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Epigenetic Aging in Alzheimer's Disease: Molecular Mechanisms Linking Chromatin Remodeling, Neuroinflammation, and Progressive Neurodegeneration

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Abstract

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder and represents a major global health burden associated with aging populations. Although amyloid-β deposition and tau pathology remain classical hallmarks of AD, increasing evidence suggests that epigenetic aging critically contributes to disease initiation and progression through dynamic alterations in chromatin organization, DNA methylation, histone modifications, and non-coding RNA regulation. Epigenetic drift during aging promotes transcriptional instability, neuroinflammatory activation, mitochondrial dysfunction, synaptic impairment, and neuronal vulnerability, thereby accelerating neurodegenerative processes. Emerging studies further demonstrate that chromatin remodeling complexes and age-associated epigenomic alterations influence microglial activation, blood-brain barrier integrity, and cellular senescence within the Alzheimer's brain microenvironment. Advances in multi-omics technologies and epigenetic profiling have substantially improved the understanding of molecular interactions linking aging biology with neurodegeneration. Furthermore, the reversibility of epigenetic modifications has generated significant interest in epigenetic-targeted therapeutic interventions, including histone deacetylase inhibitors, DNA methylation modulators, senolytic approaches, and precision medicine strategies. This review discusses the mechanistic interplay between epigenetic aging and Alzheimer's disease, emphasizing chromatin remodeling, neuroinflammation, and emerging translational opportunities for therapeutic intervention.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, synaptic dysfunction, neuronal loss, and progressive impairment of memory and executive function [1]. As the most common cause of dementia worldwide, AD poses substantial medical, social, and economic challenges, particularly in aging populations [2]. Classical neuropathological hallmarks of the disease include extracellular amyloid-β (Aβ) plaque accumulation and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein [3]. However, increasing evidence suggests that these pathological features alone do not fully explain the molecular

complexity and heterogeneity observed during disease progression [4] (Figure 1).

Aging remains the strongest risk factor for AD, and recent investigations increasingly implicate epigenetic aging as a critical contributor to neurodegenerative vulnerability [5]. Epigenetic aging refers to the progressive accumulation of alterations in chromatin organization and epigenomic regulation that occur over time, influencing gene expression patterns without altering the underlying DNA sequence [6]. These changes encompass DNA methylation drift, histone modification imbalance, chromatin remodeling dysfunction, and dysregulated non-coding RNA expression, collectively contributing to cellular senescence and neuronal dysfunction [7].

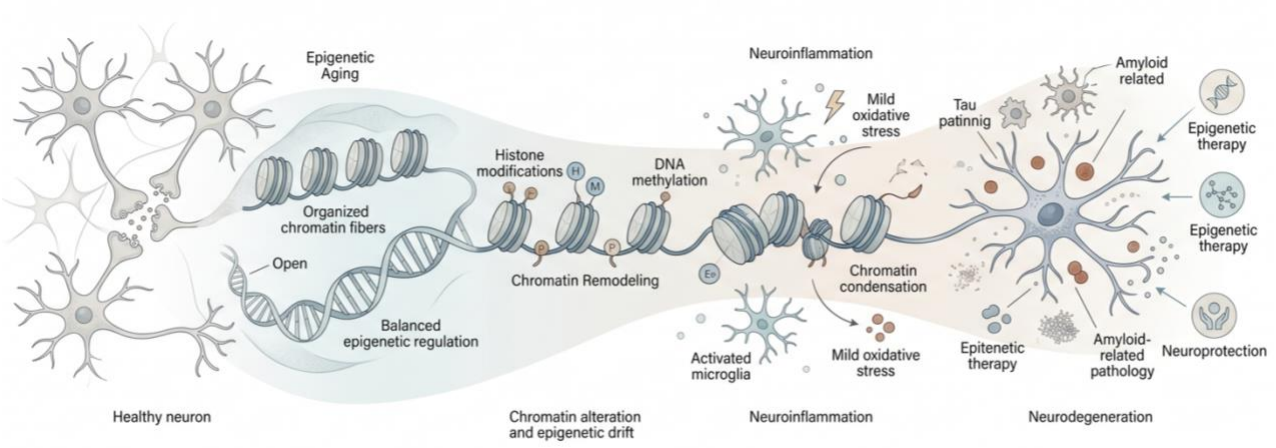

Figure 1: Schematic representation of the molecular interplay between epigenetic aging and Alzheimer's disease progression. Aging-associated chromatin alterations, including disrupted histone modifications, DNA methylation imbalance, and chromatin remodeling dysfunction, contribute to neuroinflammation, oxidative stress, and progressive neuronal degeneration. These epigenetic abnormalities ultimately promote amyloid-related pathology and synaptic impairment, highlighting potential therapeutic opportunities in epigenetic intervention and neuroprotective strategies.

DNA methylation represents one of the most extensively studied epigenetic mechanisms in AD. Aberrant methylation profiles affecting genes associated with synaptic transmission, inflammation, and amyloid processing have been identified in both human brain tissues and experimental models of AD [8]. Age-associated alterations in CpG methylation signatures have further enabled the development of "epigenetic clocks," which correlate biological aging with neurodegenerative disease susceptibility [9]. Accelerated epigenetic aging within the hippocampus and cortical regions has been associated with increased cognitive decline and pathological progression in AD patients [10].

In addition to DNA methylation, histone modifications play central roles in regulating neuronal plasticity and memory formation. Dysregulation of histone acetylation and methylation contributes to impaired transcriptional homeostasis, synaptic dysfunction, and neuroinflammatory signaling in AD [11]. Reduced histone acetylation, particularly involving histone H3 and H4, has been linked to transcriptional repression of neuroprotective genes and memory-associated pathways [12]. Consequently, histone deacetylases (HDACs) have emerged as potential therapeutic targets for restoring cognitive function and neuronal resilience [13]. Chromatin remodeling complexes also contribute significantly to neurodegenerative mechanisms. ATP-dependent chromatin remodelers regulate nucleosome positioning and chromatin accessibility required for neuronal differentiation, DNA repair, and stress responses [14]. Dysfunction of chromatin remodeling machinery may exacerbate genomic instability and inflammatory signaling during aging, thereby promoting neurodegeneration [15]. Recent studies indicate that altered chromatin accessibility in microglia and astrocytes contributes to sustained neuroinflammatory activation within the AD brain microenvironment [16].

Neuroinflammation has emerged as another fundamental driver of AD progression. Activated microglia and astrocytes release pro-inflammatory cytokines, reactive oxygen species, and neurotoxic mediators that accelerate neuronal damage and synaptic loss [17]. Importantly, epigenetic mechanisms substantially regulate inflammatory signaling pathways, including NF-κB activation, inflammasome assembly, and cytokine production

[18]. Chronic neuroinflammation may therefore establish a self-perpetuating cycle of epigenetic dysregulation and neuronal degeneration. Recent advances in transcriptomics, epigenomics, and single-cell sequencing technologies have significantly enhanced the understanding of molecular heterogeneity in AD [19]. Integrative multi-omics approaches now provide insights into the complex interactions between epigenetic aging, cellular senescence, mitochondrial dysfunction, and neuroimmune responses [20]. These technological developments are facilitating the identification of novel biomarkers and therapeutic targets for precision medicine strategies in neurodegenerative disorders.

Importantly, unlike irreversible genetic mutations, epigenetic modifications are potentially reversible, making them attractive therapeutic targets [21]. Emerging therapeutic interventions including HDAC inhibitors, DNA methylation modulators, senolytic compounds, and epigenetic editing technologies are currently being explored for their capacity to mitigate neurodegenerative progression and improve cognitive outcomes [22]. Collectively, accumulating evidence indicates that epigenetic aging constitutes a central mechanistic axis linking aging biology with Alzheimer's disease pathogenesis. Understanding the molecular interplay between chromatin remodeling, neuroinflammation, and neuronal degeneration may therefore provide critical insights into the development of innovative therapeutic approaches for AD.

2. Methodology

This review was conducted through a comprehensive literature search of peer-reviewed publications indexed in PubMed, Scopus, Web of Science, and Google Scholar databases. Relevant articles published primarily between 2000 and 2026 were identified using combinations of keywords including "Alzheimer's disease", "epigenetic aging", "chromatin remodeling", "DNA methylation", "histone modification", "neuroinflammation", "epigenomics", "cellular senescence", and "neurodegeneration". Original research articles, systematic reviews, meta-analyses, and landmark mechanistic studies were prioritized. Particular emphasis was placed on studies investigating molecular interactions between aging-associated epigenetic alterations and neurodegenerative processes in Alzheimer's disease. Additional studies focusing on translational applications, therapeutic interventions, and multi-omics technologies were also included. References cited within selected publications were manually screened to ensure comprehensive coverage and scientific relevance.

3. Epigenetic Drift, Chromatin Instability, and Cellular Senescence as Central Drivers of Alzheimer's Disease Progression

Aging is accompanied by profound alterations in epigenetic architecture that collectively reshape transcriptional homeostasis, chromatin accessibility, and cellular functionality across multiple tissues, including the central nervous system [23]. In the aging brain, progressive epigenetic drift contributes substantially to neuronal vulnerability and establishes a permissive molecular environment for neurodegenerative disease development. Epigenetic drift refers to the gradual accumulation of stochastic and environmentally influenced epigenomic alterations over time, leading to aberrant gene expression profiles and impaired cellular resilience [24]. These changes affect DNA methylation patterns, histone modifications, chromatin remodeling activity, enhancer accessibility, and non-coding RNA regulation, ultimately disrupting neuronal integrity and synaptic plasticity.

One of the most extensively investigated features of epigenetic aging in Alzheimer's disease involves alterations in DNA methylation landscapes. Global hypomethylation accompanied by focal promoter hypermethylation has been consistently observed in aged neuronal tissues and AD patient brains [25]. Such changes alter transcriptional regulation of genes involved in synaptic transmission, amyloid precursor protein processing, neuroinflammatory signaling, oxidative stress responses, and mitochondrial function [26]. Notably, methylation abnormalities in genes such as ANK1, BIN1, SORL1, and APP have been associated with accelerated cognitive decline and enhanced neuropathological burden [27].

Epigenetic clock studies have further demonstrated that biological aging of the brain frequently exceeds chronological aging in individuals with AD [28]. Accelerated epigenetic age is particularly evident in the hippocampus, entorhinal cortex, and prefrontal cortex, regions critically involved in memory and cognition [29]. This accelerated epigenomic aging correlates strongly with tau pathology, amyloid deposition, and neuronal loss, suggesting that epigenetic alterations are not merely secondary phenomena but active contributors to disease progression [30]. Histone modifications represent another major component of age-associated chromatin dysregulation in AD. Histone acetylation

is essential for transcriptional activation and memory consolidation through relaxation of chromatin architecture and facilitation of transcription factor binding [31]. However, aging and neurodegeneration are frequently associated with reduced histone acetylation, particularly involving histone H3 lysine 9 acetylation (H3K9ac) and histone H4 lysine 12 acetylation (H4K12ac) [32]. These epigenetic alterations suppress expression of neuroprotective and synaptic plasticity-related genes, thereby impairing neuronal adaptability and cognitive performance.

Conversely, increased histone deacetylase activity has been implicated in transcriptional repression and neurodegenerative pathology [33]. Elevated expression of HDAC2 and other class I histone deacetylases has been observed in AD brains and experimental models, contributing to synaptic dysfunction and impaired learning [34]. Importantly, pharmacological inhibition of HDACs has demonstrated promising neuroprotective effects in preclinical studies, including restoration of memory-associated gene expression, reduction of neuroinflammation, and improvement of cognitive outcomes [35].

Chromatin remodeling abnormalities also play central roles in neurodegenerative aging. ATP-dependent chromatin remodelers regulate nucleosome positioning, DNA accessibility, and transcriptional fidelity required for neuronal differentiation and survival [36]. During aging, disruption of chromatin remodeling machinery contributes to genomic instability, impaired DNA repair capacity, and aberrant stress responses [37]. Reduced chromatin accessibility in neuronal enhancer regions has been linked to impaired expression of synaptic and neuroprotective genes, further accelerating neuronal degeneration [38]. An additional hallmark of epigenetic aging in AD is the emergence of cellular senescence within neural and glial populations. Cellular senescence is characterized by irreversible cell-cycle arrest accompanied by altered metabolic activity, inflammatory signaling, and secretion of pro-inflammatory mediators collectively termed the senescence-associated secretory phenotype (SASP) [39]. Senescent astrocytes, microglia, oligodendrocyte progenitor cells, and endothelial cells accumulate within the aging brain and contribute substantially to neurodegenerative pathology [40].

Senescence-associated inflammatory mediators including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and matrix metalloproteinases promote chronic neuroinflammation, synaptic toxicity, and blood-brain barrier disruption [41]. Importantly, epigenetic dysregulation strongly influences senescence pathways through modulation of p16INK4a, p21, NF-κB, and DNA damage response signaling [42]. Consequently, senolytic interventions targeting senescent cell populations have emerged as promising therapeutic approaches for mitigating neurodegeneration and cognitive decline. Mitochondrial dysfunction represents another interconnected consequence of epigenetic aging and chromatin instability. Neurons possess exceptionally high metabolic demands, rendering them particularly susceptible to mitochondrial impairment and oxidative stress [43]. Age-associated epigenetic alterations disrupt expression of mitochondrial biogenesis regulators, electron transport chain components, and antioxidant defense pathways, thereby exacerbating reactive oxygen species accumulation and neuronal injury [44]. Oxidative DNA damage further destabilizes chromatin architecture and reinforces epigenetic dysregulation in a self-amplifying pathological cycle. Collectively, epigenetic drift, chromatin instability, and cellular senescence constitute fundamental mechanistic pillars linking aging biology with Alzheimer's disease pathogenesis. These interconnected processes establish a chronically dysregulated transcriptional environment that promotes neurodegeneration, neuroinflammation, and cognitive deterioration.

4. Neuroinflammatory Signaling, Microglial Epigenomics, and the Molecular Crosstalk Between Immune Dysfunction and Neurodegeneration

Neuroinflammation has emerged as one of the most significant pathogenic mechanisms underlying Alzheimer's disease progression [45]. While acute inflammatory responses may initially serve protective functions by facilitating clearance of amyloid aggregates and damaged cellular components, chronic and dysregulated neuroinflammation ultimately promotes neuronal injury, synaptic dysfunction, and cognitive decline [46]. Recent evidence increasingly demonstrates that epigenetic mechanisms critically regulate neuroimmune signaling pathways and contribute to persistent inflammatory activation within the Alzheimer's brain microenvironment. Microglia, the resident immune cells of the central nervous system,

occupy central positions in AD-associated neuroinflammation [47]. Under physiological conditions, microglia maintain tissue homeostasis through synaptic pruning, phagocytosis of cellular debris, and immune surveillance [48]. However, aging and epigenetic dysregulation induce profound transcriptional reprogramming of microglial populations, resulting in exaggerated inflammatory responses and impaired clearance of amyloid-β aggregates [49].

Single-cell transcriptomic and epigenomic analyses have identified disease-associated microglia (DAM) phenotypes characterized by altered chromatin accessibility and inflammatory gene expression patterns in AD brains [50]. These microglial populations exhibit increased expression of genes involved in inflammasome activation, cytokine secretion, oxidative stress responses, and antigen presentation [51]. Importantly, epigenetic remodeling of enhancer regions and histone modification landscapes significantly contributes to these transcriptional transitions. NF-κB signaling represents a major inflammatory pathway regulated by epigenetic mechanisms in AD [52]. Activation of NF-κB promotes transcription of pro-inflammatory cytokines including IL-1β, IL-6, TNF-α, and chemokines that exacerbate neuronal toxicity and synaptic degeneration [53]. Histone acetylation and methylation dynamics at NF-κB-responsive promoters critically determine inflammatory transcriptional intensity and duration [54]. Chronic activation of these pathways establishes persistent inflammatory states that accelerate disease progression.

NLRP3 inflammasome activation has also emerged as a major contributor to AD-associated neuroinflammation [55]. Inflammasome activation triggers maturation of IL-1β and IL-18, amplifying inflammatory signaling and neuronal injury [56]. Epigenetic regulation of inflammasome-associated genes through histone modifications and DNA methylation significantly influences microglial inflammatory phenotypes [57]. Experimental inhibition of inflammasome signaling has demonstrated neuroprotective effects in preclinical AD models, highlighting its therapeutic relevance. Astrocytes also contribute substantially to neuroinflammatory pathology. Reactive astrocytes undergo epigenetically regulated transcriptional changes that promote secretion of inflammatory mediators, glutamate excitotoxicity, and metabolic dysfunction [58]. Aging-associated chromatin remodeling abnormalities enhance astrocytic inflammatory responsiveness and impair neuroprotective support functions required for neuronal survival [59].

Another major consequence of chronic neuroinflammation involves blood-brain barrier disruption. The blood-brain barrier maintains central nervous system homeostasis through tightly regulated endothelial junctions and selective molecular transport [60]. In AD, inflammatory cytokines, oxidative stress, and epigenetic dysregulation impair endothelial integrity, facilitating peripheral immune cell infiltration and further amplification of inflammatory signaling [61]. Importantly, recent investigations have demonstrated bidirectional interactions between amyloid pathology and neuroinflammation. Amyloid-β aggregates activate inflammatory pathways through pattern recognition receptors including TREM2, CD36, and Toll-like receptors [62]. Simultaneously, chronic inflammation promotes enhanced amyloidogenic processing of amyloid precursor protein and tau hyperphosphorylation, thereby reinforcing neurodegenerative cascades [63].

Epigenetic alterations also influence adaptive immune responses within the AD microenvironment. T-cell infiltration, altered antigen presentation, and dysregulated immune checkpoint signaling have been observed in neurodegenerative tissues [64]. Emerging evidence suggests that chromatin remodeling and histone modification patterns regulate neuroimmune communication and contribute to disease heterogeneity among patients. Collectively, neuroinflammation in Alzheimer's disease is tightly interconnected with epigenetic dysregulation, chromatin remodeling abnormalities, and immune dysfunction. Understanding these complex molecular interactions may facilitate development of targeted anti-inflammatory and epigenetic therapeutic strategies for neurodegenerative disorders.

5. Multi-Omics Technologies, Epigenomic Biomarkers, and Emerging Precision Therapeutic Strategies in Alzheimer's Disease

The rapid evolution of multi-omics technologies has fundamentally transformed the understanding of Alzheimer's disease pathogenesis and molecular heterogeneity [65]. Integrative analyses combining genomics, transcriptomics, epigenomics, proteomics, metabolomics, and single-cell sequencing now provide unprecedented insights into the complex interactions linking aging biology with neurodegeneration [66]. These technologies are

facilitating identification of disease-associated molecular signatures, novel biomarkers, and individualized therapeutic targets that may improve early diagnosis and precision medicine approaches in AD. Epigenomic profiling studies have identified extensive chromatin accessibility alterations and DNA methylation abnormalities across multiple brain regions affected by AD [67]. Genome-wide methylation analyses have consistently revealed differential methylation of genes associated with inflammation, synaptic function, mitochondrial metabolism, and amyloid processing [68]. Importantly, these epigenetic signatures may emerge during early preclinical stages of disease progression, thereby offering opportunities for earlier diagnostic intervention.

Histone modification profiling has further expanded the understanding of transcriptional dysregulation in neurodegeneration. Altered histone acetylation and methylation landscapes affect enhancer activity and neuronal gene expression programs required for cognitive function [69]. Recent chromatin immunoprecipitation sequencing (ChIP-seq) studies have demonstrated widespread enhancer dysregulation and chromatin accessibility alterations in AD patient brains [70]. Single-cell transcriptomics and epigenomics have proven particularly valuable for dissecting cellular heterogeneity within the Alzheimer's brain microenvironment [71]. These approaches reveal distinct neuronal, astrocytic, oligodendroglial, endothelial, and microglial transcriptional states associated with disease progression [72]. Importantly, disease-associated microglial populations display unique epigenetic and inflammatory signatures that may represent potential therapeutic targets.

Artificial intelligence and machine learning algorithms are increasingly integrated with multi-omics datasets to identify predictive biomarkers and therapeutic response signatures [73]. Deep learning models capable of integrating methylation patterns, transcriptomic profiles, imaging data, and clinical variables may improve diagnostic accuracy and patient stratification [74]. Such computational approaches are expected to accelerate precision medicine implementation in neurodegenerative disorders. The reversibility of epigenetic modifications has generated substantial interest in epigenetic-targeted therapies for Alzheimer's disease. Histone deacetylase inhibitors represent among the most extensively investigated therapeutic strategies [75]. Experimental HDAC inhibition has demonstrated restoration of synaptic plasticity, reduction of inflammatory signaling, enhancement of memory-associated gene expression, and improvement of cognitive performance in animal models [76].

DNA methylation-targeted therapies are also under investigation. Modulation of DNA methyltransferase activity may restore transcriptional balance and mitigate neurodegenerative progression [77]. Furthermore, CRISPR-based epigenome editing technologies now permit locus-specific modification of epigenetic marks without altering genomic sequences, offering highly precise therapeutic possibilities [78]. Senolytic therapies targeting senescent cells have emerged as another promising intervention strategy [79]. Experimental clearance of senescent glial and endothelial populations reduces neuroinflammation, improves vascular integrity, and attenuates cognitive decline in preclinical models [80]. Similarly, anti-inflammatory approaches targeting inflammasome signaling and cytokine pathways may mitigate chronic neuroimmune activation associated with neurodegeneration.

Mitochondrial-targeted interventions also possess therapeutic potential due to the close relationship between epigenetic aging and metabolic dysfunction [81]. Pharmacological activation of mitochondrial biogenesis pathways and antioxidant defense systems may improve neuronal resilience and reduce oxidative stress-mediated chromatin instability. Despite these advances, substantial challenges remain in translating epigenetic therapies into clinical practice. Blood-brain barrier penetration, off-target effects, cellular specificity, and long-term safety represent major obstacles requiring further investigation [82]. Additionally, the remarkable molecular heterogeneity observed among AD patients underscores the need for individualized therapeutic strategies guided by molecular profiling and biomarker-based patient stratification. Future precision medicine approaches will likely integrate epigenomics, neuroimaging, artificial intelligence, and longitudinal biomarker analyses to optimize therapeutic selection and disease monitoring [83]. Continued advances in multi-omics technologies and functional genomics are therefore expected to significantly reshape the future landscape of Alzheimer's disease diagnosis and treatment.

6. Conclusion

Alzheimer's disease is increasingly recognized as a multifactorial neurodegenerative disorder profoundly influenced by epigenetic aging and chromatin dysregulation. Beyond classical amyloid

and tau pathology, accumulating evidence demonstrates that alterations in DNA methylation, histone modifications, chromatin remodeling, and non-coding RNA regulation contribute substantially to neuronal dysfunction, neuroinflammation, cellular senescence, and progressive cognitive decline. Aging-associated epigenetic drift establishes a permissive molecular environment that amplifies inflammatory signaling, mitochondrial dysfunction, genomic instability, and synaptic impairment within vulnerable brain regions. Recent advances in multi-omics technologies, single-cell sequencing, and epigenomic profiling have significantly enhanced the mechanistic understanding of molecular interactions linking aging biology with neurodegeneration. These discoveries have further facilitated identification of novel biomarkers and therapeutic vulnerabilities with substantial translational potential. Importantly, the reversibility of epigenetic modifications positions chromatin-targeted interventions as promising therapeutic strategies for Alzheimer's disease. Emerging approaches involving histone deacetylase inhibition, senolytic therapies, inflammasome modulation, epigenome editing, and precision medicine-guided interventions may collectively transform future management of neurodegenerative disorders. Nevertheless, additional investigations remain essential to clarify disease heterogeneity, optimize therapeutic specificity, and improve clinical translation. Continued integration of epigenomics, neurobiology, immunology, and computational medicine will therefore be critical for advancing innovative diagnostic and therapeutic strategies capable of mitigating the global burden of Alzheimer's disease.

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