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Epigenetic-Based Therapeutics for Aging: Uncovering Mechanisms and Advancing Interventions for Disorders That Emerge with Age

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ABSTRACT

Aging arises from a complex convergence of inherited influences and lifelong environmental exposures, with epigenetic remodeling positioned at the core of this process. Disruptions in DNA methylation landscapes, altered activity of histone-modifying regulators such as SIRT1 and EZH2, and shifts in non-coding RNA pathways collectively rewire transcriptional programs that govern essential functions, including senescence control and mitochondrial integrity. These changes form a mechanistic "environment–epigenome–pathology" continuum that underlies diverse age-associated conditions, ranging from β-amyloid accumulation in Alzheimer's disease to atherosclerotic progression, immune aging, bone and muscle degeneration, and cancer development. Because epigenetic marks are fundamentally reversible, the field of epigenetic pharmacology has gained prominence as a strategy to counteract aging biology and related disorders. Manipulating pivotal regulators—such as DNA methyltransferases and histone deacetylases—offers a means to reset maladaptive epigenetic states implicated in disease. This review brings together current knowledge on how epigenetic mechanisms shape aging trajectories, their involvement in major age-linked diseases, and recent progress in developing epigenetic-based therapeutics from foundational studies through clinical advancement. It also evaluates key translational barriers, including precision of target engagement, durability of treatment, and delivery to specific tissues, with the goal of supporting future approaches for diagnosing and treating age-associated disorders.

Keywords: Epigenetic modifiers, Aging, Epigenetics, DNA methylation, Age-related diseases, Pharmacological epigenetics

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Introduction

The rapid shift in global demographics over the past several decades has positioned population aging and the surge in age-associated disorders as defining public health concerns of the 21st century. Estimates from the World Health Organization indicate that individuals aged 60 and above increased from roughly 600 million in 2000 to 1 billion in 2023, with projections reaching 2.1 billion by 2050—representing nearly one-fifth of the world's population [1]. This demographic expansion is paralleled by escalating rates of chronic, age-linked illnesses, such as cardiovascular diseases, neurodegenerative disorders including Alzheimer's disease (AD) and Parkinson's disease (PD), various cancers, type 2 diabetes mellitus (T2DM), immune decline, skeletal degeneration, and conditions rooted in mitochondrial impairment [2]. These disorders substantially elevate disability in older adults, shorten healthy lifespan, and impose unsustainable demands on healthcare systems. In the United States alone, chronic and mental health conditions consume 90% of the nation's $4.9 trillion healthcare expenditure [3]. Global socioeconomic stability is also threatened: projections suggest a 13-million shortfall in long-term care workers by 2050, and in several industrialized nations, individuals aged ≥65 already surpass 28% of the adult population, straining pension systems and long-term economic resilience [4, 5]. These trends underscore the urgent need to dissect the biological foundations of aging and formulate targeted strategies to mitigate its health impacts.

Biologically, aging unfolds as a multidimensional process marked by accumulating functional deficits at the cellular, tissue, and organ levels. Classical aging research describes 12 hallmarks—including genomic instability, telomere attrition, epigenetic remodeling, loss of proteostasis, impaired autophagy, perturbed nutrient signaling, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, disrupted intercellular communication, chronic inflammation, and microbiome imbalance [6]. In 2025, this framework expanded to 14 hallmarks with the addition of extracellular matrix remodeling and psychosocial isolation [7]. Of these hallmarks, epigenetic alterations stand out as a dynamic interface through which genetic background interacts with environmental exposures to shape aging trajectories. Epigenetics modulates gene activity primarily through three interconnected mechanisms: DNA methylation, histone post-translational modifications (such as acetylation and methylation), and regulatory non-coding RNAs—including miRNAs and lncRNAs [7].

Typical age-associated DNA methylation changes include hypermethylation of CpG islands and global DNA hypomethylation—patterns which contribute to transcriptomic shifts that can activate the senescence-associated secretory phenotype (SASP) [8]. Similarly, alterations in histone-regulating enzymes such as SIRT1 and EZH2 affect telomeric maintenance and mitochondrial homeostasis, embedding these enzymes directly within core aging pathways [8, 9]. Environmental influences—ranging from dietary modulation and pollutants to persistent inflammation—can also induce heritable or age-dependent epigenetic transitions, contributing to an "environment–epigenome–disease" continuum [10, 11]. In disease-focused investigations, epigenetic disturbances have been implicated in β-amyloid buildup in AD, phenotypic modulation of vascular smooth muscle cells in atherosclerosis, and widespread genomic instability in cancer. These associations highlight both the malleability of epigenetic landscapes and the opportunity to exploit them in early diagnostics and therapeutic target discovery [12-16].

Owing to the reversible character of epigenetic marks, pharmacological epigenetics has emerged as a leading approach for reshaping disease-associated gene regulatory environments. This field integrates medicinal chemistry, molecular biology, and high-resolution epigenomics to examine how agents such as DNA methyltransferase (DNMT) inhibitors (e.g., decitabine), histone deacetylase (HDAC) inhibitors (e.g., vorinostat), and RNA-based therapeutics can remodel aberrant epigenetic states [13, 17]. At the experimental level, the combination of organoid technologies with advanced mapping tools—such as ATAC-seq and ChIP-seq—has enabled unprecedented insight into drug-induced chromatin dynamics [13, 15, 18]. Clinically, epigenetic drugs have already transformed the treatment landscape for hematologic malignancies [19]. DNMT inhibitors, for instance, have shown substantial efficacy in myelodysplastic syndromes (MDS), with oral decitabine–cedazuridine demonstrating pharmacological equivalence to intravenous dosing [20]. Expanding these therapies beyond oncology remains challenging, though ongoing trials exploring combinations such as HDAC inhibitors with immunotherapy (e.g., NCT03298905, gov.uk, 2025[21]) show promise. Meanwhile, experiments on reprogramming epigenetic aging signatures—such as DNA methylation age—have achieved partial tissue rejuvenation in mouse models, offering proof that the aging process may be modifiable [22]. Nevertheless, obstacles remain: specificity of target engagement, long-term safety, and effective tissue-targeted delivery continue to restrict broader application of epigenetic therapeutics.

This review aims to comprehensively examine the central components of epigenetic regulation, explore how DNA methylation, histone modifications, and non-coding RNAs orchestrate gene expression, and detail how dysregulated epigenetic mechanisms contribute to disorders such as AD and cancer **(Figure 1)**. Additionally, the review highlights cutting-edge progress in epigenetic pharmacology across both foundational research and clinical development while outlining current barriers and future directions needed to fully harness epigenetic interventions for aging and age-related diseases.

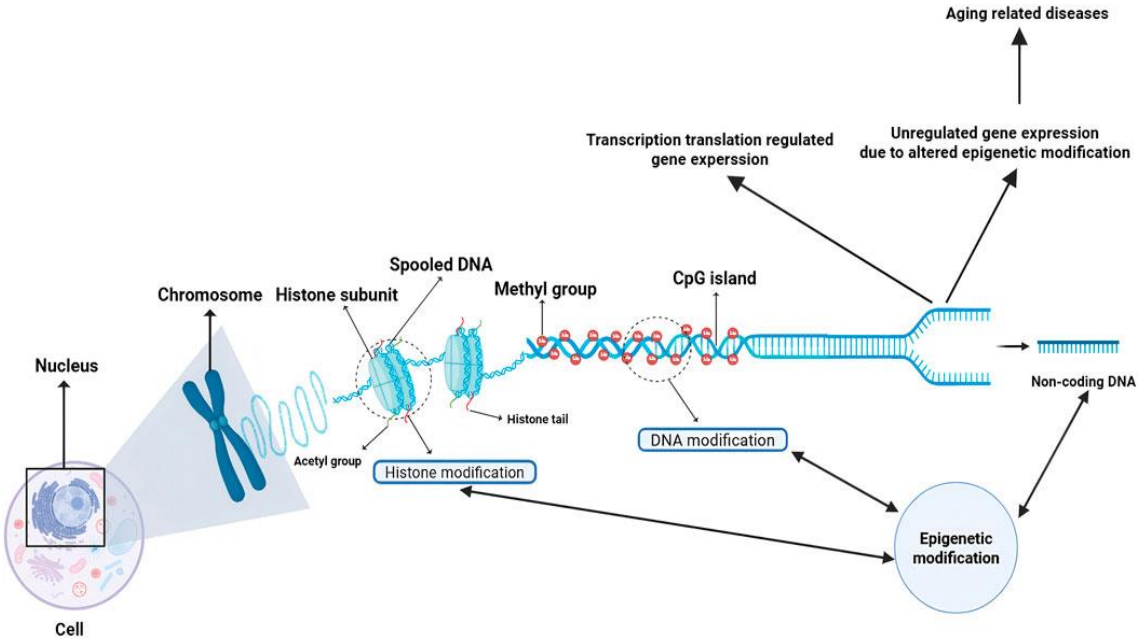

Figure 1. Diagram of epigenetic regulation and its implications in aging-related disorders

This schematic illustrates how epigenetic mechanisms orchestrate gene regulation within the nucleus. DNA is organized around histone proteins to form chromatin structures. Gene activity is controlled through: (i) histone modifications, including acetylation and methylation of histone tails, mediated by enzymes such as HATs and HDACs, which influence chromatin accessibility; (ii) DNA methylation at CpG sites, catalyzed by DNA methyltransferases (DNMTs), generally repressing transcription; and (iii) non-coding RNAs transcribed from non-coding genomic regions, providing additional post-transcriptional regulatory layers. Dysregulation of these mechanisms disrupts normal gene expression, contributing to the onset and progression of numerous age-related conditions, including cancer, neurodegenerative disorders, cardiovascular diseases, immune dysfunction, and metabolic syndromes [23]. (Created with BioRender.com)
Abbreviations: HATs, Histone Acetyltransferases; HDACs, Histone Deacetylases; DNMTs, DNA Methyltransferases.

Epigenetic advances and therapeutic applications in age-related diseases
DNA methylation and the epigenetic clock
Epigenetic regulation, particularly DNA methylation, has gained increasing recognition as a pivotal factor in aging research. DNA methylation involves the covalent addition of a methyl group to the 5-carbon of cytosine residues, predominantly within CpG dinucleotides, a process catalyzed by DNMTs. These modifications modulate gene expression patterns, shaping cellular behavior and fate decisions. Aging is accompanied by widespread alterations in DNA methylation, which correlate with functional decline and represent potential intervention points for epigenetic-based anti-aging strategies [24, 25].
The link between DNA methylation and aging was initially observed in yeast, where age-associated shifts in histone modifications and DNA methylation altered transcriptional programs, accelerating cellular senescence [26]. In mammals, this relationship is more complex. Horvath's "epigenetic clock" estimates biological age by assessing methylation at specific CpG sites, demonstrating remarkable consistency across tissues and reflecting individual health status and disease susceptibility [27, 28].
Mechanistically, aging typically involves global hypomethylation accompanied by hypermethylation at specific gene promoters, leading to transcriptional silencing. Polycomb Repressive Complex 2 (PRC2) contributes to stem cell aging by catalyzing H3K27 trimethylation, thereby reinforcing DNA methylation at target loci [29]. Age-related increases in PRC2-targeted methylation are strongly associated with stem cell functional decline [30]. Additionally, methylation dynamics at CTCF binding sites influence the maintenance of hemimethylated DNA, further altering gene regulatory networks over time [31].
DNA methylation alterations are not limited to cellular aging but also intersect with age-related diseases. For example, patients with progeria exhibit DNA repair mutations that drive abnormal methylation and accelerated

aging [32]. In murine models with impaired DNA repair, methylation age is elevated, emphasizing the interplay between DNA damage and epigenetic regulation [33]. Furthermore, methylation changes are implicated in the pathogenesis of inflammation, metabolic disorders, and cancer [34].

The epigenetic clock provides a framework for interventions aimed at reversing or slowing aging. Cellular reprogramming techniques can reset DNA methylation patterns, partially rejuvenating aged cells [35]. Lifestyle interventions, including dietary restriction, and pharmacological approaches have also been shown to slow the progression of methylation-based clocks [36, 37]. These findings highlight the therapeutic potential of modulating DNA methylation to delay aging and reduce susceptibility to age-associated diseases.

Despite these advances, several challenges remain. The causal relationship between DNA methylation changes and aging is not fully resolved, and tissue- and cell-type-specific variations in methylation complicate the development of unified aging models [38, 39].

In conclusion, DNA methylation is a central mechanism in epigenetic regulation of aging. Epigenetic clocks offer powerful tools for aging research and potential therapeutic targets, but future studies must clarify the mechanisms driving methylation changes and evaluate their translational applications in anti-aging interventions.

Dynamic alterations in histone modifications

Histones are positively charged DNA-binding proteins enriched in lysine and arginine that serve as the structural core around which DNA is packaged to form chromatin. Maintaining a dynamic equilibrium of histone modification states is essential for proper epigenetic regulation throughout aging. By modulating chromatin compaction, these modifications directly affect transcriptional activity and a range of cellular processes, playing a pivotal role in senescence and age-associated organ dysfunction [38]. Among the most critical modifications are acetylation—largely controlled by HDACs and SIRT family proteins—and methylation at key residues, such as H3K27me3 and H3K4me3, both of which are closely linked to lifespan regulation and age-related functional decline.

At the molecular level, specific imbalances in histone modifications during aging disrupt genomic and cellular homeostasis. For instance, H3K4me3 can accumulate abnormally, particularly under energy stress, which may induce aberrant transcriptional elongation, promote R-loop formation, and compromise genome integrity [40]. Meanwhile, histone acetylation generally declines, especially within ribosomal DNA regions. Reduced activity of the deacetylase Sir2 destabilizes rDNA, leading to excessive rRNA production and proteostatic collapse, a defect that intensifies with age [41]. Additionally, abnormal H4K20 methylation perturbs the balance of BRCA1 and 53BP1 at stalled replication forks, promoting nascent DNA degradation, genomic instability, and accelerated cellular senescence [42, 43].

Histone modifications operate within intricate regulatory networks that influence aging by coordinating chromatin accessibility and transcriptional silencing. Histone demethylases target core longevity pathways, such as the insulin/IGF-1 signaling cascade, thereby affecting lifespan regulation. Members of the SIRT family, possessing deacetylase and ADP-ribosyltransferase activity, are essential for healthy aging. Overexpression of SIRT1 in transgenic mice enhances genomic stability and metabolic efficiency without extending lifespan [38], while mitochondrial SIRT3 restores regenerative capacity in aged hematopoietic stem cells and mediates dietary restriction benefits. SIRT6 demonstrates bidirectional regulation: knockout accelerates aging, whereas overexpression prolongs lifespan by coupling chromatin dynamics to DNA repair and metabolism. Conversely, SIRT7 deficiency results in genomic instability and metabolic dysfunction, producing progeroid phenotypes. Knockdown of histone acetyltransferase KAT7 in human stem cells reduces H3K14ac levels, alleviating senescence markers, and delivery of Cas9/sg-KAT7 via lentiviral vectors mitigates liver aging and extends survival in both normal and progeroid mice. Pharmacological manipulation, including HAT inhibitors and HDAC activators that enhance SIRT1 activity, has similarly shown potential to improve aging phenotypes and promote longevity [38, 42].

Histone modification imbalances are tightly connected to age-related pathologies. In neurodegenerative diseases, aberrant methylation of H3K9 and H3K27 disrupts gene silencing, contributing to neuronal loss [44]. In cancers such as melanoma, dysregulated histone modifications accelerate tumor progression by reshaping transcriptional programs [44]. As a result, targeting histone modifications through HDAC inhibitors or HMT inhibitors has become a key strategy for anti-aging interventions and treatment of age-associated diseases [38, 45].

Emerging technologies, including single-cell imaging and microfluidic platforms, reveal increased heterogeneity in histone modifications in senescent cells, linking these changes to rDNA instability and mitochondrial

dysfunction [41]. Protein engineering and chromatin reconstitution approaches further allow precise analysis of histone modification effects at the molecular level, providing a foundation for therapeutic exploration [35]. Despite growing recognition of histone modifiers in aging, it remains unclear whether their beneficial effects are mediated solely through epigenetic mechanisms such as chromatin remodeling, or also via DNA repair, genomic stability, and transcriptional reprogramming of metabolic and signaling pathways. Future studies must dissect these multi-layered regulatory networks to guide targeted interventions for age-related diseases [38, 42, 44].

Regulatory networks of non-coding RNAs

Non-coding RNAs (ncRNAs), which do not code for proteins, have emerged as key regulators within the complex network controlling aging and age-related processes. Advances in high-throughput sequencing and bioinformatics have revealed the diverse forms and functions of ncRNAs, highlighting their critical contributions to age-associated pathologies and offering novel avenues for understanding aging mechanisms and developing anti-aging strategies.

Among ncRNAs, long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) are the most extensively studied. lncRNAs regulate gene expression through multiple mechanisms. For instance, in neurons, the lncRNA UBE3A-ATS silences the paternal UBE3A allele in cis, a process implicated in neurodevelopmental disorders like Angelman syndrome [46]. lncRNAs can also modulate mRNA translation and degradation by forming ribonucleoprotein (RNP) condensates, whose composition and function change with age, leading to selective inhibition of mRNA translation and altered cellular homeostasis [47]. miRNAs primarily bind to the 3′ untranslated regions of target mRNAs, inducing degradation or translational repression, enabling fine-tuned control of gene expression. Age-related changes in miRNA profiles are linked to phenotypes such as inflammation, apoptosis, and metabolic dysfunction [48]. For example, miR-346 participates in transcriptional regulation and DNA repair, and its dysregulation is associated with age-related diseases including prostate cancer [49]. miRNAs also hold promise as biomarkers for monitoring aging and evaluating therapeutic interventions [48, 50].

Other ncRNAs, such as circular RNAs (circRNAs) and small nucleolar RNAs (snoRNAs), also contribute to aging regulation. CircRNAs can act as miRNA sponges or interact with RNA-binding proteins to modulate gene expression and signaling pathways [50]. SnoRNAs primarily guide rRNA modification and processing, and their dysfunction can disrupt ribosome homeostasis, promoting cellular senescence [46]. For instance, the Snord115 cluster regulates UBE3A-ATS expression, influencing UBE3A silencing in neurons and presenting a potential therapeutic target for Angelman syndrome. ncRNAs can impact gene expression and cell fate by modulating DNA methylation, histone modifications, and chromatin structure. The lncRNA ncRNA-a3, for example, recruits the p300/BRG1 complex to the TAL1 locus, activating erythroid-specific transcription programs crucial for red blood cell differentiation [51]. ncRNAs can also stabilize genomic integrity and influence senescence via R-loop formation and regulation of transposon activity, as seen with Pbp1/ATXN2, which limits RNA-DNA hybrid accumulation to maintain rDNA stability and delay senescence.

Therapeutically, ncRNAs offer promising strategies for age-related diseases. RNA-based interventions targeting miRNAs and lncRNAs have applications in cancer, cardiovascular disease, and neurodegeneration [52, 53]. Antisense oligonucleotides (ASOs) or RNA mimics can precisely modulate ncRNA activity to influence disease progression [52]. Additionally, ncRNAs serve as non-invasive liquid biopsy biomarkers for monitoring aging and health status [50, 54]. Nevertheless, challenges remain: the diverse and context-dependent roles of ncRNAs, their tissue-specific expression, and incomplete understanding of interactions with other epigenetic regulators complicate clinical translation [48, 55].

In conclusion, ncRNAs are versatile regulators of aging, influencing gene expression, cellular homeostasis, and genomic integrity. Research on ncRNAs not only deepens our understanding of molecular aging mechanisms but also provides innovative avenues for anti-aging interventions. Future technological advances and mechanistic studies will likely expand their potential for diagnosing, monitoring, and treating age-related diseases, underscoring their promise as targets for promoting healthy longevity. These findings emphasize that miRNAs and other ncRNAs are central both to the aging process and to therapeutic strategies aimed at delaying age-related pathologies.

Degradation of three-dimensional chromatin structure: heterochromatin loss, lamin dysfunction, and genomic instability

The deterioration of the three-dimensional (3D) architecture of chromatin—commonly referred to as chromatin remodeling—is a pivotal area of study in aging epigenetics. By reshaping chromatin's spatial organization, this process exerts direct control over gene expression programs, thereby influencing cellular aging and the functional decline of tissues and organs. Key hallmarks of chromatin remodeling include heterochromatin loss and nuclear lamina dysfunction, which together promote genomic instability and act as major epigenetic drivers of aging and associated pathologies [56, 57].

Heterochromatin, a densely packed and transcriptionally silent chromatin region, progressively deteriorates during aging. It is classified into facultative heterochromatin, marked by H3K27me3, and constitutive heterochromatin, marked by H3K9me3. These subtypes undergo distinct remodeling: facultative heterochromatin often shifts from repressive B compartments to transcriptionally active A compartments, while constitutive heterochromatin strengthens internal self-interactions [57]. This compartment switching increases chromatin accessibility, leading to the inappropriate expression of normally silenced genes, including early developmental genes and repetitive sequences. Aging also increases accessibility at CTCF binding sites, promoting the formation of novel chromatin loops and further disrupting 3D genome organization [57]. Regulatory proteins such as heterochromatin protein 1a (HP1a), Polycomb group proteins, and PIN1 prolyl isomerase are crucial in this context. HP1a loss shortens lifespan in invertebrates, whereas its overexpression extends both healthspan and lifespan. PIN1 stabilizes heterochromatin across species, with deficiencies linked to premature aging and neurodegeneration; conversely, preserved PIN1 function delays heterochromatin relaxation [57]. Aging-associated histone modifications, including elevated H3K36me2 and reduced H3K27me3, further promote chromatin relaxation, accelerating heterochromatin breakdown and facilitating aberrant gene activation, including stem cell–related and potentially oncogenic genes [56].

Lamin dysfunction constitutes another critical aspect of 3D chromatin deterioration. The nuclear lamina anchors heterochromatin and genomic regions at the inner nuclear membrane. Lamina abnormalities disrupt this spatial organization, causing heterochromatin detachment and mislocalization, which, together with heterochromatin loss, blurs chromatin compartment boundaries and disrupts topologically associating domains (TADs). Such structural disorganization deregulates transcriptional programs, including inappropriate activation of senescence-associated secretory phenotype (SASP) genes, thereby accelerating cellular senescence [56, 57].

A direct consequence of 3D chromatin disruption is heightened genomic instability. Heterochromatin loss activates repetitive elements such as LTR retrotransposons and satellite DNA, whose aberrant amplification threatens genomic integrity [57]. Structural disruptions, including TAD disintegration and compartment fusion, impair recruitment of DNA repair proteins (e.g., BRCA1, 53BP1), leading to DNA damage accumulation and a feedback loop of structural disorder and accelerated aging [56, 57].

The degradation of 3D chromatin architecture is closely linked to age-related diseases. In Alzheimer's disease, compromised compartmental boundaries and domain fusion correlate with reduced expression of neuronal genes essential for synaptic maintenance, exacerbating neurodegeneration [58]. In cancers such as lymphoma, histone H1 mutations induce large-scale chromatin decompaction, activating developmental genes and driving tumorigenesis [56].

Technological advances have facilitated the detailed analysis of chromatin remodeling. Single-cell techniques like Droplet Hi-C allow mapping of 3D genome structures in heterogeneous tissues, capturing age-related structural changes [59]. Computational tools such as C.Origami predict 3D chromatin architecture from DNA sequences and accessibility data, enabling high-throughput identification of regulatory factors [60]. Nevertheless, challenges remain, including elucidating causal links between chromatin factors (e.g., HP1a, PIN1) and mammalian lifespan, clarifying lamin–chromatin interactions, and translating structural interventions into therapeutic strategies for aging-related diseases.

In summary, the deterioration of 3D chromatin architecture—marked by heterochromatin loss, laminopathy, and genomic instability—constitutes a central epigenetic mechanism of aging. Investigating these processes deepens our understanding of the molecular basis of aging and highlights potential targets for interventions aimed at delaying age-related pathologies, including neurodegeneration and cancer. Future research should focus on conserved chromatin remodeling mechanisms, regulatory network mapping, and translational strategies to support healthy longevity.

Suppression of retrotransposons

Retrotransposons, particularly Long Interspersed Nuclear Element-1 (LINE-1 or L1), are key players in the epigenetic regulation of aging. These elements, which constitute roughly 17% of the human genome, propagate via a "copy-and-paste" mechanism using their self-encoded ORF1 and ORF2 proteins to reverse transcribe RNA and integrate it into new genomic locations [61, 62]. While retrotransposons have historically contributed to genomic diversity and evolution, their aberrant activation during aging and in neurodegenerative diseases is strongly linked to DNA damage, mutations, and inflammatory responses [63, 64].

Epigenetic dysregulation is a primary trigger for retrotransposon activation in aging. Age-related global DNA hypomethylation, particularly in repetitive sequences such as LINE-1 and Alu elements, leads to their reactivation [65, 66]. In aged human umbilical vein endothelial cells (HUVECs) and skin fibroblasts (NHDFs), LINE-1 and Alu RNA levels increase markedly, accompanied by higher cytoplasmic DNA copy numbers from reverse-transcribed retrotransposons, exacerbating genomic instability [67, 68]. Chromatin remodeling further regulates retrotransposon activity, as aging-associated heterochromatin de-condensation can lift the silencing of these elements [69]. SIRT6, for example, mono-ADP-ribosylates KAP1, facilitating its interaction with HP1 to package LINE-1 DNA into transcriptionally repressive heterochromatin. SIRT6 deficiency results in LINE-1 activation, increased DNA damage, and genomic instability, highlighting the link between retrotransposon activity and age-associated pathology [70, 71].

Emerging strategies to suppress retrotransposons have demonstrated potential for delaying aging and mitigating age-related disease. Inhibition of LINE-1 via antiretroviral drugs or RNA interference alleviates progeroid phenotypes in SIRT6-deficient mice [72]. Epigenetic drugs, including DNMT and HDAC inhibitors, can re-establish retrotransposon silencing, reducing their contribution to genomic instability and inflammatory responses [73]. However, research is complicated by the intricate epigenetic and chromatin-based regulation of retrotransposons and their tissue-specific activity. For instance, neuronal LINE-1 activity differs from that in other tissues, as observed in Huntington's disease mouse models where elevated LINE-1 copy numbers in the brain correlate with disease progression [74, 75].

Retrotransposon reactivation is increasingly recognized as a contributor to aging in complex organisms. In senescent cells, LINEs and SINEs become derepressed, causing genomic and epigenetic alterations and activating immune pathways [64]. Epigenetic derepression of LINE-1 RNA reduces Suv39H1 activity, lowering H3K9me3 levels and heterochromatin integrity, while reverse-transcribed LINE-1 cDNA triggers the cGAS/STING/interferon pathway. Treatment with nucleoside reverse transcriptase inhibitors (NRTIs) suppresses retrotransposition, extending lifespan and healthspan in SIRT6-deficient mice and improving musculoskeletal phenotypes. Antisense oligonucleotide (ASO) therapy targeting retrotransposons similarly prolongs lifespan in progeroid models. Notably, rare SIRT6 variants in centenarians exhibit enhanced LINE-1 suppression, improved genomic stability, and greater apoptosis induction in cancer cells compared to wild-type SIRT6, underscoring a causal role for retrotransposons in aging. Targeting retrotransposon activity may therefore offer promising avenues for extending healthspan and treating age-related diseases.

Gene expression changes

Epigenetic regulation ultimately converges on the dynamic control of gene expression, which is profoundly altered during aging. Over time, the cellular transcriptional network becomes increasingly imbalanced, accompanied by heightened transcriptional noise, aberrant mRNA synthesis, and defects in mRNA maturation. Core epigenetic mechanisms—DNA methylation, histone modifications, and non-coding RNA (ncRNA) regulation—collectively reshape the transcriptional landscape, leading to diminished cellular function and disrupted tissue homeostasis. These changes, influenced by both environmental exposures and technological advances, provide critical insights into the molecular underpinnings of aging and the development of interventions for age-related diseases [76-78].

Environmental factors further modulate gene expression during aging by altering DNA methylation patterns and histone modification states, thereby accelerating the progression of the epigenetic clock. Concurrently, technological innovations—such as microarrays, single-cell transcriptomics, plasma proteomics, and CRISPR-dCas9-based epigenome editing (CRISPRa/CRISPRi)—offer unprecedented resolution for profiling age-associated transcriptional changes [79, 80]. For example, single-cell analyses reveal heterogeneity in gene expression across individual cells and tissues, while CRISPR-dCas9 tools allow experimental simulation of age-related methylation changes and their functional consequences. Studies in mice have shown that aging leads to widespread transcriptional remodeling across multiple organs, affecting inflammatory pathways, protein folding,

extracellular matrix maintenance, and mitochondrial function. Reduced efficiency in transcriptional and post-transcriptional regulation further disrupts proteostasis, highlighting new targets for anti-aging interventions.

Dysregulated epigenetic control of gene expression is also closely linked to age-related diseases. In Alzheimer's disease (AD), hypermethylation of gene promoters leads to downregulation of synaptic and neuronal function genes, exacerbating cognitive decline. Similarly, in cancer, epigenetic silencing of tumor suppressor genes drives tumor progression and malignancy [12, 81, 82].

In summary, epigenetic regulation of gene expression during aging involves the coordinated action of multiple modifications, influenced by both environmental and technological factors. Future research should aim to disentangle the complexity of these regulatory networks and develop precision interventions based on epigenetic editing, providing both theoretical foundations and translational potential for delaying aging and mitigating age-related diseases [83, 84].

Epigenetic advances and therapeutic implications in age-related diseases

Epigenetics plays a pivotal role in both the onset and progression of aging and associated disorders, orchestrating gene expression and cellular function through DNA methylation, diverse histone modifications (acetylation, ubiquitination, methylation), and ncRNA-mediated mechanisms. Mounting evidence implicates epigenetic dysregulation in the pathogenesis of multiple age-related conditions, including cancer, metabolic diseases such as type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVDs), neurodegenerative disorders, and immune dysfunction **(Figure 2)**. These diseases arise from complex molecular perturbations in which epigenetic imbalance disrupts homeostatic cellular networks, precipitating functional decline. Importantly, because epigenetic changes are theoretically reversible, they present promising avenues for the development of novel anti-aging and disease-modifying therapies. The following sections delve into the specific epigenetic mechanisms underlying age-related diseases, highlighting their contribution to disease pathology and potential as therapeutic targets.

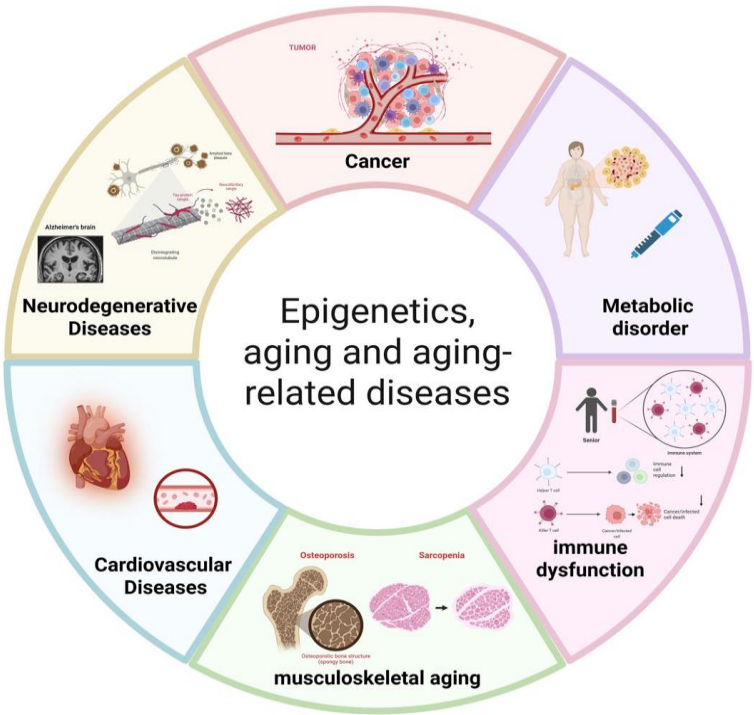

Figure 2. Central role of epigenetic dysregulation in aging and age-related diseases. This illustration depicts how age-related epigenetic changes contribute to the development of major disease groups: Cancer: driven by global DNA hypomethylation and hypermethylation of tumor suppressor gene promoters (e.g., p16INK4a, RASSF1A); Metabolic disorders (e.g., T2DM): linked to methylation changes in insulin-signaling genes (e.g., INS promoter) and overexpression of HDACs; Immune dysfunction: involving DNA methylation alterations in immune-related genes (e.g., IL-7Rα) and imbalanced histone modifications; Musculoskeletal aging (e.g., osteoporosis, sarcopenia): associated with methylation of osteogenic genes (e.g., RUNX2, SOST) and miRNA dysregulation (e.g., miR-29); Cardiovascular diseases: influenced by methylation of vascular genes

(e.g., NOS3, ABCA1) and HDAC-driven chromatin remodeling; Neurodegenerative diseases (e.g., Alzheimer's, Parkinson's, Huntington's): linked to DNA methylation abnormalities in synaptic genes, histone deacetylation, and non-coding RNA dysregulation [9]. Abbreviations: LINE-1, Long Interspersed Nuclear Element-1; p16INK4a, Cyclin-Dependent Kinase Inhibitor 2A; RASSF1A, Ras Association Domain Family Member 1A; INS, Insulin; HDAC, Histone Deacetylase; PPARγ, Peroxisome Proliferator-Activated Receptor γ; IL-7Rα, Interleukin-7 Receptor α; IFN-γ, Interferon γ; RUNX2, Runt-Related Transcription Factor 2; SOST, Sclerostin; miR-29, microRNA-29; NOS3, Nitric Oxide Synthase 3; ABCA1, ATP-Binding Cassette Sub-Family A Member 1; SERCA2a, Sarcoplasmic Reticulum Calcium ATPase 2a; BDNF, Brain-Derived Neurotrophic Factor; miR-132, microRNA-132. (Created with BioRender.com).

Neurodegenerative diseases

Aging is a primary contributor to the onset of neurodegenerative disorders such as Alzheimer's Disease (AD), Parkinson's Disease (PD), and Huntington's Disease (HD), and mounting evidence highlights the pivotal role of epigenetic mechanisms in their pathogenesis, forming the basis of "neuroepigenetics." DNA methylation, a central epigenetic regulator, is involved in gene silencing and crucially supports memory formation, with DNMT1, DNMT3A, and DNMT3B being key for normal brain function.

In PD, the hallmark pathology is dopaminergic neuron loss in the substantia nigra and alpha-synuclein (SNCA) aggregation. Epigenetic dysregulation in PD centers on SNCA promoter methylation imbalances and reduced histone acetylation. Hyper-methylation of the SNCA promoter has been observed in alcohol-dependent anorexia patients, leading to decreased expression, whereas inhibition of DNMT activity restores SNCA expression, indicating fine-tuning by DNA methylation [85]. Aggregated alpha-synuclein also binds histones, suppressing histone acetyltransferase activity, condensing chromatin, and reducing neuroprotective gene expression while worsening mitochondrial dysfunction. HDAC inhibitors can reverse these effects by restoring acetylation, activating mitophagy-related genes (e.g., PINK1, Parkin), and improving mitochondrial homeostasis [85, 86].

AD is marked by progressive neuronal loss in the cortex and hippocampus, β-amyloid deposition, tau hyperphosphorylation, and cognitive decline. Aging-related epigenetic alterations are closely linked to these processes. Histone H3 phosphorylation and H4 deacetylation in the hippocampus suppress genes vital for synaptic plasticity, such as BDNF [87]. DNA methylation abnormalities also occur in synaptic and neuroinflammatory genes, including APOEε4 pathways, intensifying neuronal injury [87]. HDAC inhibitors, like HDAC6 inhibitor PB118, can enhance Aβ clearance, stabilize microtubules via α-tubulin acetylation, reduce phosphorylated tau levels, regulate inflammatory mediators, and restore autophagy-lysosomal function [86, 88].

HD results from expanded CAG repeats in the HTT gene, producing mutant huntingtin (mHTT), which disrupts transcription, mitochondria, and neuronal survival, with epigenetic imbalance driving pathology. Studies show global DNA methylation changes and disrupted H3K9/H3K14 acetylation in HD brains. mHTT interacts with HDACs, increasing their activity and repressing autophagy genes (e.g., ATG5, LC3), promoting protein aggregation [86]. Additionally, mHTT's aberrant modulation of Polycomb Repressive Complex 2 (PRC2) leads to H3K27me3 accumulation on neural differentiation genes, accelerating neuronal degeneration [89].

In conclusion, age-related epigenetic dysregulation is a central mechanism in neurodegenerative disease development, offering insights for therapeutic strategies. Future research should integrate multi-omics datasets, deepen understanding of epigenetic networks, and advance epigenetically targeted therapies from basic research to clinical application for the prevention and treatment of aging-associated neurodegeneration.

Cardiovascular diseases

Cardiovascular diseases (CVDs) remain the leading cause of death and morbidity worldwide, with aging being a major contributing factor. Disruption of epigenetic homeostasis—including abnormal DNA methylation, altered histone modifications, and dysregulation of non-coding RNAs (ncRNAs)—forms a key molecular link between aging and cardiovascular pathology. These epigenetic alterations dynamically regulate gene expression in cardiomyocytes, vascular smooth muscle cells, and immune cells, disturbing cardiovascular equilibrium and promoting conditions such as atherosclerosis, coronary artery disease (CAD), and heart failure, while also offering potential targets for diagnosis and therapy [90-92].

With aging, an imbalance between DNA methyltransferases (DNMTs) and the ten-eleven translocation 2 (TET2) enzyme initiates cardiovascular epigenetic disruption. This discord between DNMT-mediated methylation and TET2-driven 5-methylcytosine hydroxylation perturbs genomic methylation homeostasis, impacting genes

critical for heart and vascular function. For example, mutations in DNMT3A, TET2, or extra sex combs-like genes can modify leukocyte inflammatory responses, enhance pro-inflammatory factor release, and accelerate atherosclerotic plaque formation [90]. Age-related methylation changes in metabolic genes, such as CPT1A, disrupt lipoprotein and triglyceride balance, whereas hypermethylation of ABCA1 impairs reverse cholesterol transport, promoting hypercholesterolemia and atherosclerosis [90, 93]. Other genes, including NOS3, APOE, RELA, and KLF4, are epigenetically modified in aging, influencing vasodilation, lipid transport, inflammation, and vascular homeostasis, all contributing to atherosclerosis initiation and progression [90, 92]. In atherosclerotic lesions, aberrant methylation of genes such as COL15A1 and TGFBR3 regulates vascular smooth muscle cell proliferation and migration, while dysfunction of chromatin remodelers like the BAF (SWI/SNF) complex exacerbates pathological vascular remodeling [90, 92].

Histone modification imbalances, particularly reduced acetylation due to altered histone deacetylase (HDAC) activity, are strongly linked to cardiovascular inflammation, impaired myocardial function, and vascular dysfunction. Aging affects HDAC expression profiles; for instance, HDAC9 polymorphisms increase the risk of large vessel atherosclerotic stroke by modulating genes involved in inflammation, lipid metabolism, and platelet activity [94]. Increased expression of HDAC1, HDAC2, and HDAC4 in peripheral blood mononuclear cells of CAD patients correlates with cardiac function metrics such as ejection fraction and diastolic performance, highlighting their potential as diagnostic and prognostic biomarkers [91]. Mechanistically, HDACs remove histone acetyl groups, silencing vasoprotective genes (e.g., endothelial nitric oxide synthase, IL-10) and activating pro-inflammatory pathways (e.g., NF-κB) and genes promoting vascular smooth muscle proliferation, thereby accelerating atherosclerosis and myocardial remodeling [34, 91].

Age-related alterations in ncRNA expression also critically affect cardiovascular cell function and serve as diagnostic markers. Reduced miRNA-425 and miRNA-744 in cardiac fibroblasts is linked to cardiac fibrosis and heart failure, whereas miRNA-15 upregulation during myocardial ischemia promotes cardiomyocyte apoptosis by targeting anti-apoptotic genes. Conversely, miRNA-204 and miRNA-34b protect vasculature by suppressing genes such as RUNX2 involved in vascular smooth muscle calcification [90, 92]. Long non-coding RNAs (lncRNAs) like ANRIL are upregulated in heart failure, correlating with cardiac remodeling and reduced ejection fraction, making them potential prognostic markers [90, 95]. lncRNAs can also modulate CAD-related genes (e.g., HCFC1, RNF8) by regulating chromatin remodeling complexes such as BAF, linking aging to increased CVD susceptibility [92].

Because epigenetic modifications are reversible, they represent promising therapeutic targets in age-related CVDs. HDAC inhibitors can restore histone acetylation, activate anti-inflammatory and vascular homeostasis genes, suppress vascular smooth muscle proliferation, and slow atherosclerosis progression [91, 94]. DNMT inhibitors can reverse hypermethylation of key genes such as ABCA1 and NOS3, improving cholesterol metabolism and vasodilation [90, 92]. Furthermore, profiling HDACs (HDAC1, HDAC2, HDAC4, HDAC9), DNA methylation markers (CPT1A, ABCA1), and ncRNA levels (miRNA-15, lncRNA ANRIL) provides valuable tools for early diagnosis and risk stratification in CAD and heart failure, forming the basis for “epigenetic diagnosis” [91, 92, 95].

In summary, epigenetic regulation is essential for maintaining cardiovascular homeostasis during aging, and its disruption underlies the development of age-related CVDs. Comprehensive exploration of these mechanisms offers new strategies and targets for the prevention, diagnosis, and treatment of cardiovascular diseases.

Metabolic syndrome

Metabolic Syndrome (MetS) is a complex and prevalent condition strongly associated with aging and represents a key risk factor for chronic diseases, including cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM), with its prevalence rising significantly in older populations [76]. Recent evidence indicates that disruptions in epigenetic homeostasis serve as a crucial molecular bridge linking aging to MetS pathogenesis. Altered DNA methylation, abnormal histone modifications, and dysregulated non-coding RNAs (ncRNAs) collectively influence the expression of genes involved in metabolism, impairing insulin signaling, lipid homeostasis, and inflammatory balance, and thereby driving MetS development. Understanding these mechanisms offers novel insights for disease management and targeted interventions.

During aging, an imbalance between DNA methyltransferases (DNMTs) and demethylases, including TET family enzymes, leads to abnormal genomic methylation that disrupts metabolic pathways. In MetS patients, aberrant methylation of genes in the insulin signaling pathway—such as insulin receptor substrates in peripheral blood and

adipose tissue—contributes to insulin resistance, a hallmark of age-related adipocyte dysfunction. Altered methylation of genes regulating lipid metabolism further disturbs lipid balance, promoting features of MetS such as hypertriglyceridemia and low HDL cholesterol levels [96]. Notably, 5-hydroxymethylcytosine (5hmC), a key intermediate in DNA demethylation, has a stronger regulatory role than 5-methylcytosine (5mC) in age-related cardiometabolic conditions, for example enhancing myocardial energy metabolism in MetS-associated cardiovascular injury, highlighting its therapeutic potential [97].

DNA methylation changes are particularly significant in T2DM, a common MetS complication. Age-associated methylation of CpG islands upstream of the human insulin gene promoter reduces gene expression, disrupting insulin and glucagon balance, accelerating hyperglycemia, and promoting T2DM onset. These findings emphasize the pivotal role of methylation imbalance in metabolic disease progression.

Histone modifications, especially acetylation and methylation, are also disrupted with aging. Overactivation of histone deacetylases (HDACs) in adipose tissue and liver of MetS patients alters chromatin structure, suppressing anti-inflammatory genes (e.g., IL-10) and metabolic protective genes (e.g., adiponectin), while enhancing adipose inflammation and hepatic lipid accumulation via transcription factors such as NF-κB. This creates a cycle of inflammation, insulin resistance, and metabolic dysfunction [96]. HDAC inhibition can restore acetylation, activate protective metabolic pathways, and improve insulin sensitivity and lipid regulation, representing a clear intervention strategy.

Age-related ncRNA expression changes also modulate metabolic pathways and provide potential diagnostic markers. For instance, aberrant miR-30c-1 is linked to MetS-related cardiovascular complications, including myocardial hypertrophy and heart failure, by targeting myocardial metabolic genes such as GLUT4. Downregulation of miRNAs like miR-143/145, which regulate insulin signaling, exacerbates insulin resistance. Long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) influence adipocyte differentiation and hepatic gluconeogenesis through miRNA sponging or interactions with RNA-binding proteins, though their precise roles in aging remain to be fully elucidated [97].

The reversibility of epigenetic modifications makes them attractive therapeutic targets in MetS. DNMT inhibitors (e.g., RG108) can partially restore myocardial metabolism and contractile function by reversing abnormal methylation of metabolic genes. HDAC inhibitors reduce adipose inflammation, improve hepatic insulin sensitivity, and lower glucose and lipid levels in MetS patients [96]. Moreover, CRISPR/Cas9 technology enables precise editing of epigenetic loci, including insulin promoter CpG islands and HDAC regulatory regions, providing a platform for personalized epigenetic therapies [97]. Epigenetic-based drugs and gene-editing approaches therefore offer innovative strategies for precise MetS management. Future studies should focus on clarifying the links between aging, epigenetics, and metabolism, addressing tissue-specificity and safety concerns, and translating these findings into clinical applications to advance the prevention and treatment of age-related MetS.

Cancer

Aging represents the most significant risk factor for cancer, primarily through the interconnected processes of accumulated cellular damage, genomic instability, and epigenetic disruption. Over time, environmental stresses such as oxidative damage, radiation, and dietary factors induce DNA lesions—including single- and double-strand breaks—and cause telomere attrition. Epigenetic dysregulation amplifies the age-related decline in genomic stability and functions as a core molecular mechanism that facilitates the transformation of normal cells into malignant ones [34, 98]. DNA methylation, histone modification, and non-coding RNA regulation act as reversible modulators of gene expression, driving both the functional deterioration of senescent cells and the initiation, progression, and therapeutic resistance of tumors, providing a comprehensive framework to link aging with cancer pathogenesis [34, 99].

During aging, the dysregulation of DNA methyltransferases (DNMTs), particularly reduced DNMT1 activity, leads to aberrant methylation patterns characterized by widespread hypomethylation and focal hypermethylation. Genome-wide hypomethylation—especially within repetitive elements such as satellite DNA and LINEs—destabilizes chromatin, activates transposable elements, induces insertion/deletion mutations, and accelerates oncogenesis. Evidence from the Apc^Min/+ mouse model shows that complete DNMT1 loss markedly accelerates intestinal tumorigenesis, highlighting the role of hypomethylation in tumor development [34]. In parallel, hypermethylation of tumor suppressor gene promoters silences critical anti-cancer pathways, as seen with p16INK4a and TIMP3 in oropharyngeal cancer, RASSF1A and GSTP1 in hepatocellular carcinoma, and multiple

suppressor genes in colorectal cancer, which also serve as early detection biomarkers [34]. These methylation imbalances accumulate with age, progressively rendering senescent cells epigenetically vulnerable to malignant transformation.

Alterations in histone modifications further disrupt chromatin architecture and transcriptional regulation, fostering tumor development. For instance, reductions in H3K4me3 in senescent cells compromise genomic stability and transcriptional precision. Mutations or abnormal activation of histone-modifying enzymes such as EZH2 result in the accumulation of repressive marks like H3K27me3 on tumor suppressor loci, promoting cancers including lymphoma and breast cancer [34, 99]. Aging also perturbs the balance between histone acetyltransferases (HATs) and histone deacetylases (HDACs): heightened HDAC activity drives hypoacetylation, suppressing tumor suppressor genes like p53, while aberrant HAT function can enhance proto-oncogene expression, such as MYC, collectively encouraging the malignant transformation of aged cells [99].

Epigenetic alterations are increasingly recognized as sensitive biomarkers for aging-related cancers. Detection of hypermethylated tumor suppressor genes in circulating tumor DNA (ctDNA) provides a non-invasive approach for early cancer diagnosis and therapy monitoring, with superior specificity compared to traditional markers [99]. Likewise, histone modification patterns—such as alterations in H3K4me3 and H3K27me3—can serve as prognostic indicators; for example, loss of H3K27me3 correlates with poorer survival in lung cancer patients [100].

The reversible nature of epigenetic marks makes them promising therapeutic targets. DNMT inhibitors, including Azacitidine and Decitabine, reverse tumor suppressor gene hypermethylation and are clinically approved for myelodysplastic syndromes (MDS) and acute myeloid leukemia [34]. HDAC inhibitors, such as Vorinostat and Romidepsin, restore acetylation, reactivate suppressed genes, and demonstrate efficacy against peripheral T-cell lymphoma (PTCL), offering significant advances in T-cell malignancy treatment [99]. Emerging combination approaches that pair epigenetic drugs with immunotherapy—such as HDAC inhibitors enhancing PD-1 checkpoint blockade—are under clinical investigation, providing new strategies for the targeted management of cancers associated with aging [99].

Epigenetics and immunosenescence

Immunosenescence reflects the progressive deterioration of immune system function with age, encompassing reduced generation and activity of immune cells—including T cells, B cells, macrophages, and dendritic cells—alongside heightened chronic inflammation and impaired immune surveillance. These changes contribute to increased vulnerability to infections, autoimmune disorders, and cancers in elderly populations [101, 102]. Emerging evidence indicates that epigenetic drift—including altered DNA methylation, disrupted histone modifications, and aberrant non-coding RNA regulation—serves as a central molecular mechanism driving these age-related immune deficits. By modulating gene expression programs governing immune cell development, differentiation, and functionality, epigenetic changes form a mechanistic link between aging, immune decline, and disease susceptibility, offering novel insights into immunosenescence and potential therapeutic strategies [97, 103].

DNA methylation functions as a precise biomarker of biological aging, and its perturbation directly compromises immune cell homeostasis. In hematopoietic stem cells (HSCs), age-related declines in TET enzyme expression (TET1/2/3) impair proliferation and differentiation, while concurrent dysregulation of DNMTs—particularly DNMT1, a critical regulator of B-cell development—disrupts hematopoietic lineage output. Reductions in DNMT3A and DNMT3B further diminish HSC regenerative capacity [104, 105]. Functionally, global hypomethylation of CpG sites in aged cells can activate pattern recognition receptors such as Toll-like receptors, interfering with apoptotic cell clearance. Re-methylation of hypomethylated DNA has been shown to restore immunosuppressive properties, highlighting hypomethylated DNA as a “molecular switch” for immune dysfunction [103]. Specific promoter hypermethylation events, such as at IL-7Rα, decrease CD8+ T-cell proliferation and cytotoxicity, whereas hypomethylation in dendritic cells enhances interferon-alpha secretion, fueling chronic inflammation and autoimmune responses [103, 105].

Age-associated histone modifications, including aberrant methylation and acetylation, further remodel chromatin structure, thereby influencing immune gene transcription and promoting immunosenescence. In aged HSCs, elevated levels of H3R4me3 and H3R27me3 repress stem cell differentiation genes, reducing immune cell output [103]. Conversely, diminished H3K27me3 derepresses pro-inflammatory genes such as TNF-α and IL-6, exacerbating chronic inflammation and impairing T-cell responses [106]. Dysregulated histone acetylation, driven

by increased HDAC activity with age, results in hypoacetylation that suppresses immunoregulatory genes like IL-10, further aggravating inflammatory signaling [107].

Non-coding RNAs also play a critical role in shaping immune function during aging. Upregulation of miR-21 and miR-146a in aged immune cells targets genes such as PTEN and TLR4, inhibiting T-cell proliferation and skewing macrophages toward a pro-inflammatory M1 phenotype while limiting M2 anti-inflammatory polarization, thereby reinforcing immunosenescence [108, 109]. Long non-coding RNAs such as MALAT1, downregulated in aged T cells, can restore T-cell activity and antitumor immunity through recruitment of chromatin remodeling complexes, highlighting lncRNAs as potential targets for intervention [110].

Epigenetic interventions offer promising strategies to counter immunosenescence. DNMT inhibitors can reverse hypermethylation of genes like IL-7Rα, restoring T-cell proliferation and cytotoxic function [111]. HDAC inhibitors enhance macrophage immunoregulatory capacity and reduce pro-inflammatory cytokine secretion by promoting histone acetylation and activating anti-inflammatory genes [107]. Combining these epigenetic drugs with immune checkpoint blockade (ICB) therapies can further potentiate anti-tumor immunity in elderly patients, while CRISPR-Cas9 epigenome editing enables precise correction of dysregulated loci, such as IL-7Rα promoters and H3K27me3-related genes, to rejuvenate immune cell function [112-114]. Additionally, targeting ncRNAs—by inhibiting miR-21/miR-146a or overexpressing MALAT1—can restore anti-inflammatory and immune surveillance functions [96, 110].

In conclusion, epigenetic regulation constitutes a key driver of immunosenescence. Understanding these mechanisms provides a framework for developing interventions—including epigenetic drugs, gene-editing approaches, and ncRNA-targeted therapies—that can restore immune function in aging populations, reduce susceptibility to infections, autoimmune diseases, and cancer, and guide future research into immune cell-specific epigenetic networks for precise and safe therapeutic applications.

Epigenetics of the musculoskeletal system (Osteoporosis and Sarcopenia)

The aging process poses significant challenges to musculoskeletal health, most notably through the high prevalence of osteoporosis (OP) and sarcopenia, which often co-exist as the combined syndrome termed "osteosarcopenia." These conditions are closely linked to age-related disruptions in epigenetic regulation [115, 116]. Epigenetic mechanisms—including DNA methylation, histone modifications, and non-coding RNA (ncRNA) regulation—modulate the differentiation and activity of osteoblasts, osteoclasts, and muscle satellite cells, thereby affecting both bone metabolism and muscle regeneration. This dynamic regulation forms a key molecular bridge connecting aging with musculoskeletal deterioration, offering insights into pathophysiology and potential therapeutic targets [34, 117].

Aging induces notable changes in the methylation of genes central to bone metabolism. For example, comparisons between healthy individuals and postmenopausal women with osteoporosis revealed elevated CpG methylation in the SOST gene promoter, which encodes the bone formation inhibitor sclerostin. However, other studies have reported SOST promoter hypomethylation in bone cells, highlighting tissue-specific effects that regulate sclerostin expression and influence bone formation [115]. In mesenchymal stem cells (hMSCs), epigenomic analyses have identified differential methylation of osteogenic regulators, including RUNX2 and OSX, in cells from osteoporotic fracture patients versus healthy donors. Age-associated hypermethylation of HOXA and RUNX2 CpG islands in hMSCs from older adults suppresses their transcription and reduces osteoblast differentiation capacity [117]. Furthermore, Tet1 and Tet2 DNA demethylases, which normally promote osteogenesis by interacting with Osx enhancers and cooperating with RUNX2 and Dlx5, decline with age in bone marrow stromal cells, leading to diminished RUNX2 expression and osteopenia, as confirmed in Tet1/Tet2 knockout mouse models [117].

Altered histone methylation is another hallmark of age-related osteoporosis. Levels of the repressive mark H3K27me3 increase with aging during osteogenesis, largely regulated by EZH2, a PRC2 complex component. Elevated EZH2 in adult bone marrow suppresses RUNX2 transcription via increased H3K27me3, inhibiting osteoblast differentiation and providing a rationale for using EZH2 inhibitors in OP therapy [34, 117]. Aberrant HDAC activation further contributes to bone dysfunction, with inhibitors like SAHA/Vorinostat enhancing osteoblast activity, suppressing osteoclast function, and improving bone structure and mechanical properties in osteoporotic animal models [34, 118].

Sarcopenia, marked by progressive loss of muscle mass and strength, is tightly linked to the declining regenerative potential of muscle satellite cells and epigenetic silencing of muscle metabolic genes. Muscle tissue comparisons

between younger and older individuals reveal differentially methylated CpG sites (dmCpGs) in genes controlling cytoskeletal organization, axon guidance, calcium signaling, and the mTOR pathway [119]. Mitochondrial dysfunction and reduced oxidative phosphorylation gene expression in sarcopenic muscle further underscore the role of epigenetic dysregulation. Many of these dmCpGs are enriched in EZH2 targets and H3K27me3-modified regions, indicating that DNA methylation and histone modifications jointly suppress mitochondrial and metabolic genes, worsening muscle decline [116, 120]. In addition, age-related increases in HDAC activity cause histone hypoacetylation, inhibiting muscle-specific genes such as myosin heavy chain (MyHC) and impairing muscle repair [34].

The miRNA expression landscape also shifts with age, significantly influencing sarcopenia. For instance, upregulation of the miR-29 family in aged muscle promotes fibrosis and functional deterioration by targeting collagen synthesis genes and suppressing anti-atrophy genes, such as AKT [119, 121].

Epigenetic interventions demonstrate promise in mitigating musculoskeletal aging. HDAC inhibitors like SAHA can simultaneously improve bone and muscle health by enhancing osteogenic differentiation and activating muscle regeneration pathways [34, 118]. DNMT inhibitors can reverse the hypermethylation of RUNX2 and Tet1/Tet2, restoring the functionality of osteogenic and muscle stem cells [117]. Targeted inhibition of miR-29 using antisense oligonucleotides (ASOs) has also been shown to promote muscle regeneration and increase strength in sarcopenia models [119].

In conclusion, epigenetic mechanisms are central drivers of musculoskeletal aging. Understanding these regulatory processes provides critical insights into the pathophysiology of osteoporosis and sarcopenia and facilitates the development of targeted therapeutics and diagnostic tools. Future research should focus on the integrated 'bone-muscle' epigenetic network, leveraging technological advances and interdisciplinary approaches to design precise interventions that maintain musculoskeletal health in the elderly [34, 115, 117].

Targets of aging and epigenetic-based anti-aging therapeutics

Aging is a complex biological process driven by the disruption of multiple molecular and cellular pathways, with epigenetic dysregulation being a central contributor. Alterations in DNA methylation, histone modifications, and chromatin remodeling affect gene expression and cell fate decisions, thereby promoting age-related functional decline and disease onset. Understanding these epigenetic mechanisms provides a framework for developing anti-aging interventions that specifically target these pathways [122-124].

DNA methylation modulators: correcting methylation imbalance

Age-related DNA methylation patterns are characterized by global hypomethylation alongside hypermethylation of certain gene promoters, contributing to genomic instability and the silencing of longevity-associated genes [125]. Drugs that inhibit DNA methyltransferases (DNMTs), such as 5-Azacytidine and Decitabine, can reverse these aberrant methylation states. In aged mouse models, 5-Azacytidine restores the expression of neuroprotective and anti-inflammatory genes, improving cognitive performance and reducing age-associated inflammation [126]. Clinically, these modulators have shown efficacy against age-related malignancies, including myelodysplastic syndromes (MDS), and metabolic disorders, demonstrating their broad therapeutic potential [127]. However, limitations exist: for example, poor blood-brain barrier penetration reduces efficacy in Alzheimer's disease, and prolonged use may exacerbate genomic instability.

HDAC inhibitors: modulating chromatin to activate repair mechanisms

Histone deacetylases (HDACs) remove acetyl groups from histones, leading to chromatin compaction and transcriptional repression of genes involved in repair and metabolism. HDAC activity increases with age, contributing to neurodegenerative and cardiovascular disorders [128]. HDAC inhibitors, such as Trichostatin A and Vorinostat, restore histone acetylation, relax chromatin, and reactivate protective gene expression. Mechanistic studies show that HDAC1 deficiency accelerates DNA damage and cognitive decline, whereas HDAC1 activators enhance DNA repair and cognitive performance in aged and Alzheimer's model mice via recruitment of repair enzymes like OGG1 [129]. Additionally, HDAC inhibitors modulate mitochondrial gene expression, reduce oxidative stress, and delay cellular senescence [130]. Challenges include limited tissue specificity and insufficient long-term safety data in elderly populations.

Histone methylation and chromatin remodeling agents: maintaining epigenetic homeostasis

Histone methylation regulates chromatin structure through lysine and arginine modifications, such as H3K27me3 and H3K4me3. Excessive H3K27me3 accumulation is associated with stem cell dysfunction and gene silencing during aging [131]. Therapeutic approaches targeting these pathways include histone methyltransferase (HMT) inhibitors, like GSK126, which reduces H3K27me3 via EZH2 inhibition, and histone demethylase (HDM) inhibitors, such as JIB-04, which preserve protective methylation marks by targeting the JMJD family. These interventions can restore methylation balance, enhancing proliferation and differentiation capacity [132]. Chromatin remodeling dysfunction, exemplified by impaired SWI/SNF complexes, also contributes to age-associated tissue degeneration, including cardiac fibrosis and neuronal apoptosis, making small molecule modulators of these complexes promising anti-aging targets.

Multi-target synergistic therapies: enhancing anti-aging efficacy

Due to the interplay of multiple aging pathways, single-target therapies often show limited effects. Multi-target strategies are gaining attention, aiming for a synergistic effect where combined interventions exceed the sum of individual outcomes ("1 + 1 > 2"). For example, combining HDAC inhibitors with DNA methylation modulators has been shown to improve cognitive function and metabolic health in aged mice by simultaneously restoring gene expression and opening chromatin [133]. Similarly, integrating epigenetic drugs with senolytics, which eliminate senescent cells, or autophagy activators can suppress both epigenetic dysfunction and the accumulation of senescent cells. In mouse models, such combinatorial approaches have reduced senescent cardiomyocytes, improved exercise capacity, and extended healthspan [134, 135].

In summary, targeting epigenetic regulators—including DNA methylation, histone modifications, and chromatin remodeling—represents a promising avenue for anti-aging therapy. Multi-pathway synergistic strategies further enhance their potential. Future studies should leverage single-cell epigenomic technologies and AI-assisted drug design to deepen the understanding of epigenetic contributions to aging and optimize the translation of these therapies into clinical applications, ultimately providing precise strategies for delaying aging and mitigating age-related diseases [136, 137].

Advances and obstacles in epigenetic anti-aging interventions

Recent breakthroughs in epigenetic research are creating new possibilities to reverse age-associated molecular changes, surpassing the limits of conventional strategies. One promising approach is partial epigenetic reprogramming, which selectively resets aging-associated epigenetic marks without altering overall cell identity, avoiding the risks of full genome reprogramming. Likewise, CRISPR/dCas9 epigenetic editing—which couples an inactive Cas9 enzyme with modifiers of DNA or histones—enables precise adjustments to critical genes, including those regulating cell cycle arrest (p16INK4a) and telomere maintenance, reducing unintended effects on unrelated genomic regions [138, 139]. Other tools, such as nanoparticle-based delivery systems, allow drugs like DNMT and HDAC inhibitors to reach target tissues efficiently, while single-cell epigenomic analyses provide insights into cellular variability, guiding more personalized and precise interventions [31, 140, 141]. Together, these techniques are enhancing both specificity and adaptability in anti-aging therapeutics.

Despite these innovations, significant challenges remain. Off-target consequences pose a major concern: conventional DNMT inhibitors may unintentionally trigger widespread epigenetic alterations, including activation of oncogenes or suppression of tumor suppressors, raising risks for genomic instability and malignancy [25, 61, 142]. Similarly, even highly targeted CRISPR/dCas9 interventions can affect neighboring genes due to non-specific guide RNA binding or prolonged enzymatic activity [34, 138]. Long-term epigenetic memory presents another hurdle: improper partial reprogramming can blur cell identity, while conventional epigenetic drugs may disrupt stable patterns, such as X-chromosome inactivation or imprinting, leading to chronic metabolic or reproductive disorders [39, 143, 144].

Future progress must focus on precision and controllability. At the technical level, innovations such as inducible dCas9 systems and high-accuracy guide RNA design could allow temporally and spatially controlled epigenetic modulation. Optimizing partial reprogramming regimens alongside continuous monitoring using single-cell epigenomics is essential to reverse aging changes while preserving cell-specific functions [138, 139]. On a personalized medicine front, integrating genome-wide epigenetic data with multi-omics profiles could enable tailored interventions—for example, DNMT inhibitors for individuals with accelerated DNA methylation aging, or HDAC inhibitors combined with targeted epigenetic editing for those with histone modification imbalances [34, 139].

From a translational perspective, rigorous evaluation is critical. Long-term clinical trials must assess safety, including potential immunogenicity of nanocarriers and effects of epigenetic editing on germ cells. Additionally, standardized frameworks for measuring therapeutic success—combining DNA methylation age, organ function metrics, and other biomarkers—are needed to quantify outcomes [25, 34]. Finally, combining epigenetic therapies with complementary approaches such as senolytic treatments may produce a synergistic "reset plus clearance" effect, facilitating the movement from experimental research to clinical application and providing a novel paradigm for the prevention and management of age-related diseases [25, 34, 138, 139].

Conclusion

Recent advances in aging epigenetics have focused on three main areas: integrating multi-omics datasets, discovering innovative biomarkers, and addressing ethical considerations in translational applications [145]. This review consolidates current progress, offering a comprehensive understanding of the "epigenetic imbalance–aging–disease" pathway and providing a framework to bridge fundamental research with clinical implementation. By combining multi-omics approaches with deep learning algorithms, it is now possible to predict individual-specific epigenetic changes and identify precise therapeutic targets, even for tissues that are difficult to access [146], enabling the development of highly personalized interventions. Concurrently, emerging tools such as multi-modal aging clocks and liquid biopsies allow for non-invasive, precise monitoring of aging processes and age-related conditions [147].

Despite these promising advances, clinical translation of epigenetic therapies faces several critical challenges. The first is tissue-specific delivery, as efficient targeting strategies are essential to maximize therapeutic effects while minimizing off-target consequences [148]. The second challenge is long-term safety, necessitating extensive preclinical studies to evaluate potential risks such as drug-induced genomic instability [149]. The third is the development of aging-specific biomarkers, requiring a multi-layered system that incorporates DNA methylation, non-coding RNA profiles, and other omics data to reliably measure treatment outcomes [150].

Moving forward, the field should emphasize several key strategies: creating multi-omics biomarkers capable of accurately reflecting drug efficacy; developing animal models that more faithfully replicate human aging for pharmacological research; and exploring synergistic combinations of epigenetic therapies with lifestyle or other non-drug interventions [151]. In summary, aging epigenetics stands as a foundational discipline for elucidating the biological mechanisms of aging and represents a vital avenue for promoting healthy aging and combating age-associated diseases. As methodological challenges are overcome, this field will provide essential insights and tools for extending healthspan and enhancing the quality of life in older populations.

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