term "anabolism" is employed in its broadest thermodynamic sense to represent the energy-consuming synthesis of macromolecules from precursors; this definition rigorously applies not only to protein translation and lipid biosynthesis but also to template-directed processes such as DNA replication and RNA transcription.

loss of proteostasis, and disabled macroautophagy (protein turnover).⁶ It extends the primary causes of aging to RNA and metabolite layers, including disturbed information flow from DNA to RNA, and RNA to protein, metabolite, defective function (e.g., rRNA, tRNA, miRNA, lncRNA), decay, and metabolic reprogramming, encompassing deregulated nutrient sensing, and mitochondrial dysfunction. It posits that aging arises from imbalances in anabolism, modification, and catabolism across the four layers. Exposome covers microenvironment, systemic factors, microbiota, diet, lifestyle, mental stress and space elements. The aging-causal microenvironment changes include not only ECM changes, but also altered O₂, H₂O, ions, hormones, cytokines, growth factors, metabolites, antibodies, and extracellular vesicles (EVs) that influence the intercellular communication, and cellular senescence. Systemic disturbances comprise deregulated endocrine, water and electrolyte imbalance, hypertension, disturbed body temperature, immune surveillance decline, as well as chronic inflammation, and stem cell exhaustion. Dysbiosis, irregular lifestyle, and psychosocial stress comprise aging-accelerating macroenvironment alteration. The environmental degradation emphasizes earth deterioration (e.g., heavy metals, radiation, fluctuation of ambient temperature, oxygen, light, and microgravity). The Central Dogma of Aging and the exposome collectively influence cellular senescence and lead to systemic aging. The four layers, DNA, RNA, protein, and metabolite, with biological function, aging-causal anabolic, modificatory, catabolic deficits, and representative biomarkers, are summarized (Table 1).

Genomic instability

The DNA serves as the foundational layer in the Central Dogma of Aging, encoding the genetic information that is essential for cellular, tissue and organismal function and homeostasis.^{7,160} Aging is profoundly influenced by defective maintenance of genomic integrity,⁵² including inherited/somatic mutations,^{55,57-59} chromosomal rearrangements,⁵³⁻⁵⁵ and structural changes.^{56,60} The perturbations arise from intrinsic processes like DNA replication errors¹⁶¹ and extrinsic factors such as oxidative stress.^{162,163} Accumulation of mutations, as revealed by whole-genome sequencing (WGS) and single-cell genomics, is correlated with declined DNA repair efficiency and increased age-related disease risk.^{58,164,165} Mitochondrial DNA (mtDNA) also acts as a potent driver of aging, wherein metabolic dysregulation and nucleotide imbalance promote ribonucleotide misincorporation; this leads to cytosolic release of mtDNA and activation of the innate immune sensor cyclic GMP-AMP synthase (cGAS), which activates stimulator of interferon genes (STING) pathway, thereby fueling aging-related inflammation and the senescence-associated secretory phenotype (SASP).¹⁶⁶ Below, we dissect the role of genome alteration in aging through the lenses of anabolism (synthesis, repair), modification (epigenetic modification, chromatin remodeling), and catabolism (DNA fragmentation, telomere attrition) (Figure 2).

DNA replication collapse and impaired repair. DNA anabolism primarily involves replication and repair. DNA polymerases replicate the genome with high fidelity, but inherent errors occur at a rate of approximately 10⁻⁸ to 10⁻¹⁰ per nucleotide per replication cycle,¹⁶⁷ leading to point mutations, insertions or deletions.¹⁶⁸ These errors accumulate over time due to replication stress, caused by DNA lesions and secondary structures.^{169,170} DNA replication stress

Table 1. Layer-specific aging hallmarks across the Central Dogma of Aging.

Layer	Biological function	Anabolic deficit	Modification deficit	Catabolic deficit	Representative biomarkers
DNA	Repository of genetic information	DNA replication collapse; replication errors and stress; inherited/somatic mutations and chromosomal rearrangements. ⁵²⁻⁵⁰	Altered DNA methylation; loss of heterochromatin; chromatin remodeling failure; histone modification dysregulation; epigenetic drift. ⁶¹⁻⁶⁹	Telomere attrition; DNA fragmentation; cytosolic DNA leakage; mitochondrial DNA instability. ⁷⁰⁻⁷⁹	γH2AX, ⁸⁰ 5mC, ⁸¹ telomere length, ^{82,83} SAHF. ⁸⁴
RNA	Intermediary for genetic information transfer and regulation	Transcription inefficiency; stalling; fidelity loss; Pol II/Pol decline; increased transcriptional noise. ⁸⁵⁻⁹⁶	RNA alternative splicing defects; dysregulated RNA modifications; editing decline; aberrant processing. ⁹⁷⁻¹⁰⁰	Impaired RNA decay; exosome failure; circular/lncRNA accumulation; toxic RNA aggregation; RNA exosome dysfunction. ¹⁰¹⁻¹⁰⁵	<i>CDKN2A</i> (p16) mRNA, ¹⁰³ m ⁶ A levels. ¹⁰⁶
Protein	Functional executor of cellular activities	Translational stalling; anabolic resistance; ribosome pausing and dysfunction; reduced mTOR activation; impaired translation initiation and elongation. ¹⁰⁷⁻¹¹⁴	Aberrant enzymatic PTMs (phosphorylation, acetylation, ubiquitination, glycosylation); protein carbonylation and oxidation; PTM crosstalk disruption. ¹¹⁵⁻¹²³	UPS and ALP failure; disabled macroautophagy; chaperone-mediated autophagy decline; amyloid aggregation; proteasome activity decreases. ¹²⁴⁻¹³⁰	Carbonylated proteins ¹³¹ , IL6, ¹³² histone modification. ¹³³
Metabolite	Metabolic readout; energy and signaling source	Biosynthetic wane; decline in <i>de novo</i> lipogenesis (DNL), purine, and pyrimidine synthesis; reduced anabolic intermediates; metabolic anabolic resistance. ¹³⁴⁻¹⁴¹	Non-enzymatic glycation (AGEs); altered chemical conjugations; increased oxidation of metabolites; aberrant metabolite modifications. ¹⁴²⁻¹⁴⁶	Glycolytic/TCA pathway slowing; BCAA and lipid catabolic block; reduced mitochondrial catabolic flux; impaired glycolysis and β-oxidation. ¹⁴⁷⁻¹⁵⁷	NAD ⁺ , ⁴¹ SAM, ¹⁵⁸ PGE ₂ , ¹⁵⁹ advanced glycation end-products. ¹⁴⁵

can also arise from transcription-replication conflicts, notably through the accumulation of unresolved R-loops—three-stranded RNA-DNA hybrids with a displaced single-stranded DNA.¹⁷¹ DNA replication stress activates DNA damage response (DDR), mediated by kinases including ataxia-telangiectasia-mutated (ATM),¹⁷² and ataxia telangiectasia and Rad3-related (ATR),¹⁷³ which phosphorylate checkpoint proteins to halt cell cycle progression and recruit repair machinery. With aging, DDR efficiency diminishes, accumulating unresolved damage and increasing genomic instability, a fundamental hallmark of aging.^{5,12,174,175}

Telomeres, repetitive TTAGGG sequences at chromosome ends, protect against end-fusion and degradation,^{70,71} however, they are shortened by 50-200 bp per division due to the end-replication issue.^{72,73} When critically short, the telomeric ends trigger DDR via ATM/p53 signaling, inducing senescence or apoptosis.^{74,75} Reactive oxygen species (ROS) accelerate attrition,⁷⁷⁻⁷⁹ which is correlated with cardiovascular diseases.^{21,73,176} Heterogeneous telomere lengths are identified by single-cell genomics in tissues,^{82,83} with shorter ones driving inflammation via senescence associated secretory phenotype (SASP).^{177,178} The telomerase, with reverse transcriptase (TERT) and RNA component (TERC), extends telomeres in stem cells, but its activity declines with age, accelerating telomere shortening.^{179,180}

DNA repair machinery constitutes a critical anabolic countermeasure against genomic instability,^{5,181} which encompasses multiple specialized pathways: base excision repair (BER) addresses oxidative lesions by excising damaged bases (e.g., via 8-Oxoguanine-DNA glycosylase-1, OGG1) followed by DNA polymerase/ligase-mediated gap filling and ligation;^{182,183} nucleotide excision repair (NER) resolves helix-distorting DNA lesions;¹⁸⁴ and mismatch repair (MMR) corrects replication errors.¹⁸⁵ Double-strand breaks (DSBs), the most severe lesions, are repaired via cell-cycle restricted and error-free homologous recombination (HR),¹⁸⁶⁻¹⁸⁸ or error-prone non-homologous end joining (NHEJ).¹⁸⁹ Aging impairs these pathways: e.g., reduced expression of repair enzymes like BER endonuclease AP-endonuclease 1 (APE1) leads to persistent single-strand breaks, which can be converted to DSBs during replication.¹⁹⁰⁻¹⁹² Oxidative stress from mitochondrial dysfunction exacerbates genomic instability, as ROS induce lesions that overwhelm repair capacity.^{193,194} The WGS and exome sequencing reveal age-related somatic mutations in tissues like brain and heart, and the downregulation of repair genes (e.g., BRCA1 in HR) in aged cells are correlated with increased mutation burden.^{164,195,196} The cellular genomic instability is heterogeneous, i.e., stem cells accumulate mutations faster than somatic cells, contributing to tissue degeneration.¹⁹⁷ Unrepaired DNA lesions can trigger persistent DDR

signaling via p53 and p16Ink4a pathways.^{198,199} In addition, the DNA anabolic deficits not only build up a fundamental layer of aging, but also drive other hallmarks such as inflammation and senescence.^{200,201}

Epigenetic alteration and chromatin remodeling. Genomic modifications encompass epigenetic alterations that regulate gene expression, such as DNA methylation,^{202,203} histone modification,^{69,133} and chromatin remodeling.⁶⁴ These changes are dynamic and reversible but dysregulated during aging, leading to aberrant gene expression.²⁵ DNA methylation involves an addition of methyl groups to cytosine residues (5-methylcytosine, 5mC) by DNA methyltransferases (DNMTs) like DNMT1 (maintenance) and DNMT3a/b (*de novo*).^{61,62} While global hypomethylation is uncovered, some allelic specific hypermethylation is responsible for silencing tumor suppressors and longevity genes during aging.⁶⁵

Histone modifications, such as lysine acetylation by histone acetyltransferases (HATs) like p300⁶⁶ and deacetylation by histone deacetylases (HDACs) like sirtuin 1 (SIRT1), alter chromatin accessibility.⁶³ Histone acetylation opens chromatin for transcription, while deacetylation compacts it. Aging-related decline in SIRT1 expression and activity increases global histone acetylation, causing inappropriate gene expression and loss of heterochromatin.^{67,68} Aging shifts histone marks like methylation (e.g., H3K27me3 for repression of gene expression, H3K4me3 for activation), of which the increase of H3K27me3 represses stem cell self-renewal, while the decrease of H3K9me3 erodes heterochromatin, causing transposon activation and inflammation.^{23,204-207} During aging, dysfunction of ATP-dependent chromatin remodelers like SWI/SNF complexes, which reposition nucleosomes, and alter the genome architecture, including loss of topologically associating domains (TADs).²⁰⁸⁻²¹⁰ The epigenetic modifications usually interact with DDR: the modifying enzymes are recruited to facilitate DNA repair, while persistent damage in aging leads to "epigenetic scars".²¹¹⁻²¹⁴ Epigenetic de-repression (e.g., loss of heterochromatin) activates the dormant endogenous retroviruses (ERVs),²¹⁵ which induce senescence and inflammation by activating the cGAS-STING pathway.²¹⁵⁻²¹⁷ Age-specific epigenetic patterns, e.g., DNA methylation at specific CpGs, predict epigenetic drift and biological age, namely, epigenetic clocks.^{23,218,219} By incorporating physiological decline, organ-system vulnerability, and mortality risk, next-generation clocks, PhenoAge (trained on clinical biomarkers),²²⁰ GrimAge (trained on mortality risk),²²¹ and DunedinPACE (trained on longitudinal biological aging rate), are built.²²² These multi-dimensional clocks align more closely with multi-layered, self-reinforcing systemic collapse central to the Central Dogma of Aging model.

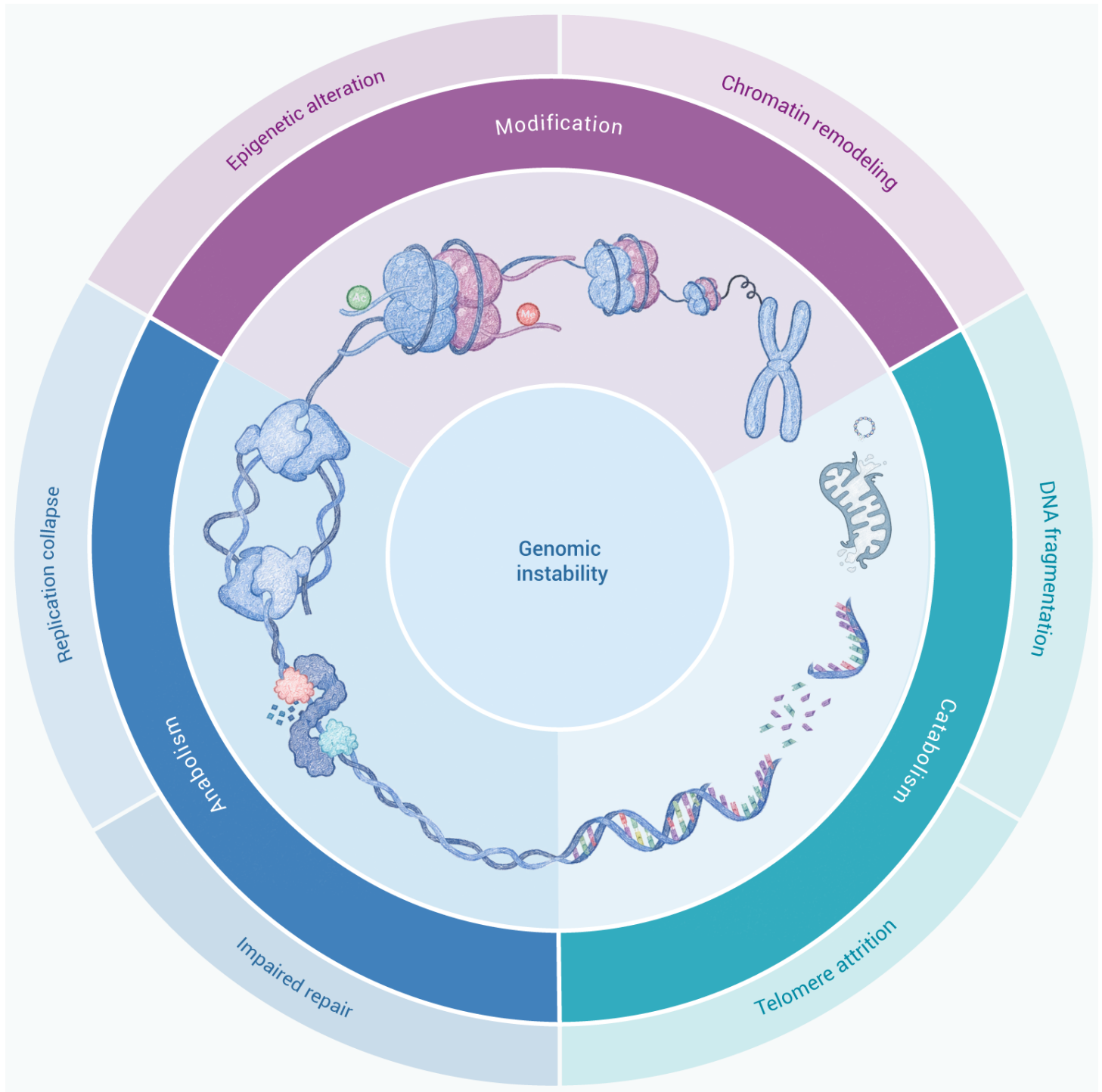


Figure 2. Genomic instability This model delineates the causal roles of genomic instability in aging through the lenses of three interconnected processes: anabolism, encompassing DNA synthesis and repair, whose decline leads to replication errors and DNA damage accumulation; modification, involving epigenetic modification and chromatin remodeling, such as aberrant histone modifications that regulate gene expression; and catabolism, characterized by telomere attrition and DNA fragmentation, contributing to cellular senescence and functional decline. Mitochondrial DNA instability is included.

DNA fragmentation and telomere attrition. Catabolism encompasses degradative process that erodes genome structure, e.g., DNA fragmentation, which is a key feature of aging. Cumulative DNA damage leads to the leakage of genomic DNA fragments into the cytoplasm,⁷⁶ which are recognized by the cGAS-STING pathway, and drive chronic inflammation and the SASP, exacerbating local aging and inducing paracrine senescence in neighboring cells.^{200,223} During DDR, exonucleases and endonucleases process damaged ends to facilitate repair; however, during aging, unresolved lesions may lead to chromosomal aberrations like fusions and dicentric.²⁵ The Shelterin complex (e.g., telomere repeat binding factor 1/2 (TRF1/2), protection of telomeres 1 (POT1)) shields telomeres, but its disruption in aging exposes

ends to nucleases.²²⁴ In telomerase-deficient animal models, the inhibition of the cGAS-STING signaling rescues premature aging, and extends healthspan, showing that innate immune activation by genomic instability—including telomere attrition and DNA fragmentation—is a key mechanism driving organismal aging.²²⁵

Transcriptomic alteration

The transcriptome represents a dynamic ensemble of RNA molecules transcribed from the genome. It serves as an intermediary in the Central Dogma of Aging by translating genetic information into functional proteins, responding to cellular and environmental cues. During aging, profound tran-

scriptomic alterations occur, including shifts in gene expression profiles that reflect deregulated pathways such as inflammation, immune response, and synaptic function, often manifesting as a hallmark of altered intercellular communication and chronic inflammation.²²⁶⁻²³⁰ Transcriptomic dysregulation involves errors in RNA synthesis, aberrant processing, and impaired degradation, contributing to cellular senescence and age-related diseases like neurodegeneration.²³¹⁻²³³ Advanced techniques such as RNA-seq and single-cell RNA-seq capture these perturbations; multi-omics link them to genomic instability and proteostatic collapse, highlighting the interconnected central dogma of aging (Figure 3).³⁸

Transcription efficacy decline. During RNA synthesis, RNA polymerase II (Pol II) and associated factors convert DNA templates into messenger RNA (mRNA), long non-coding RNA (lncRNA), and other transcripts. Transcription initiation involves the assembly of the pre-initiation complex (PIC) at promoters, including general transcription factors (TFs) like TFIID and TFIIF, which unwind DNA and phosphorylate the C-terminal domain (CTD) of Pol II to enable elongation.^{85,88,90} Pol II advances at variable rates, modulated by chromatin state and pausing factors like the 5,6-dichloro-1- β -D-ribofuranosylbenzimidazole sensitivity-inducing factor (DSIF) and negative elongation factor (NELF), which are disengaged following positive transcription elongation factor b (P-TEFb)-mediated CTD phosphorylation.^{96,91,93} During aging, the Pol II stalling diminishes transcriptional fidelity, culminating in decreased transcription and altered gene expression. This is attributed to accumulated DNA damage, oxidative stress, as well as diminished levels of elongation factors, which result in transcription errors—including base misincorporations—that ultimately lead to defective protein synthesis.^{26,234} Notably, these errors can generate damaged mRNAs, such as those containing 8-oxoG, which cause mistranslation and the production of aberrant proteins.⁹² Likewise, ribosomal RNA (rRNA) synthesis by Pol I decreases with age,⁹⁴ linked to promoter hypermethylation and diminished nucleolar activity, impairing ribosome biogenesis and overall protein synthesis.^{87,89,95} Age-related gene expression alteration is exemplified by increased p16^{Ink4a}, pro-inflammatory genes (e.g., nuclear factor kappa B (NF- κ B)), and the downregulation of those involved in metabolism and repair, with epigenetic shift that facilitate aberrant transcription.^{234,235} P16^{Ink4a}-positive cells accumulate with aging,²³⁶ which are heterogeneous, with distinct types playing different roles in pathology.²³⁷

Post-transcriptional modification abnormality. Transcriptomic modification involves post-transcriptional alterations that refine RNA structure and function, including alternative splicing, editing, and chemical modifications. The alternative splicing is orchestrated by spliceosomes—complexes of small nuclear ribonucleoproteins (snRNPs) and splicing factors (e.g., serine/arginine-rich splicing factor (SRSF))—that excise introns and join exons, generating isoform diversity.^{97,100} The altered splicing factor expression and localization lead to intron retention and exon skipping, which produce dysfunctional isoforms implicated in senescence and diseases like Alzheimer's.^{92,98} During aging, remodeling of alternative splicing favors isoforms that promote inflammation or reduce metabolic efficiency.⁹⁸ Age-associated chromatin changes drive RNA alternative splicing, as seen in hematopoietic stem cells (HSCs), where modified RNAs influence lineage commitment and aging.^{26,99}

RNA editing, primarily adenosine-to-inosine (A-to-I) by adenosine deaminases acting on RNA (ADAR) enzymes, recodes transcripts to alter protein sequence; aging declines ADAR activity, reducing RNA editing efficiency, and causing neurological decline.²⁸ RNA m6A methylation, deposited by writers like methyltransferase-like 3 (METTL3), regulate RNA stability, translation, and splicing; its reduction in aging impairs synaptic protein synthesis and correlates with cognitive deficits.^{29,30,77,238} Other modifications, like pseudouridylation and 5-methylcytosine (m5C), modulate RNA folding and export, but their dysregulation in aging promotes misfolded RNAs and cellular stress.²³⁹⁻²⁴²

Impaired RNA decay. Proper RNA decay provides both quality control and swift adaptation to cellular stress. mRNA decay involves the deadenylation by the CCR4-NOT complex, decapping by DCP1/2, and 5'-3' exonucleolytic digestion by XRN1, while 3'-5' degradation through the exosome complex.¹⁰² Nonsense-mediated decay (NMD) targets aberrant transcripts with premature stop codons, mediated by UPF proteins.¹⁰¹ During aging, RNA turnover slows due to reduced exosome activity and mislocalization of RNA-binding proteins (RBPs), leading to accumulation of damaged or long-lived RNAs and

thus promoting senescence.^{104,105} RNA-binding protein AUF1 promotes *INK4A* mRNA decay via its 3'UTR; AUF1 decline leads to *INK4A* stabilization¹⁰³ in senescent cells. Circular RNAs (circRNAs) and lncRNAs become resistant to exonucleases and accumulate with age, sequestering miRNAs and dysregulating gene networks.^{243,244} RNA helicases, like DDX family members, unwind structures for degradation, but their downregulation exacerbates aging.^{245,246} Increased RNA stability is evidenced in aged cells.^{247,248} Beyond enzymatic decay, RNA metabolism is increasingly recognized to be governed by liquid-liquid phase separation (LLPS), a process that concentrates RBPs and RNAs into membraneless organelles such as stress granules and P-bodies; LLPS facilitates rapid and spatially regulated RNA processing, storage, and decay.^{249,250} Aged cells exhibit reduced RNA concentration, leading to SGs with elevated RBP-to-RNA ratios and increased viscosity, termed "alt-SGs", which persist after stress removal and directly link RNA metabolic decline, altered condensate dynamics to cellular aging.²⁵¹ The RNA exosome serves as a guardian of nuclear homeostasis, and its failure triggers a cascade of nuclear RNA aggregation, disrupted transcription, and collapsed translation that directly drives cellular senescence.⁹⁸ Impaired RNA exosome function promotes cellular senescence by enabling the accumulation of endogenous retrotransposon-rich cytoplasmic double-stranded RNAs (dsRNAs). These dsRNAs activate an interferon-mediated viral response pathway, establishing a chronic inflammatory state that acts independently of, or in parallel to, the cytoplasmic DNA/cGAS-STING axis to drive the SASP.¹⁰⁵ Depletion of spliceosome components and accumulated unspliced RNAs suggest RNA catabolic defects in aged neurons.^{252,253}

The transcriptome not only serves as a decisive regulatory hub, where the compounding deficits in anabolism, modification, and catabolism reflect upstream genomic instability and actively drive the downstream collapse of proteostasis and metabolic equilibrium, the alteration of itself also directly drive senescence, thereby propelling the systemic failure encoded by the Central Dogma of Aging.

Proteostasis collapse

The proteome represents the entire set of proteins expressed by a genome under specific conditions, and its alterations in aging are pivotal, manifesting as loss of proteostasis—a core hallmark involving protein synthesis abnormality, the accumulation of misfolded, aggregated proteins, PTM changes, and impaired turnover.²⁵⁴ These changes contribute to inflammation, cell dysfunction, and age-related diseases like neurodegeneration and sarcopenia. We summarize roles of proteostasis loss in aging through the perspectives of anabolism (biosynthesis), modification, and catabolism (turnover) (Figure 4).

Protein synthesis changes. Protein synthesis is a highly regulated process where ribosomes assemble amino acids into polypeptides based on mRNA templates, which comprises initiation (assembly of the 43S pre-initiation complex with eukaryotic initiation factor 2 (eIF2), GTP, and Met-tRNAi), elongation (aminoacyl-tRNA delivery by eukaryotic elongation factor 1 alpha (eEF1A) and peptide bond formation), and termination (release factors recognizing stop codons). This process is energy-intensive and modulated by signalings like mechanistic target of rapamycin complex 1 (mTORC1), which phosphorylates the eIF4E-binding protein 1 (4E-BP1) and ribosomal protein S6 kinase (S6K1) to enhance cap-dependent translation.^{247,255} During muscular aging, the anabolic efficiency declines, leading to "anabolic resistance", wherein protein synthesis responds poorly to stimuli like amino acids or exercise, contributing to sarcopenia. This resistance stems from reduced mTOR activation, ribosomal stalling, and lower levels of initiation factors.^{107,109,111} A moderate suppression of translation in early adulthood extends lifespan by reducing proteotoxic stress and error-prone protein production, as seen in models with inhibited eIF4E or eIF4G.^{108,110,114} Age-related ribosomal dysfunction, including rRNA modifications and reduced polysome formation, impair translational fidelity and favor the synthesis of shorter, dysfunctional proteins.^{94,113,242} Reduction of translation machinery proteins, such as ribosomal subunits and elongation factors, was also evidenced by quantitative proteomic, across aged tissues like skeletal muscle and brain.^{112,113} The anabolic deficits are correlated with upstream transcriptomic changes, such as reduced mRNA levels for eIFs, and downstream metabolomic shifts in amino acid pools, forming feedback loops that exacerbate aging.²⁵⁶ A large-

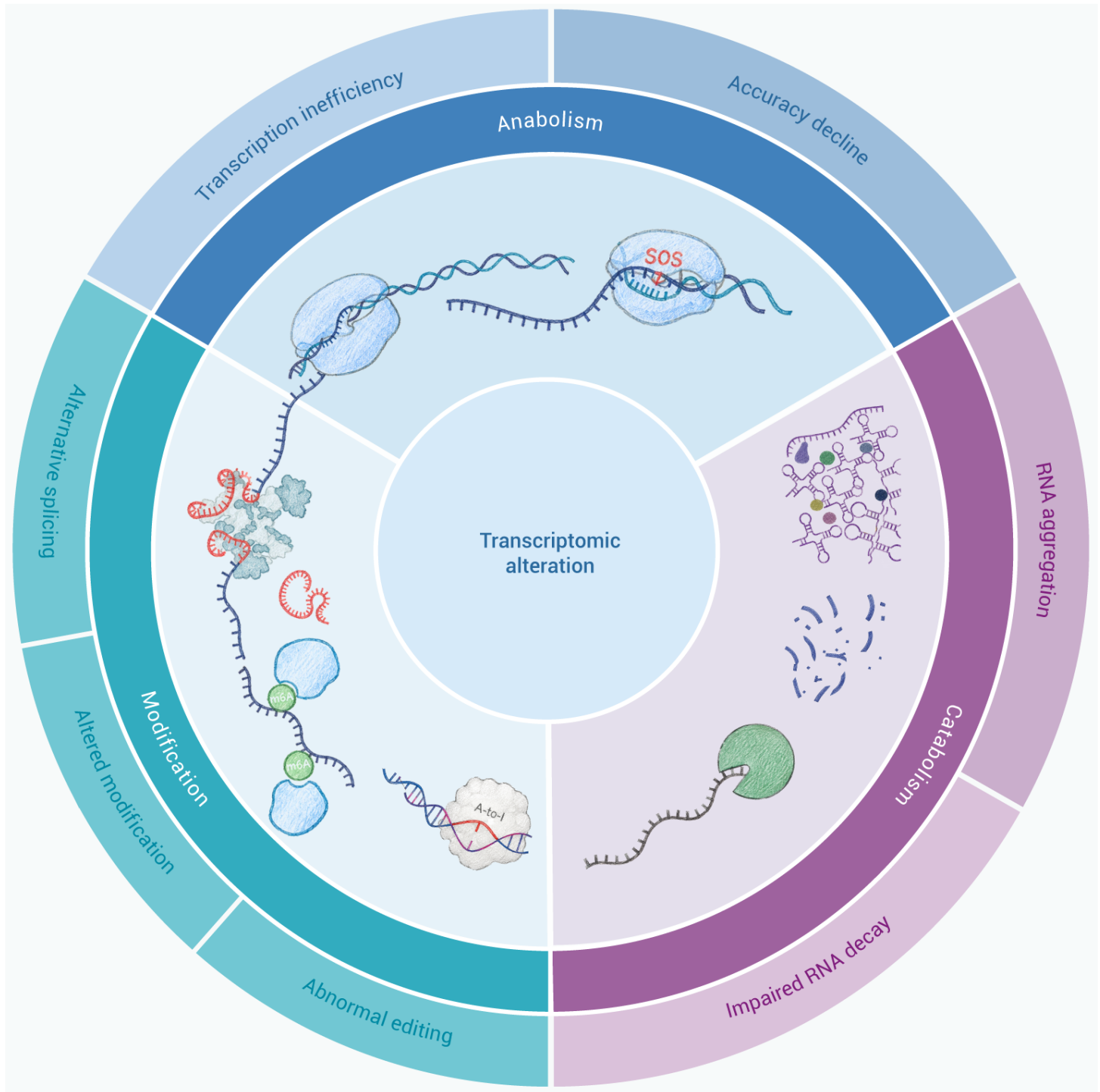


Figure 3. Transcriptomic alteration This model delineates the core mechanisms underlying transcriptomic alteration during aging, which stems from the dysregulation of three fundamental processes: anabolism, modification (processing), and catabolism. The decline in biosynthesis is characterized by diminished transcriptional efficiency and reduced fidelity, leading to increased gene expression noise. The abnormal modification encompasses erroneous alternative splicing, altered RNA modifications, and aberrant RNA editing such as A-to-I conversion, which collectively compromise RNA maturation and function. The collapse of catabolism is manifested as impaired RNA decay and toxic RNA aggregation. These processes are interconnected, forming a self-reinforcing vicious cycle: the errors and noise from the synthesis stage burden the modification systems, while the failures in modifications and degradation further amplify transcriptomic chaos, driving senescence and contributing to functional decline.

scale human proteomic study reveals blood vessels as an early-aging tissue and the elevated growth arrest-specific 6 (GAS6) as a causal driver of vascular and systemic aging.²⁵⁷

Altered post-translational modifications (PTMs). Proteome modifications involve a diverse array of PTMs, including phosphorylation, acylation, ubiquitination, glycosylation, and oxidation, which dynamically regulate the protein function, stability, localization, and interactions without altering the underlying sequence. Molecularly, enzymatic PTMs like phosphorylation by kinases (e.g., AMP-activated protein kinase (AMPK), cAMP/protein kinase A

(PKA) or acetylation by HATs (e.g., p300) enable rapid signaling transduction, while deacylases like SIRT1 reverse them to maintain homeostasis.^{117,121,258}

During aging, the PTM landscapes shift: increased non-enzymatic modifications from ROS, such as carbonylation and nitration, cause protein misfolding and aggregation.^{115,120} PTM crosstalk amplifies the effects; for example, ubiquitination can follow phosphorylation, directing proteins to degradation, however, aging disrupts this, leading to proteotoxic buildup.¹¹⁹ Enrichment-based PTM proteomics (e.g., phospho- or glyco-proteomics), identify thousands of age-specific sites; for instance, muscle PTM profiling reveals func-

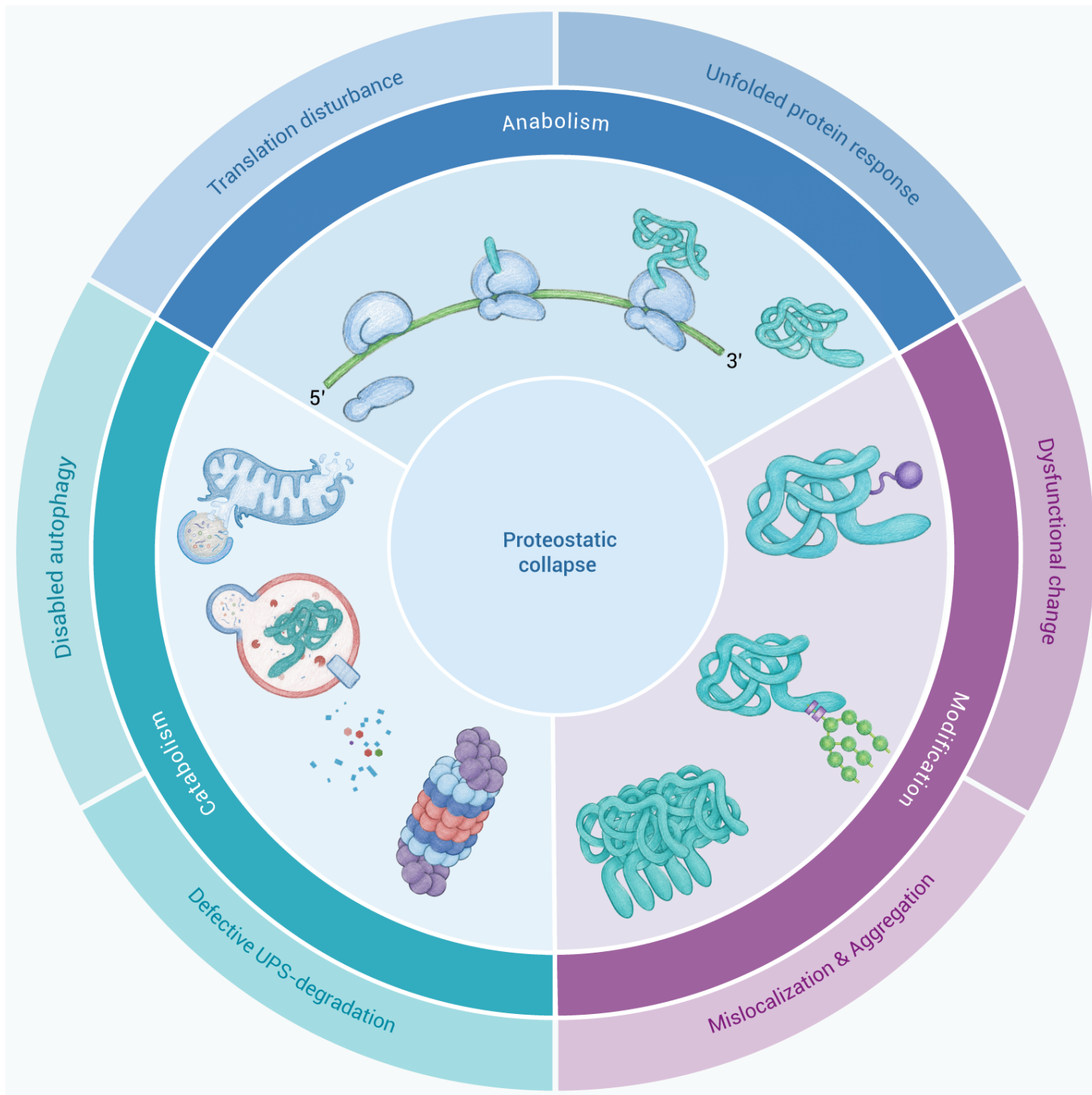


Figure 4. Proteostasis collapse This model delineates the contributing role of proteostatic collapse in aging through three interconnected processes—anabolism, modification, and catabolism—revealing a self-reinforcing cycle of proteostasis failure. The impaired protein synthesis in aging manifests as translational disturbance and unresolved unfolded protein response (UPR), generating error-prone polypeptides. Aberrant post-translational modifications (PTM), including single-type and chain-type modifications, cause function changes, or promote mislocalization and toxic aggregation. The catabolic abnormality depicts the ubiquitin-proteasome system and autophagy-lysosome pathway becomes overwhelmed, resulting in defective protein degradation and disabled macroautophagy. These synchronously dysregulated processes create a vicious cycle that perpetuates and amplifies proteome collapse during aging.

tion decline markers in long-lived species.¹²³ Novel PTMs, like citrullination and deamidation, are revealed and correlated with age-related disease risk.^{116,118,122}

Loss of proteostasis. Catabolism involves the breakdown of proteins to maintain quality control, primarily through the ubiquitin-proteasome system (UPS) and the autophagy-lysosome pathway (ALP), collectively ensuring proteostasis. UPS conjugates ubiquitin chains via E1 (activating), E2 (conjugating), and E3 (ligating) enzymes, marking proteins for 26S proteasome degradation.¹²⁷ Autophagy, categorized into macroautophagy, chaperone-

mediated autophagy (CMA), and microautophagy, sequesters substrates for lysosomal fusion and hydrolysis.^{124,126} During aging, the catabolic capacity wanes: proteasome activity decreases due to oxidative damage and subunit disassembly, while autophagic flux impairs owing to mTOR hyperactivation, lysosomal acidification loss, and reduced ATG level, leading to aggregates accumulation.^{127,259,260} In neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and prion disorders, specific proteins (e.g., A β , tau, α -synuclein, and PrP) undergo misfolding and aggregation, forming amyloid fibrils.¹²⁵ These aggregates exhibit prion-like properties and can

promote the misfolding and aggregation of other native proteins via cross-seeding or trans-seeding mechanisms.²⁶¹ This proteostatic collapse triggers cell aging and neurodegeneration.²⁶² Cells are primarily equipped with autophagy, a selective form of autophagy, to clear these toxic aggregates. This relies on a coordinated action of DNAJB6–HSPA/HSP70–HSPH1/HSP110 chaperone module and the proteasomal 19S regulatory particle (RPs), which collectively fragment and condense amorphous aggregates, thus facilitating the clustering of selective autophagy receptor (SAR) and formation of local phagophores.²⁶³ With advancing age, the efficiency of this clearance mechanism declines, leading to the accumulation of toxic aggregates and exacerbating cellular dysfunction and aging. Emerging evidence establishes LLPS as a critical mechanism linking proteostasis loss to aging. RNA-binding protein RBM33 undergoes LLPS to bind CDKN1A promoter and induce microglial senescence, accelerating hippocampal aging;¹²⁸ conversely, MRG15 condensation via its intrinsically disordered region delays senescence in human mesenchymal stem cells (MSCs).¹²⁹ Pharmacological modulation of LLPS is emerging as a promising therapeutic to counteract protein aggregation and restore proteostatic balance during aging.¹³⁰

Metabolic reprogramming

The metabolome encompasses the complete set of small-molecule metabolites within a biological system, reflecting the end products of cellular processes and serving as a dynamic readout of physiological status in the Central Dogma of Aging. Metabolome maintains its functional fidelity through stoichiometric balance, metabolic fluxes, and enzyme kinetics.⁴⁰ Aging disrupts metabolic homeostasis, contributing to the hallmarks like deregulated nutrient sensing, mitochondrial dysfunction, and altered intercellular communication, which manifest in metabolic shifts toward inefficiency, inflammation, and disease susceptibility.^{77,158,264} Metabolic perturbations include declines in energy metabolites like NAD⁺, accumulations of pro-inflammatory lipids, and imbalances in amino acid pools.^{265–269} Polyamines, such as spermidine, also decline with age; this impairs eIF5A hypusination and reduces TFEB-driven autophagy.²⁷⁰ NAD⁺,²⁷¹ spermidine, S-adenosylmethionine (SAM),²⁷² and gut-derived compounds, also regulate modifications and functions of DNA, RNA and protein,^{48,273–275} linking metabolic disturbance to genomic instability, declined transcription and translation, and disrupted nutrient signaling,^{276,277} driving senescence and tissue functional decline.²⁷⁸ Age-specific metabolic waves are revealed by integrated genomics, transcriptomics, proteomics and metabolomics, where dysregulated metabolites correlate with genomic instability and proteostasis loss.⁹ At the molecular level, metabolomic changes arise from imbalances in synthesis, chemical modifications, and degradation.^{9,279} Advanced techniques, like liquid chromatography-mass spectrometry (LC-MS) and nuclear magnetic resonance (NMR), enable profiling of metabolomic alterations, developing of aging clocks and identifying intervention targets.²⁸⁰ We dissect the role of metabolites in aging through anabolism (biosynthesis), modification (chemical alteration), and catabolism (breakdown), incorporating both molecular and omics evidence (Figure 5).

Deregulated biosynthesis. Metabolome anabolism encompasses the biosynthesis of diverse molecules, including nucleotides, amino acids, lipids, and carbohydrates. These metabolites are integral to inter- and intra-cellular signaling, energy metabolism, and the construction of cellular structures,¹³⁵ which rely on enzymatic cascades; for instance, *de novo* lipogenesis (DNL) synthesizes fatty acids via acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), regulated by sterol regulatory element-binding protein-1c (SREBP-1c) and AMPK.^{136,138,139,141} During aging, anabolic efficiency wanes, leading to "metabolic anabolic resistance"; e.g., the branched-chain amino acids (BCAAs) synthesis in muscle respond poorly to nutrients, resulting in sarcopenia and insulin resistance.^{134,137,140} The resistance may arise from reduced enzyme activity, cofactor depletion (e.g., NAD⁺ for sirtuins), and mitochondrial impairments that limit precursor availability, resulting in lowered levels of anabolic intermediates like citrate in the TCA cycle.²⁸¹ Aging declines the biosynthesis of purine and pyrimidine, reducing folate cycle activity while increasing oxidative burden.^{282–284} The metabolism of arachidonic acid (AA), a polyunsaturated fatty acid, represents another central metabolic pathway linking inflammation and aging.^{285,286} AA is metabolized via the cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP) enzyme path-

ways into a series of highly bioactive eicosanoids, including prostaglandins (e.g., PGE₂), thromboxanes, and leukotrienes.¹⁵⁹ In aging, increased oxidative stress and altered enzymatic activity often lead to enhanced production of pro-inflammatory eicosanoids (e.g., PGE₂, LTB₄), while synthesis of anti-inflammatory or pro-resolving metabolites (such as lipoxins) may be reduced.^{159,287} This imbalance drives chronic, low-grade systemic inflammation, which in turn affects other hierarchical levels—such as epigenetic regulation and protein function—through signaling mechanisms, thereby promoting aging and related pathologies.²⁸⁶ The essential cofactor riboflavin (vitamin B2) exhibits a paradoxical role in aging. Its uptake via the p53-target SLC52A1 alleviates senescence by supporting mitochondrial complex II,²⁸⁸ whereas its moderate depletion extends lifespan in *C. elegans* through AMPK activation,²⁸⁹ indicating that its optimal regulatory level is critical for metabolic health. The targeted metabolomics reveals age-associated reductions in anabolic metabolites, such as BCAAs and lipids, correlating with muscle loss across cohorts.²⁷⁹ Nonlinear anabolic shifts were evidenced by longitudinal studies, with midlife drops in synthesis rates, and as seen in metabolomic aging.²⁹⁰ Single-Cell metabolomics uncovers aged fibroblasts with impaired glucose anabolism leading to glycolytic intermediates buildup.^{291,292}

Chemical alterations and conjugations. Modification of metabolome refers to chemical changes that alter metabolite structure and function, including oxidation, methylation, and acetylation etc., and conjugations like glucuronidation and sulfation. At the molecular level, ROS induce oxidation, such as lipid peroxidation forming malondialdehyde (MDA) or protein carbonylation;¹⁴² the enzymatic modifications like N-acetyltransferase (NAT) activity add acetyl groups to amines for excretion.^{143,144} During aging, these modifications accumulate aberrantly: increased ROS from mitochondrial dysfunction leads to elevated oxidized metabolites (e.g., 8-oxo-dG), promoting genomic instability. One-carbon metabolism (e.g., SAM for methylation) declines, reducing metabolite methylation and altering histone/DNA marks.¹⁵⁸ AGEs accumulate via non-enzymatic glycation of sugars with amines, cross-linking macromolecules and activating RAGE receptors to drive chronic inflammation.¹⁴⁵ The untargeted metabolomics identifies age-specific modified metabolites, like dimethyl-guanosine and acetyl-carnosine, serving as biomarkers in frailty studies.¹⁴⁴ Cohort analyses show ethnic and sex differences in modification profiles, with higher oxidative markers in aging populations predicting disease.¹⁴⁶

Disturbed degradation and breakdown. Catabolism in the metabolome encompasses the breakdown of metabolites to generate energy and eliminate waste, including pathways like glycolysis, β -oxidation, and the urea cycle. Molecularly, glycolysis degrades glucose via enzymes like pyruvate kinase (PK) to pyruvate, feeding the TCA cycle, while β -oxidation in mitochondria breaks fatty acids into acetyl-CoA via acyl-CoA dehydrogenases.^{150,152} Catabolic flux impairs during aging: reduced mitochondrial efficiency slows down TCA cycle; accumulating intermediates like succinate promote pseudohypoxia and inflammation.^{147,149,157} During aging, catabolism of BCAAs declines due to lowered BCKDH activity, causing BCAAs buildup and hyperactivation of mTOR, exacerbating insulin resistance.^{148,151} Metabolomics shows that aging increases gut-derived toxins.^{154,155} Multi-omics links metabolic aging to mutations in catabolic genes and enzyme declines.^{153,156} Catabolic signatures predict human longevity, with protective metabolites from the gut microbiome, and glucose metabolism slowdowns in liver.^{155,293}

Interactions between the four layers

While the classical central dogma posits a partial bidirectional flow from DNA to RNA to protein, the expanded Central Dogma recognizes bidirectional and cyclic interactions (4C rule) among DNA, RNA, protein, and metabolite, forming a complex regulatory network. The interactions are not merely linear; they involve feedback loops, cross-talk, and nonlinear dynamics, for instance, metabolites modulate epigenetic marks, proteins regulate transcriptome stability, and genomic variants affect metabolism.^{294–296} During aging, the interactions weaken, causing systemic collapse; for instance, genomic instability alters transcriptome, which in turn disrupt proteostasis and metabolomic flux, creating vicious cycles that accelerate the hallmarks of aging like mitochondrial dysfunction and chronic inflammation.^{46,296,297}

Genome-transcriptome interplay and feedback. Genomic mutations

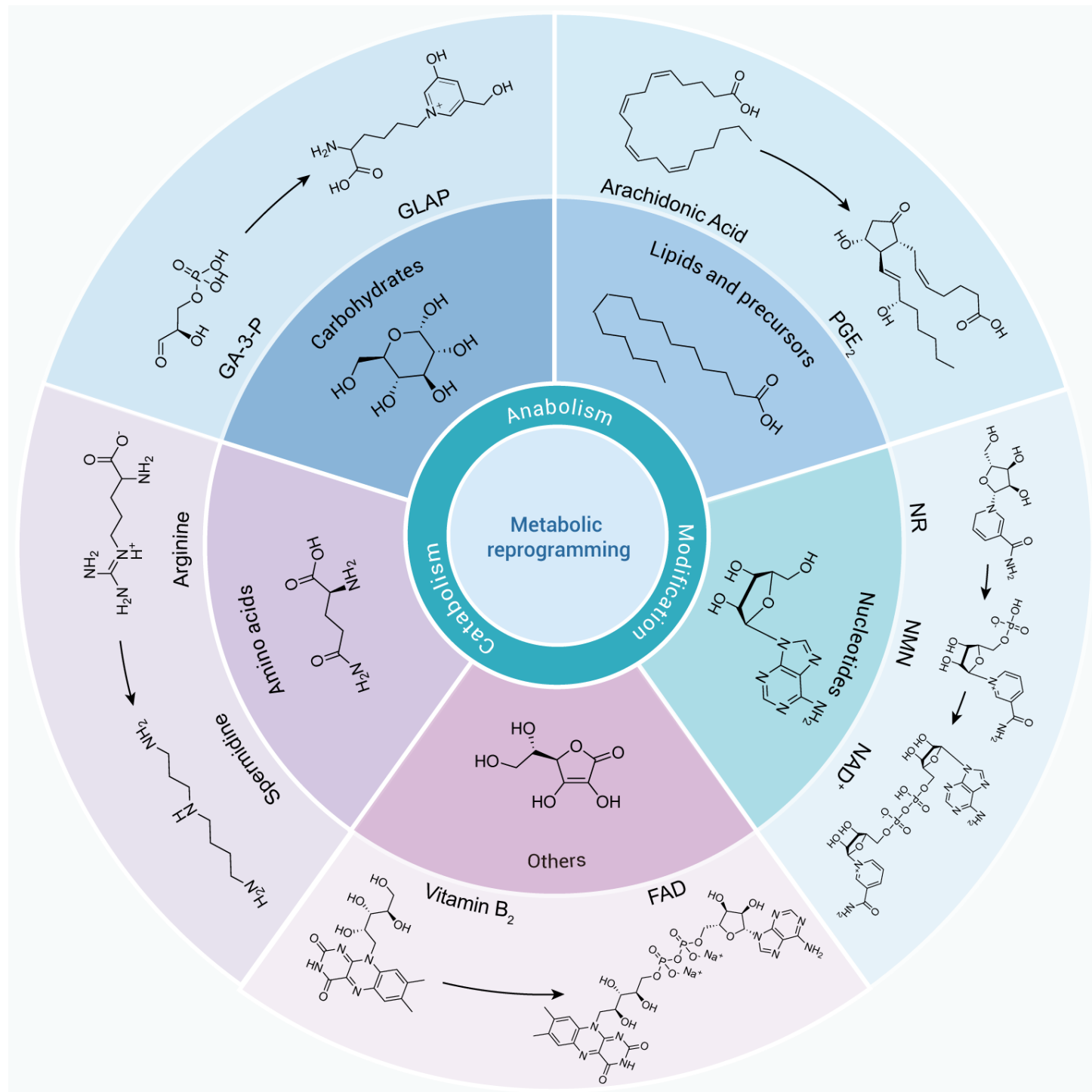


Figure 5. Metabolic reprogramming This model elucidates the hierarchical architecture of metabolic reprogramming during aging, arising from the dysregulation of three interconnected processes: imbalanced anabolism, altered modification, and catabolic disturbance. The chemical foundation of age-related metabolic deterioration is represented by major metabolite classes—amino acids, carbohydrates, lipids and precursors, nucleotides, and other essential molecules. The manifestation of these processes in specific age-related metabolic transformations is exemplified by their structural conversions: arginine-to-spermidine in polyamine metabolism, GA-3-P (D-Glyceraldehyde 3-phosphate)-to-GLAP (Glyceraldehyde-derived pyridinium) transition in carbohydrate processing, arachidonic acid (AA)-to-prostaglandin E_2 (PGE_2) transformation in inflammation, NR (nicotinamide riboside)-to-NMN (nicotinamide mononucleotide)-to- NAD^+ (nicotinamide adenine dinucleotide) pathway in nucleotide metabolism and redox homeostasis, and vitamin B_2 -to-FAD conversion in cofactor regulation. These structural conversions create a self-reinforcing cycle that propagates metabolic dysfunction throughout the Central Dogma of Aging, positioning metabolic reprogramming as both driver and manifestation of organismal aging.

and/or telomere shortening can lead to aberrant transcription, such as increased noise or stochastic gene expression, contributing to cellular heterogeneity as well as senescence.^{33,298} A multi-omics study of human prefrontal cortex across the lifespan found short, highly expressed house-keeping genes accumulate mutations at the highest rate in aged neurons, which is correlated with the transcription downregulation, and provides a direct mechanistic link whereby genomic instability shapes the aging transcriptome.²⁹⁹ R-loops, RNA-DNA hybrids that form during transcription,

provide a direct transcriptome-to-genome feedback. Age-related declines in RNase H2 and Rat1 nucleases cause pathological R-loop persistence, which stalls replication forks, triggers ATM/p53-mediated DNA damage response, accelerates telomere attrition and cellular senescence.¹⁷¹ Feedback also occurs via lncRNAs that modulate chromatin structure, creating epigenetic loops that stabilize or destabilize genome.^{300,301} At molecular level, histone modifications and DNA methylation that evolve with aging, often lead to global hypomethylation but local hypermethylation, and repress longevity

genes but activate inflammatory pathways.³⁰²⁻³⁰⁴ The integration of epigenomics and transcriptomics in human cohorts demonstrate age-related nonlinear shifts: midlife epigenetic changes are correlated with transcriptomic deregulation in DNA repair genes.^{213,297,305} Aging disrupts the coherence of methylome-transcriptome, leading to proteotoxic stress,^{300,306} chronic stress exacerbates the genome-transcriptome interplay by inducing ROS which damages DNA, propagating errors to the transcriptome in model organisms.³⁰⁷

Transcriptome-proteome interface and dysregulation. The transcriptome directs the proteome via translation, where mRNAs are decoded by ribosomes into proteins. A panoramic proteomic atlas, for the first time, systematically reveals the dynamic evolution of the proteome over a 50-year lifespan, identifying transcriptome-proteome expression decoupling during aging.²⁵⁷ This interface further weakens with age,³⁰⁸ transcriptomic upregulation of inflammatory genes (e.g., NF- κ B targets) may not translate proportionally to proteins due to ribosomal stalling or mRNA decay, leading to proteostatic collapse.³⁰⁹ Senescence drives proteostasis collapse by crippling stress-responsive transcription: despite intact stress sensing, senescent cells fail to activate key transcriptional programs, including heat shock response, alternative splicing, and ATF6-mediated UPR, leading to irrecoverable proteasome dysfunction.³¹⁰ Feedback from the proteome includes RBPs stabilizing or splicing the transcripts, with age-related RBP mislocalization causing transcript accumulation and errors.²⁵³ Multi-omics reveals nonlinear dynamics in human plasma: midlife transcriptomic waves predict proteomic shifts.^{9,297}

Proteome-metabolome mutual shaping. The proteome shapes the metabolome through enzymatic catalysis, where proteins like kinases and oxidases convert substrates into metabolites, regulating energy homeostasis and signaling. Aging-related loss of proteostasis impairs enzyme activity, leading to metabolomic shifts such as NAD⁺ depletion and lipid peroxidation accumulation.^{278,311} Reciprocal interactions occur as metabolites modulate protein function via PTMs; for example, acetyl-CoA levels influence protein acetylation, affecting enzyme kinetics. In human studies, proteomic aging clocks predict metabolomic biomarkers of frailty, with shared pathways in nucleotide metabolism.³⁰⁰ These protein-metabolite interactions collectively form a higher-level regulatory network of aging, provide a systems biology foundation for developing precision geroprotective strategies.³¹²

Metabolome-to-genome feedback and loop closure. Metabolome feeds back to genome via metabolites acting as epigenetic cofactors: SAM enables DNA methylation,³¹³ NAD⁺ activates sirtuins for protein deacetylation.^{314,315} Aging-related metabolomic declines (e.g., one-carbon metabolites reduction) lead to epigenetic drift, altering genomic stability and gene expression.³⁰⁰ This creates cycles: genomic changes affect metabolism via altered enzyme expression, in turn, metabolic byproducts influence DNA repair. The metabolome-transcriptome integration shows microbiome-dependent metabolic declines that impact nucleotide synthesis in aged mice.³¹⁶ In humans, joint analyses link metabolomic signatures to the epigenetic clocks, predicting mortality.³¹⁷

A hierarchy of evidence for metabolite-driven aging regulation

Evaluating the causal role of a given metabolite in aging requires integrating multiple lines of evidence: the strength of association with aging, specificity of molecular targets, and sufficiency and necessity via genetic or pharmacological manipulations at cellular or organismal level. Based on these criteria, evidence for metabolite-mediated regulation are categorized into three tiers. (1) Causally established drivers possess well-defined molecular targets and mechanisms, with both genetic and pharmacological interventions establishing causality at the organismal level. For instance, NAD⁺ serves as the obligate co-substrate for sirtuins and declines with age; its precursor nicotinamide riboside (NR) elevates NAD⁺ levels in aged muscle stem cells, improves mitochondrial function, and extends lifespan in mice, whereas *Sirt1* conditional knockout abrogates the benefits, firmly establishing the NAD⁺-SIRT1-mitochondria axis.³¹⁸ SAM functions as methyl donor for H3K9me3 and maintains heterochromatin integrity; its age-related depletion causes heterochromatin loss and DNA damage, while supplementation restores these defects and improves muscle regeneration in aged mice.^{319,320} β -Hydroxybutyrate (BHB) inhibits class I HDACs, suppresses NLRP3 inflammasome, and extends lifespan in *C. elegans*,³²¹ while cyclic ketogenic diet

reduces mid-life mortality in mice.³²² Spermidine induces autophagy, regulates translation, and extends lifespan across yeast, worms, flies, and mice.^{270,323,324} α -Ketoglutarate (α -KG) supplementation compresses morbidity and extends median lifespan in aged mice, with attenuation of systemic inflammation and SASP.³²⁵ In each case, multi-layered evidence, spanning molecular mechanism, genetic manipulation, and organismal healthspan, supports a causal role. (2) Indirect modulators exhibit compelling mechanistic links to aging, but complete organismal validation of causality remains incomplete. Acetyl-CoA acts as substrate for HATs driving H3K27ac and *INK4a* transcription; its nuclear depletion induced by ACLY/ACSS2 deficiency or microbiota ablation triggers senescence, a phenotype reversible by supplementation of acetate or SAHA.^{326,327} FAD directly binds to the catalytic pockets of cGAS and RIG-I, suppressing nucleic acid sensing and type I interferon-mediated inflammation; FLAD1 loss reduces FAD levels, aggravating inflammation and senescence; FAD supplementation reverses the effects.³²⁸ UDP-GlcNAc, an end-product of hexosamine pathway and a donor for N-glycosylation and O-GlcNAcylation, enhances ER proteostasis via the IRE-1/XBP-1 axis; its enhanced level alleviates proteotoxicity and extends lifespan in *C. elegans*.³²⁹ Among short-chain fatty acids (SCFAs), acetate activates the SIRT1-NRF2 antioxidant axis, suppresses NF- κ B-mediated SASP, rescues endothelial aging, and extends lifespan in *C. elegans* and *Drosophila*.^{330,331} Yet, these metabolites lack complete reverse-genetic evidence that chronic deficiency shortens lifespan; whether their supplementation consistently extends lifespan in normal aging also remains to be systematically validated. (3) Associative candidates have been linked to aging through multi-omics or observational studies, but causal mechanisms remain unclear. Succinate level is elevated in aged hearts and correlate with fibrosis severity; exogenous succinate inhibits autophagy and UPR^{mt}, promotes α -synuclein aggregation and shortens lifespan in *C. elegans*.³³² Lactate regulates senescence through histone lactylation, modifying p53, NF- κ B, and other regulators.³³³ Ceramides accumulate in senescent T cells driven by GIMAP5 deficiency.³³⁴ However, whether these metabolites are primary drivers of aging or secondary consequences remains to be determined. Collectively, this evidence spectrum, from causally established drivers through indirect modulators to associative candidates, reinforces the metabolome's dual role as both a readout and a driver of aging. It provides a framework for distinguishing which metabolic changes are causal to aging and which are merely correlative, a distinction that is essential for prioritizing targets for geroprotective intervention.

Overall, the four layers form a resilient yet vulnerable network; aging erodes their coherence, with reduced inter-layer correlations and increased stochasticity.²⁹⁸ Constraint-based modeling integrates layers to predict fluxes and reveals aging-associated declines in microbial-host metabolic interactions.³¹⁶ Targeting aging hubs (e.g., NAD⁺ pathways) could restore balance and mitigate disruptions.²⁹⁷

Lessons from nature

The remarkable diversity of aging trajectories and lifespans across the animal kingdom provides compelling natural evidence that validates and refines the Central Dogma of Aging. Genomic analyses of Pacific Ocean rockfishes, with lifespans ranging from 11 to over 200 years, pinpointed the positive selection of DNA repair pathways as a key genetic adaptation for extreme longevity.³³⁵ Copy number expansion in the butyrophilin gene family, involved in modulating inflammation, suggests a co-evolved adaptation at the transcriptomic and proteomic layers to mitigate a major age-related disturbance.³³⁵ Research in diverse insects and *Caenorhabditis elegans* has identified nuclear gene CG11837 (a DIMT1 ortholog) as a conserved regulator of lifespan, which enhances mitochondrial oxidative phosphorylation and links a transcriptomic regulator to the core of metabolomic anabolism.³³⁶ Evolution has optimized the proteome and metabolome layers for longevity. The naked mole-rat exhibits exceptional resistance to age-related diseases, owing to abundant high-molecular-mass hyaluronic acid (HMM-HA).^{337,338} It directly protects cells from oxidative stress, improves gut barrier function (preserving proteomic integrity), and systemically attenuates inflammation. When the naked mole-rat HA synthase gene (*nmrHas2*) was overexpressed in mice, it increased HA levels, reduced cancer incidence, extended lifespan, and shifted transcriptome signature toward that of longer-lived species.³³⁸

Thus, nature's longevity solutions are not linear but orchestrated across the genome, transcriptome, proteome, and metabolome, which bolster anabolic repair, introduce protective modifications, and maintain efficient catabolic turnover, thereby preserving the integrity and crosstalk between all layers of the Central Dogma of Aging.

Exposome challenge: External modulators of aging

Exposome is conceptualized as the cumulative measure of environment exposures that cells, tissues, organs, and individuals encounter, including microenvironment change, systemic disturbance, dysbiosis, irregular lifestyle, psychosocial pressure, and environment exacerbation. The exposome factors constitute an integrated, multi-layered regulatory network that impinges on the inner 4-layer core through a hierarchical relay architecture (Figure 6). The microenvironment factor (e.g., H_2O , O_2 , hormones, metabolite, ions, cytokines, growth factors, immunoglobins, ECM and EVs etc.) directly interface with cells and exert layer-specific effects. Some factors enter the cell by passive diffusion, channels, carriers, endocytosis or membrane fusion, and influence all four layers; others influence the surface proteins (receptors, antigens) and lipid layer via direct interaction, and elicit cascading effect on the inner four layers. Systemic disturbances (e.g., hypertension, loss of immune surveillance, diminished stem cell rejuvenation, deregulated CBT, and altered microenvironmental factors that circulate systemically), dysbiosis (bacteria, and virus), irregular lifestyle, psychosocial stress are transmitted, filtered, and amplified through microenvironment changes before reaching the intracellular molecular layers and perturb the entire Central Dogma. Environment exacerbation affects cell states via directly interfacing with the inner four layers (microgravity, radiation, disturbed light, oxygen, magnetic fields, or ambient temperature), microenvironment change or systemic disturbance (pollutants).

Microenvironment change

Tissue microenvironment constitutes a proximate layer of exposome, serving as a primary interface through which systemic and some external exposures exert their influence on cellular senescence.

Soluble factors. Dysregulated ionic homeostasis constitutes a critical microenvironmental stressor that propagates aging. Central to this is the calcium (Ca^{2+}) signaling. For instance, the age-related downregulation of the TRPC3 channel leads to elevated mitochondrial Ca^{2+} load, increasing oxidative stress and driving cells to a pro-inflammatory, senescent state.³³⁹ In acidic microenvironment, acid-sensing ion channels (ASIC1a) and mechanosensitive channels (Piezo1) are activated, triggering Ca^{2+} influx and accumulation of ROS, which directly damage DNA and compromise RNA polymerase II activity.^{193,194,340,341} ASIC1a degrades nuclear lamina protein Lamin B1 via autophagy, a hallmark of senescence.³⁴²⁻³⁴⁴ The inhibition of Na^+/K^+ -ATPase pump by compounds like ouabain selectively eliminates senescent cells by disrupting crucial signal transduction and autophagy.³⁴⁵

Growth factors, cytokines, and immunoglobulins accelerate aging via interconnected mechanisms that disrupt the Central Dogma of Aging. The age-related decline in growth hormone (GH) and insulin-like growth factor 1 (IGF-1), a phenomenon known as "somatopause", is associated with detrimental changes in physical function.³⁴⁶ Reduced activity of the GH/IGF-1 axis is associated with longevity and may lower the risk of diabetes and cancer.³⁴⁷ In contrast, estrogen decline exacerbates osteoporosis and metabolic inflammation.^{348,349} The vascular endothelial growth factor (VEGF) signaling declines with aging owing to increased soluble VEGF receptor 1 (sVEGFR1), leading to reduced tissue perfusion and capillary loss.^{350,351} Transforming growth factor- β (TGF- β) induces deep senescent state under conditions like hypoxia.^{352,353} Fibroblast growth factor 21 (FGF21) activates autophagy, thus alleviating osteoarthritis.³⁵⁴ The accumulation of IgG across aged tissues induces senescence in macrophages, fueling a pro-aging microenvironment.³⁵⁵ The chronically elevated inflammatory cytokines, such as IL-1 β , IL-6, and TNF- α , can drive genomic instability, and proteostatic collapse, referred to as "inflammaging".^{5,356} These diverse stressors converge to amplify SASP, which reinforces inflammation, induces paracrine senescence, and disrupts tissue structure, creating a feed-forward loop that systemically drives age-related functional decline.³⁵⁷

Extracellular matrix and vesicles. During aging, ECM alters in composition, stiffness, and organization, and serves as a dynamic signaling hub that

actively modulates the Central Dogma of Aging. Matrix stiffening promotes aberrant mechanotransduction, primarily through altered integrin-YAP/TAZ signaling, which unleashes cGAS-STING signaling, while sustaining YAP function rejuvenates senescent cells.³⁵⁸ It accelerates chondrocyte senescence via the modification changes of the central dogma, such as HDAC3-mediated deacetylation of Parkin and promoter methylation of α -Klotho, leading to mitochondrial dysfunction and age-related osteoarthritis.^{359,360} Postmenopausal decline in estrogen and progesterone exacerbates ECM disassembly and senescence.³⁶¹ Age-related bone marrow stiffening induces HSC aging and engineering a soft microenvironment *ex vivo* reverse HSC aging and restore regenerative capacity.³⁶² ECM fragments, e.g., elastin-derived peptides, serve as matrilins disrupting intracellular proteostasis.^{363,364}

EVs are critical mediators of intercellular communication, and their cargo of proteins, nucleic acids, lipids, and metabolites is essential for maintaining cell homeostasis. EVs become dysregulated during aging and transforming from vehicles for maintenance into potent vectors of aging. Senescent cells secrete EVs that transfer specific microRNAs (like miR-34a) and proteins to recipient cells, which may exacerbate genomic instability, disrupt proteostasis, and fuel chronic inflammation, thus creating a feed-forward loop that disseminates senescence.³⁶⁵ EVs derived from young sources, such as the plasma of young mice or human adipose-derived MSCs, counteract aging at molecular, cellular, and physiological levels.^{366,367} The rejuvenating effects are mediated by cargos, which stimulate mitochondrial biogenesis via PGC-1 α activation and enhance antioxidant capacity via transfer of GSTM2.^{368,369,370} Thus, EVs offer a promise as regenerative therapies to counteract aging and age-related decline.

Systemic disturbance

Hormones. Age-related hormonal imbalances constitute a critical systemic factor that accelerates organismal aging. Estrogen promotes the premature fusion of epiphyses by accelerating senescence of growth plate chondrocytes.³⁷¹ In human aging, menopausal transition represents a notable shift in estrogen signaling, where the depletion of ovarian follicular reserves causes circulating estrogen levels to drop precipitously to dramatically; this is associated with a range of broader changes, including increased fracture risk, accelerated bone turnover, and a heightened risk of cardiovascular disorders.³⁴⁸ Non-pituitary-derived GH increases with age and fosters a proliferative but repair-deficient microenvironment by suppressing p53 and attenuating DDR, thus accelerating aging-related pathologies.^{372,373}

Water and electrolyte. With advancing age, the ability to maintain water and electrolyte balance declines. This micro-environmental factor directly interferes with all layers of the Central Dogma by affecting molecular solubility, ion gradients, and enzyme activity. Aging is often accompanied by diminished thirst sensation, declining renal function, and altered hormonal regulation (such as antidiuretic hormone), leading to mild dehydration and electrolyte imbalances.³⁷⁴ Common electrolyte abnormalities, such as hyponatremia and hypernatremia, occur more frequently in the elderly.³⁷⁵⁻³⁷⁷ Aging is associated with reduced activity of the renin-angiotensin-aldosterone system (RAAS), leading to decreased potassium excretion capacity, and compensatory acid excretion under increased acid load.³⁷⁷

Blood pressure (hypertension). Chronic dysregulation of blood pressure (BP) constitutes a significant systemic factor that accelerates aging through chronic inflammation, oxidative stress, and endothelial dysfunction.³⁷⁸ These processes promote genomic instability, epigenetic alterations, and mitochondrial damage, linking elevated BP and increased BP variability (BPV) directly to the hallmarks of aging. Therefore, hypertension is not only a primary risk factor for cardiovascular and cerebrovascular disease but also a major contributor to collateral age-related conditions, including cognitive decline, frailty, and loss of autonomy.³⁷⁸⁻³⁸⁰ Beyond its traditional clinical implications, BP dysregulation acts as a potent, systemic driver of aging, propagating molecular and functional decline from the genome to the metabolome.

Immune surveillance. Immune surveillance machinery serves as a critical mechanism for maintaining tissue health by efficiently eliminating senescent cells,³⁸¹ however, which declines with aging, leading to the accumulation of senescent cells in various tissues.³⁸¹ The senescent cells can evade immune clearance by expressing "senescence immune checkpoint" molecules. A subset of senescent cells upregulates the immune checkpoint protein PD-L1;

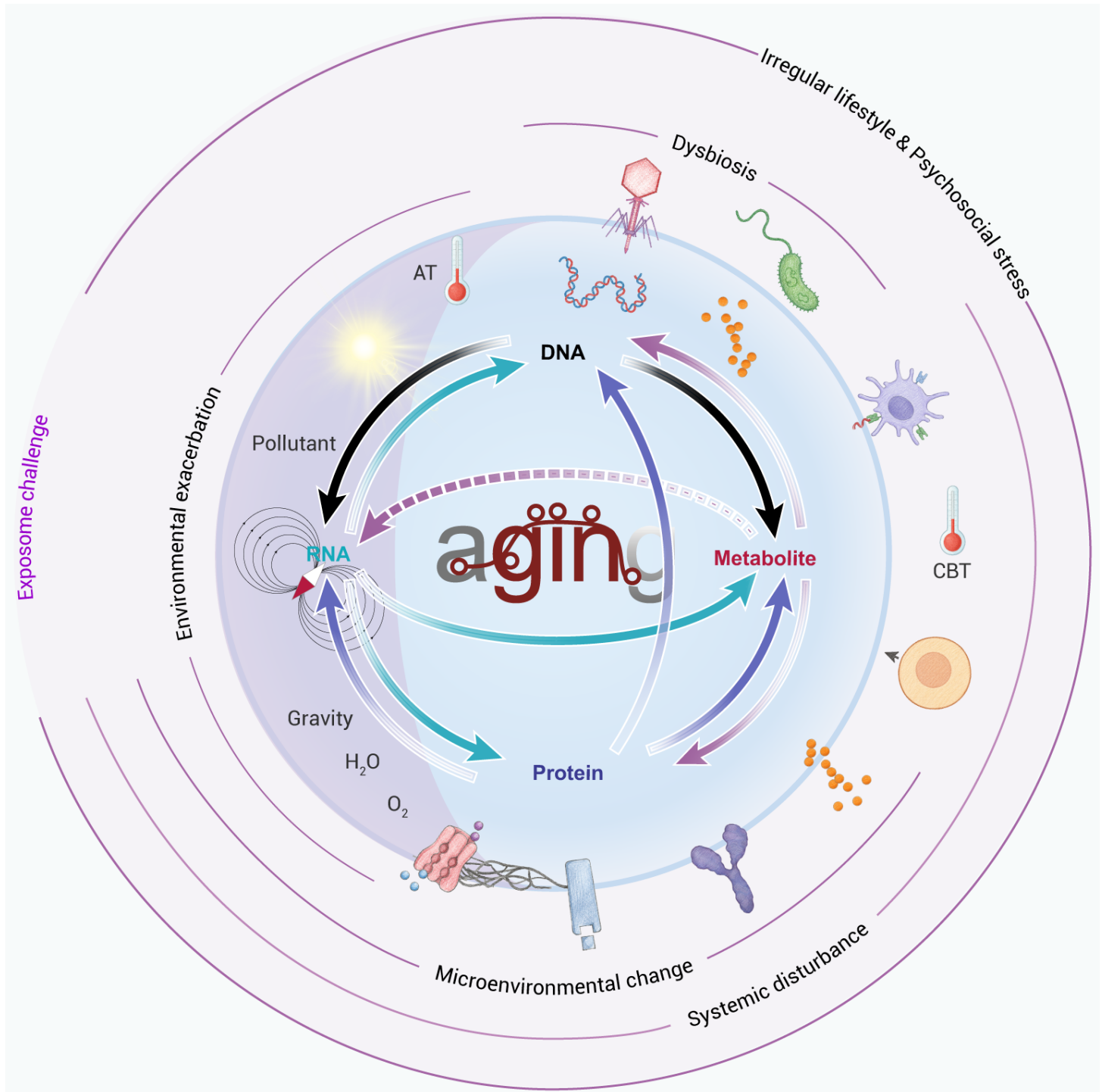


Figure 6. The Exposome: A hierarchical modulator of aging Schematic representation of the exposome as a multi-layered modulator of Aging. The innermost core depicts the four layers; the outside circles represent exposome factors.

by interacting with its receptor PD-1, it inhibits the cytotoxic function of CD8⁺ T cells, allowing these PD-L1-positive cells to survive and accumulate. Administration of PD-1 antibody in aged mice effectively removes these cells and ameliorates aging.³⁸² In non-oncogene induced senescent cells, sialyltransferase ST8SIA1 and subsequent disialylated ganglioside GD3 were upregulated; the latter suppresses the cytotoxicity of natural killer (NK) cells, conferring immune privilege to senescent cells; targeting GD3 successfully attenuates pulmonary, liver fibrosis, and bone remodeling in aged animal models.³⁸³ Understanding the immune evasion mechanisms provides promising targets for novel anti-aging strategies, such as immune checkpoint blockade-based "senolytic" therapies, aiming to restore the body's capacity to clear senescent cells and treat aging-associated diseases.³⁸¹⁻³⁸³

Stem cell rejuvenation. During aging, tissue-specific stem cells manifest as a decline in their self-renewal and regenerative capacity, directly contributing to degeneration and function decline.^{5,384,385} This is driven by intracellular cumulative damage across the Central Dogma of Aging, detrimental changes in local microenvironment, and high turnover demand. Strategies for stem cell rejuvenation have emerged as a convergent therapeutic avenue, reversing this age-related functional decay.^{384,386} These approaches integrate interventions across genome, transcriptome, proteome, and metabolome, leveraging intrinsic and extrinsic factors—from epigenetic remodeling (such as partial reprogramming with Yamanaka factors) and metabolic manipulation to niche modification (via parabiosis or senolytic clearance)—to restore stem cell function.^{384,385,387} By targeting the core mechanisms of stem cell aging,

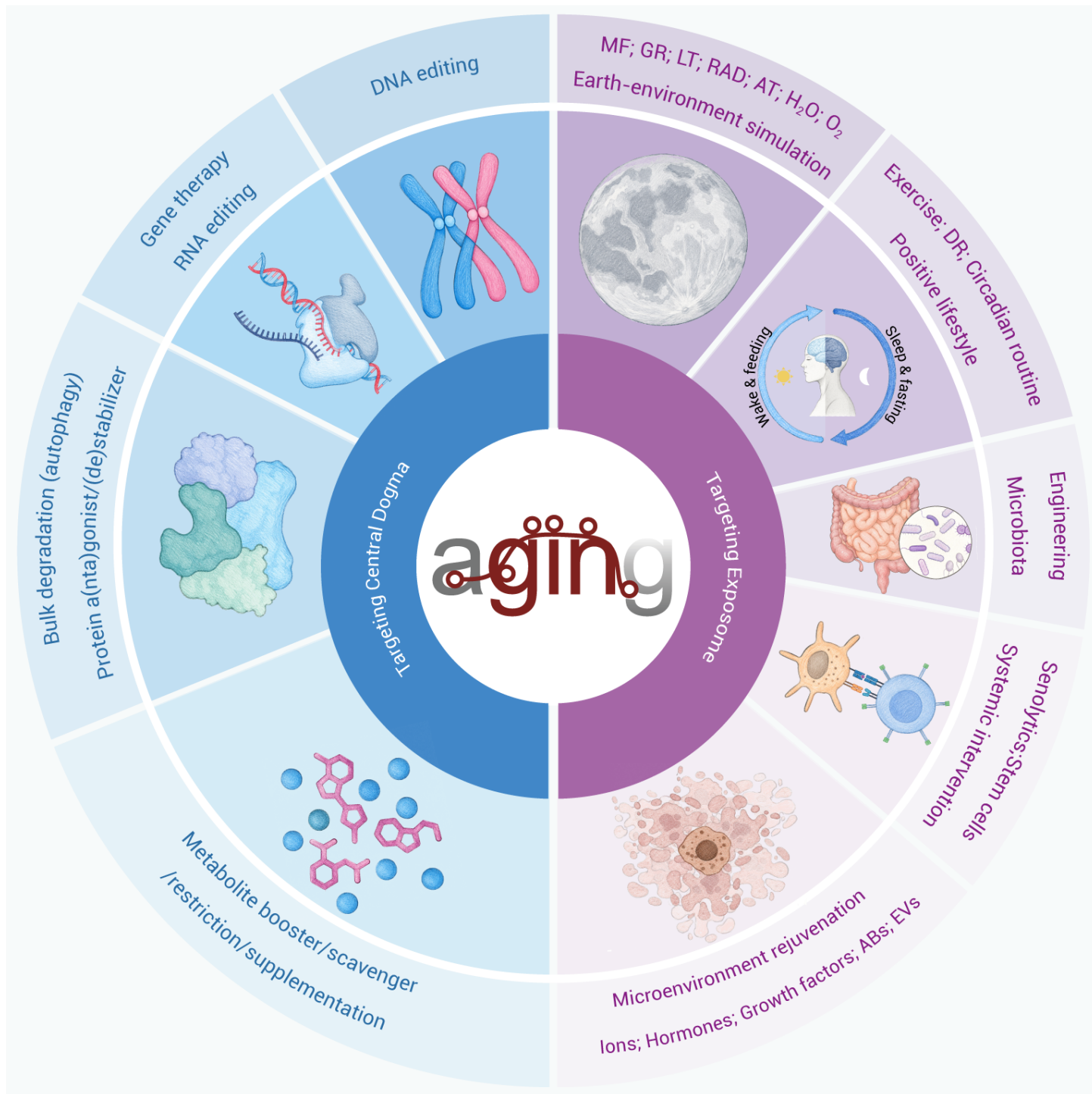


Figure 7. Targeting the central dogma to mitigate aging This schematic illustrates a comprehensive strategy to combat aging through synergistic interventions that target both its intrinsic biological and extrinsic environmental drivers. The framework concurrently addresses the core molecular hierarchies of the Central Dogma of Aging—encompassing DNA (via DNA editing), RNA (through RNA editing and gene therapy), protein (by the activation, inhibition, and restoration of proteostasis), and metabolite (through metabolic recalibration and redox balance restoration). In parallel, it implements active countermeasures against exposomal drivers, including: remodeling the tissue microenvironment via cytokine neutralization, replenishment, ion rebalancing, and aggregate clearance; senolytic clearance, stem cell rejuvenation and serum replacement; reprogramming the microbiome; optimizing lifestyle with dietary restriction, circadian entrainment, exercise and joyful environment; and the developing of protective strategies against macro-environmental challenges, such as ultraviolet ray, temperature extremes, and alterations in atmospheric composition, etc. This integrated paradigm preserves molecular fidelity and physiological resilience by simultaneously stabilizing cellular processes and modulating external environmental exposures. MF, magnetic fields; GR, gravity; LT, light; RAD, radiation; AT, ambient temperature.

these promising strategies seek to enhance tissue homeostasis, improve recovery from injury, and ultimately extend healthspan.

Dysbiosis. Microbial exposure serves as a critical exposome factor in aging, driving systemic aging through diverse mechanisms: bacterial infections directly induce tissue damage,³⁸⁸ the depletion of specific beneficial microbes (e.g., *Akkermansia muciniphila*, AKK) erodes essential barrier and metabolic support of the gut,³⁸⁹ pathogens like viruses and prions induce

systemic inflammation and exacerbate neurodegeneration.³⁹⁰ These elements form a multidimensional network through which microbes influence aging.

Bacterial infection. Lung tissues from tuberculosis patients are characterized by senescence, inflammation, and fibrosis, with downregulated FOXO3 signaling and enhanced NF- κ B-dependent thromboinflammation.³⁸⁸ Beyond *Mycobacterium tuberculosis*, a broader mechanism involves bacte-

rial genotoxins, such as cytolethal distending toxin (CDT), which induces DNA damage in immune cells, leading to senescence in activated CD4⁺ T cells.³⁹¹ During chronic mycobacterial infection, ensuing interferon- γ (IFN γ) response provides a selective advantage for *Dnmt3a*-deficient HSCs, promoting clonal expansion and linking chronic infection to aging-related clonal hematopoiesis.³⁹²

Gut microbiota. Emerging evidence positions gut microbiota, particularly AKK, as a critical exposome factor that systemically influences aging. A decline in AKK abundance is a hallmark of aged gut microbiomes across species, from aging mice to centenarians, wherein its presence is notably associated with longevity.³⁸⁹ Age-related decline of AKK causes translocation of endotoxins, triggers CCR2⁺ monocyte-mediated inflammation, and causes insulin resistance via the expansion of 4-1BBL⁺ B1a cells.³⁹³ AKK also acts as a key source of beneficial metabolites, notably acetic acid, which extends healthspan in both invertebrate and mammalian models.³⁸⁹

Viral and prion. Viral infections, such as persistent cytomegalovirus (CMV) and SARS-CoV-2, induce chronic inflammation and SASP, promoting senescence and tissue dysfunction.^{394,395} Reactivation of ancient viruses produces reverse transcription products (e.g., dsRNA) and viral particles, which transmit intercellularly through paracrine or fluid-mediated mechanisms, amplifying senescence signals in distal cells.²¹⁵ Prion represents another viral exposome factor that promotes age-related diseases. Prion protein (PrP) activates the endoplasmic reticulum (ER) glutathione peroxidase GPX8, reduces ROS, and leads to polyunsaturated fatty acid phospholipids (PUFA-PLs) accumulation, thus increasing cellular susceptibility to ferroptosis.³⁹⁶ N-terminal soluble region of PrP is neurotoxic *in vivo*; key sequence KKRPKP (CC1 region) surpasses a toxicity threshold and binds to membrane surfaces, triggering rapid and lethal neurodegeneration.³⁹⁰

Irregular lifestyle

Irregular lifestyle constitutes a major modifiable exposome factor, exerting profound and systemic influences on the Central Dogma of Aging. Dietary components, such as specific amino acids, and fat, along with physical activity, serve as key environmental inputs that modulate metabolic homeostasis, epigenetic regulation and gene expression, and proteostasis. These factors either promote longevity, physiological resilience or accelerate aging, depending on their nature, timing, and context.

Amino acids. Specific amino acids, as exposome factors, act as potent modulators of aging, with both restrictive and supplemental strategies showing promise. Dietary restriction (DR) of certain amino acids emerges as a powerful intervention. Methionine restriction (MetR) initiated in late life (18 months) improves metabolic health, neuromuscular and lung function, and reduces frailty in mice.³⁹⁷ BCAAs restriction promotes metabolic health, reduces frailty in midlife mice and extends lifespan.³⁹⁸ Conversely, impaired BCAA catabolism in visceral adipose tissue activates mTORC1 signaling and senescence.³⁹⁹ Beyond restriction, supplementation of non-essential amino acid asparagine (Asn) activates autophagy, inhibits intestinal stem cell (ISC) hyperproliferation, and extends lifespan.⁴⁰⁰

Lipids. Lipids constitute a critical exposome factor, with the systemic and cellular deregulation being a central mechanism in aging. Circulating lipidome undergoes significant, non-linear shifts, characterized by the accumulation of specific lipid species like ceramides and a marked decline in ether-linked phospholipids during aging.⁴⁰¹ The changes occur in a gender-specific manner, with men and women exhibiting distinct 'aging crests' at different life stages, and point to impairments in lipid-driven bioenergetics, antioxidant defense, and cellular signaling.⁴⁰¹ Specific lipids, e.g., bis (monoacylglycerol)phosphate (BMP), accumulate in aged mice tissues and in human muscle, which can be mitigated by physical intervention.⁴⁰² Molecularly, epigenetic regulation of lipid metabolism is a key driver of aging, as exemplified by *Elovl2*; its suppression disrupts polyunsaturated fatty acid synthesis, induces ER and mitochondrial stress, and accelerates cellular and organismal aging.⁴⁰³ Senescent cells accumulate cholesterol in lysosomes to sustain mTORC1 activity and SASP, linking lipid dyshomeostasis to chronic inflammation.⁴⁰⁴

High-fat diet (HFD) acts as an exogenous lipid stressor, rapidly inducing cellular senescence in white adipose tissue (WAT), a process driven by ATP overproduction that acts as a local danger signal.⁴⁰⁵ Senescent cells express-

ing glycoprotein non-metastatic melanoma protein B (GPNMB) accumulate under HFD, and senolytic elimination via a vaccination strategy ameliorates metabolic dysfunction and reduces atherosclerotic burden.⁴⁰⁶ Interventions that bolster metabolic resilience by overexpression of FGF21 counter HFD induced aging.⁴⁰⁷ Thus, lipid-exposures, from systemic metabolic shifts to dietary intake, are powerful modulators of aging, operating via convergent pathways of metabolic dysfunction, chronic inflammation, and cellular senescence.

Caloric restriction (CR). CR elicits anti-aging benefits through remodeling cellular and systemic landscape by slowing growth and development while enhancing metabolic homeostasis.⁴⁰⁸ A key mediator is lithocholic acid (LCA), which accumulates, binds to intracellular receptor, TUB-like protein 3 (TULP3), and activates the TULP3-Sirtuin-v-ATPase-AMPK axis to extend healthspan and lifespan.⁴⁰⁸ Beyond specific molecules, CR reverses aging-associated alterations in cell-type composition, reducing the accumulation of pro-inflammatory immune cells like neutrophils, and rescues the expression of aging-related genes across tissues.⁴⁰⁹ CR benefits are maximized not just by calorie reduction, but also by circadian rhythms through daily fasting.⁴¹⁰ Collectively, these findings delineate a multi-layered framework for CR, encompassing a defined nutrient-sensing pathway, a systemic reversal of transcriptional aging, and the potential for timing and diet quality to emulate its potent geroprotective effects.⁴⁰⁸⁻⁴¹²

Exercise. Exercise stands as a potent, non-pharmacological factor that systemically counteracts the aging process. Exercise promotes a youthful methylome and transcriptome profile in human skeletal muscle.⁴¹³ Exercise upregulates myokine Cardiotrophin-like cytokine factor 1 (CLCF1), improving physical performance, glucose tolerance, mitochondrial activity, and bone health in aged mice.⁴¹⁴ Exercise also enriches the metabolite betaine, which exerts geroprotective effects by inhibiting TBK1.⁴¹⁵ At the cellular level, exercise ameliorates age-associated inflammation, reduces senescence, and rejuvenates stem cell function by restoring the transcriptomic landscape and intercellular communication within stem cell niches.^{415,416} Critically, these molecular benefits can translate into long-term systemic improvements, as early-life exercise in mice confers lasting healthspan benefits, including enhanced metabolism and reduced frailty in old age.⁴¹⁷ Collectively, by clearing senescent cells, reducing the burden of SASP, and counteracting age-related ECM stiffening, exercise remodels tissue microenvironment, and solidifies its role as a cornerstone of healthy aging.^{357,414,415}

Psychosocial stress. Psychological and social stress, and depression constitute potent exposome factors that systemically accelerate aging by dysregulating neuroendocrine pathways and inducing measurable molecular alterations. Chronic social stress can directly induce neuronal DNA damage and senescence in a p16^{Ink4a}-dependent manner, particularly in the brain and peripheral tissues, linking psychosocial adversity to hallmark of aging.⁴¹⁸ Social stress is independently associated with accelerated immune aging, marked by reduced naïve but increased terminally differentiated T cells.⁴¹⁹ Chronic stress is associated with accelerated epigenetic aging as measured by clocks like GrimAge.⁴²⁰ The underlying mechanism involves specific neural circuits like the central amygdala to dorsal motor nucleus of the vagus pathway, which impairs ISC function and promotes an aging-like decline through cholinergic signaling, independent of inflammation or microbiota.⁴²¹

Environment exacerbation

Earth elements such as light, irradiation, oxygen, temperature, gravity, magnetic field, and pollutants serve as critical environmental inputs that disrupt the molecular circadian clock, trigger genomic instability, induce oxidative stress, and overwhelm proteostatic capacity. These factors either accelerate functional decline or be harnessed for potential interventions, depending on their nature, intensity, and timing. Environment exposures, except some pollutants, can directly assault the four intracellular layers, e.g., damaging DNA, disrupting transcription, translation, compromising proteostasis and disturbing energy metabolism, which underscore environment exacerbation as pivotal drivers of aging.

Light-dark cycle. Earth's rotation around the sun creates a light-dark cycle and controls circadian rhythms, which enable organisms to synchronize internal biological processes.⁴²² This systemic timekeeper comprises a central pacemaker in the suprachiasmatic nucleus (SCN) that coordinates

peripheral cellular clocks via humoral, neural signals, temperature, feeding and fasting.⁴²³ At the molecular level, the cell-intrinsic clocks are driven by a series of transcriptional-translational feedback loops of core clock genes (e.g., *CLOCK*, *BMAL1*, *PER*, *CRY*), which in turn regulate rhythmic expression of numerous genes governing cellular functions.⁴²⁴ The endocrine system exhibits circadian oscillations, with insulin, cortisol, melatonin, and growth hormone displaying diurnal patterns that synchronize feeding, sleep, peripheral clocks and activities.^{425,426} The integrity of these rhythms is intrinsically linked to aging. High-amplitude circadian rhythms are associated with well-being and longevity in animals,⁴²⁷ whereas circadian amplitude dampens and phase shifts accelerate aging.^{428,429} Mice with genetically disrupted *Bmal1* exhibit shortened lifespan and premature aging.⁴³⁰ Senescence impairs circadian gene expression.⁴³¹ Core molecular clocks like *BMAL1* and *CLOCK* also play non-canonical, transcription-independent roles in stabilizing heterochromatin and repressing retrotransposons, thus counteracting cellular senescence in primate stem cells.^{432,433}

Oxygen. Both hyperoxia and hypoxia constitute significant exposome factors. Chronic exposure to high O₂ level induces oxidative damage to DNA, proteins, and lipids, accelerating age-related decline.⁴³⁴ Conversely, intermittent hypoxia, as in sleep apnea, is linked to inflammation, and increased risk for cardiovascular and cognitive decline.⁴³⁵ Notably, housing mice in a hypoxic environment (11% oxygen, equivalent to an altitude of 5000 meters) extends lifespan by approximately 50% and delays the onset of neurasthenia. Thus, tight regulation of oxygen homeostasis is critical for health and longevity.⁴³⁶

Ambient temperature (AT). AT is a critical exposome factor that bidirectionally modulates aging via its profound impact on cellular and systemic homeostasis. Chronic exposure to high temperatures accelerates molecular aging, as sustained heat stress overwhelms the proteostatic capacity of molecular chaperones, leading to proteasome overload and protein aggregation.⁴³⁷ This is compounded by heat-induced declines in transcriptional fidelity and elevated replication error rates, with epidemiological studies showing that for every 1.3°C increase in AT, biological age increases by an average of 0.023–0.031 years.⁴³⁸ On the other side, cold exposure extends lifespan by enhancing proteostasis through the activation of the proteasome. In *Caenorhabditis elegans*, cold temperature (e.g., 15°C) upregulates PSME-3, the orthologue of human PA28γ/PSME3, which selectively activates trypsin-like proteasome, improving protein degradation and reducing aggregation of disease-related proteins, thereby promoting longevity.⁴³⁹ Cold acclimation in humans enhances autophagy and reduces apoptotic signaling, improving cellular cold tolerance.⁴⁴⁰ In rodents, lower the core body temperature (CBT) is linked to extended lifespan, and interventions that reduce the CBT, such as CR, contribute to longevity.⁴⁴¹

AT is sensed by cutaneous nerves via the transient receptor potential (TRP) channels;⁴⁴² the signals are then transmitted to the preoptic area (POA) in the hypothalamus, which initiates/suppresses thermogenesis in brown adipose tissues (BAT) to maintain CBT.⁴⁴³ Aging impairs cold adaptation, primarily attributable to senescence of beige adipocyte progenitors, which blunts thermogenesis.⁴⁴⁴ Subcutaneous white adipose lipotrophy in a progeria mouse model exacerbates cold stress, induces PGE₂, and causes high CBT and accelerated aging.⁴⁴⁵ Overexpression of uncoupling protein 2 (UCP2) in hypocretin neurons reduces CBT and prolongs murine lifespan;⁴⁴⁶ conversely, mice exposed to hot AT display elevated CBT and reduced lifespan.⁴⁴¹ Indeed, modest, sustained reduction in CBT is a key feature of CR, which is mechanistically linked to enhanced metabolic efficiency, and raising AT to thermoneutrality reverse a significant portion of systemic and hypothalamic metabolic benefits.^{446,447} Thus, thermal exposome factor serves as a potent modulator of aging: excessive heat promotes molecular decay and accelerates epigenetic age, while regulated hypothermia and preserved cold adaptation are linked to longevity and metabolic vitality.

Irradiation, microgravity and pollutants. Environment degradation, especially loss of irradiation protection and microgravity, creates a distinct exposome factor. Ionizing and ultraviolet radiation are potent inducers of DNA damage, including DSBs and oxidative base modifications. Sustained DDR triggers cellular senescence.^{448,449} Microgravity induces cardiovascular deconditioning, musculoskeletal atrophy, and immune dysregulation,^{450–452} and inhibits embryonic stem cells (mESCs) proliferation and induce senes-

cence and apoptosis.⁴⁵³ At the molecular level, Piezo1 acts as a mechanical sensor; its activation by a stiffened microenvironment induces calcium overload, resulting in mitochondrial dysfunction.⁴⁵⁴ These findings highlight roles of mechanical forces in tissue homeostasis and mirror aspects of terrestrial aging.

Pollutants like arsenic and benzene cause DNA hypermethylation, thus silencing DNA repair genes via DNMT upregulation.⁴⁵⁵ Components like pesticides are correlated with epigenomic shifts in aging.⁴⁵⁶ Phthalates and bisphenols can impair RNA polymerase II recruitment, reducing transcription rates,⁴⁵⁷ and atmospheric pollutants like nitrogen dioxide (NO₂) directly interact with RNA Pol II, resulting in aberrant transcriptional elongation and increased alternative splicing events.⁴⁵⁸

Therefore, the exposome function as key drivers of aging, systemically corrupting the delicate balance of anabolic, modificatory, and catabolic fluxes across the Central Dogma of Aging. This central role positions the exposome as prime targets for strategic interventions aimed at preserving molecular fidelity and promoting healthy longevity.

Targeting the central dogma to mitigate aging

The Central Dogma of Aging provides a structured framework for the identification of therapeutics to mitigate age-related decline, aiming to restore the balances in anabolism, modification, and catabolism across the genome, transcriptome, proteome, metabolome, and address exposome influences. To this end, a diverse arsenal of targeted strategies is emerging, which are broadly categorized into interventions targeting the intrinsic layers of the Central Dogma and those modulating the extrinsic exposome (Figure 7).

At the genomic level, interventions aim to boost endogenous DNA repair capacity and counteract instability.¹⁴ Relaxing chromatin structure by chloroquine extends lifespan via the ATM-SIRT6 axis.⁴⁵⁹ DNA editing using CRISPR-Cas9 system on aging-related loci (e.g., *FOXO3*) alleviate genomic damages.⁴⁶⁰ Targeting master regulators like the DREAM complex elevates global DNA repair gene expression,⁴⁶¹ and gene editing is employed to correct specific repair defects, as demonstrated in progeria models.⁴⁶² At the transcriptomic level, partial reprogramming through short-term cyclic expression of Yamanaka factors reverses cellular and physiological hallmarks of aging and extends lifespan in progeroid mice.³⁸⁷ RNA therapeutics with antisense oligonucleotides (ASOs) correct splicing defects in neurodegeneration.⁴⁶³

Proteomic strategies focus on protein a(nta)gonists, (de)stabilizers and bulk degradation, collectively proteostasis restoration. PTM modulators, such as sirtuin activators (e.g., resveratrol) or kinase inhibitors, show potentials to correct PTM errors, restore youthful profiles and extend healthspan.^{66,464–466} The treatment with HDAC inhibitor vorinostat and DNMT inhibitor azacitidine reverses age-related methylation patterns in human trials.⁶⁸ Telomerase activator TA-65 extends telomeres, delaying cellular senescence, and improves healthiness.⁴⁶⁷ Exosome activator can enhance RNA turnover, preventing accumulation of damaged transcripts in senescence models.²³¹ Enhancing the function of elongation factor P-TEFb alleviates age-related transcriptional noise and errors.⁴⁶⁸ Specifically targeting the cGAS-STING pathway suppresses SASP and inflammation that drive aging.⁴⁶⁹ A cocktail of chemical reprogramming restore youthful transcript profiles in human cells.⁴⁷⁰ Enhancing proteome catabolism with autophagy inducers (e.g., spermidine, rapamycin) or proteasome activators restores proteostatic balance and extends lifespan.^{471,472} Metformin activates AMPK for efficient breakdown, predicting longevity in metabolomic clocks.⁴⁷³ Natural compound myricetin activates proteasome, improving clearance of damaged proteins in aging cells.⁴⁷⁴

Metabolomic interventions recalibrate homeostasis by metabolite boosting, scavenging, restriction and supplementation. NAD⁺ boosters (e.g., nicotinamide mononucleotide, NMN; nicotinamide riboside, NR) activate sirtuins, improve mitochondrial function, ameliorate pulmonary hypertension, and extend lifespan in rodent models.^{158,475} SAM supplementation improves muscle regeneration;^{319,320} α-KG extends median lifespan in aged mice,³²⁵ and spermidine extends lifespan across species.^{270,323,324} Antioxidant NAC alleviate oxidative stress and AGE accumulation.²⁷⁹ Supplementation of Omega-3 polyunsaturated fatty acid (PUFAs) counteracts aging by activating PPARα, enhancing fatty acid β-oxidation, and improving energy metabolism.^{476,477} Methionine restriction extends lifespan in models by improving metabolic

homeostasis.¹⁵⁸

Targeting the exposome

The pervasive influence of the exposome on the Central Dogma of Aging necessitates strategic intervention by mitigating harmful exposure and reinforcing protective factors. Targeting the exposome is not merely about avoiding toxins; it is about actively shaping the molecular microenvironment to maintain fidelity across the genome, transcriptome, proteome, and metabolome. The interventions are categorized based on their level of action, from targeted molecular approaches to systemic lifestyle changes (Figure 7).

The proximate cellular environment is a critical therapeutic target. Interventions include replenishing depleted growth factors, such as restoring GDF11 levels to reverse age-related cardiac hypertrophy⁴⁷⁸, and neutralizing harmful cytokines, e.g., deploying anti-IL-11 therapy to extend lifespan⁴⁷⁹ or targeting IL-17 to ameliorate skin aging.⁴⁸⁰ The administration of youthful EVs is an experimental frontier aiming to directly supply rejuvenating cargo to aged cells, which restores transcriptional networks, mitochondrial metabolism, and antioxidant defenses.^{369,370} Targeting senescent cells and thereby the deleterious SASP has emerged as a powerful strategy to break the vicious cycle of aging.⁴⁸¹ The genetic ablation of p16^{ink4}-positive cells delays age-related deterioration and extends healthy lifespan in transgenic models.⁴⁸² Pharmacologically, senolytics such as the combined dasatinib and quercetin (D + Q) or Venetoclax inhibit anti-apoptotic genes (BCL-2, BCL-XL), thereby selectively eliminating senescent cells.⁴⁸³⁻⁴⁸⁵ This clearance has been shown to reduce the systemic burden of key aging biomarkers (IL-23R, CCL5), ameliorate physical dysfunction, and increase lifespan in aged mice.^{357,485,486} In parallel, senomorphics such as metformin, rapamycin, or ruxolitinib suppress the SASP without eliminating senescent cells, offering a complementary pharmacological approach to reduce the aging-related chronic inflammation.⁴⁸⁷ Beyond small molecules, innovative strategies are harnessing the immune system for senolytic activity. Vaccination targeting senescent cell-specific antigens, such as GPNMB or the surface protein CD153, has been shown to generate antibody responses that facilitate the clearance of senescent cells, improving metabolic health and extending lifespan in mice models of aging and atherosclerosis.^{406,488} Taking this a step further, adoptive cell therapy using chimeric antigen receptor (CAR) T cells engineered to target senescent cell surface markers (such as uPAR or NKG2D ligands) has demonstrated remarkable efficacy in treating aging and age-related diseases.⁴⁸⁹⁻⁴⁹¹

Complementing the clearance of senescent cells, stem cell rejuvenation is a powerful regenerative strategy. Direct supplementation with young or healthy stem cells, such as CD133⁺ endothelial-like cells, has been shown to restore tissue function and extend lifespan in both progeroid and naturally aged mice.⁴⁹² The efficacy of this approach can be enhanced through genetic engineering; for instance, the senescence-resistant human mesenchymal progenitor cells (SRCs) systemically reduce aging hallmarks and improved cognitive function without adverse effects in aged non-human primates.⁴⁹³ In addition, a single transfer of aged blood is sufficient to induce cellular senescence and tissue aging phenotypes in young mice; crucially, this pro-geronic effect is abrogated if the aged blood is first cleared of senescent cells, proving that senescence is not merely a cell-intrinsic fate but a systemically transmissible phenomenon that can be countered by senolytic interventions.⁴⁹⁴

Microbiome engineering via prebiotics, probiotics, or fecal microbiota transplantation favorably alters the gut-derived metabolome, which in turn influences host epigenetic marks and dampens inflammation, thereby alleviating aging.^{389,414,495} Dietary patterns like CR or its mimetics act as systemic exposomal modulators.^{77,408} A specific high-fiber diet that replaces 30% of macronutrients with indigestible cellulose was found to induce robust CR-like transcriptomic and metabolomic profiles, and reverse declines in motor and cognitive functions in aging mice.⁴¹² Circadian-aligned lifestyles, including regular sleep-wake cycles and timed feeding, reinforce robust transcriptional rhythms, enhance proteostasis, and optimize metabolomic flux, thereby buffering against the disruptive effects of shift work and light pollution.^{424,496} Structured exercise remodels the systemic milieu by reducing the SASP factors, promoting youthful epigenetic and transcriptomic patterns in muscle, and stimulating the release of protective myokines and metabolites like

betaine, which systemically improve proteostasis and mitochondrial function.⁴¹³⁻⁴¹⁵

Collectively, a multi-pronged strategy that concurrently reduces damaging exposures, amplifies protective signals (e.g., through diet and exercise), and corrects the aged microenvironment (e.g., via senolytics) holds immense promise for intervening in aging. The framework of Central Dogma of Aging posits that the most effective interventions will be those that create a virtuous cycle, stabilizing one layer to impart resilience to others, e.g., exercise (proteome/metabolome) induces epigenetic changes (genome) that favor metabolic health, which in turn supports genomic stability.

CONCLUSIONS

The Central Dogma of Aging integrates the four layers with dynamic processes and exposome influences, offering a novel lens for understanding and combating aging and age-related decline. It enhances our understanding of aging in the following aspects: (1) The 4C rule (C¹oding, C²atalysis, C³onstitution, C⁴atabolism) provides a mechanistic grammar for inter-layer communication, explicitly defines bidirectional feedback loops, and transforms aging from a list of parallel events into a closed-loop system. (2) The RNA layer is elevated from a passive intermediary to an active regulatory hub. It is not merely an outcome of transcriptional or epigenetic changes, but also is an independent and critical aging driver, with its own anabolic-modulatory-catabolic imbalances. (3) The framework identifies a directional cascade, termed as "first trigger" logic. Unlike the co-occurring hallmarks, the framework posits a propagation sequence: the genomic insults to transcriptomic errors, RNA defects to dysregulated translation, proteostatic collapse to metabolic reprogramming, and feedback to genome via metabolites (loop closure), thereby generating experimentally testable predictions. (4) The model positions the metabolite as not only a readout but a driver of aging, which functions as signaling molecules, enzyme cofactors, and epigenetic substrates that feed back to the genome, transcriptome, and proteome. (5) The framework positions exposome as a hierarchical modulator that impinges on intracellular molecular layers, bridging external drivers to internal molecular circuitry of aging. The five aspects—4C rules, RNA layer as active hub, directional propagation logic, metabolomic causality, and exposome integration—are woven to a unified framework that organizes known phenomena into a predictive, and hierarchical architecture. The framework underscores that aging is not merely a linear decline but a nonlinear, self-reinforcing process wherein dysfunction at any level propagates across layers, accelerating systemic failure. It offers practical guidance for aging biomarker discovery, intervention design, and experimental validation. The most informative biomarkers are those that capture information flow across layers not static single-layer measurement. The hierarchical and "first trigger" logic provides a basis for distinguishing causal drivers from correlative readouts, enabling rational prioritization of intervention targets. The exposome integration highlights the need for multi-scale strategies.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work author(s) used DeepSeek to improve language and readability. After using this tool, author(s) reviewed and edited the content as needed and take full responsibility for the content.

REFERENCES

- Hou Y., Dan X., Babbar M., et al. (2019). Ageing as a risk factor for neurodegenerative disease. *Nat. Rev. Neurol.* **15**:565–581. DOI:10.1038/s41582-019-0244-7
- Guo J., Huang X., Dou L., et al. (2022). Aging and aging-related diseases: From molecular mechanisms to interventions and treatments. *Signal Transduct. Target Ther.* **7**:391. DOI:10.1038/s41392-022-01251-0
- Pu F., Chen W., Li C., et al. (2024). Heterogeneous associations of multiplexed environmental factors and multidimensional aging metrics. *Nat. Commun.* **15**:4921. DOI:10.1038/s41467-024-49283-0
- Argentieri M. A., Amin N., Nevado-Holgado A. J., et al. (2025). Integrating the environmental and genetic architectures of aging and mortality. *Nat. Med.* **31**:1016–1025. DOI:10.1038/s41591-024-03483-9
- Lopez-Otin C., Blasco M. A., Partridge L., et al. (2023). Hallmarks of aging: An expanding universe. *Cell* **186**:243–278. DOI:10.1016/j.cell.2022.11.001
- Kroemer G., Maier A. B., Cuervo A. M., et al. (2025). From geroscience to precision

- geromedicine: Understanding and managing aging. *Cell* **188**:2043–2062. DOI:10.1016/j.cell.2025.03.011
7. Crick F. (1970). Central dogma of molecular biology. *Nature* **227**:561–563. DOI:10.1038/227561a0
 8. Cheng F. and Wang L. (2024). Slowing down the central dogma rate for alleviating aging. *Innov. Life* **2**:100049. DOI:10.59717/j.xinn-life.2024.100049
 9. Shen X., Wang C., Zhou X., et al. (2024). Nonlinear dynamics of multi-omics profiles during human aging. *Nat. Aging* **4**:1619–1634. DOI:10.1038/s43587-024-00692-2
 10. Ahadi S., Zhou W., Schussler-Florenza Rose S. M., et al. (2020). Personal aging markers and ageotypes revealed by deep longitudinal profiling. *Nat. Med.* **26**:83–90. DOI:10.1038/s41591-019-0719-5
 11. Rutledge J., Oh H. and Wyss-Coray T. (2022). Measuring biological age using omics data. *Nat. Rev. Genet.* **23**:715–727. DOI:10.1038/s41576-022-00511-7
 12. Niedernhofer L. J., Garinis G. A., Raams A., et al. (2006). A new progeroid syndrome reveals that genotoxic stress suppresses the somatotroph axis. *Nature* **444**:1038–1043. DOI:10.1038/nature05456
 13. Schumacher B., Pothof J., Vijg J., et al. (2021). The central role of DNA damage in the ageing process. *Nature* **592**:695–703. DOI:10.1038/s41586-021-03307-7
 14. Bujarrabal-Dueso A., Garinis G. A., Robbins P. D., et al. (2025). Targeting DNA damage in ageing: Towards supercharging DNA repair. *Nat. Rev. Drug Discovery* **24**:785–807. DOI:10.1038/s41573-025-01212-6
 15. Kunkel T. A. (2004). DNA replication fidelity. *J. Biol. Chem.* **279**:16895–16898. DOI:10.1074/jbc.R400006200
 16. Loeb L. A. and Monnat R. J., Jr. (2008). DNA polymerases and human disease. *Nat. Rev. Genet.* **9**:594–604. DOI:10.1038/nrg2345
 17. Harley C. B., Futcher A. B. and Greider C. W. (1990). Telomeres shorten during ageing of human fibroblasts. *Nature* **345**:458–460. DOI:10.1038/345458a0
 18. Chang E. and Harley C. B. (1995). Telomere length and replicative aging in human vascular tissues. *Proc. Natl. Acad. Sci. USA* **92**:11190–11194. DOI:10.1073/pnas.92.24.11190
 19. Herbig U., Jobling W. A., Chen B. P., et al. (2004). Telomere shortening triggers senescence of human cells through a pathway involving ATM, p53, and p21(CIP1), but not p16(INK4a). *Mol. Cell* **14**:501–513. DOI:10.1016/s1097-2765(04)00256-4
 20. Crabbe L., Jauch A., Naeger C. M., et al. (2007). Telomere dysfunction as a cause of genomic instability in Werner syndrome. *Proc. Natl. Acad. Sci. USA* **104**:2205–2210. DOI:10.1073/pnas.0609410104
 21. Rossiello F., Jurk D., Passos J. F., et al. (2022). Telomere dysfunction in ageing and age-related diseases. *Nat. Cell Biol.* **24**:135–147. DOI:10.1038/s41556-022-00842-x
 22. Benayoun B. A., Pollina E. A. and Brunet A. (2015). Epigenetic regulation of ageing: Linking environmental inputs to genomic stability. *Nat. Rev. Mol. Cell Biol.* **16**:593–610. DOI:10.1038/nrm4048
 23. Pal S. and Tyler J. K. (2016). Epigenetics and aging. *Sci. Adv.* **2**e1600584. DOI:10.1126/sciadv.1600584
 24. Yang J. H., Hayano M., Griffin P. T., et al. (2023). Loss of epigenetic information as a cause of mammalian aging. *Cell* **186**:305–326 e327. DOI:10.1016/j.cell.2022.12.027
 25. Wu Z., Qu J. and Liu G. H. (2024). Roles of chromatin and genome instability in cellular senescence and their relevance to ageing and related diseases. *Nat. Rev. Mol. Cell Biol.* **25**:979–1000. DOI:10.1038/s41580-024-00775-3
 26. Debes C., Papadakis A., Gronke S., et al. (2023). Ageing-associated changes in transcriptional elongation influence longevity. *Nature* **616**:814–821. DOI:10.1038/s41586-023-05922-y
 27. Papantonis A., Antebi A., Partridge L., et al. (2025). Age-associated changes in transcriptional elongation and their effects on homeostasis. *Trends Cell Biol.* **35**:645–650. DOI:10.1016/j.tcb.2024.11.005
 28. Hao X., Shiromoto Y., Sakurai M., et al. (2022). ADAR1 downregulation by autophagy drives senescence independently of RNA editing by enhancing p16(INK4a) levels. *Nat. Cell Biol.* **24**:1202–1210. DOI:10.1038/s41556-022-00959-z
 29. Zhang J., Ao Y., Zhang Z., et al. (2020). Lamin A safeguards the m(6) A methylase METTL14 nuclear speckle reservoir to prevent cellular senescence. *Aging Cell* **19**:e13215. DOI:10.1111/acer.13215
 30. Wu Z., Lu M., Liu D., et al. (2023). M(6)A epitranscriptomic regulation of tissue homeostasis during primate aging. *Nat. Aging* **3**:705–721. DOI:10.1038/s43587-023-00393-2
 31. Fu Y., Jiang F., Zhang X., et al. (2024). Perturbation of METTL1-mediated tRNA N(7)-methylguanosine modification induces senescence and aging. *Nat. Commun.* **15**:5713. DOI:10.1038/s41467-024-49796-8
 32. van Sluis M., Gonzalo-Hansen C., Li Q., et al. (2026). Mechanisms of transcription-coupled repair and DNA damage surveillance in health and disease. *Nat. Rev. Mol. Cell Biol.* **27**:234–251. DOI:10.1038/s41580-025-00915-3
 33. Bahar R., Hartmann C. H., Rodriguez K. A., et al. (2006). Increased cell-to-cell variation in gene expression in ageing mouse heart. *Nature* **441**:1011–1014. DOI:10.1038/nature04844
 34. Wei Y. N., Hu H. Y., Xie G. C., et al. (2015). Transcript and protein expression decoupling reveals RNA binding proteins and miRNAs as potential modulators of human aging. *Genome Biol.* **16**:41. DOI:10.1186/s13059-015-0608-2
 35. Zheng H., Seit-Nebi A., Han X., et al. (2013). A posttranslational modification cascade involving p38, Tip60, and PRAK mediates oncogene-induced senescence. *Mol. Cell* **50**:699–710. DOI:10.1016/j.molcel.2013.04.013
 36. Zhang C. and Cuervo A. M. (2008). Restoration of chaperone-mediated autophagy in aging liver improves cellular maintenance and hepatic function. *Nat. Med.* **14**:959–965. DOI:10.1038/nm.1851
 37. Bobkova N. V., Evgen'ev M., Garbuz D. G., et al. (2015). Exogenous Hsp70 delays senescence and improves cognitive function in aging mice. *Proc. Natl. Acad. Sci. USA* **112**:16006–16011. DOI:10.1073/pnas.1516131112
 38. Edifizi D., Nolte H., Babu V., et al. (2017). Multilayered reprogramming in response to persistent DNA damage in *C. elegans*. *Cell Rep.* **20**:2026–2043. DOI:10.1016/j.celrep.2017.08.028
 39. Stein K. C., Morales-Polanco F., van der Lienden J., et al. (2022). Ageing exacerbates ribosome pausing to disrupt cotranslational proteostasis. *Nature* **601**:637–642. DOI:10.1038/s41586-021-04295-4
 40. Jankowski C. S. R., Samarah L. Z., MacArthur M. R., et al. (2025). Aged mice exhibit widespread metabolic changes but preserved major fluxes. *Cell Metab.* **37**:2280–2294 e2284. DOI:10.1016/j.cmet.2025.09.009
 41. Alonso-Lavin A. J., Bajic D. and Poyatos J. F. (2021). Tolerance to NADH/NAD(+) imbalance anticipates aging and anti-aging interventions. *iScience* **24**:102697. DOI:10.1016/j.isci.2021.102697
 42. Menendez J. A., Alarcon T. and Joven J. (2014). Gerometabolites: The pseudohypoxic aging side of cancer oncometabolites. *Cell Cycle* **13**:699–709. DOI:10.4161/cc.28079
 43. Grimbs S., Selbig J., Bulik S., et al. (2007). The stability and robustness of metabolic states: Identifying stabilizing sites in metabolic networks. *Mol. Syst. Biol.* **3**:146. DOI:10.1038/msb4100186
 44. Lopez-Otin C., Blasco M. A., Partridge L., et al. (2013). The hallmarks of aging. *Cell* **153**:1194–1217. DOI:10.1016/j.cell.2013.05.039
 45. Li S., Agudelo Garcia P. A., Aliferis C., et al. (2025). Advancing biological understanding of cellular senescence with computational multiomics. *Nat. Genet.* **57**:2381–2394. DOI:10.1038/s41588-025-02314-y
 46. Hoffman J. M., Lyu Y., Pletcher S. D., et al. (2017). Proteomics and metabolomics in ageing research: From biomarkers to systems biology. *Essays Biochem.* **61**:379–388. DOI:10.1042/EBC20160083
 47. Imai S. and Guarente L. (2014). NAD⁺ and sirtuins in aging and disease. *Trends Cell Biol.* **24**:464–471. DOI:10.1016/j.tcb.2014.04.002
 48. Villa E., Sahu U., O'Hara B. P., et al. (2021). mTORC1 stimulates cell growth through SAM synthesis and m(6)A mRNA-dependent control of protein synthesis. *Mol. Cell* **81**:2076–2093 e2079. DOI:10.1016/j.molcel.2021.03.009
 49. Hu W. L., Jin L., Xu A., et al. (2018). GUARDIN is a p53-responsive long non-coding RNA that is essential for genomic stability. *Nat. Cell Biol.* **20**:492–502. DOI:10.1038/s41556-018-0066-7
 50. de Lorenzo V. (2014). From the selfish gene to selfish metabolism: Revisiting the central dogma. *Bioessays* **36**:226–235. DOI:10.1002/bies.201300153
 51. Hernandez H., Santamaria-Garcia H., Moguilner S., et al. (2025). The exposome of healthy and accelerated aging across 40 countries. *Nat. Med.* **31**:3089–3100. DOI:10.1038/s41591-025-03808-2
 52. Johnson F. B., Sinclair D. A. and Guarente L. (1999). Molecular biology of aging. *Cell* **96**:291–302. DOI:10.1016/s0092-8674(00)80567-x
 53. Jacobs P. A., Court Brown W. M. and Doll R. (1961). Distribution of human chromosome counts in relation to age. *Nature* **191**:1178–1180. DOI:10.1038/1911178a0
 54. Vijg J. and Dolle M. E. (2002). Large genome rearrangements as a primary cause of aging. *Mech. Ageing Dev.* **123**:907–915. DOI:10.1016/s0047-6374(02)00028-3
 55. Dolle M. E. and Vijg J. (2002). Genome dynamics in aging mice. *Genome Res.* **12**:1732–1738. DOI:10.1101/gr.125502
 56. Chandra T., Ewels P. A., Schoenfelder S., et al. (2015). Global reorganization of the nuclear landscape in senescent cells. *Cell Rep.* **10**:471–483. DOI:10.1016/j.celrep.2014.12.055
 57. Lodato M. A., Rodin R. E., Bohrsen C. L., et al. (2018). Aging and neurodegeneration are associated with increased mutations in single human neurons. *Science* **359**:555–559. DOI:10.1126/science.aao4426
 58. Choudhury S., Huang A. Y., Kim J., et al. (2022). Somatic mutations in single human cardiomyocytes reveal age-associated DNA damage and widespread oxidative genotoxicity. *Nat. Aging* **2**:714–725. DOI:10.1038/s43587-022-00261-5
 59. Vijg J., Schumacher B., Abakir A., et al. (2023). Mitigating age-related somatic mutation burden. *Trends Mol. Med.* **29**:530–540. DOI:10.1016/j.molmed.2023.04.002
 60. Shaban H. A. and Gasser S. M. (2025). Dynamic 3D genome reorganization during senescence: Defining cell states through chromatin. *Cell Death Differ.* **32**:9–15. DOI:10.1038/s41418-023-01197-y
 61. Bacolla A., Pradhan S., Roberts R. J., et al. (1999). Recombinant human DNA (cytosine-5) methyltransferase. II. Steady-state kinetics reveal allosteric activation by methylated DNA. *J. Biol. Chem.* **274**:33011–33019. DOI:10.1074/jbc.274.46.33011
 62. Suetake I., Shinozaki F., Miyagawa J., et al. (2004). DNMT3L stimulates the DNA methylation activity of Dnmt3a and Dnmt3b through a direct interaction. *J. Biol. Chem.* **279**:27816–27823. DOI:10.1074/jbc.M400181200
 63. Oberdoerffer P., Michan S., McVay M., et al. (2008). SIRT1 redistribution on chromatin promotes genomic stability but alters gene expression during aging. *Cell*

- 135:907–918. DOI:10.1016/j.cell.2008.10.025
64. Pazolli E., Alspach E., Milczarek A., et al. (2012). Chromatin remodeling underlies the senescence-associated secretory phenotype of tumor stromal fibroblasts that supports cancer progression. *Cancer Res.* **72**:2251–2261. DOI:10.1158/0008-5472.CAN-11-3386
 65. Marttila S., Kananen L., Hayrynen S., et al. (2015). Ageing-associated changes in the human DNA methylome: Genomic locations and effects on gene expression. *BMC Genomics* **16**:179. DOI:10.1186/s12864-015-1381-z
 66. Sen P., Lan Y., Li C. Y., et al. (2019). Histone acetyltransferase p300 induces de novo super-enhancers to drive cellular senescence. *Mol. Cell* **73**:684–698 e688. DOI:10.1016/j.molcel.2019.01.021
 67. Xu C., Wang L., Fozouni P., et al. (2020). SIRT1 is downregulated by autophagy in senescence and ageing. *Nat. Cell Biol.* **22**:1170–1179. DOI:10.1038/s41556-020-00579-5
 68. Wang K., Liu H., Hu Q., et al. (2022). Epigenetic regulation of aging: Implications for interventions of aging and diseases. *Signal Transduct. Target Ther.* **7**:374. DOI:10.1038/s41392-022-01211-8
 69. Weaver K. J., Holt R. A., Henry E., et al. (2023). Effects of hunger on neuronal histone modifications slow aging in *Drosophila*. *Science* **380**:625–632. DOI:10.1126/science.ade1662
 70. Makarov V. L., Hirose Y. and Langmore J. P. (1997). Long G tails at both ends of human chromosomes suggest a C strand degradation mechanism for telomere shortening. *Cell* **88**:657–666. DOI:10.1016/s0092-8674(00)81908-x
 71. Wright W. E., Tesmer V. M., Huffman K. E., et al. (1997). Normal human chromosomes have long G-rich telomeric overhangs at one end. *Genes Dev.* **11**:2801–2809. DOI:10.1101/gad.11.21.2801
 72. Huffman K. E., Levene S. D., Tesmer V. M., et al. (2000). Telomere shortening is proportional to the size of the G-rich telomeric 3'-overhang. *J. Biol. Chem.* **275**:19719–19722. DOI:10.1074/jbc.M002843200
 73. Shammam M. A. (2011). Telomeres, lifestyle, cancer, and aging. *Curr. Opin. Clin. Nutr. Metab. Care* **14**:28–34. DOI:10.1097/MCO.0b013e32834121b1
 74. Hewitt G., Jurk D., Marques F. D., et al. (2012). Telomeres are favoured targets of a persistent DNA damage response in ageing and stress-induced senescence. *Nat. Commun.* **3**:708. DOI:10.1038/ncomms1708
 75. Wang Y., Wang X., Flores E. R., et al. (2016). Dysfunctional telomeres induce p53-dependent and independent apoptosis to compromise cellular proliferation and inhibit tumor formation. *Aging Cell* **15**:646–660. DOI:10.1111/acel.12476
 76. Lan Y. Y., Heather J. M., Eisenhaure T., et al. (2019). Extranuclear DNA accumulates in aged cells and contributes to senescence and inflammation. *Aging Cell* **18**:e12901. DOI:10.1111/acel.12901
 77. Li Y., Tian X., Luo J., et al. (2024). Molecular mechanisms of aging and anti-aging strategies. *Cell Commun. Signal* **22**:285. DOI:10.1186/s12964-024-01663-1
 78. Goncalves T., Cunniffe S., Ma T. S., et al. (2025). Elevated reactive oxygen species can drive the alternative lengthening of telomeres pathway in ATRX-null cancers. *Nucleic Acids Res.* **53**:gkaf061. DOI:10.1093/nar/gkaf061
 79. Wang C., Martens D. S., Bustamante M., et al. (2025). The multi-omics signatures of telomere length in childhood. *BMC Genomics* **26**:75. DOI:10.1186/s12864-025-11209-5
 80. Sedelnikova O. A., Horikawa I., Zimonjic D. B., et al. (2004). Senescing human cells and ageing mice accumulate DNA lesions with unreparable double-strand breaks. *Nat. Cell Biol.* **6**:168–170. DOI:10.1038/ncb1095
 81. Morandini F., Lu J. Y., Rechsteiner C., et al. (2025). Transposable element 5mC methylation state of blood cells predicts age and disease. *Nat. Aging* **5**:193–204. DOI:10.1038/s43587-024-00757-2
 82. Wang F., Pan X., Kalmbach K., et al. (2013). Robust measurement of telomere length in single cells. *Proc. Natl. Acad. Sci. USA* **110**:E1906–E1912. DOI:10.1073/pnas.1306639110
 83. Rowland T. J., Dumbovic G., Hass E. P., et al. (2019). Single-cell imaging reveals unexpected heterogeneity of telomerase reverse transcriptase expression across human cancer cell lines. *Proc. Natl. Acad. Sci. USA* **116**:18488–18497. DOI:10.1073/pnas.1908275116
 84. Narita M., Nunez S., Heard E., et al. (2003). Rb-mediated heterochromatin formation and silencing of E2F target genes during cellular senescence. *Cell* **113**:703–716. DOI:10.1016/s0092-8674(03)00401-x
 85. Nikolov D. B. and Burley S. K. (1997). RNA polymerase II transcription initiation: A structural view. *Proc. Natl. Acad. Sci. USA* **94**:15–22. DOI:10.1073/pnas.94.1.15
 86. Yamaguchi Y., Takagi T., Wada T., et al. (1999). NELF, a multisubunit complex containing RD, cooperates with DSIF to repress RNA polymerase II elongation. *Cell* **97**:41–51. DOI:10.1016/s0092-8674(00)80713-8
 87. Oakes C. C., Smiraglia D. J., Plass C., et al. (2003). Aging results in hypermethylation of ribosomal DNA in sperm and liver of male rats. *Proc. Natl. Acad. Sci. USA* **100**:1775–1780. DOI:10.1073/pnas.0437971100
 88. Cheung A. C., Sainsbury S. and Cramer P. (2011). Structural basis of initial RNA polymerase II transcription. *EMBO J.* **30**:4755–4763. DOI:10.1038/emboj.2011.396
 89. D'Aquila P., Montesanto A., Mandala M., et al. (2017). Methylation of the ribosomal RNA gene promoter is associated with aging and age-related decline. *Aging Cell* **16**:966–975. DOI:10.1111/acel.12603
 90. Sharifi S. and Bierhoff H. (2018). Regulation of RNA polymerase I transcription in development, disease, and aging. *Annu. Rev. Biochem.* **87**:51–73. DOI:10.1146/annurev-biochem-062917-012612
 91. Vos S. M., Farnung L., Urlaub H., et al. (2018). Structure of paused transcription complex Pol II-DSIF-NELF. *Nature* **560**:601–606. DOI:10.1038/s41586-018-0442-2
 92. Dai D. P., Gan W., Hayakawa H., et al. (2018). Transcriptional mutagenesis mediated by 8-oxoG induces translational errors in mammalian cells. *Proc. Natl. Acad. Sci. USA* **115**:4218–4222. DOI:10.1073/pnas.1718363115
 93. Kang D., Baek Y. and Lee J. S. (2022). Mechanisms of RNA and protein quality control and their roles in cellular senescence and age-related diseases. *Cells* **11**:4062. DOI:10.3390/cells11244062
 94. Sharifi S., Chaudhari P., Martirosyan A., et al. (2024). Reducing the metabolic burden of rRNA synthesis promotes healthy longevity in *Caenorhabditis elegans*. *Nat. Commun.* **15**:1702. DOI:10.1038/s41467-024-46037-w
 95. Schiksnis E. C., Nicastro I. A. and Pasquinelli A. E. (2024). Full-length direct RNA sequencing reveals extensive remodeling of RNA expression, processing and modification in aging *Caenorhabditis elegans*. *Nucleic Acids Res.* **52**:13896–13913. DOI:10.1093/nar/gkae1064
 96. Sun P., Miller B. A., Sakai A. P., et al. (2026). RNA imbalance as a hallmark of cellular ageing. *Nat. Cell Biol.* **28**:1102–1112. DOI:10.1038/s41556-026-01946-4
 97. Lee Y. and Rio D. C. (2015). Mechanisms and regulation of alternative pre-mRNA splicing. *Annu. Rev. Biochem.* **84**:291–323. DOI:10.1146/annurev-biochem-060614-034316
 98. Han X., Xing L., Hong Y., et al. (2024). Nuclear RNA homeostasis promotes systems-level coordination of cell fate and senescence. *Cell Stem Cell* **31**:694–716 e611. DOI:10.1016/j.stem.2024.03.015
 99. van der Werf I., Sneider J. and Jamieson C. (2024). RNA modifications shape hematopoietic stem cell aging: Beyond the code. *FEBS Lett.* **598**:2774–2775. DOI:10.1002/1873-3468.15014
 100. Wang Y., Wang C., Dai X., et al. (2025). Deciphering the multifaceted role of circular RNA in aging: From molecular mechanisms to therapeutic potentials. *Noncoding RNA Res.* **14**:129–144. DOI:10.1016/j.ncrna.2025.05.015
 101. Lykke-Andersen J., Shu M. D. and Steitz J. A. (2000). Human Upf proteins target an mRNA for nonsense-mediated decay when bound downstream of a termination codon. *Cell* **103**:1121–1131. DOI:10.1016/s0092-8674(00)00214-2
 102. Brewer G. (2002). Messenger RNA decay during aging and development. *Ageing Res. Rev.* **1**:607–625. DOI:10.1016/s1568-1637(02)00023-5
 103. Wang W., Martindale J. L., Yang X., et al. (2005). Increased stability of the p16 mRNA with replicative senescence. *EMBO Rep.* **6**:158–164. DOI:10.1038/sj.embor.7400346
 104. Son H. G., Seo M., Ham S., et al. (2017). RNA surveillance via nonsense-mediated mRNA decay is crucial for longevity in *daf-2/insulin/IGF-1* mutant *C. elegans*. *Nat. Commun.* **8**:14749. DOI:10.1038/ncomms14749
 105. Mullani N., Porozhan Y., Manginck A., et al. (2021). Reduced RNA turnover as a driver of cellular senescence. *Life Sci. Alliance* **4**:e20200809. DOI:10.26508/lisa.20200809
 106. Wu Z., Zhang W., Qu J., et al. (2024). Emerging epigenetic insights into aging mechanisms and interventions. *Trends Pharmacol. Sci.* **45**:157–172. DOI:10.1016/j.tips.2023.12.002
 107. Guillet C., Prod'homme M., Balage M., et al. (2004). Impaired anabolic response of muscle protein synthesis is associated with S6K1 dysregulation in elderly humans. *FASEB J.* **18**:1586–1587. DOI:10.1096/fj.03-1341fje
 108. Syntichaki P., Troulinaki K. and Tavernarakis N. (2007). eIF4E function in somatic cells modulates ageing in *Caenorhabditis elegans*. *Nature* **445**:922–926. DOI:10.1038/nature05603
 109. Fry C. S., Drummond M. J., Glynn E. L., et al. (2011). Aging impairs contraction-induced human skeletal muscle mTORC1 signaling and protein synthesis. *Skelet. Muscle* **1**:11. DOI:10.1186/2044-5040-1-11
 110. Rogers A. N., Chen D., McColl G., et al. (2011). Life span extension via eIF4G inhibition is mediated by posttranscriptional remodeling of stress response gene expression in *C. elegans*. *Cell Metab.* **14**:55–66. DOI:10.1016/j.cmet.2011.05.010
 111. You J. S., Anderson G. B., Dooley M. S., et al. (2015). The role of mTOR signaling in the regulation of protein synthesis and muscle mass during immobilization in mice. *Dis. Model Mech.* **8**:1059–1069. DOI:10.1242/dmm.019414
 112. Plubell D. L., Wilmarth P. A., Zhao Y., et al. (2017). Extended multiplexing of Tandem Mass Tags (TMT) labeling reveals age and high fat diet specific proteome changes in mouse epididymal adipose tissue. *Mol. Cell. Proteomics* **16**:873–890. DOI:10.1074/mcp.M116.065524
 113. Anisimova A. S., Meerson M. B., Gerashchenko M. V., et al. (2020). Multifaceted deregulation of gene expression and protein synthesis with age. *Proc. Natl. Acad. Sci. USA* **117**:15581–15590. DOI:10.1073/pnas.2001788117
 114. Kim H. S. and Pickering A. M. (2023). Protein translation paradox: Implications in translational regulation of aging. *Front. Cell Dev. Biol.* **11**:1129281. DOI:10.3389/fcell.2023.1129281
 115. Choksi K. B., Boylston W. H., Rabek J. P., et al. (2004). Oxidatively damaged proteins of heart mitochondrial electron transport complexes. *Biochim. Biophys. Acta* **1688**:95–101. DOI:10.1016/j.bbadis.2003.11.007
 116. Hains P. G. and Truscott R. J. (2010). Age-dependent deamidation of lifelong proteins in the human lens. *Invest. Ophthalmol. Vis. Sci.* **51**:3107–3114. DOI:10.1167/iiovs.09-4308

117. Beltrao P., Bork P., Krogan N. J., et al. (2013). Evolution and functional cross-talk of protein post-translational modifications. *Mol. Syst. Biol.* **9**:714. DOI:10.1002/msb.201304521
118. Hollingsworth T. J., Radic M. Z., Beranova-Giorgianni S., et al. (2018). Murine retinal citrullination declines with age and is mainly dependent on peptidyl arginine deiminase 4 (PAD4). *Invest. Ophthalmol. Vis. Sci.* **59**:3808–3815. DOI:10.1167/iov.18-24118
119. Leutert M., Entwisle S. W. and Villen J. (2021). Decoding post-translational modification crosstalk with proteomics. *Mol. Cell. Proteomics* **20**:100129. DOI:10.1016/j.mcpro.2021.100129
120. Murphy M. P., Bayir H., Belousov V., et al. (2022). Guidelines for measuring reactive oxygen species and oxidative damage in cells and in vivo. *Nat. Metab.* **4**:651–662. DOI:10.1038/s42255-022-00591-z
121. Lee J. M., Hammaren H. M., Savitski M. M., et al. (2023). Control of protein stability by post-translational modifications. *Nat. Commun.* **14**:201. DOI:10.1038/s41467-023-35795-8
122. Johnston E. and Buckley M. (2023). Age-related changes in post-translational modifications of proteins from whole male and female skeletal elements. *Molecules* **28**:4899. DOI:10.3390/molecules28134899
123. Poudel S., Chuang C.-L., Shrestha H. K., et al. (2025). Pan-PTM profiling identifies post-translational modifications associated with exceptional longevity and preservation of skeletal muscle function in *Drosophila*. *npj Aging* **11**:23. DOI:10.1038/s41514-025-00215-2
124. Klionsky D. J. (2007). Autophagy: From phenomenology to molecular understanding in less than a decade. *Nat. Rev. Mol. Cell Biol.* **8**:931–937. DOI:10.1038/nrm2245
125. Cuanalo-Contreras K., Mukherjee A. and Soto C. (2013). Role of protein misfolding and proteostasis deficiency in protein misfolding diseases and aging. *Int. J. Cell Biol.* **2013**:638083. DOI:10.1155/2013/638083
126. Aman Y., Schmauck-Medina T., Hansen M., et al. (2021). Autophagy in healthy aging and disease. *Nat. Aging* **1**:634–650. DOI:10.1038/s43587-021-00098-4
127. Hamazaki J. and Murata S. (2024). Relationships between protein degradation, cellular senescence, and organismal aging. *J. Biochem.* **175**:473–480. DOI:10.1093/jb/mvae016
128. Yang X., Wei L., Zhong S., et al. (2025). Liquid-liquid phase separation of RBM33 facilitates hippocampus aging by inducing microglial senescence by activating CDKN1A. *Int. J. Biol. Macromol.* **310**:142986. DOI:10.1016/j.ijbiomac.2025.142986
129. Li Y., Jin X., Yu C., et al. (2025). Phase separation of MRG15 delays cellular senescence. *Commun. Biol.* **8**:688. DOI:10.1038/s42003-025-08071-2
130. Lian K. and Nan F. (2026). Small molecules modulate the biomolecular condensates and liquid-liquid phase separation. *Acta Pharm. Sin. B* **16**:2756–2772. DOI:10.1016/j.apsb.2026.01.032
131. Nyström T. (2005). Role of oxidative carbonylation in protein quality control and senescence. *EMBO J.* **24**:1311–1317. DOI:10.1038/sj.emboj.7600599
132. Olinger B. and Basisty N. (2026). A compendium of circulating biomarkers of senescence in humans: Insights on mechanistic impact across health domains and modulation by therapeutic interventions. *Ageing Res. Rev.* **121**:103254. DOI:10.1016/j.arr.2026.103254
133. de Lima Camillo L. P., Asif M. H., Horvath S., et al. (2025). Histone mark age of human tissues and cell types. *Sci. Adv.* **11**:eadk9373. DOI:10.1126/sciadv.adk9373
134. Breen L. and Phillips S. M. (2011). Skeletal muscle protein metabolism in the elderly: Interventions to counteract the 'anabolic resistance' of ageing. *Nutr. Metab. (Lond.)* **8**:68. DOI:10.1186/1743-7075-8-68
135. Zhu J. and Thompson C. B. (2019). Metabolic regulation of cell growth and proliferation. *Nat. Rev. Mol. Cell Biol.* **20**:436–450. DOI:10.1038/s41580-019-0123-5
136. Han Y., Hu Z., Cui A., et al. (2019). Post-translational regulation of lipogenesis via AMPK-dependent phosphorylation of insulin-induced gene. *Nat. Commun.* **10**:623. DOI:10.1038/s41467-019-08585-4
137. Le Couteur D. G., Solon-Biet S. M., Cogger V. C., et al. (2020). Branched chain amino acids, aging and age-related health. *Ageing Res. Rev.* **64**:101198. DOI:10.1016/j.arr.2020.101198
138. Lee G., Kim Y. Y., Jang H., et al. (2022). SREBP1c-PARP1 axis tunes anti-senescence activity of adipocytes and ameliorates metabolic imbalance in obesity. *Cell Metab.* **34**:702–718 e705. DOI:10.1016/j.cmet.2022.03.010
139. Bonnet L., Alexandersson I., Baboota R. K., et al. (2022). Cellular senescence in hepatocytes contributes to metabolic disturbances in NASH. *Front. Endocrinol. (Lausanne)* **13**:957616. DOI:10.3389/fendo.2022.957616
140. Vanweert F., Schrauwen P. and Phielix E. (2022). Role of branched-chain amino acid metabolism in the pathogenesis of obesity and type 2 diabetes-related metabolic disturbances BCAA metabolism in type 2 diabetes. *Nutr. Diabetes* **12**:35. DOI:10.1038/s41387-022-00213-3
141. Moldakozhayev A. and Gladyshev V. N. (2023). Metabolism, homeostasis, and aging. *Trends Endocrinol. Metab.* **34**:158–169. DOI:10.1016/j.tem.2023.01.003
142. Ayala A., Munoz M. F. and Arguelles S. (2014). Lipid peroxidation: Production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. *Oxid. Med. Cell. Longev.* **2014**:360438. DOI:10.1155/2014/360438
143. Furman D., Chang J., Lartigue L., et al. (2017). Expression of specific inflammasome gene modules stratifies older individuals into two extreme clinical and immunological states. *Nat. Med.* **23**:174–184. DOI:10.1038/nm.4267
144. Adav S. S. and Wang Y. L. (2021). Metabolomics signatures of aging: Recent advances. *Ageing Dis.* **12**:646–661. DOI:10.14336/Ad.2020.0909
145. Balashova E. E., Maslov D. L., Trifonova O. P., et al. (2022). Metabolome profiling in aging studies. *Biology (Basel)* **11**:1570. DOI:10.3390/biology11111570
146. Trivedi D., Hollywood K. A., Xu Y., et al. (2024). Metabolomic heterogeneity of ageing with ethnic diversity: A step closer to healthy ageing. *Metabolomics* **21**:9. DOI:10.1007/s11306-024-02199-8
147. Roubenoff R. (2003). Catabolism of aging: Is it an inflammatory process. *Curr. Opin. Clin. Nutr.* **6**:295–299. DOI:10.1097/01.mco.0000068965.34812.62
148. Newgard C. B., An J., Bain J. R., et al. (2009). A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. *Cell Metab.* **9**:311–326. DOI:10.1016/j.cmet.2009.02.002
149. Mills E. L., Kelly B., Logan A., et al. (2016). Succinate dehydrogenase supports metabolic repurposing of mitochondria to drive inflammatory macrophages. *Cell* **167**:457–470 e413. DOI:10.1016/j.cell.2016.08.064
150. Ravera S., Podesta M., Sabatini F., et al. (2019). Discrete changes in glucose metabolism define aging. *Sci. Rep.* **9**:10347. DOI:10.1038/s41598-019-46749-w
151. Biswas D., Dao K. T., Mercer A., et al. (2020). Branched-chain ketoacid overload inhibits insulin action in the muscle. *J. Biol. Chem.* **295**:15597–15621. DOI:10.1074/jbc.RA120.013121
152. Parkhitko A. A., Filine E., Mohr S. E., et al. (2020). Targeting metabolic pathways for extension of lifespan and healthspan across multiple species. *Ageing Res. Rev.* **64**:101188. DOI:10.1016/j.arr.2020.101188
153. Lu Y., Xu K., Lin D., et al. (2022). Multi-omics analysis reveals neuroinflammation, activated glial signaling, and dysregulated synaptic signaling and metabolism in the hippocampus of aged mice. *Front. Aging Neurosci.* **14**:964429. DOI:10.3389/fnagi.2022.964429
154. Sun L., Li Z., Hu C., et al. (2023). Age-dependent changes in the gut microbiota and serum metabolome correlate with renal function and human aging. *Ageing Cell* **22**:e14028. DOI:10.1111/ace1.14028
155. Sebastiani P., Monti S., Lustgarten M. S., et al. (2024). Metabolite signatures of chronological age, aging, survival, and longevity. *Cell Rep.* **43**:114913. DOI:10.1016/j.celrep.2024.114913
156. Perez R. F., Tezanos P., Penarroya A., et al. (2024). A multiomic atlas of the aging hippocampus reveals molecular changes in response to environmental enrichment. *Nat. Commun.* **15**:5829. DOI:10.1038/s41467-024-49608-z
157. Xu F., Guo Y., Thomas S. C., et al. (2025). Succinate modulates oral dysbiosis and inflammation through a succinate receptor 1 dependent mechanism in aged mice. *Int. J. Oral Sci.* **17**:47. DOI:10.1038/s41368-025-00376-6
158. Panyard D. J., Yu B. and Snyder M. P. (2022). The metabolomics of human aging: Advances, challenges, and opportunities. *Sci. Adv.* **8**:eadd6155. DOI:10.1126/sciadv.add6155
159. Goncalves S., Yin K., Ito Y., et al. (2021). COX2 regulates senescence secretome composition and senescence surveillance through PGE(2). *Cell Rep.* **34**:108860. DOI:10.1016/j.celrep.2021.108860
160. Balakrishnan R., Mori M., Segota I., et al. (2022). Principles of gene regulation quantitatively connect DNA to RNA and proteins in bacteria. *Science* **378**:eabk2066. DOI:10.1126/science.abk2066
161. Cortez D. (2019). Replication-Coupled DNA Repair. *Mol. Cell* **74**:866–876. DOI:10.1016/j.molcel.2019.04.027
162. Finkel T. and Holbrook N. J. (2000). Oxidants, oxidative stress and the biology of ageing. *Nature* **408**:239–247. DOI:10.1038/35041687
163. Poetsch A. R., Boulton S. J. and Luscombe N. M. (2018). Genomic landscape of oxidative DNA damage and repair reveals regioselective protection from mutagenesis. *Genome Biol.* **19**:215. DOI:10.1186/s13059-018-1582-2
164. Kiseleva O. I., Arzumanyan V. A., Ikhalaynen Y. A., et al. (2024). Multiomics of aging and aging-related diseases. *Int. J. Mol. Sci.* **25**:13671. DOI:10.3390/ijms252413671
165. Ren P., Zheng C., Pang Y., et al. (2025). Single-cell analysis of the somatic mutational landscape in human chondrocytes during aging and in osteoarthritis. *Nat. Aging* **5**:2417–2431. DOI:10.1038/s43587-025-01011-z
166. Bahat A., Milenkovic D., Cors E., et al. (2025). Ribonucleotide incorporation into mitochondrial DNA drives inflammation. *Nature* **647**:726–734. DOI:10.1038/s41586-025-09541-7
167. McCulloch S. D. and Kunkel T. A. (2008). The fidelity of DNA synthesis by eukaryotic replicative and translesion synthesis polymerases. *Cell Res.* **18**:148–161. DOI:10.1038/cr.2008.4
168. Gao Z., Moorjani P., Sasani T. A., et al. (2019). Overlooked roles of DNA damage and maternal age in generating human germline mutations. *Proc. Natl. Acad. Sci. USA* **116**:9491–9500. DOI:10.1073/pnas.1901259116
169. Burhans W. C. and Weinberger M. (2007). DNA replication stress, genome instability and aging. *Nucleic Acids Res.* **35**:7545–7556. DOI:10.1093/nar/gkm1059
170. Alexander J. L., Barrasa M. I. and Orr-Weaver T. L. (2015). Replication fork progression during re-replication requires the DNA damage checkpoint and double-strand break repair. *Curr. Biol.* **25**:1654–1660. DOI:10.1016/j.cub.2015.04.058
171. Graf M., Bonetti D., Lockhart A., et al. (2017). Telomere length determines TERRA and R-loop regulation through the cell cycle. *Cell* **170**:72–85.e14. DOI:10.1016/j.cell.2017.06.006
172. Banin S., Moyal L., Shieh S., et al. (1998). Enhanced phosphorylation of p53 by ATM

- in response to DNA damage. *Science* **281**:1674–1677. DOI:10.1126/science.281.5383.1674
173. Matsuoka S., Ballif B. A., Smogorzewska A., et al. (2007). ATM and ATR substrate analysis reveals extensive protein networks responsive to DNA damage. *Science* **316**:1160–1166. DOI:10.1126/science.1140321
 174. Liu B., Wang J., Chan K. M., et al. (2005). Genomic instability in laminopathy-based premature aging. *Nat. Med.* **11**:780–785. DOI:10.1038/nm1266
 175. Herr L. M., Schaffer E. D., Fuchs K. F., et al. (2024). Replication stress as a driver of cellular senescence and aging. *Commun. Biol.* **7**:616. DOI:10.1038/s42003-024-06263-w
 176. Serrano A. L. and Andres V. (2004). Telomeres and cardiovascular disease: Does size matter. *Circ. Res.* **94**:575–584. DOI:10.1161/01.RES.0000122141.18795.9C
 177. Victororelli S. and Passos J. F. (2020). Telomeres: Beacons of autocrine and paracrine DNA damage during skin aging. *Cell Cycle* **19**:532–540. DOI:10.1080/15384101.2020.1728016
 178. Di Micco R., Krizhanovsky V., Baker D., et al. (2021). Cellular senescence in ageing: From mechanisms to therapeutic opportunities. *Nat. Rev. Mol. Cell Biol.* **22**:75–95. DOI:10.1038/s41580-020-00314-w
 179. Yamaguchi H., Calado R. T., Ly H., et al. (2005). Mutations in TERT, the gene for telomerase reverse transcriptase, in aplastic anemia. *N. Engl. J. Med.* **352**:1413–1424. DOI:10.1056/NEJMoa042980
 180. Jaskieloff M., Muller F. L., Paik J. H., et al. (2011). Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice. *Nature* **469**:102–106. DOI:10.1038/nature09603
 181. Jiricny J. (2006). The multifaceted mismatch-repair system. *Nat. Rev. Mol. Cell Biol.* **7**:335–346. DOI:10.1038/nrm1907
 182. Hegde M. L., Hazra T. K. and Mitra S. (2008). Early steps in the DNA base excision/single-strand interruption repair pathway in mammalian cells. *Cell Res.* **18**:27–47. DOI:10.1038/cr.2008.8
 183. Xu Z., Zhang L., Zhang W., et al. (2015). SIRT6 rescues the age related decline in base excision repair in a PARP1-dependent manner. *Cell Cycle* **14**:269–276. DOI:10.4161/15384101.2014.980641
 184. Durik M., Kavousi M., van der Pluijm I., et al. (2012). Nucleotide excision DNA repair is associated with age-related vascular dysfunction. *Circulation* **126**:468–478. DOI:10.1161/CIRCULATIONAHA.112.104380
 185. Kunkel T. A. and Erie D. A. (2015). Eukaryotic mismatch repair in relation to DNA replication. *Annu. Rev. Genet.* **49**:291–313. DOI:10.1146/annurev-genet-112414-054722
 186. Mao X., Tian X., Van Meter M., et al. (2012). Sirtuin 6 (SIRT6) rescues the decline of homologous recombination repair during replicative senescence. *Proc. Natl. Acad. Sci. USA* **109**:11800–11805. DOI:10.1073/pnas.1200583109
 187. White R. R. and Vijg J. (2016). Do DNA double-strand breaks drive aging. *Mol. Cell* **63**:729–738. DOI:10.1016/j.molcel.2016.08.004
 188. Pal S., Postnikoff S. D., Chavez M., et al. (2018). Impaired cohesion and homologous recombination during replicative aging in budding yeast. *Sci. Adv.* **4**:eaq0236. DOI:10.1126/sciadv.aag0236
 189. Seluanov A., Mittelman D., Pereira-Smith O. M., et al. (2004). DNA end joining becomes less efficient and more error-prone during cellular senescence. *Proc. Natl. Acad. Sci. USA* **101**:7624–7629. DOI:10.1073/pnas.0400726101
 190. Lombard D. B., Chua K. F., Mostoslavsky R., et al. (2005). DNA repair, genome stability, and aging. *Cell* **120**:497–512. DOI:10.1016/j.cell.2005.01.028
 191. Li M., Yang X., Lu X., et al. (2018). APE1 deficiency promotes cellular senescence and premature aging features. *Nucleic Acids Res.* **46**:5664–5677. DOI:10.1093/nar/gky326
 192. Lin Y., Raj J., Li J., et al. (2020). APE1 senses DNA single-strand breaks for repair and signaling. *Nucleic Acids Res.* **48**:1925–1940. DOI:10.1093/nar/gkz1175
 193. Liu L., Trimarchi J. R., Smith P. J., et al. (2002). Mitochondrial dysfunction leads to telomere attrition and genomic instability. *Aging Cell* **1**:40–46. DOI:10.1046/j.1474-9728.2002.00004.x
 194. Yousefzadeh M., Henpita C., Vyas R., et al. (2021). DNA damage-how and why we age. *eLife* **10**:e62852. DOI:10.7554/eLife.62852
 195. Titus S., Li F., Stobezki R., et al. (2013). Impairment of BRCA1-related DNA double-strand break repair leads to ovarian aging in mice and humans. *Sci. Transl. Med.* **5**:172ra121. DOI:10.1126/scitranslmed.3004925
 196. Sedic M., Skibinski A., Brown N., et al. (2015). Haploinsufficiency for BRCA1 leads to cell-type-specific genomic instability and premature senescence. *Nat. Commun.* **6**:7505. DOI:10.1038/ncomms8505
 197. Panier S., Wang S. and Schumacher B. (2024). Genome instability and DNA repair in somatic and reproductive aging. *Annu. Rev. Pathol.* **19**:261–290. DOI:10.1146/annurev-pathmechdis-051122-093128
 198. Robles S. J. and Adami G. R. (1998). Agents that cause DNA double strand breaks lead to p16INK4a enrichment and the premature senescence of normal fibroblasts. *Oncogene* **16**:1113–1123. DOI:10.1038/sj.onc.1201862
 199. Clarke T. L. and Mostoslavsky R. (2022). DNA repair as a shared hallmark in cancer and ageing. *Mol. Oncol.* **16**:3352–3379. DOI:10.1002/1878-0261.13285
 200. Gluck S., Guey B., Gulen M. F., et al. (2017). Innate immune sensing of cytosolic chromatin fragments through cGAS promotes senescence. *Nat. Cell Biol.* **19**:1061–1070. DOI:10.1038/ncb3586
 201. Liu H., Zhang H., Wu X., et al. (2018). Nuclear cGAS suppresses DNA repair and promotes tumorigenesis. *Nature* **563**:131–136. DOI:10.1038/s41586-018-0629-6
 202. Horvath S. (2013). DNA methylation age of human tissues and cell types. *Genome Biol.* **14**:R115. DOI:10.1186/gb-2013-14-10-r115
 203. Lu A. T., Fei Z., Haghani A., et al. (2023). Universal DNA methylation age across mammalian tissues. *Nat. Aging* **3**:1144–1166. DOI:10.1038/s43587-023-00462-6
 204. Agger K., Cloos P. A., Rudkjaer L., et al. (2009). The H3K27me3 demethylase JMD3 contributes to the activation of the INK4A-ARF locus in response to oncogene- and stress-induced senescence. *Genes Dev.* **23**:1171–1176. DOI:10.1101/gad.510809
 205. Ito T., Teo Y. V., Evans S. A., et al. (2018). Regulation of cellular senescence by polycomb chromatin modifiers through distinct DNA damage- and histone methylation-dependent pathways. *Cell Rep.* **22**:3480–3492. DOI:10.1016/j.celrep.2018.03.002
 206. Li R., Teng Y., Guo Y., et al. (2023). Aging-related decrease of histone methyltransferase SUV39H1 in adipose-derived stem cells enhanced SASP. *Mech. Ageing Dev.* **215**:111868. DOI:10.1016/j.mad.2023.111868
 207. Bracken A. P., Dietrich N., Pasini D., et al. (2006). Genome-wide mapping of Polycomb target genes unravels their roles in cell fate transitions. *Genes Dev.* **20**:1123–1136. DOI:10.1101/gad.381706
 208. Tordella L., Khan S., Hohmeyer A., et al. (2016). SWI/SNF regulates a transcriptional program that induces senescence to prevent liver cancer. *Genes Dev.* **30**:2187–2198. DOI:10.1101/gad.286112.116
 209. Wolf B. K., Zhao Y., McCray A., et al. (2023). Cooperation of chromatin remodeling SWI/SNF complex and pioneer factor AP-1 shapes 3D enhancer landscapes. *Nat. Struct. Mol. Biol.* **30**:10–21. DOI:10.1038/s41594-022-00880-x
 210. Wu Y. L., Lin Z. J., Li C. C., et al. (2023). Epigenetic regulation in metabolic diseases: Mechanisms and advances in clinical study. *Signal Transduct. Target Ther.* **8**:98. DOI:10.1038/s41392-023-01333-7
 211. Mortusewicz O., Schermelleh L., Walter J., et al. (2005). Recruitment of DNA methyltransferase I to DNA repair sites. *Proc. Natl. Acad. Sci. USA* **102**:8905–8909. DOI:10.1073/pnas.0501034102
 212. Dabin J., Fortuny A. and Polo S. E. (2016). Epigenome maintenance in response to DNA damage. *Mol. Cell* **62**:712–727. DOI:10.1016/j.molcel.2016.04.006
 213. Soto-Palma C., Niedernhofer L. J., Faulk C. D., et al. (2022). Epigenetics, DNA damage, and aging. *J. Clin. Invest.* **132**:e158446. DOI:10.1172/JCI158446
 214. Qiu L., Xu W., Lu X., et al. (2023). The HDAC6-RNF168 axis regulates H2A/H2A. X ubiquitination to enable double-strand break repair. *Nucleic Acids Res.* **51**:9166–9182. DOI:10.1093/nar/gkad631
 215. Liu X., Liu Z., Wu Z., et al. (2023). Resurrection of endogenous retroviruses during aging reinforces senescence. *Cell* **186**:287–304 e226. DOI:10.1016/j.cell.2022.12.017
 216. Yang H., Wang H., Ren J., et al. (2017). cGAS is essential for cellular senescence. *Proc. Natl. Acad. Sci. USA* **114**:E4612–E4620. DOI:10.1073/pnas.1705499114
 217. Mao J., Zhang Q., Zhuang Y., et al. (2024). Reactivation of senescence-associated endogenous retroviruses by ATF3 drives interferon signaling in aging. *Nat. Aging* **4**:1794–1812. DOI:10.1038/s43587-024-00745-6
 218. Kerepesi C., Zhang B., Lee S. G., et al. (2021). Epigenetic clocks reveal a rejuvenation event during embryogenesis followed by aging. *Sci. Adv.* **7**:eabg6082. DOI:10.1126/sciadv.abg6082
 219. Kabacik S., Lowe D., Fransen L., et al. (2022). The relationship between epigenetic age and the hallmarks of aging in human cells. *Nat. Aging* **2**:484–493. DOI:10.1038/s43587-022-00220-0
 220. Levine M. E., Lu A. T., Quach A., et al. (2018). An epigenetic biomarker of aging for lifespan and healthspan. *Aging (Albany N.Y.)* **10**:573–591. DOI:10.18632/aging.101414
 221. Lu A. T., Quach A., Wilson J. G., et al. (2019). DNA methylation GrimAge strongly predicts lifespan and healthspan. *Aging (Albany N.Y.)* **11**:303–327. DOI:10.18632/aging.101684
 222. Belsky D. W., Caspi A., Arseneault L., et al. (2020). Quantification of the pace of biological aging in humans through a blood test, the DunedinPoAm DNA methylation algorithm. *eLife* **9**:e54870. DOI:10.7554/eLife.54870
 223. Dou Z., Ghosh K., Vizioli M. G., et al. (2017). Cytoplasmic chromatin triggers inflammation in senescence and cancer. *Nature* **550**:402–406. DOI:10.1038/nature24050
 224. Martinez P. and Blasco M. A. (2017). Telomere-driven diseases and telomere-targeting therapies. *J. Cell Biol.* **216**:875–887. DOI:10.1083/jcb.201610111
 225. Serifoglu N., Allavena G., Lopes-Bastos B., et al. (2025). cGAS-STING are responsible for premature aging of telomerase-deficient zebrafish. *EMBO J.* **44**:4666–4680. DOI:10.1038/s44318-025-00482-5
 226. Cheng H., Xuan H., Green C. D., et al. (2018). Repression of human and mouse brain inflammaging transcriptome by broad gene-body histone hyperacetylation. *Proc. Natl. Acad. Sci. USA* **115**:7611–7616. DOI:10.1073/pnas.1800656115
 227. Boisvert M. M., Erikson G. A., Shokhirev M. N., et al. (2018). The aging astrocyte transcriptome from multiple regions of the mouse brain. *Cell Rep.* **22**:269–285. DOI:10.1016/j.celrep.2017.12.039
 228. Tabula Muris C., Overall C., Logistical C., et al. (2018). Single-cell transcriptomics of 20 mouse organs creates a Tabula Muris. *Nature* **562**:367–372. DOI:10.1038/s41586-018-0590-4
 229. Ham S. and Lee S. V. (2020). Advances in transcriptome analysis of human brain

- aging. *Exp. Mol. Med.* **52**:1787–1797. DOI:10.1038/s12276-020-00522-6
230. Tabula Muris C. (2020). A single-cell transcriptomic atlas characterizes ageing tissues in the mouse. *Nature* **583**:590–595. DOI:10.1038/s41586-020-2496-1
231. Perez-Gomez A, Buxbaum J. N. and Petrascheck M. (2020). The aging transcriptome: Read between the lines. *Curr. Opin. Neurobiol.* **63**:170–175. DOI:10.1016/j.conb.2020.05.001
232. Soheili-Nezhad S, Ibanez-Sole O, Izeta A., et al. (2024). Time is ticking faster for long genes in aging. *Trends Genet.* **40**:299–312. DOI:10.1016/j.tig.2024.01.009
233. Arif M., Lehoczi A., Hasko G., et al. (2025). Global and tissue-specific transcriptomic dysregulation in human aging: Pathways and predictive biomarkers. *Geroscience* **47**:5917–5936. DOI:10.1007/s11357-025-01672-z
234. Gyenis A, Chang J, Demmers J., et al. (2023). Genome-wide RNA polymerase stalling shapes the transcriptome during aging. *Nat. Genet.* **55**:268–279. DOI:10.1038/s41588-022-01279-6
235. Varga B. and Kerepesi C. (2025). CpGeneAge: Multi-omics aging clocks associated with NF- κ B signaling pathway in aging. *bioRxiv*:2025.2006.2026.661785. DOI:10.1101/2025.06.26.661785
236. Liu J. Y., Souroullas G. P., Diekmann B. O., et al. (2019). Cells exhibiting strong p16(INK4a) promoter activation in vivo display features of senescence. *Proc. Natl. Acad. Sci. USA* **116**:2603–2611. DOI:10.1073/pnas.1818313116
237. Zhao H., Liu Z., Chen H., et al. (2024). Identifying specific functional roles for senescence across cell types. *Cell* **187**:7314–7334 e7321. DOI:10.1016/j.cell.2024.09.021
238. Wu Z., Shi Y., Lu M., et al. (2020). METTL3 counteracts premature aging via m6A-dependent stabilization of MIS12 mRNA. *Nucleic Acids Res.* **48**:11083–11096. DOI:10.1093/nar/gkaa816
239. Cookson M. R. (2012). Aging--RNA in development and disease. *Wiley Interdiscip. Rev. RNA* **3**:133–143. DOI:10.1002/wrna.109
240. Li Q., Li X., Tang H., et al. (2017). NSUN2-mediated m5C methylation and METTL3/METTL14-mediated m6A methylation cooperatively enhance p21 translation. *J. Cell Biochem.* **118**:2587–2598. DOI:10.1002/jcb.25957
241. Casella G., Tsitsipatis D., Abdelmohsen K., et al. (2019). mRNA methylation in cell senescence. *Wiley Interdiscip. Rev. RNA* **10**:e1547. DOI:10.1002/wrna.1547
242. Cheng Y., Wang S., Zhang H., et al. (2024). A non-canonical role for a small nucleolar RNA in ribosome biogenesis and senescence. *Cell* **187**:4770–4789 e4723. DOI:10.1016/j.cell.2024.06.019
243. Cortes-Lopez M., Gruner M. R., Cooper D. A., et al. (2018). Global accumulation of circRNAs during aging in *Caenorhabditis elegans*. *BMC Genomics* **19**:8. DOI:10.1186/s12864-017-4386-y
244. Anver S., Sumit A. F., Sun X. M., et al. (2024). Ageing-associated long non-coding RNA extends lifespan and reduces translation in non-dividing cells. *EMBO Rep.* **25**:4921–4949. DOI:10.1038/s44319-024-00265-9
245. Seo M., Seo K., Hwang W., et al. (2015). RNA helicase HEL-1 promotes longevity by specifically activating DAF-16/FOXO transcription factor signaling in *Caenorhabditis elegans*. *Proc. Natl. Acad. Sci. USA* **112**:E4246–E4255. DOI:10.1073/pnas.1505451112
246. Park S., Park H.-E. H., Son H. G., et al. (2017). The role of RNA helicases in aging and lifespan regulation. *Transl. Med. Aging* **1**:24–31. DOI:10.1016/j.tma.2017.08.001
247. Anisimova A. S., Alexandrov A. I., Makarova N. E., et al. (2018). Protein synthesis and quality control in aging. *Aging (Albany N.Y.)* **10**:4269–4288. DOI:10.18632/aging.101721
248. Huang Y., Zhu S., Yao S., et al. (2025). Unraveling aging from transcriptomics. *Trends Genet.* **41**:218–235. DOI:10.1016/j.tig.2024.09.006
249. Luo Y., Na Z. and Slavoff S. A. (2018). P-bodies: Composition, properties, and functions. *Biochemistry* **57**:2424–2431. DOI:10.1021/acs.biochem.7b01162
250. Li J., Chen K., Dong X., et al. (2022). YTHDF1 promotes mRNA degradation via YTHDF1-AGO2 interaction and phase separation. *Cell Prolif.* **55**:e13157. DOI:10.1111/cpr.13157
251. Rajappa A., Patel T., Raju S. S., et al. (2026). Aging associated RNA loss impairs the dynamics of RNA and protein condensates. *bioRxiv*:2026.2002.2016.705223. DOI:10.64898/2026.02.16.705223
252. Moaddel R., Ubaida-Mohien C., Tanaka T., et al. (2021). Proteomics in aging research: A roadmap to clinical, translational research. *Aging Cell* **20**:e13325. DOI:10.1111/acer.13325
253. Rhine K., Li R., Koppale H. M., et al. (2025). Neuronal aging causes mislocalization of splicing proteins and unchecked cellular stress. *Nat. Neurosci.* **28**:1174–1184. DOI:10.1038/s41593-025-01952-z
254. Johnson A. A., Shokhiev M. N., Wyss-Coray T., et al. (2020). Systematic review and analysis of human proteomics aging studies unveils a novel proteomic aging clock and identifies key processes that change with age. *Ageing Res. Rev.* **60**:101070. DOI:10.1016/j.arr.2020.101070
255. Jackson R. J., Hellen C. U. and Pestova T. V. (2010). The mechanism of eukaryotic translation initiation and principles of its regulation. *Nat. Rev. Mol. Cell Biol.* **11**:113–127. DOI:10.1038/nrm2838
256. Kim H. S., Parker D. J., Hardiman M. M., et al. (2023). Early-adulthood spike in protein translation drives aging via juvenile hormone/germline signaling. *Nat. Commun.* **14**:5021. DOI:10.1038/s41467-023-40618-x
257. Ding Y., Zuo Y., Zhang B., et al. (2025). Comprehensive human proteome profiles across a 50-year lifespan reveal aging trajectories and signatures. *Cell* **188**:5763–5784.e5726. DOI:10.1016/j.cell.2025.06.047
258. Spoel S. H. (2018). Orchestrating the proteome with post-translational modifications. *J. Exp. Bot.* **69**:4499–4503. DOI:10.1093/jxb/ery295
259. Kaushik S. and Cuervo A. M. (2018). The coming of age of chaperone-mediated autophagy. *Nat. Rev. Mol. Cell Biol.* **19**:365–381. DOI:10.1038/s41580-018-0001-6
260. Hipp M. S., Kasturi P. and Hartl F. U. (2019). The proteostasis network and its decline in ageing. *Nat. Rev. Mol. Cell Biol.* **20**:421–435. DOI:10.1038/s41580-019-0101-y
261. Strang K. H., Croft C. L., Sorrentino Z. A., et al. (2018). Distinct differences in prion-like seeding and aggregation between Tau protein variants provide mechanistic insights into tauopathies. *J. Biol. Chem.* **293**:2408–2421. DOI:10.1074/jbc.M117.815357
262. Ottens F., Franz A. and Hoppe T. (2021). Build-UPS and break-downs: Metabolism impacts on proteostasis and aging. *Cell Death Differ.* **28**:505–521. DOI:10.1038/s41418-020-00682-y
263. Mauthe M., Kampinga H. and Reggiori F. (2025). Aggregate fragmentation: The ticket to aggregate phagocytosis. *Autophagy* **21**:3422–3424. DOI:10.1080/15548627.2025.2562893
264. Brestoff J. R. and Artis D. (2015). Immune regulation of metabolic homeostasis in health and disease. *Cell* **161**:146–160. DOI:10.1016/j.cell.2015.02.022
265. Marschallinger J., Iram T., Zardeneta M., et al. (2020). Lipid-droplet-accumulating microglia represent a dysfunctional and proinflammatory state in the aging brain. *Nat. Neurosci.* **23**:194–208. DOI:10.1038/s41593-019-0566-1
266. McReynolds M. R., Chellappa K., Chiles E., et al. (2021). NAD(+) flux is maintained in aged mice despite lower tissue concentrations. *Cell Syst.* **12**:1160–1172 e1164. DOI:10.1016/j.cels.2021.09.001
267. Hornburg D., Wu S., Mogri M., et al. (2023). Dynamic lipidome alterations associated with human health, disease and ageing. *Nat. Metab.* **5**:1578–1594. DOI:10.1038/s42255-023-00880-1
268. Halade G. V., Upadhyay G., Marimuthu M., et al. (2024). Exercise reduces pro-inflammatory lipids and preserves resolution mediators that calibrate macrophage-centric immune metabolism in spleen and heart following obesogenic diet in aging mice. *J. Mol. Cell. Cardiol.* **188**:79–89. DOI:10.1016/j.jmcc.2024.02.004
269. Wang Z., Zhu H. and Xiong W. (2025). Metabolism and metabolomics in senescence, aging, and age-related diseases: A multiscale perspective. *Front. Med.* **19**:200–225. DOI:10.1007/s11684-024-1116-0
270. Madeo F., Eisenberg T., Pietrocola F., et al. (2018). Spermidine in health and disease. *Science* **359**:eaan2788. DOI:10.1126/science.aan2788
271. Lin S. J., Defossez P. A. and Guarente L. (2000). Requirement of NAD and SIR2 for life-span extension by calorie restriction in *Saccharomyces cerevisiae*. *Science* **289**:2126–2128. DOI:10.1126/science.289.5487.2126
272. Ogawa T., Tsubakiyama R., Kanai M., et al. (2016). Stimulating S-adenosyl-L-methionine synthesis extends lifespan via activation of AMPK. *Proc. Natl. Acad. Sci. USA* **113**:11913–11918. DOI:10.1073/pnas.1604047113
273. Selberg S., Blokhina D., Aatonen M., et al. (2019). Discovery of small molecules that activate RNA methylation through cooperative binding to the METTL3-14-WTAP complex active site. *Cell Rep.* **26**:3762–3771 e3765. DOI:10.1016/j.celrep.2019.02.100
274. Zhang H., Alsaleh G., Feltham J., et al. (2019). Polyamines control eIF5A hypusination, TFEB translation, and autophagy to reverse B cell senescence. *Mol. Cell* **76**:110–125 e119. DOI:10.1016/j.molcel.2019.08.005
275. Ao Y., Zhang J., Liu Z., et al. (2019). Lamin A buffers CK2 kinase activity to modulate aging in a progeria mouse model. *Sci. Adv.* **5**:eaav5078. DOI:10.1126/sciadv.aav5078
276. Xie N., Zhang L., Gao W., et al. (2020). NAD(+) metabolism: Pathophysiologic mechanisms and therapeutic potential. *Signal Transduct. Target Ther.* **5**:227. DOI:10.1038/s41392-020-00311-7
277. Hwang I., Uchida H., Dai Z., et al. (2021). Cellular stress signaling activates type-I IFN response through FOXO3-regulated lamin posttranslational modification. *Nat. Commun.* **12**:640. DOI:10.1038/s41467-020-20839-0
278. Covarrubias A. J., Perrone R., Grozio A., et al. (2021). NAD(+) metabolism and its roles in cellular processes during ageing. *Nat. Rev. Mol. Cell Biol.* **22**:119–141. DOI:10.1038/s41580-020-00313-x
279. Fang W., Chen S., Jin X., et al. (2023). Metabolomics in aging research: Aging markers from organs. *Front. Cell Dev. Biol.* **11**:1198794. DOI:10.3389/fcell.2023.1198794
280. Huang H., Chen Y., Xu W., et al. (2025). Decoding aging clocks: New insights from metabolomics. *Cell Metab.* **37**:34–58. DOI:10.1016/j.cmet.2024.11.007
281. Aragon A. A., Tipton K. D. and Schoenfeld B. J. (2023). Age-related muscle anabolic resistance: Inevitable or preventable. *Nutr. Rev.* **81**:441–454. DOI:10.1093/nutrit/nuac062
282. Khutornenko A. A., Roudko V. V., Chernyak B. V., et al. (2010). Pyrimidine biosynthesis links mitochondrial respiration to the p53 pathway. *Proc. Natl. Acad. Sci. USA* **107**:12828–12833. DOI:10.1073/pnas.0910885107
283. Avanesov A. S., Ma S., Pierce K. A., et al. (2014). Age- and diet-associated metabolome remodeling characterizes the aging process driven by damage accumulation. *eLife* **3**:e02077. DOI:10.7554/eLife.02077
284. Yang L., You J., Yang X., et al. (2025). ACS2 drives senescence-associated

- secretory phenotype by limiting purine biosynthesis through PAICS acetylation. *Nat. Commun.* **16**:2071. DOI:10.1038/s41467-025-57334-3
285. Wiley C. D., Sharma R., Davis S. S., et al. (2021). Oxylipin biosynthesis reinforces cellular senescence and allows detection of senolysis. *Cell Metab.* **33**:1124–1136 e1125. DOI:10.1016/j.cmet.2021.03.008
 286. Qian C., Wang Q., Qiao Y., et al. (2025). Arachidonic acid in aging: New roles for old players. *J. Adv. Res.* **70**:79–101. DOI:10.1016/j.jare.2024.05.003
 287. Chen J., Deng J. C., Zemans R. L., et al. (2022). Age-induced prostaglandin E(2) impairs mitochondrial fitness and increases mortality to influenza infection. *Nat. Commun.* **13**:6759. DOI:10.1038/s41467-022-34593-y
 288. Nagano T., Awai Y., Kuwaba S., et al. (2021). Riboflavin transporter SLC52A1, a target of p53, suppresses cellular senescence by activating mitochondrial complex II. *Mol. Biol. Cell* **32**:br10. DOI:10.1091/mbc.E21-05-0262
 289. Yerevanian A., Murphy L. M., Emans S., et al. (2022). Riboflavin depletion promotes longevity and metabolic hormesis in *Caenorhabditis elegans*. *Aging Cell* **21**:e13718. DOI:10.1111/accel.13718
 290. Zhu D., Wu J. Z., Griffin P. T., et al. (2025). Metabolomics biomarkers of frailty: A longitudinal study of aging female and male mice. *NPJ Aging* **11**:40. DOI:10.1038/s41514-025-00237-w
 291. Brookes P. S. and Jimenez A. G. (2021). Metabolomics of aging in primary fibroblasts from small and large breed dogs. *Geroscience* **43**:1683–1696. DOI:10.1007/s11357-021-00388-0
 292. Xu P., Kong Y. M., Palmer N. D., et al. (2024). Integrated multi-omic analyses uncover the effects of aging on cell-type regulation in glucose-responsive tissues. *Aging Cell* **23**:e14199. DOI:10.1111/accel.14199
 293. Basu R., Dalla Man C., Campioni M., et al. (2006). Effects of age and sex on postprandial glucose metabolism: Differences in glucose turnover, insulin secretion, insulin action, and hepatic insulin extraction. *Diabetes* **55**:2001–2014. DOI:10.2337/db05-1692
 294. Hasin Y., Seldin M. and Lusis A. (2017). Multi-omics approaches to disease. *Genome Biol.* **18**:83. DOI:10.1186/s13059-017-1215-1
 295. Aging Atlas C. (2021). Aging Atlas: A multi-omics database for aging biology. *Nucleic Acids Res.* **49**:D825–D830. DOI:10.1093/nar/gkaa894
 296. Ji Q., Jiang X., Wang M., et al. (2024). Multimodal omics approaches to aging and age-related diseases. *Phenomics* **4**:56–71. DOI:10.1007/s43657-023-00125-x
 297. Solovov I., Shaposhnikov M. and Moskalev A. (2020). Multi-omics approaches to human biological age estimation. *Mech. Ageing Dev.* **185**:111192. DOI:10.1016/j.mad.2019.111192
 298. Singh P. P. and Benayoun B. A. (2023). Considerations for reproducible omics in aging research. *Nat. Aging* **3**:921–930. DOI:10.1038/s43587-023-00448-4
 299. Jeffries A. M., Yu T., Ziegenfuss J. S., et al. (2025). Single-cell transcriptomic and genomic changes in the ageing human brain. *Nature* **646**:657–666. DOI:10.1038/s41586-025-09435-8
 300. Rivero-Segura N. A., Bello-Chavolla O. Y., Barrera-Vazquez O. S., et al. (2020). Promising biomarkers of human aging: In search of a multi-omics panel to understand the aging process from a multidimensional perspective. *Ageing Res. Rev.* **64**:101164. DOI:10.1016/j.arr.2020.101164
 301. Mattick J. S., Amaral P. P., Carninci P., et al. (2023). Long non-coding RNAs: Definitions, functions, challenges and recommendations. *Nat. Rev. Mol. Cell Biol.* **24**:430–447. DOI:10.1038/s41580-022-00566-8
 302. Cruickshanks H. A., McBryan T., Nelson D. M., et al. (2013). Senescent cells harbour features of the cancer epigenome. *Nat. Cell Biol.* **15**:1495–1506. DOI:10.1038/ncb2879
 303. Xie W., Kagiampakis I., Pan L., et al. (2018). DNA methylation patterns separate senescence from transformation potential and indicate cancer risk. *Cancer Cell* **33**:309–321 e305. DOI:10.1016/j.ccell.2018.01.008
 304. Vaidya H., Jelinek J. and Issa J. J. (2025). DNA methylation, aging, and cancer. *Epigenomes* **9**:18. DOI:10.3390/epigenomes9020018
 305. Fleming A. M., Ding Y. and Burrows C. J. (2017). Oxidative DNA damage is epigenetic by regulating gene transcription via base excision repair. *Proc. Natl. Acad. Sci. USA* **114**:2604–2609. DOI:10.1073/pnas.1619809114
 306. Stoeger T., Grant R. A., McQuattie-Pimentel A. C., et al. (2022). Aging is associated with a systemic length-associated transcriptome imbalance. *Nat. Aging* **2**:1191–1206. DOI:10.1038/s43587-022-00317-6
 307. Donnio L. M. and Giglia-Mari G. (2025). Keep calm and reboot - how cells restart transcription after DNA damage and DNA repair. *FEBS Lett.* **599**:275–294. DOI:10.1002/1873-3468.14964
 308. Walther D. M., Kasturi P., Zheng M., et al. (2017). Widespread proteome remodeling and aggregation in aging *C. elegans*. *Cell* **168**:944. DOI:10.1016/j.cell.2016.12.041
 309. Chien Y., Scuoppo C., Wang X., et al. (2011). Control of the senescence-associated secretory phenotype by NF- κ B promotes senescence and enhances chemosensitivity. *Genes Dev.* **25**:2125–2136. DOI:10.1101/gad.17276711
 310. Sabath N., Levy-Adam F., Younis A., et al. (2020). Cellular proteostasis decline in human senescence. *Proc. Natl. Acad. Sci. USA* **117**:31902–31913. DOI:10.1073/pnas.2018138117
 311. Maan K., Baghel R., Dhariwal S., et al. (2023). Metabolomics and transcriptomics based multi-omics integration reveals radiation-induced altered pathway networking and underlying mechanism. *npj Syst. Biol. Appl.* **9**:42. DOI:10.1038/s41540-023-00305-5
 312. Xiong J., Zhu X., Guo Y., et al. Multi-omic underpinnings of heterogeneous aging across multiple organ systems. *Cell Genomics* **5**:101032. DOI:10.1016/j.xgen.2025.101032
 313. Mori M. P., Lozoya O. A., Brooks A. M., et al. (2025). Mitochondrial membrane hyperpolarization modulates nuclear DNA methylation and gene expression through phospholipid remodeling. *Nat. Commun.* **16**:4029. DOI:10.1038/s41467-025-59427-5
 314. Bonkowski M. S. and Sinclair D. A. (2016). Slowing ageing by design: The rise of NAD(+) and sirtuin-activating compounds. *Nat. Rev. Mol. Cell Biol.* **17**:679–690. DOI:10.1038/nrm.2016.93
 315. Etchegaray J. P. and Mostoslavsky R. (2016). Interplay between metabolism and epigenetics: A nuclear adaptation to environmental changes. *Mol. Cell* **62**:695–711. DOI:10.1016/j.molcel.2016.05.029
 316. Best L., Dost T., Esser D., et al. (2025). Metabolic modelling reveals the aging-associated decline of host-microbiome metabolic interactions in mice. *Nat. Microbiol.* **10**:973–991. DOI:10.1038/s41564-025-01959-z
 317. Wen J. (2025). Refining the generation, interpretation and application of multi-organ, multi-omics biological aging clocks. *Nat. Aging* **5**:1897–1913. DOI:10.1038/s43587-025-00928-9
 318. Zhang H., Ryu D., Wu Y., et al. (2016). NAD⁺ repletion improves mitochondrial and stem cell function and enhances life span in mice. *Science* **352**:1436–1443. DOI:10.1126/science.aaf2693
 319. Kang J., Benjamin D. I., Kim S., et al. (2024). Depletion of SAM leading to loss of heterochromatin drives muscle stem cell ageing. *Nat. Metab.* **6**:153–168. DOI:10.1038/s42255-023-00955-z
 320. Perez J. M. J., Lam A., Weissleder C., et al. (2026). The mitochondrial unfolded protein response in human microglia disrupts neuronal-glia communication and promotes senescence. *Nat. Neurosci.* **29**:1858–1872. DOI:10.1038/s41593-026-02320-1
 321. Han Y.-M., Ramprasath T. and Zou M.-H. (2020). β -hydroxybutyrate and its metabolic effects on age-associated pathology. *Exp. Mol. Med.* **52**:548–555. DOI:10.1038/s12276-020-0415-z
 322. Newman J. C., Covarrubias A. J., Zhao M., et al. (2017). Ketogenic diet reduces midlife mortality and improves memory in aging mice. *Cell Metab.* **26**:547–557.e548. DOI:10.1016/j.cmet.2017.08.004
 323. Eisenberg T., Abdellatif M., Schroeder S., et al. (2016). Cardioprotection and lifespan extension by the natural polyamine spermidine. *Nat. Med.* **22**:1428–1438. DOI:10.1038/nm.4222
 324. Hofer S. J., Daskalaki I., Bergmann M., et al. (2024). Spermidine is essential for fasting-mediated autophagy and longevity. *Nat. Cell Biol.* **26**:1571–1584. DOI:10.1038/s41556-024-01468-x
 325. Asadi Shahmirzadi A., Edgar D., Liao C. Y., et al. (2020). Alpha-ketoglutarate, an endogenous metabolite, extends lifespan and compresses morbidity in aging mice. *Cell Metab.* **32**:447–456 e446. DOI:10.1016/j.cmet.2020.08.004
 326. Yamauchi S., Sugiura Y., Yamaguchi J., et al. (2024). Mitochondrial fatty acid oxidation drives senescence. *Sci. Adv.* **10**:eado5887. DOI:10.1126/sciadv.ado5887
 327. Du J., Sarkar R., Wang L., et al. (2026). Gut microbiota-derived acetate safeguards the colonic epithelial acetyl-CoA reserve to avert colonic senescence. *bioRxiv*. DOI:10.64898/2026.05.15.725523
 328. Wang Y., Shen Y., Liu J., et al. (2026). Flavin adenine dinucleotide is an endogenous suppressor for cytosolic DNA and RNA sensors to modulate innate immunity. *Immunity* **59**:2413–2428.e2419. DOI:10.1016/j.immuni.2026.06.010
 329. Denzel M. S., Storm N. J., Gutschmidt A., et al. (2014). Hexosamine pathway metabolites enhance protein quality control and prolong life. *Cell* **156**:1167–1178. DOI:10.1016/j.cell.2014.01.061
 330. Saeedi Saravi S. S., Pugin B., Constancias F., et al. (2025). Gut microbiota-dependent increase in phenylacetic acid induces endothelial cell senescence during aging. *Nat. Aging* **5**:1025–1045. DOI:10.1038/s43587-025-00864-8
 331. Zhou Y., Hu G. and Wang M. C. (2021). Host and microbiota metabolic signals in aging and longevity. *Nat. Chem. Biol.* **17**:1027–1036. DOI:10.1038/s41589-021-00837-z
 332. Akbar M., Yadav S., Naseer A., et al. (2026). Gut microbiota-derived succinate links proteostasis collapse to α -synuclein pathology and aging. *iScience* **29**:115941. DOI:10.1016/j.isci.2026.115941
 333. Sun C., Li J., Dong L., et al. (2025). Lactylation: A novel epigenetic regulator of cellular senescence. *Aging Dis.* **17**:890–906. DOI:10.14336/ad.2025.0277
 334. Park A. Y., Leney-Greene M., Lynberg M., et al. (2024). GIMAP5 deficiency reveals a mammalian ceramide-driven longevity assurance pathway. *Nat. Immunol.* **25**:282–293. DOI:10.1038/s41590-023-01691-y
 335. Kolora S. R. R., Owens G. L., Vazquez J. M., et al. (2021). Origins and evolution of extreme life span in Pacific Ocean rockfishes. *Science* **374**:842–847. DOI:10.1126/science.abg5332
 336. Tao M., Chen J., Cui C., et al. (2024). Identification of a longevity gene through evolutionary rate covariation of insect mito-nuclear genomes. *Nat. Aging* **4**:1076–1088. DOI:10.1038/s43587-024-00641-z
 337. Bou Sleiman M., Roy S., Gao A. W., et al. (2022). Sex- and age-dependent genetics of longevity in a heterogeneous mouse population. *Science* **377**:eabo3191. DOI:10.1126/science.abo3191

338. Zhang Z., Tian X., Lu J. Y., et al. (2023). Increased hyaluronan by naked mole-rat Has2 improves healthspan in mice. *Nature* **621**:196–205. DOI:10.1038/s41586-023-06463-0
339. Farfariello V., Gordienko D. V., Mesilmany L., et al. (2022). TRPC3 shapes the ER-mitochondria Ca(2+) transfer characterizing tumour-promoting senescence. *Nat. Commun.* **13**:956. DOI:10.1038/s41467-022-28597-x
340. Morgan M. J. and Liu Z. G. (2011). Crosstalk of reactive oxygen species and NF-kappaB signaling. *Cell Res.* **21**:103–115. DOI:10.1038/cr.2010.178
341. Jiapaer Z., Su D., Hua L., et al. (2022). Regulation and roles of RNA modifications in aging-related diseases. *Aging Cell* **21**:e13657. DOI:10.1111/ace1.13657
342. Freund A., Laberge R. M., Demaria M., et al. (2012). Lamin B1 loss is a senescence-associated biomarker. *Mol. Biol. Cell* **23**:2066–2075. DOI:10.1091/mbc.E11-10-0884
343. Ren X., Li B., Xu C., et al. (2022). High expression of Piezo1 induces senescence in chondrocytes through calcium ions accumulation. *Biochem. Biophys. Res. Commun.* **607**:138–145. DOI:10.1016/j.bbrc.2022.03.119
344. Ding J., Chen Y., Zhao Y. J., et al. (2022). Acid-sensitive ion channel 1a mediates osteoarthritis chondrocyte senescence by promoting Lamin B1 degradation. *Biochem. Pharmacol.* **202**:115107. DOI:10.1016/j.bcp.2022.115107
345. L'Hôte V., Courbeyrette R., Pinna G., et al. (2021). Ouabain and chloroquine trigger senolysis of BRAF-V600E-induced senescent cells by targeting autophagy. *Aging Cell* **20**:e13447. DOI:10.1111/ace1.13447
346. Sattler F. R. (2013). Growth hormone in the aging male. *Best Pract. Res. Clin. Endocrinol. Metab.* **27**:541–555. DOI:10.1016/j.beem.2013.05.003
347. Junnila R. K., List E. O., Berryman D. E., et al. (2013). The GH/IGF-1 axis in ageing and longevity. *Nat. Rev. Endocrinol.* **9**:366–376. DOI:10.1038/nrendo.2013.67
348. Camon C., Garratt M. and Correa S. M. (2024). Exploring the effects of estrogen deficiency and aging on organismal homeostasis during menopause. *Nat. Aging* **4**:1731–1744. DOI:10.1038/s43587-024-00767-0
349. Monteiro R., Teixeira D. and Calhau C. (2014). Estrogen signaling in metabolic inflammation. *Mediators Inflamm.* **2014**:615917. DOI:10.1155/2014/615917
350. Coppe J. P., Kauser K., Campisi J., et al. (2006). Secretion of vascular endothelial growth factor by primary human fibroblasts at senescence. *J. Biol. Chem.* **281**:29568–29574. DOI:10.1074/jbc.M603307200
351. Grunewald M., Kumar S., Sharife H., et al. (2021). Counteracting age-related VEGF signaling insufficiency promotes healthy aging and extends life span. *Science* **373**:eabc8479. DOI:10.1126/science.abc8479
352. Matsuda S., Revandkar A., Dubash T. D., et al. (2023). TGF-beta in the microenvironment induces a physiologically occurring immune-suppressive senescent state. *Cell Rep.* **42**:112129. DOI:10.1016/j.celrep.2023.112129
353. Kiourtis C., Terradas-Terradas M., Gee L. M., et al. (2024). Hepatocellular senescence induces multi-organ senescence and dysfunction via TGFbeta. *Nat. Cell Biol.* **26**:2075–2083. DOI:10.1038/s41556-024-01543-3
354. Lu H., Jia C., Wu D., et al. (2021). Fibroblast growth factor 21 (FGF21) alleviates senescence, apoptosis, and extracellular matrix degradation in osteoarthritis via the SIRT1-mTOR signaling pathway. *Cell Death Dis.* **12**:865. DOI:10.1038/s41419-021-04157-x
355. Ma S., Ji Z., Zhang B., et al. (2024). Spatial transcriptomic landscape unveils immunoglobulin-associated senescence as a hallmark of aging. *Cell* **187**:7025–7044 e7034. DOI:10.1016/j.cell.2024.10.019
356. Franceschi C., Garagnani P., Parini P., et al. (2018). Inflammaging: A new immune-metabolic viewpoint for age-related diseases. *Nat. Rev. Endocrinol.* **14**:576–590. DOI:10.1038/s41574-018-0059-4
357. Wang B., Han J., Elisseeff J. H., et al. (2024). The senescence-associated secretory phenotype and its physiological and pathological implications. *Nat. Rev. Mol. Cell Biol.* **25**:958–978. DOI:10.1038/s41580-024-00727-x
358. Sladitschek-Martens H. L., Guarnieri A., Brumana G., et al. (2022). YAP/TAZ activity in stromal cells prevents ageing by controlling cGAS-STING. *Nature* **607**:790–798. DOI:10.1038/s41586-022-04924-6
359. Iijima H., Gilmer G., Wang K., et al. (2023). Age-related matrix stiffening epigenetically regulates alpha-Klotho expression and compromises chondrocyte integrity. *Nat. Commun.* **14**:18. DOI:10.1038/s41467-022-35359-2
360. Fu B., Shen J., Zou X., et al. (2024). Matrix stiffening promotes chondrocyte senescence and the osteoarthritis development through downregulating HDAC3. *Bone Res.* **12**:32. DOI:10.1038/s41413-024-00333-9
361. Gilmer G., Iijima H., Hettlinger Z. R., et al. (2025). Menopause-induced 17beta-estradiol and progesterone loss increases senescence markers, matrix disassembly and degeneration in mouse cartilage. *Nat. Aging* **5**:65–86. DOI:10.1038/s43587-024-00773-2
362. Zhang X., Cao D., Xu L., et al. (2023). Harnessing matrix stiffness to engineer a bone marrow niche for hematopoietic stem cell rejuvenation. *Cell Stem Cell* **30**:378–395 e378. DOI:10.1016/j.stem.2023.03.005
363. Sephel G. C. and Davidson J. M. (1986). Elastin production in human skin fibroblast cultures and its decline with age. *J. Invest. Dermatol.* **86**:279–285. DOI:10.1111/1523-1747.ep12285424
364. Skora B. and Szychowski K. A. (2025). Proteostasis and autophagy disruption by the aging-related VGVAPG hexapeptide - preliminary insights into a potential novel elastin-induced neurodegeneration pathway in an in vitro human cellular neuron model. *Neurochem. Int.* **187**:105992. DOI:10.1016/j.neuint.2025.105992
365. Alfonzo M. C., Al Saedi A., Fulzele S., et al. (2022). Extracellular vesicles as communicators of senescence in musculoskeletal aging. *JBMR Plus* **6**:e10686. DOI:10.1002/jbmr.4.10686
366. Sanz-Ros J., Romero-Garcia N., Mas-Bargues C., et al. (2022). Small extracellular vesicles from young adipose-derived stem cells prevent frailty, improve health span, and decrease epigenetic age in old mice. *Sci. Adv.* **8**:eabq2226. DOI:10.1126/sciadv.abq2226
367. Chen X., Luo Y., Zhu Q., et al. (2024). Small extracellular vesicles from young plasma reverse age-related functional declines by improving mitochondrial energy metabolism. *Nat. Aging* **4**:814–838. DOI:10.1038/s43587-024-00612-4
368. Fafian-Labora J. A., Rodriguez-Navarro J. A. and O'Loughlin A. (2020). Small extracellular vesicles have GST activity and ameliorate senescence-related tissue damage. *Cell Metab.* **32**:71–86 e75. DOI:10.1016/j.cmet.2020.06.004
369. Hu S., Li Z., Zhu D., et al. (2026). Microneedle delivery of small extracellular vesicles from young blood to treat endothelial senescence. *Adv. Mater.* **38**:e2418352. DOI:10.1002/adma.202418352
370. Hou J., Chen K. X., He C., et al. (2024). Aged bone marrow macrophages drive systemic aging and age-related dysfunction via extracellular vesicle-mediated induction of paracrine senescence. *Nat. Aging* **4**:1562–1581. DOI:10.1038/s43587-024-00694-0
371. Weise M., De-Levi S., Barnes K. M., et al. (2001). Effects of estrogen on growth plate senescence and epiphyseal fusion. *Proc. Natl. Acad. Sci. USA* **98**:6871–6876. DOI:10.1073/pnas.121180498
372. Chesnokova V., Zhou C., Ben-Shlomo A., et al. (2013). Growth hormone is a cellular senescence target in pituitary and nonpituitary cells. *Proc. Natl. Acad. Sci. USA* **110**:E3331–E3339. DOI:10.1073/pnas.1310589110
373. Chesnokova V., Zonis S., Apostolou A., et al. (2021). Local non-pituitary growth hormone is induced with aging and facilitates epithelial damage. *Cell Rep.* **37**:110068. DOI:10.1016/j.celrep.2021.110068
374. Phillips P. A., Rolls B. J., Ledingham J. G., et al. (1984). Reduced thirst after water deprivation in healthy elderly men. *N. Engl. J. Med.* **311**:753–759. DOI:10.1056/NEJM198409203111202
375. Luckey A. E. and Parsa C. J. (2003). Fluid and electrolytes in the aged. *Arch. Surg.* **138**:1055–1060. DOI:10.1001/archsurg.138.10.1055
376. Farrell M. J., Zamarripa F., Shade R., et al. (2008). Effect of aging on regional cerebral blood flow responses associated with osmotic thirst and its satiation by water drinking: A PET study. *Proc. Natl. Acad. Sci. USA* **105**:382–387. DOI:10.1073/pnas.0710572105
377. Schlanger L. E., Bailey J. L. and Sands J. M. (2010). Electrolytes in the aging. *Adv. Chronic Kidney Dis.* **17**:308–319. DOI:10.1053/j.ackd.2010.03.008
378. Bencivenga L., De Souto Barreto P., Rolland Y., et al. (2022). Blood pressure variability: A potential marker of aging. *Ageing Res. Rev.* **80**:101677. DOI:10.1016/j.arr.2022.101677
379. Higashi Y., Kihara Y. and Noma K. (2012). Endothelial dysfunction and hypertension in aging. *Hypertens. Res.* **35**:1039–1047. DOI:10.1038/hr.2012.138
380. Benetos A., Petrovic M. and Strandberg T. (2019). Hypertension management in older and frail older patients. *Circ. Res.* **124**:1045–1060. DOI:10.1161/CIRCRESAHA.118.313236
381. Majewska J. and Krizhanovsky V. (2025). Immune surveillance of senescent cells in aging and disease. *Nat. Aging* **5**:1415–1424. DOI:10.1038/s43587-025-00910-5
382. Wang T. W., Johmura Y., Suzuki N., et al. (2022). Blocking PD-L1-PD-1 improves senescence surveillance and ageing phenotypes. *Nature* **611**:358–364. DOI:10.1038/s41586-022-05388-4
383. Iltis C., Moskalevska I., Debiesse A., et al. (2025). A ganglioside-based immune checkpoint enables senescent cells to evade immunosurveillance during aging. *Nat. Aging* **5**:219–236. DOI:10.1038/s43587-024-00776-z
384. Cai Y., Wang S., Qu J., et al. (2022). Rejuvenation of tissue stem cells by intrinsic and extrinsic factors. *Stem Cells Transl. Med.* **11**:231–238. DOI:10.1093/stcltm/szab012
385. Brunet A., Goodell M. A. and Rando T. A. (2023). Ageing and rejuvenation of tissue stem cells and their niches. *Nat. Rev. Mol. Cell Biol.* **24**:45–62. DOI:10.1038/s41580-022-00510-w
386. Matteini F., Montserrat-Vazquez S. and Florian M. C. (2024). Rejuvenating aged stem cells: Therapeutic strategies to extend health and lifespan. *FEBS Lett.* **598**:2776–2787. DOI:10.1002/1873-3468.14865
387. Ocampo A., Reddy P., Martinez-Redondo P., et al. (2016). In vivo amelioration of age-associated hallmarks by partial reprogramming. *Cell* **167**:1719–1733 e1712. DOI:10.1016/j.cell.2016.11.052
388. Sun G., Li K., Ping J., et al. (2025). A single-cell transcriptomic atlas reveals senescence and inflammation in the post-tuberculosis human lung. *Nat. Microbiol.* **10**:2073–2091. DOI:10.1038/s41564-025-02050-3
389. Barcena C., Valdes-Mas R., Mayoral P., et al. (2019). Healthspan and lifespan extension by fecal microbiota transplantation into progeroid mice. *Nat. Med.* **25**:1234–1242. DOI:10.1038/s41591-019-0504-5
390. Yan R., Zhang Y., Zhang J., et al. (2025). Soluble N-terminal region of prion protein causes rapid neurodegeneration in prion disease. *Sci. Adv.* **11**:eadw6867. DOI:10.1126/sciadv.adw6867
391. Mathiasen S. L., Gall-Mas L., Pateras I. S., et al. (2021). Bacterial genotoxins induce T cell senescence. *Cell Rep.* **35**:109220. DOI:10.1016/j.celrep.2021.109220

392. Hormaechea-Agulla D., Matallà K. A., Le D. T., et al. (2021). Chronic infection drives Dnmt3a-loss-of-function clonal hematopoiesis via IFN γ signaling. *Cell Stem Cell* **28**:1428–1442 e1426. DOI:10.1016/j.stem.2021.03.002
393. Bodogai M., O'Connell J., Kim K., et al. (2018). Commensal bacteria contribute to insulin resistance in aging by activating innate B1a cells. *Sci. Transl. Med.* **10**:eaat4271. DOI:10.1126/scitranslmed.aat4271
394. Zheng Y., Liu X., Le W., et al. (2020). A human circulating immune cell landscape in aging and COVID-19. *Protein Cell* **11**:740–770. DOI:10.1007/s13238-020-00762-2
395. Wang S., Yao X., Ma S., et al. (2021). A single-cell transcriptomic landscape of the lungs of patients with COVID-19. *Nat. Cell Biol.* **23**:1314–1328. DOI:10.1038/s41556-021-00796-6
396. Peng H., Pfeiffer S., Varynskyi B., et al. (2025). Prion-induced ferroptosis is facilitated by RAC3. *Nat. Commun.* **16**:5385. DOI:10.1038/s41467-025-60793-3
397. Hernandez-Arciga U., Stamenkovic C., Yadav S., et al. (2025). Dietary methionine restriction started late in life promotes healthy aging in a sex-specific manner. *Sci. Adv.* **11**:eads1532. DOI:10.1126/sciadv.ads1532
398. Richardson N. E., Konon E. N., Schuster H. S., et al. (2021). Lifelong restriction of dietary branched-chain amino acids has sex-specific benefits for frailty and life span in mice. *Nat. Aging* **1**:73–86. DOI:10.1038/s43587-020-00006-2
399. Han H. S., Ahn E., Park E. S., et al. (2023). Impaired BCAA catabolism in adipose tissues promotes age-associated metabolic derangement. *Nat. Aging* **3**:982–1000. DOI:10.1038/s43587-023-00460-8
400. Luo T., Zhao L., Feng C., et al. (2025). Asparagine prevents intestinal stem cell aging via the autophagy-lysosomal pathway. *Aging Cell* **24**:e14423. DOI:10.1111/acef.14423
401. Sol J., Fernandez-Bernal A., Mota-Martorell N., et al. (2025). Ether lipids and sphingolipids drive sex-specific human aging dynamics. *Redox Biol.* **85**:103779. DOI:10.1016/j.redox.2025.103779
402. Janssens G. E., Molenaars M., Herzog K., et al. (2024). A conserved complex lipid signature marks human muscle aging and responds to short-term exercise. *Nat. Aging* **4**:681–693. DOI:10.1038/s43587-024-00595-2
403. Li X., Wang J., Wang L., et al. (2022). Lipid metabolism dysfunction induced by age-dependent DNA methylation accelerates aging. *Signal Transduct. Target Ther.* **7**:162. DOI:10.1038/s41392-022-00964-6
404. Roh K., Noh J., Kim Y., et al. (2023). Lysosomal control of senescence and inflammation through cholesterol partitioning. *Nat. Metab.* **5**:398–413. DOI:10.1038/s42255-023-00747-5
405. Pini M., Czibik G., Sawaki D., et al. (2021). Adipose tissue senescence is mediated by increased ATP content after a short-term high-fat diet exposure. *Aging Cell* **20**:e13421. DOI:10.1111/acef.13421
406. Suda M., Shimizu I., Katsuumi G., et al. (2021). Senolytic vaccination improves normal and pathological age-related phenotypes and increases lifespan in progeroid mice. *Nat. Aging* **1**:1117–1126. DOI:10.1038/s43587-021-00151-2
407. Gliniak C. M., Gordillo R., Youm Y. H., et al. (2025). FGF21 promotes longevity in diet-induced obesity through metabolic benefits independent of growth suppression. *Cell Metab.* **37**:1547–1567 e1546. DOI:10.1016/j.cmet.2025.05.011
408. Qu Q., Chen Y., Wang Y., et al. (2025). Lithocholic acid binds TULP3 to activate sirtuins and AMPK to slow down ageing. *Nature* **643**:201–209. DOI:10.1038/s41586-024-08348-2
409. Ma S., Sun S., Geng L., et al. (2020). Caloric restriction reprograms the single-cell transcriptional landscape of Rattus norvegicus aging. *Cell* **180**:984–1001.e1022. DOI:10.1016/j.cell.2020.02.008
410. Acosta-Rodríguez V., Rijo-Ferreira F., Izumo M., et al. (2022). Circadian alignment of early onset caloric restriction promotes longevity in male C57BL/6J mice. *Science* **376**:1192–1202. DOI:10.1126/science.abk0297
411. Hofer S. J. and Madoe F. (2023). Sex- and timing-specific effects of fasting and caloric restriction. *Cell Metab.* **35**:1091–1093. DOI:10.1016/j.cmet.2023.06.001
412. Hu F., Yu L., Tu X., et al. (2025). A high-fiber diet mimics aging-related signatures of caloric restriction in mammals. *Nat. Commun.* **16**:5917. DOI:10.1038/s41467-025-61046-z
413. Voisin S., Seale K., Jacques M., et al. (2024). Exercise is associated with younger methylome and transcriptome profiles in human skeletal muscle. *Aging Cell* **23**:e13859. DOI:10.1111/acef.13859
414. Kang J. S., Kim J. H., Kim M. J., et al. (2025). Exercise-induced CLCF1 attenuates age-related muscle and bone decline in mice. *Nat. Commun.* **16**:4743. DOI:10.1038/s41467-025-59959-w
415. Geng L., Ping J., Wu R., et al. (2025). Systematic profiling reveals betaine as an exercise mimetic for geroprotection. *Cell* **188**:5426–5428. DOI:10.1016/j.cell.2025.07.030
416. Liu L., Kim S., Buckley M. T., et al. (2023). Exercise reprograms the inflammatory landscape of multiple stem cell compartments during mammalian aging. *Cell Stem Cell* **30**:689–705 e684. DOI:10.1016/j.stem.2023.03.016
417. Feng M., Li M., Lou J., et al. (2025). Early-life exercise extends healthspan but not lifespan in mice. *Nat. Commun.* **16**:6328. DOI:10.1038/s41467-025-61443-4
418. Lyons C. E., Pallais J. P., McGonigle S., et al. (2025). Chronic social stress induces p16-mediated senescent cell accumulation in mice. *Nat. Aging* **5**:48–64. DOI:10.1038/s43587-024-00743-8
419. Klopock E. T., Crimmins E. M., Cole S. W., et al. (2022). Social stressors associated with age-related T lymphocyte percentages in older US adults: Evidence from the US Health and Retirement Study. *Proc. Natl. Acad. Sci. USA* **119**:e2202780119. DOI:10.1073/pnas.2202780119
420. Harvanek Z. M., Fogelman N., Xu K., et al. (2021). Psychological and biological resilience modulates the effects of stress on epigenetic aging. *Transl. Psychiatry* **11**:601. DOI:10.1038/s41398-021-01735-7
421. Zhang G., Lian Y., Li Q., et al. (2025). Vagal pathway activation links chronic stress to decline in intestinal stem cell function. *Cell Stem Cell* **32**:778–794.e710. DOI:10.1016/j.stem.2025.02.016
422. Patke A., Young M. W. and Axelrod S. (2020). Molecular mechanisms and physiological importance of circadian rhythms. *Nat. Rev. Mol. Cell Biol.* **21**:67–84. DOI:10.1038/s41580-019-0179-2
423. Mohawk J. A., Green C. B. and Takahashi J. S. (2012). Central and peripheral circadian clocks in mammals. *Annu. Rev. Neurosci.* **35**:445–462. DOI:10.1146/annurev-neuro-060909-153128
424. Takahashi J. S. (2017). Transcriptional architecture of the mammalian circadian clock. *Nat. Rev. Genet.* **18**:164–179. DOI:10.1038/nrg.2016.150
425. Gamble K. L., Berry R., Frank S. J., et al. (2014). Circadian clock control of endocrine factors. *Nat. Rev. Endocrinol.* **10**:466–475. DOI:10.1038/nrendo.2014.78
426. Challet E. (2019). The circadian regulation of food intake. *Nat. Rev. Endocrinol.* **15**:393–405. DOI:10.1038/s41574-019-0210-x
427. Katewa S. D., Akagi K., Bose N., et al. (2016). Peripheral circadian clocks mediate dietary restriction-dependent changes in lifespan and fat metabolism in Drosophila. *Cell Metab.* **23**:143–154. DOI:10.1016/j.cmet.2015.10.014
428. Yamazaki S., Straume M., Tei H., et al. (2002). Effects of aging on central and peripheral mammalian clocks. *Proc. Natl. Acad. Sci. USA* **99**:10801–10806. DOI:10.1073/pnas.152318499
429. Chen C. Y., Logan R. W., Ma T., et al. (2016). Effects of aging on circadian patterns of gene expression in the human prefrontal cortex. *Proc. Natl. Acad. Sci. USA* **113**:206–211. DOI:10.1073/pnas.1508249112
430. Kondratov R. V., Kondratova A. A., Gorbacheva V. Y., et al. (2006). Early aging and age-related pathologies in mice deficient in BMAL1, the core component of the circadian clock. *Genes Dev.* **20**:1868–1873. DOI:10.1101/gad.1432206
431. Kunieda T., Minamino T., Katsuno T., et al. (2006). Cellular senescence impairs circadian expression of clock genes in vitro and in vivo. *Circ. Res.* **98**:532–539. DOI:10.1161/01.RES.0000204504.25798.a8
432. Liang C., Liu Z., Song M., et al. (2021). Stabilization of heterochromatin by CLOCK promotes stem cell rejuvenation and cartilage regeneration. *Cell Res.* **31**:187–205. DOI:10.1038/s41422-020-0385-7
433. Liang C., Ke Q., Liu Z., et al. (2022). BMAL1 moonlighting as a gatekeeper for LINE1 repression and cellular senescence in primates. *Nucleic Acids Res.* **50**:3323–3347. DOI:10.1093/nar/gkac146
434. Jomova K., Raptova R., Alomar S. Y., et al. (2023). Reactive oxygen species, toxicity, oxidative stress, and antioxidants: Chronic diseases and aging. *Arch. Toxicol.* **97**:2499–2574. DOI:10.1007/s00204-023-03562-9
435. Ryan S., Taylor C. T. and McNicholas W. T. (2005). Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. *Circulation* **112**:2660–2667. DOI:10.1161/CIRCULATIONAHA.105.556746
436. Rogers R. S., Wang H., Durham T. J., et al. (2023). Hypoxia extends lifespan and neurological function in a mouse model of aging. *PLoS Biol.* **21**:e3002117. DOI:10.1371/journal.pbio.3002117
437. Ding E., Wang Y., Liu J., et al. (2022). A review on the application of the exposome paradigm to unveil the environmental determinants of age-related diseases. *Hum. Genomics* **16**:54. DOI:10.1186/s40246-022-00428-6
438. Chen S., Liu Y., Yi Y., et al. (2025). Long-term impacts of heatwaves on accelerated ageing. *Nat. Clim. Change* **15**:1000–1007. DOI:10.1038/s41558-025-02407-w
439. Lee H. J., Alirzayeva H., Koyuncu S., et al. (2023). Cold temperature extends longevity and prevents disease-related protein aggregation through PA28 γ -induced proteasomes. *Nat. Aging* **3**:546–566. DOI:10.1038/s43587-023-00383-4
440. King K. E., McCormick J. J. and Kenny G. P. (2025). The effect of 7-day cold water acclimation on autophagic and apoptotic responses in young males. *Adv. Biol. (Weinh.)* **9**:e2400111. DOI:10.1002/adbi.202400111
441. Zhao Z., Cao J., Niu C., et al. (2022). Body temperature is a more important modulator of lifespan than metabolic rate in two small mammals. *Nat. Metab.* **4**:320–326. DOI:10.1038/s42255-022-00545-5
442. Tan C. L. and Knight Z. A. (2018). Regulation of body temperature by the nervous system. *Neuron* **98**:31–48. DOI:10.1016/j.neuron.2018.02.022
443. Cannon B. and Nedergaard J. (2004). Brown adipose tissue: Function and physiological significance. *Physiol. Rev.* **84**:277–359. DOI:10.1152/physrev.00015.2003
444. Berry D. C., Jiang Y., Arpke R. W., et al. (2017). Cellular aging contributes to failure of cold-induced beige adipocyte formation in old mice and humans. *Cell Metab.* **25**:481. DOI:10.1016/j.cmet.2017.01.011
445. Liu Z., Hu W., Tan X., et al. (2026). White adipose atrophy exacerbates cold stress and accelerates aging in male mice. *Nat. Commun.* **17**:5390. DOI:10.1038/s41467-026-71857-3
446. Conti B., Sanchez-Alavez M., Winsky-Sommerer R., et al. (2006). Transgenic mice with a reduced core body temperature have an increased life span. *Science*

- 314:825–828. DOI:10.1126/science.1132191
447. Guijas C., Montenegro-Burke J. R., Cintron-Colon R., et al. (2020). Metabolic adaptation to calorie restriction. *Sci. Signal.* **13**:eabb2490. DOI:10.1126/scisignal.abb2490
448. Gao Y., Sun Y., Frank K. M., et al. (1998). A critical role for DNA end-joining proteins in both lymphogenesis and neurogenesis. *Cell* **95**:891–902. DOI:10.1016/s0092-8674(00)81714-6
449. de Feraudy S., Revet I., Bezrookove V., et al. (2010). A minority of foci or pan-nuclear apoptotic staining of gammaH2AX in the S phase after UV damage contain DNA double-strand breaks. *Proc. Natl. Acad. Sci. USA* **107**:6870–6875. DOI:10.1073/pnas.1002175107
450. Ohira Y., Yoshinaga T., Nomura T., et al. (2002). Gravitational unloading effects on muscle fiber size, phenotype and myonuclear number. *Adv. Space Res.* **30**:777–781. DOI:10.1016/s0273-1177(02)00395-2
451. Scott J. M., Stoudemire J., Dolan L., et al. (2022). Leveraging spaceflight to advance cardiovascular research on earth. *Circ. Res.* **130**:942–957. DOI:10.1161/CIRCRESAHA.121.319843
452. Wu F., Du H., Overbey E., et al. (2024). Single-cell analysis identifies conserved features of immune dysfunction in simulated microgravity and spaceflight. *Nat. Commun.* **15**:4795. DOI:10.1038/s41467-023-42013-y
453. Mao W., Huai Y., An L., et al. (2024). Microgravity inhibits cell proliferation and promotes senescence and apoptosis in embryonic stem cells. *Space Sci. Technol.* **4**:0104. DOI:10.34133/space.0104
454. Huang J., Sun L., Yin Y., et al. (2025). High matrix stiffness triggers testosterone decline in aging males by disrupting stem Leydig cell pool homeostasis. *Cell Rep.* **44**:116207. DOI:10.1016/j.celrep.2025.116207
455. Dutta S., Goodrich J. M., Dolinsky D. C., et al. (2023). Biological aging acceleration due to environmental exposures: An exciting new direction in toxicogenomics research. *Genes (Basel)* **15**:16. DOI:10.3390/genes15010016
456. Khodasevich D., Gladish N., Daredia S., et al. (2025). Exposome-wide association study of environmental chemical exposures and epigenetic aging in the national health and nutrition examination survey. *Aging (Albany N.Y.)* **17**:408–430. DOI:10.18632/aging.206201
457. Maitre L., Bustamante M., Hernandez-Ferrer C., et al. (2022). Multi-omics signatures of the human early life exposome. *Nat. Commun.* **13**:7024. DOI:10.1038/s41467-022-34422-2
458. Peters A., Nawrot T. S. and Baccarelli A. A. (2021). Hallmarks of environmental insults. *Cell* **184**:1455–1468. DOI:10.1016/j.cell.2021.01.043
459. Qian M., Liu Z., Peng L., et al. (2018). Boosting ATM activity alleviates aging and extends lifespan in a mouse model of progeria. *eLife* **7**:e34836. DOI:10.7554/eLife.34836
460. Yu J., Li T. and Zhu J. (2023). Gene therapy strategies targeting aging-related diseases. *Aging Dis.* **14**:398–417. DOI:10.14336/AD.2022.00725
461. Bujarrabal-Dueso A., Sendtner G., Meyer D. H., et al. (2023). The DREAM complex functions as conserved master regulator of somatic DNA-repair capacities. *Nat. Struct. Mol. Biol.* **30**:475–488. DOI:10.1038/s41594-023-00942-8
462. Koblan L. W., Erdos M. R., Wilson C., et al. (2021). In vivo base editing rescues Hutchinson-Gilford progeria syndrome in mice. *Nature* **589**:608–614. DOI:10.1038/s41586-020-03086-7
463. Plesa A. M., Shadpour M., Boyden E., et al. (2023). Transcriptomic reprogramming for neuronal age reversal. *Hum. Genet.* **142**:1293–1302. DOI:10.1007/s00439-023-02529-1
464. Dang W., Steffen K. K., Perry R., et al. (2009). Histone H4 lysine 16 acetylation regulates cellular lifespan. *Nature* **459**:802–807. DOI:10.1038/nature08085
465. Liu B., Ghosh S., Yang X., et al. (2012). Resveratrol rescues SIRT1-dependent adult stem cell decline and alleviates progeroid features in laminopathy-based progeria. *Cell Metab.* **16**:738–750. DOI:10.1016/j.cmet.2012.11.007
466. Liu B., Wang Z., Zhang L., et al. (2013). Depleting the methyltransferase Suv39h1 improves DNA repair and extends lifespan in a progeria mouse model. *Nat. Commun.* **4**:1868. DOI:10.1038/ncomms2885
467. Bernardes de Jesus B., Schneeberger K., Vera E., et al. (2011). The telomerase activator TA-65 elongates short telomeres and increases health span of adult/old mice without increasing cancer incidence. *Aging Cell* **10**:604–621. DOI:10.1111/j.1474-9726.2011.00700.x
468. Bugai A., Quaresma A. J. C., Friedel C. C., et al. (2019). P-TEFb activation by RBM7 shapes a pro-survival transcriptional response to genotoxic stress. *Mol. Cell* **74**:254–267 e210. DOI:10.1016/j.molcel.2019.01.033.
469. Gulen M. F., Samson N., Keller A., et al. (2023). cGAS-STING drives ageing-related inflammation and neurodegeneration. *Nature* **620**:374–380. DOI:10.1038/s41586-023-06373-1
470. Yang J. H., Petty C. A., Dixon-McDougall T., et al. (2023). Chemically induced reprogramming to reverse cellular aging. *Aging (Albany N.Y.)* **15**:5966–5989. DOI:10.18632/aging.204896
471. Labbadia J. and Morimoto R. I. (2015). The biology of proteostasis in aging and disease. *Annu. Rev. Biochem.* **84**:435–464. DOI:10.1146/annurev-biochem-060614-033955
472. Palmer J. E., Wilson N., Son S. M., et al. (2025). Autophagy, aging, and age-related neurodegeneration. *Neuron* **113**:29–48. DOI:10.1016/j.neuron.2024.09.015
473. Jia X., Fan J., Wu X., et al. (2024). A novel metabolomic aging clock predicting health outcomes and its genetic and modifiable factors. *Adv. Sci. (Weinh.)* **11**:e2406670. DOI:10.1002/adv.202406670
474. Upadhyay A. (2021). Natural compounds in the regulation of proteostatic pathways: An invincible artillery against stress, ageing, and diseases. *Acta Pharm. Sin. B.* **11**:2995–3014. DOI:10.1016/j.apsb.2021.01.006
475. Nadeem J., Sultana R., Parveen A., et al. (2025). Recent advances in anti-aging therapeutic strategies targeting DNA damage response and senescence-associated secretory phenotype-linked signaling cascade. *Cell Biochem. Funct.* **43**:e70046. DOI:10.1002/cbf.70046
476. Kain V., Ingle K. A., Kachman M., et al. (2018). Excess ω -6 fatty acids influx in aging drives metabolic dysregulation, electrocardiographic alterations, and low-grade chronic inflammation. *Am. J. Physiol. Heart Circ. Physiol.* **314**:H160–H169. DOI:10.1152/ajpheart.00297.2017
477. Xiong Y., Li X., Liu J., et al. (2024). Omega-3 PUFAs slow organ aging through promoting energy metabolism. *Pharmacol. Res.* **208**:107384. DOI:10.1016/j.phrs.2024.107384
478. Loffredo F. S., Steinhauser M. L., Jay S. M., et al. (2013). Growth differentiation factor 11 is a circulating factor that reverses age-related cardiac hypertrophy. *Cell* **153**:828–839. DOI:10.1016/j.cell.2013.04.015
479. Widjaja A. A., Lim W. W., Viswanathan S., et al. (2024). Inhibition of IL-11 signalling extends mammalian healthspan and lifespan. *Nature* **632**:157–165. DOI:10.1038/s41586-024-07701-9
480. Sola P., Mereu E., Bonjoch J., et al. (2023). Targeting lymphoid-derived IL-17 signaling to delay skin aging. *Nat. Aging* **3**:688–704. DOI:10.1038/s43587-023-00431-z
481. Baker D. J., Wijshake T., Tchkonja T., et al. (2011). Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. *Nature* **479**:232–236. DOI:10.1038/nature10600
482. Baker D. J., Childs B. G., Durik M., et al. (2016). Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. *Nature* **530**:184–189. DOI:10.1038/nature16932
483. Zhu Y., Tchkonja T., Pirtskhalava T., et al. (2015). The Achilles' heel of senescent cells: From transcriptome to senolytic drugs. *Aging Cell* **14**:644–658. DOI:10.1111/acer.12344
484. Yosef R., Pilpel N., Tokarsky-Amiel R., et al. (2016). Directed elimination of senescent cells by inhibition of BCL-W and BCL-XL. *Nat. Commun.* **7**:11190. DOI:10.1038/ncomms11190
485. Xu M., Pirtskhalava T., Farr J. N., et al. (2018). Senolytics improve physical function and increase lifespan in old age. *Nat. Med.* **24**:1246–1256. DOI:10.1038/s41591-018-0092-9
486. Carver C. M., Rodriguez S. L., Atkinson E. J., et al. (2025). IL-23R is a senescence-linked circulating and tissue biomarker of aging. *Nat. Aging* **5**:291–305. DOI:10.1038/s43587-024-00752-7
487. Zhang L., Pitcher L. E., Prahald V., et al. (2023). Targeting cellular senescence with senotherapeutics: Senolytics and senomorphics. *FEBS J.* **290**:1362–1383. DOI:10.1111/febs.16350
488. Yoshida S., Nakagami H., Hayashi H., et al. (2020). The CD153 vaccine is a senotherapeutic option for preventing the accumulation of senescent T cells in mice. *Nat. Commun.* **11**:2482. DOI:10.1038/s41467-020-16347-w
489. Amor C., Feucht J., Leibold J., et al. (2020). Senolytic CAR T cells reverse senescence-associated pathologies. *Nature* **583**:127–132. DOI:10.1038/s41586-020-2403-9
490. Yang D., Sun B., Li S., et al. (2023). NKG2D-CAR T cells eliminate senescent cells in aged mice and nonhuman primates. *Sci. Transl. Med.* **15**:eadd1951. DOI:10.1126/scitranslmed.add1951
491. Eskiocak O., Gewolb J., Shah V., et al. (2025). Anti-uPAR CAR T cells reverse and prevent aging-associated defects in intestinal regeneration and fitness. *Nat. Aging* **6**:108–126. DOI:10.1038/s43587-025-01022-w
492. Sun S., Meng Y., Li M., et al. (2023). CD133(+) endothelial-like stem cells restore neovascularization and promote longevity in progeroid and naturally aged mice. *Nat. Aging* **3**:1401–1414. DOI:10.1038/s43587-023-00512-z
493. Lei J., Xin Z., Liu N., et al. (2025). Senescence-resistant human mesenchymal progenitor cells counter aging in primates. *Cell* **188**:5039–5061 e5035. DOI:10.1016/j.cell.2025.05.021.
494. Jeon O. H., Mehdiipour M., Gil T. H., et al. (2022). Systemic induction of senescence in young mice after single heterochronic blood exchange. *Nat. Metab.* **4**:995–1006. DOI:10.1038/s42255-022-00609-6
495. Shiels P. G., Painer J., Natterson-Horowitz B., et al. (2021). Manipulating the exposome to enable better ageing. *Biochem. J.* **478**:2889–2898. DOI:10.1042/BCJ20200958
496. Kalia V., Belsky D. W., Baccarelli A. A., et al. (2022). An exposomic framework to uncover environmental drivers of aging. *Exposome* **2**:osac002. DOI:10.1093/exposome/osac002

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The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

Not applicable.

DATA AND CODE AVAILABILITY

No new data were created or analyzed in this study. Data sharing is not applicable to this article.