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RECENT UNDERSTANDING OF EPIGENETIC AGING, REJUVENATION, AND LONGEVITY PRINCIPLES FOR REVERSE AGING

Shahid Nadeem*[1], Saira Ashraf[2], Khadija Arshad[3], Fatima[4], Aqsa Shahzad[5], Laiba Shahid[6], Nimra Shahzad[7], Huneza Sharif[8], Nimra Batool[9], Amer Jamil[10]

*[1,10]*Molecular Biochemistry Lab., Department of Biochemistry, University of Agriculture, Faisalabad, Punjab, Pakistan*
*[2,3,4,5,6,7,8,9]*Barani Institute of Sciences, Arid Agriculture Burewala, Punjab, Pakistan*

*[1]shahid66nadeem@gmail.com

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Corresponding Author: *
Shahid Nadeem

Abstract

Aging is an intricate biological phenomenon driven by the progressive erosion of epigenetic landscapes, manifesting as widespread DNA methylation drift, histone modification imbalances, and large-scale chromatin reorganization. These molecular alterations collectively compromise gene regulatory networks and precipitate cellular functional decline. This review synthesizes contemporary evidence on how epigenetic dysregulation orchestrates aging and age-associated neurodegenerative conditions, evaluates the diagnostic utility of epigenetic clock technologies spanning four generations, and examines the mechanistic basis of cellular reprogramming using Yamanaka factors (OSKM) as a strategy for partial epigenetic age reversal. Key Interventions Covered: Therapeutic strategies reviewed include CRISPR-based epigenome editing, senolytic pharmacology, NAD⁺ supplementation, sirtuin modulation, mTOR pathway inhibition, and AMPK activation. Epigenetic modifications are fundamentally reversible, positioning the epigenome as a therapeutically actionable substrate for anti-aging interventions. Converging advances in precision genome editing, artificial intelligence, and multi-omics profiling are establishing a scientific foundation for extending human healthspan.

1. Introduction

Aging constitutes the single most powerful risk factor for the spectrum of non-communicable diseases, encompassing type 2 diabetes mellitus, cardiovascular disorders, and systemic metabolic dysfunction (Franzago et al., 2022). A striking and clinically consequential feature of aging is its heterogeneity: individuals sharing identical chronological ages can exhibit dramatically divergent trajectories of biological decline, a disparity attributable in substantial part to differential epigenetic profiles heritable molecular alterations that regulate gene expression independently of nucleotide sequence changes. Global demographic projections underscore the urgency of this research frontier; World Health Organization data indicate that global life expectancy reached 72.6 years in 2019, and by 2050, the cohort aged 65 years and above will numerically surpass the 15–24-year age group. This unprecedented demographic transformation has catalyzed intensive scientific inquiry into the molecular biology of aging, with particular emphasis on its mechanistic intersections with neurodegenerative pathologies such as

Alzheimer's disease and Parkinson's disease (Kandlur et al., 2020).

At the mechanistic core, epigenetic regulation encompasses three interconnected biochemical systems: DNA methylation at CpG dinucleotides generating 5-methylcytosine (5mC); histone post-translational modifications including acetylation, methylation, and phosphorylation encoding the "histone code" (Etchegaray & Mostoslavsky, 2016); and non-coding RNA species that modulate epigenetic enzyme activity in response to environmental stimuli including dietary composition, stress, and physical activity (Pagiatakis et al., 2021). Over the aging lifespan, a paradoxical dual pattern of methylation change becomes established: global hypomethylation coexisting with focal hypermethylation at CpG island-associated gene promoters. Crucially, experimental evidence confirms that cellular aging is not irreversible induced pluripotent stem cells display near-zero epigenetic age following reprogramming, and partial reprogramming strategies restore youthful epigenetic signatures while preserving cell identity (Puri & Wagner, 2023; Chiavellini et al., 2021).

Objectives:

To evaluate the feasibility of reversing aging through targeted interventions assessing the efficacy and safety of partial reprogramming (OSK/OSKM factors), senolytics, NAD^+ boosters, CRISPR-based epigenome editing, and caloric restriction in reversing epigenetic aging markers while minimizing risks such as tumor formation and loss of cellular identity.

2. Review of Literature

2.1. Mechanisms of Epigenetic Drift in Aging

2.1.1. DNA Methylation Dynamics

The concept of epigenetics was initially articulated by Conrad Waddington in the 1940s to describe gene-environment interactions governing developmental trajectories. DNA methylation the covalent attachment of a methyl moiety to cytosine bases at CpG dinucleotide sites has emerged as the most extensively studied and clinically informative epigenetic modification (Gong et al., 2015). Approximately half of all human gene promoter regions are embedded within CpG-dense domains termed CpG islands, and methylation of these regions is coupled to transcriptional repression through the recruitment of methyl-binding proteins and co-repressor complexes. The enzymatic reversal of this modification is achieved through TET family dioxygenases, which oxidize 5mC to 5-hydroxymethylcytosine (5hmC), initiating iterative demethylation via base excision repair (Issa, 2014). The enzymatic machinery governing these patterns includes de novo methyltransferases DNMT3A and DNMT3B, which establish new methylation marks, and the maintenance methyltransferase DNMT1, which faithfully replicates existing patterns following DNA replication. Age-related dysregulation of these molecular "writers," "readers," and "erasers" underpins the epigenetic instability observed in malignancy and accelerated aging (Vaidya et al., 2025).

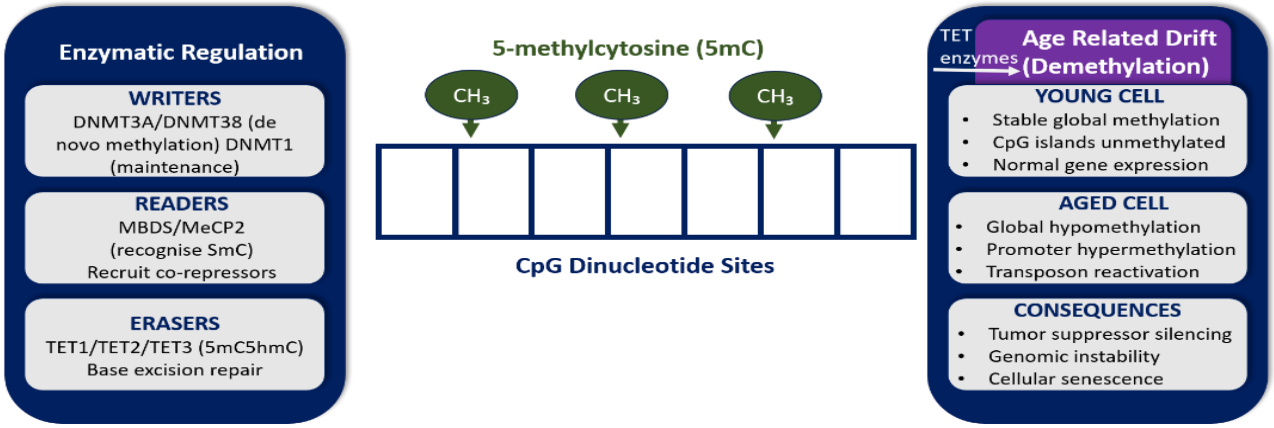

Figure 2. 1: DNA Methylation Mechanism and Age-Related Epigenetic Drift. The figure illustrates the enzymatic regulation by molecular "writers" (DNMT3A/B, DNMT1), "readers" (MBDs, MeCP2), and "erasers" (TET1-3), the CpG methylation process generating 5mC, and the contrasting methylation profiles of young versus aged cells. Age-related drift results in global hypomethylation, focal promoter hypermethylation, transposon reactivation, and tumor suppressor silencing.

2.1.2. Histone Modification Alterations

The fundamental structural unit of chromatin the nucleosome comprises 147 base pairs of DNA coiled around an octameric protein complex of histones H2A, H2B, H3, and H4. The protruding N-terminal tails of these histones are subject to an extensive repertoire of post-translational modifications that collectively orchestrate chromatin compaction and transcriptional accessibility (Maleszewska et al., 2016). Lysine acetyltransferases (KATs) deposit acetyl groups relaxing chromatin into a transcriptionally permissive euchromatic configuration, while histone deacetylases (HDACs) restore compaction. The consequences of histone methylation are residue-dependent: H3K4me3 activates transcription whereas H3K27me3 mediates Polycomb-mediated gene silencing. During aging, global histone levels decline and nucleosome occupancy becomes markedly irregular. Activating marks including H3K9ac and H4K16ac are progressively depleted, while repressive heterochromatic marks are redistributed in spatially disruptive patterns, driving cellular aging phenotypes (Yi & Kim, 2020; Molina-Serrano et al., 2019).

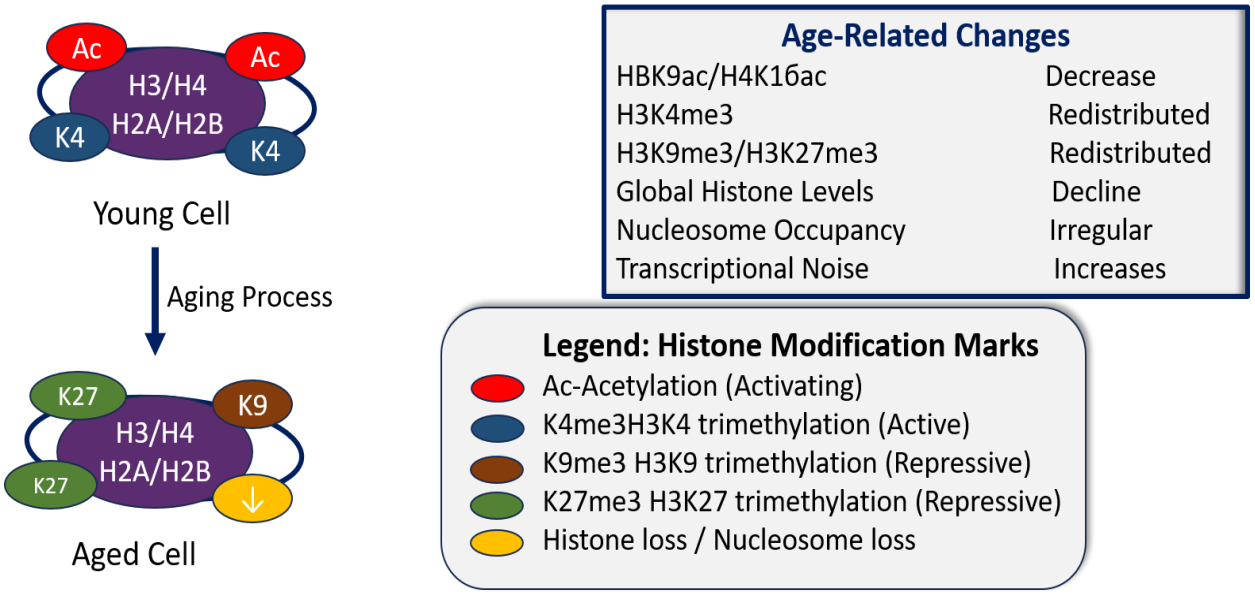

Figure 2.2: Histone Modifications and Their Dysregulation in Cellular Aging. The schematic contrasts the balanced histone modification landscape of young cells characterized by active acetylation marks (H3K9ac, H4K16ac) and precise H3K4me3 distribution with the aged cell epigenome featuring global histone depletion, redistribution of repressive marks (H3K9me3, H3K27me3), and increased transcriptional noise.

2.1.3. Heterochromatin Erosion and Epigenetic Noise

The heterochromatin loss model of aging, positing that constitutive heterochromatin domains established during embryogenesis deteriorate progressively throughout the lifespan, causing aberrant derepression of normally silenced loci. Heterochromatin stability depends on H3K9me3 marks and heterochromatin protein 1 alpha (HP1α); during aging, HP1α becomes delocalized and H3K9me3 levels diminish (Villeponteau et al., 1997). In humans, heterochromatin erosion is documented in physiological aging, replicative senescence, and accelerated progeriod syndromes including Hutchinson-Gilford Progeria Syndrome and Werner syndrome (Lee et al., 2020; Pal & Tyler, 2016). Beyond programmatic changes, aging is further characterized by the stochastic accumulation of epigenetic errors epigenetic noise at individual genomic loci. Environmental exposures including occupational noise, air pollution, and circadian disruption from night-shift work compound this stochastic drift, collectively serving as biomarkers for cumulative biological aging and disease susceptibility (Leso et al., 2020; Eze et al., 2020

Table 2.1: Principal Epigenetic Changes Associated with Aging

Epigenetic Mechanism	Age-Related Change	Functional Consequence	Key References
DNA Methylation	Global hypomethylation; focal hypermethylation at CpG island promoters	Transposon activation; tumor suppressor silencing; transcriptional dysregulation	Issa, 2014; Teschendorff et al., 2013
Histone Acetylation	Decreased H3K9ac and H4K16ac globally	Chromatin compaction; reduced transcriptional output; cellular senescence	Molina-Serrano et al., 2019

Histone Methylation	Redistributed H3K9me3 and H3K27me3; altered H3K4me3	Loss of transcriptional precision; reactivation of developmental genes	Yi & Kim, 2020
Heterochromatin	HP1α mislocalization; H3K9me3 decline; SAHF formation	Genomic instability; inflammatory signaling; premature senescence	Tsurumi & Li, 2012
Epigenetic Noise	Stochastic methylation and modification drift	Transcriptional variability; disease susceptibility; accelerated aging	Eze et al., 2020

2.2. Epigenetic Clocks: From Biomarkers to Causal Mechanisms

Epigenetic clocks represent a transformative class of computational tools leveraging site-specific DNA methylation signatures to generate quantitative estimates of biological as opposed to chronological age. Biological age reflects the cumulative molecular and functional state of the organism, integrating contributions of genetics, lifestyle, environmental exposure, and epigenetic drift. Conventional aging biomarkers including telomere attrition and immunosenescence capture isolated facets of aging, each subject to substantial inter-individual variability. A particularly illustrative limitation is the observation that African Americans demonstrate longer mean telomere lengths than Caucasians despite experiencing higher burdens of age-related disease and shorter life expectancy (Horvath et al., 2016). Epigenetic clocks transcend these limitations by integrating information across hundreds to thousands of CpG methylation sites simultaneously.

2.2.1. First-Generation Clocks (~2013): Chronological Age Prediction

The inaugural generation of epigenetic clocks predicted chronological age from DNA methylation data. The Hannum clock utilized 71 CpG sites from blood samples but demonstrated reduced accuracy in non-blood tissues (Margiotti et al., 2023). The landmark Horvath clock achieved generalizability through a pan-tissue model utilizing 353 CpG sites across diverse tissue types, attaining high predictive accuracy applicable to cancer biology, epidemiological aging research, and mortality risk prediction (Horvath, 2013).

2.2.2. Second-Generation Clocks (~2018): Health and Mortality Prediction

Second-generation clocks incorporated health-related phenotypic biomarkers alongside methylation data. PhenoAge integrates clinical laboratory markers with methylation for phenotypic age estimation. GrimAge incorporates methylation proxies of plasma protein levels, smoking history, and sex-adjusted parameters to produce mortality predictions of exceptional strength. Habitual physical activity significantly attenuates GrimAge acceleration, confirming the responsiveness of second-generation clocks to modifiable lifestyle factors (Nagata et al., 2024; Green et al., 2025).

2.2.3. Third-Generation Clocks (~2022): Pace of Aging

Third-generation clocks measure the dynamic rate of biological aging rather than a static age estimate. DunedinPACE, derived from longitudinal cohort data tracking participants across multiple time points, quantifies aging velocity as "years of biological aging per calendar year," with population mean near 1.0 and values above indicating accelerated aging (Belsky et al., 2022). This dynamic approach is particularly suited to clinical trial applications evaluating anti-aging interventions (Mavrommatis et al., 2025).

2.2.4. Fourth-Generation Clocks (2024–present): Causal Mechanisms

Fourth-generation clocks employ Mendelian randomization to distinguish DNA methylation changes causally implicated in driving aging from correlative associations. The CausAge clock

identifies causally relevant aging mechanisms; AdaptAge captures beneficial adaptive changes; DamAge quantifies harmful aging-associated epigenetic damage (Ying et al., 2024; Crimmins et al., 2024). This tripartite separation enables targeted investigation of protective versus pathogenic epigenetic aging mechanisms.

Table 2.2: Comparative Overview of Epigenetic Clock Generations

Generation	Era	Primary Objective	Exemplar Clocks	Principal Applications
First	~2013	Chronological age prediction from methylation data	Horvath Clock (353 CpGs); Hannum Clock (71 CpGs)	Forensic age estimation; baseline aging research controls
Second	~2018	Disease risk stratification and mortality prediction	PhenoAge; GrimAge (includes plasma protein proxies)	All-cause mortality prediction; health risk assessment
Third	~2022	Quantification of aging pace and velocity	DunedinPACE (longitudinal cohort-derived)	Clinical trial outcome measurement; personalized monitoring
Fourth	2024–present	Causal mechanism dissection via Mendelian randomization	CausAge; AdaptAge; DamAge	Targeted anti-aging therapy development; mechanistic research

2.3. Cellular Rejuvenation and Epigenetic Reprogramming

Rejuvenation, in the biological context, refers to the experimental restoration of youthful molecular and cellular characteristics in aged or senescent cells. The conceptual foundation was established by Takahashi and Yamanaka (2006), whose demonstration that somatic cells could be reprogrammed to a pluripotent state through transient overexpression of four transcription factors overturned the long-standing assumption that cellular differentiation was irreversible. iPSCs generated through this approach display near-zero epigenetic age, confirming that reprogramming effectively erases accumulated aging-associated epigenetic marks (Chiavellini et al., 2021). Partial reprogramming strategies can restore youthful epigenetic signatures while preserving differentiated cell identity, avoiding oncogenic risk (Puri & Wagner, 2023).

2.3.1. Yamanaka Factors and Partial Reprogramming

The four Yamanaka factors Oct4, Sox2, Klf4, and c-Myc (OSKM) reprogram somatic cells by dismantling the epigenetic architecture of the differentiated state and reinstating transcriptional networks associated with pluripotency (Takahashi & Yamanaka, 2006). Oct4 serves as the master regulator of pluripotency and self-renewal (Mohiuddin et al., 2020); Sox2 sustains the undifferentiated state (Novak et al., 2020); Klf4 exerts dual roles as activator and repressor of differentiation genes (Park et al., 2016); c-Myc enhances reprogramming efficiency but introduces significant oncogenic risk (Elbadawy et al., 2019). Modified factor combinations such as OSK (omitting c-Myc) have been developed to preserve rejuvenation efficacy while substantially reducing malignant transformation potential (Jiang et al., 2025). Partial reprogramming employs transient OSKM exposure sufficient to reset aging-associated epigenetic marks without progressing to full epigenetic erasure producing intermediate cells with improved mitochondrial

bioenergetics, restored nuclear integrity, and reduced SASP markers (Simpson et al., 2021).

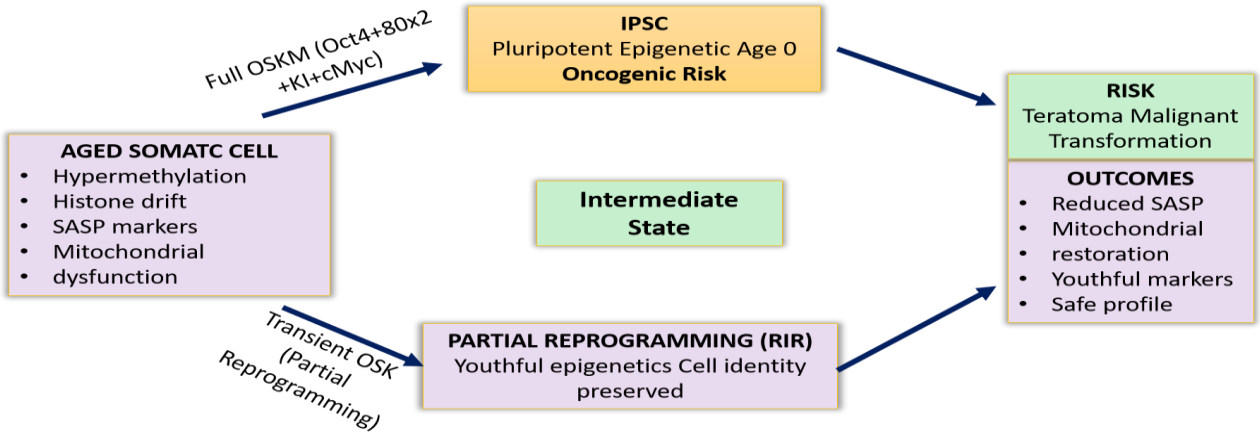

Figure 2.3: Cellular Rejuvenation Strategies: Full Reprogramming versus Partial Reprogramming (RiR). The diagram contrasts full OSKM reprogramming resulting in iPSCs with oncogenic risks against partial reprogramming (Reprogramming-induced Rejuvenation; RiR), which restores youthful epigenetic markers, mitochondrial function, and reduces SASP burden while preserving somatic cell identity. Cyclic OSKM induction (Ocampo et al., 2016) demonstrated lifespan extension without teratoma formation. OSK reprogramming restored vision in aged retinal ganglion cells (Rodriquez et al., 2022).

2.3.2. Tumor Risk Mitigation Strategies

The oncogenic potential of full OSKM reprogramming represents the most significant safety barrier to clinical translation. c-Myc's role as a proto-oncogene capable of driving uncontrolled proliferative signaling is well-established, and even c-Myc-independent reprogramming protocols carry residual risk if epigenetic resetting silences tumor suppressor networks (Lin et al., 2024; Ohnishi et al., 2014). The landmark study by Ocampo et al. (2016) demonstrated that short-term cyclic OSKM expression in a progeria mouse model produced substantial lifespan extension and tissue homeostasis improvement with reversal of DNA methylation patterns in muscle and pancreatic cells without detectable teratoma formation. This "cyclic reprogramming" paradigm, alternating periods of factor expression with factor withdrawal, has emerged as the conceptual template for safe rejuvenation.

2.4. Longevity-Regulating Molecular Pathways

2.4.1. Sirtuin-NAD$^+$ Axis

The sirtuin family of NAD$^+$-dependent protein deacylases encompassing SIRT1 through SIRT7 in mammals constitutes a central molecular nexus linking cellular metabolic status, genomic stability, epigenetic regulation, and organismal longevity (Wątroba & Szukiewicz, 2021). In mammalian systems, sirtuins are allosterically activated by elevated NAD$^+$ levels as occur during caloric restriction, producing broad beneficial effects including enhanced insulin sensitivity, stimulation of mitochondrial biogenesis via PGC-1α, and upregulation of antioxidant defense mechanisms (Imai & Guarente, 2016). Transgenic overexpression of SIRT6 in male mice produced a statistically significant 16% extension of median lifespan with improved metabolic parameters (Sen et al., 2016).

2.4.2. mTOR Inhibition, AMPK Activation, and Caloric Restriction

The mechanistic target of rapamycin (mTOR) integrates nutrient availability, growth factor signaling, and cellular energy status into two complexes: mTORC1 governing protein synthesis and autophagic flux, and mTORC2 regulating cytoskeletal dynamics. Age-associated hyperactivation of mTORC1 drives progressive muscle degeneration, neurodegeneration, and metabolic dysfunction through suppression of autophagy. Rapamycin inhibition consistently extends lifespan across yeast, nematodes, and Drosophila (Timmons et al., 2019). AMP-activated protein kinase (AMPK), activated by rising AMP/ATP ratios during exercise or caloric restriction, orchestrates coordinated metabolic adaptation including glycolysis, fatty acid oxidation, mitochondrial biogenesis, and autophagy, while directly suppressing mTORC1 via TSC2 phosphorylation (Xu et al., 2023). Caloric restriction remains the most reproducible non-genetic intervention for lifespan extension across species, mechanistically converging on sirtuin activation, AMPK stimulation, and mTOR suppression. The human CALERIE trial demonstrated that 25% caloric reduction over 24 months produced significant improvements in cardiometabolic risk markers and reductions in oxidative stress biomarkers (Das et al., 2023).

Table 2.3: Major Longevity-Regulating Pathways: Mechanisms and Interventions

Pathway	Activation Trigger	Key Molecular Targets	Anti-Aging Mechanisms	Clinical/Preclinical Evidence
Sirtuins (SIRT1–7)	Elevated NAD^+; caloric restriction	Histones; p53; NF-κB; PGC-1α; FOXO3	Deacetylation of longevity genes; mitochondrial biogenesis; DNA repair	SIRT6 overexpression: +16% lifespan in mice (Sen et al., 2016)
mTOR Inhibition	Rapamycin; nutrient deprivation	S6K1; 4E-BP1; ULK1; mTORC1 complex	Autophagy induction; proteostasis; reduced cellular hypertrophy	Lifespan extension in multiple model organisms; early human data
AMPK Activation	High AMP/ATP ratio; exercise; metformin	TSC2; mTORC1; ACC; SIRT1; ULK1	Glycolysis; fatty acid oxidation; mitochondrial biogenesis; autophagy	C. elegans lifespan extension; improved metabolic health in humans
Caloric Restriction	Reduced caloric intake (≈25–40%)	Sirtuins; AMPK; mTOR (triple convergence)	Reduced oxidative damage; improved insulin sensitivity; anti-inflammatory	CALERIE trial: improved cardiometabolic markers in humans (Das et al., 2023)

2.5. Recent Advances in Anti-Aging Therapeutics

2.5.1. CRISPR-Based Epigenome Editing

CRISPR-Cas systems were initially characterized as prokaryotic adaptive immune mechanisms. The recognition that Cas9 nuclease activity could be programmed by a synthetic single guide RNA (sgRNA) to introduce site-specific double-strand breaks established a paradigm for targeted genome modification (Pacesa et al., 2024). For epigenome editing, nuclease-inactivated "dead Cas9" (dCas9) proteins are fused with epigenetic effector domains enabling locus-specific modification without disrupting DNA sequence: dCas9-DNMT3A/3L for targeted cytosine methylation; dCas9-TET1 for site-specific demethylation; dCas9-p300 for histone acetylation; and dCas9-KRAB for transcriptional repression. CRISPR off

systems combining KRAB and DNMT fusion domains can establish and propagate stable gene silencing patterns across cell divisions (Liesenfelder et al., 2025).

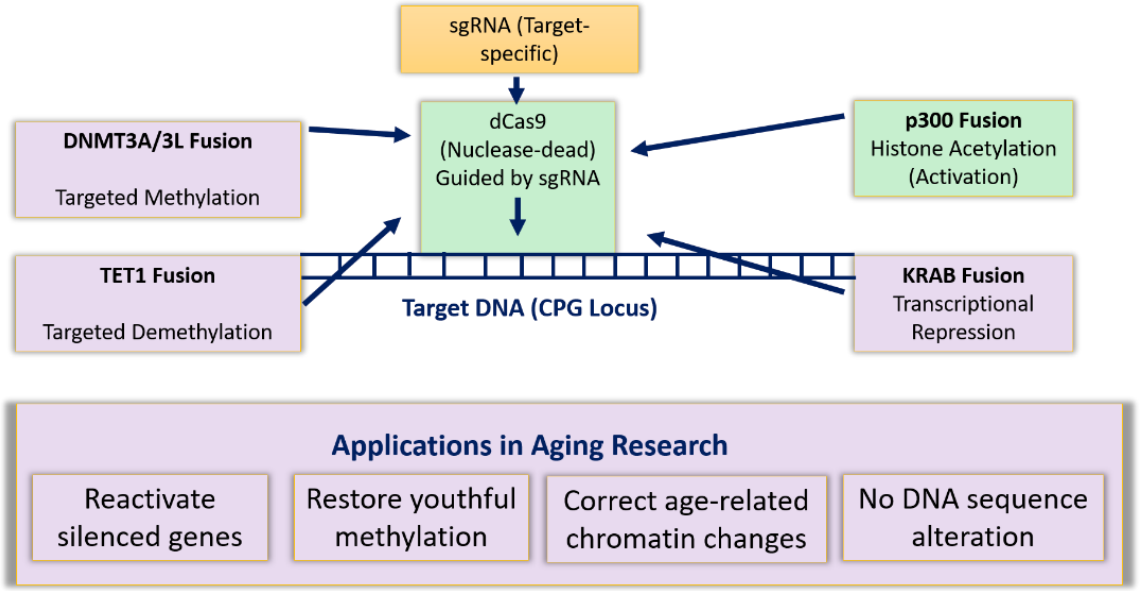

Figure 2.4: CRISPR-Based Epigenome Editing for Targeted Epigenetic Correction. The figure illustrates the dCas9-sgRNA complex directed to target CpG loci, and the four principal epigenetic effector fusion domains: DNMT3A/3L (targeted methylation), TET1 (targeted demethylation), p300 (histone acetylation/activation), and KRAB (transcriptional repression). These tools enable locus-specific epigenetic correction of age-associated aberrations without altering DNA sequence (Liesenfelder et al., 2025; Sichani et al., 2023).

2.5.2. Senolytics and Senescent Cell Clearance

Cellular senescence represents a terminal cell cycle arrest occurring in response to replicative telomere exhaustion, oncogene activation, and genotoxic stress. While initially adaptive, the progressive accumulation of senescent cells in aging tissues drives dysfunction through their senescence-associated secretory phenotype (SASP) — a sustained paracrine inflammatory program perpetuating local tissue damage and impairing progenitor cell function (Kang, 2019). Senolytics selectively eliminate senescent cells by disabling the pro-survival signaling pathways upon which they disproportionately depend. Principal agents include Navitoclax (ABT-263) and ABT-737, which inhibit anti-apoptotic BCL-2 family proteins; the FOXO4-DRI peptide disrupting the FOXO4-p53 nuclear interaction; and fisetin, a natural plant flavonoid reducing SASP burden and extending healthy lifespan in murine models (Zhang et al., 2021; Lorenzo et al., 2023).

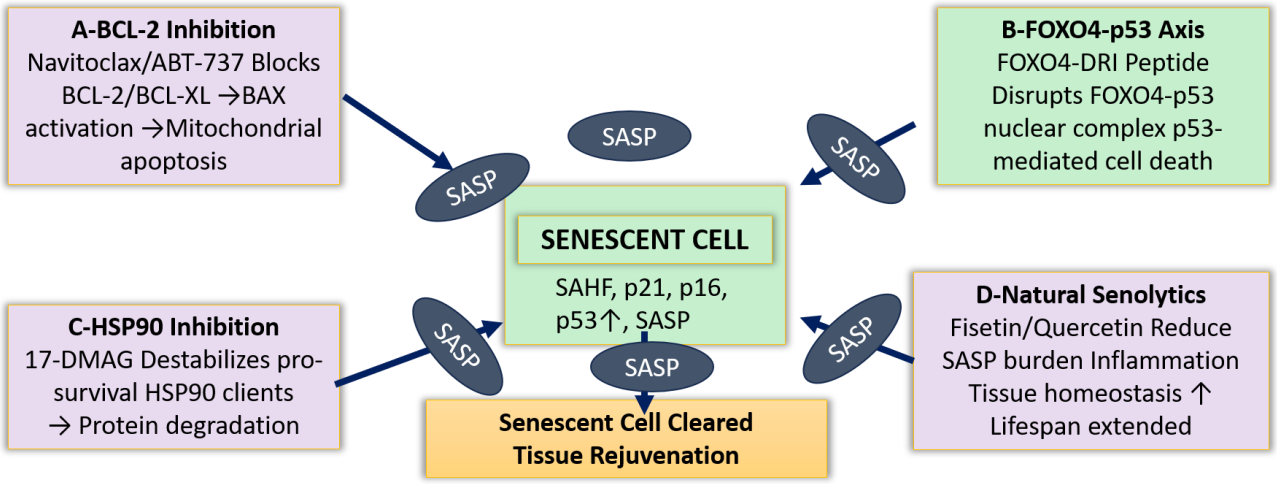

Figure 2.5: Senolytic Therapeutic Strategies for Selective Clearance of Senescent Cells. The schematic illustrates four primary therapeutic pathways: (A) BCL-2 Inhibition via Navitoclax/ABT-737 triggering BAX-mediated mitochondrial apoptosis; (B) FOXO4-p53 Axis disruption by FOXO4-DRI peptide releasing p53 to initiate cell death; (C) HSP90 Inhibition by 17-DMAG destabilizing pro-survival chaperone clients; and (D) Natural Senolytics including fisetin and quercetin reducing SASP burden and promoting tissue homeostasis. All pathways converge on elimination of the senescent cell and tissue rejuvenation (Zhang et al., 2021; Lorenzo et al., 2023; Saliev & Singh, 2025).

2.5.3. NAD^+ Augmentation and AI-Driven Aging Prediction

Nicotinamide adenine dinucleotide (NAD^+) is an essential coenzyme serving as the obligate co-substrate for sirtuin deacylases, PARPs involved in DNA repair, and CD38. Tissue NAD^+ concentrations decline substantially with aging, contributing to sirtuin inactivation, impaired DNA damage response, and mitochondrial dysfunction (Kang et al., 2020). Pharmacological restoration through biosynthetic precursors nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) has been confirmed to elevate blood NAD^+ by 50–100% in human trials, producing measurable improvements in skeletal muscle insulin sensitivity, arterial compliance, and inflammatory biomarker profiles (Freeberg et al., 2023). Complementing these approaches, AI-based biological age models trained on 10,000-individual clinical biomarker datasets achieve prediction accuracy with mean absolute error of 3.5 years, outperforming traditional regression by ~25% (Bae et al., 2021). Deep learning brain MRI analysis detects early neurocognitive decline with 85–90% accuracy, while explainable AI frameworks have identified 37 CpG sites significantly associated with accelerated immunological aging (Azzam et al., 2025; Kaulagi & Chavan, 2026).

Table 2.4: Emerging Therapeutic Strategies in Epigenetic Anti-Aging Research

Therapeutic Strategy	Mechanism of Action	Development Stage	Key Limitations	Representative References
CRISPR Epigenome Editing (dCas9 fusions)	Locus-specific methylation/demethylation/acetylation without DNA sequence change	Preclinical; early in vitro human cell studies	Delivery specificity; immunogenicity; off-target effects	Liesenfelder et al., 2025; Sichani et al., 2023
Senolytics (Navitoclax, FOXO4-DRI, Fisetin)	Selective elimination of senescent cells via pro-apoptotic pathway activation	Preclinical efficacy; Phase I-II human trials	Off-target toxicity (thrombocytopenia); tissue specificity	Zhang et al., 2021; Lorenzo et al., 2023
NAD^+ Precursors (NR, NMN)	Restoration of NAD^+ levels; sirtuin and PARP activation	Multiple completed Phase I-II randomized controlled trials	Bioavailability variability; optimal dosing unclear	Freeberg et al., 2023; Poljšak et al., 2022
Partial Reprogramming (OSKM/OSK)	Transient epigenetic age reset via pluripotency factor expression	Preclinical proof-of-concept; no human trials to date	Oncogenic risk; in vivo delivery; reprogramming fidelity	Puri & Wagner, 2023; Ocampo et al., 2016
AI-Driven Aging Prediction	Multi-omics biomarker integration for biological age estimation	Validated computational tools; clinical integration in development	Algorithmic interpretability; cross-population generalizability	Azzam et al., 2025; Meng, 2024

3. Discussion

The evidence synthesized in this review converges on a coherent framework in which aging is fundamentally orchestrated by progressive, multi-layered epigenomic remodeling that collectively erodes the fidelity and precision of gene regulatory networks (Lopez-Otin et al., 2013). The paradoxical duality of global hypomethylation coexisting with focal hypermethylation at functionally critical loci, as quantified by the Horvath 353 CpG clock model, establishes epigenetic drift as both a reliable biomarker and a potential causal driver of aging. Downstream histone modification changes including transposable element derepression through H3K9me3 loss and consequent activation of innate immune inflammatory signaling mechanistically link epigenetic aging to the chronic low-grade "inflammaging" characterizing aged organisms (De Cecco et al., 2019).

Perhaps the most conceptually transformative insight from recent aging research is the experimental confirmation that epigenetic aging is a dynamic, partially reversible molecular state. The

complete epigenetic rejuvenation of somatic cells through iPSC reprogramming established the principle. Ocampo et al. (2016) demonstrated in vivo lifespan extension through partial epigenetic reversal without oncogenic consequences. The demonstration by Rodriquez et al. (2022) that OSK-mediated reprogramming of retinal ganglion cells restores visual function in aged mice exemplifies tissue-level clinical potential. The convergence of partial reprogramming, targeted CRISPR-based epigenome editing, senolytic clearance of dysregulated senescent cells, and NAD^+-mediated sirtuin reactivation represents a powerful combinatorial therapeutic toolkit addressing complementary aspects of the aging epigenome.

Despite this momentum, fundamental obstacles remain. Oncogenic risk constitutes the most pressing safety concern, as OSKM factors particularly c-Myc are established proto-oncogenes (Nakagawa et al., 2010; Lin et al., 2024). In vivo delivery through AAV vectors carries risks of insertional mutagenesis and host immune reactivity (High & Roncarolo, 2019). The biological complexity of aging its tissue-specificity, inter-individual genetic variability, and lifelong accumulation makes universal therapeutic protocols fundamentally inadequate (Marioni et al., 2015). Ethical dimensions regarding equitable access to significant lifespan extension technologies are substantial (Gems, 2011). The near-term trajectory points toward convergence of personalized multi-omics profiling, precision epigenome editing, AI-driven biomarker development, and advanced lipid nanoparticle delivery systems enabling tissue-specific epigenetic correction approaching clinical precision (Schübeler, 2015).

4. Conclusion

Aging is fundamentally an epigenetically regulated biological process, driven by the progressive erosion of DNA methylation fidelity, histone modification homeostasis, heterochromatin stability, and epigenetic signal precision collectively dismantling the gene regulatory infrastructure upon which cellular identity and function depend. Four successive generations of epigenetic clock technologies have transformed biological age from an abstract concept into a quantifiable, clinically actionable biomarker, enabling measurement and monitoring of aging trajectories and evaluation of interventional efficacy.

The reversibility of epigenetic aging has been unambiguously established: transient Yamanaka factor expression through partial reprogramming restores youthful epigenetic signatures without the risks of full cellular dedifferentiation; CRISPR-based epigenome editing enables locus-specific correction of age-associated methylation and histone aberrations; senolytics selectively eliminate dysfunctional senescent cell populations driving tissue aging; and the convergent longevity pathways sirtuin activation, mTOR inhibition, AMPK engagement, and caloric restriction collectively promote autophagy, metabolic efficiency, and genomic stability. NAD^+ supplementation sustains these interconnected pathways in aging tissues by restoring the sirtuin substrate linking metabolic status to epigenetic regulation.

The remaining challenges of delivery specificity, long-term safety validation, inter-individual variability management, and ethical regulatory navigation must be systematically addressed before clinical translation can be responsibly pursued. The integration of artificial intelligence, multi-omics precision profiling, and advanced genome editing technologies will progressively transform epigenetic insights into actionable therapies targeting not simply the extension of chronological lifespan, but the expansion of healthspan the duration of life experienced in functional health, cognitive clarity, and physical independence.

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