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Review Article

Investigating the Mechanistic Role of piRNA Dysregulation in Amyloid-beta Toxicity and Tau Pathology in Alzheimer's Disease Pathophysiology: Implications for Therapeutic Targets

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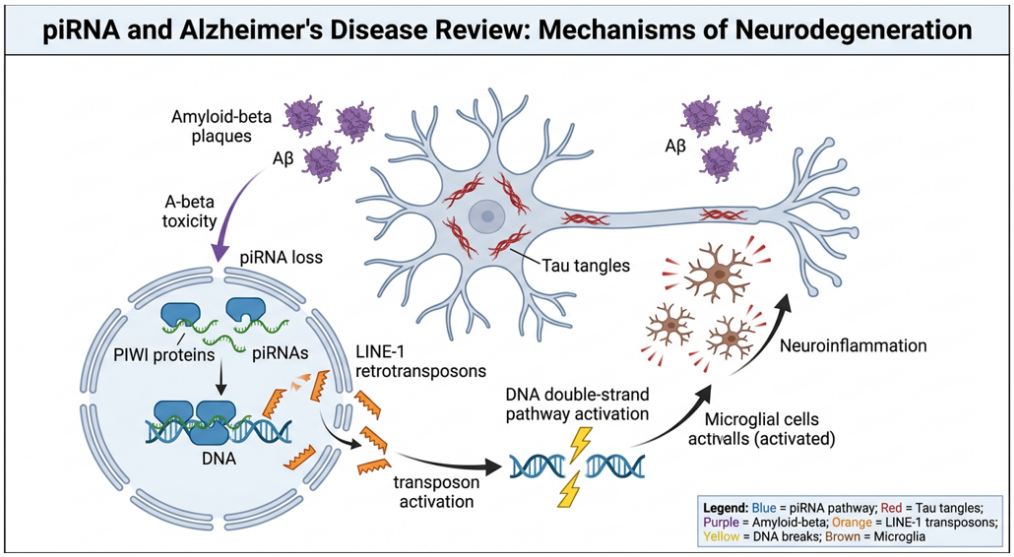
Abstract

Alzheimer's disease (AD) represents the most prevalent neurodegenerative disorder worldwide, characterized by progressive cognitive decline, amyloid-beta (Aβ) plaque deposition, and neurofibrillary tangle formation. While the amyloid cascade and tau propagation hypotheses have dominated the field for decades, emerging evidence implicates epigenetic mechanisms, particularly PIWI-interacting RNAs (piRNAs), in the early pathogenesis of sporadic AD. This review synthesizes current knowledge regarding piRNA dysregulation in AD, examining mechanistic links between piRNA loss, transposable element activation, Aβ toxicity, and tau pathology while evaluating therapeutic implications. We first discuss how AD-associated stressors, including oxidative stress and mitochondrial dysfunction, alter piRNA expression profiles in vulnerable brain regions such as the hippocampus and cortex. Next, we examine mechanistic convergence points: aberrant piRNAs may de-repress transposable elements (e.g., LINE-1), triggering cytosolic DNA sensing pathways and neuroinflammation that exacerbate Aβ aggregation. Simultaneously, piRNA imbalance is hypothesized to disrupt post-transcriptional networks governing microtubule-associated protein tau, potentially via competitive binding with microRNAs or through PIWI-clade proteins that directly interact with tau kinases (e.g., GSK-3β, CDK5). Additionally, we evaluate evidence linking piRNA-mediated epigenetic modulation of *BACE1* and *MAPT* promoters to sustained amyloidogenic and tauogenic cascades. Key databases including PubMed, Google Scholar, and Europe PMC were searched for relevant publications from 2017–2026. Multiple studies demonstrate significant piRNA dysregulation in human AD brains and cerebrospinal fluid, with specific piRNA signatures correlating with Braak staging and amyloid/tau PET biomarkers. Mechanistically, Aβ-induced oxidative stress disrupts PIWI protein expression, leading to LINE-1 retrotransposon derepression, genomic instability, and feedforward amplification of amyloidogenic processing. Tau pathology further exacerbates piRNA depletion through PIWI-piRNA complex mislocalization, creating a vicious cycle of epigenetic dysregulation and neurodegeneration. piRNA dysregulation represents a convergent node linking Aβ and tau pathologies with downstream neuroinflammation via cGAS-STING activation. Restoring piRNA function through synthetic mimics, PIWI stabilizers, or CRISPR activation of piRNA clusters offers novel therapeutic avenues for disease modification in AD.

Keywords: *PIWI-interacting RNA; Alzheimer's disease; Amyloid-beta; Tau pathology; LINE- 1; BACE1; Retrotransposon; CRISPR; Neuroinflammation*



1. Introduction

Alzheimer's disease (AD) affects approximately 55 million individuals worldwide, with prevalence projected to triple by 2050 without effective interventions [1]. The disease is neuropathologically characterized by extracellular deposits of amyloid-beta (Aβ) peptides forming senile plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein [2]. For over three decades, the amyloid cascade hypothesis has provided the dominant framework for understanding AD pathogenesis, positing that Aβ accumulation triggers downstream tau hyperphosphorylation, synaptic dysfunction, and eventual neuronal death [3]. However, accumulating evidence challenges the sufficiency of this framework. The amyloid hypothesis cannot fully explain several critical observations: (i) significant numbers of elderly individuals harbor substantial Aβ deposits without cognitive impairment [4]; (ii) anti-amyloid immunotherapies demonstrate modest clinical efficacy despite substantial plaque clearance [5]; (iii) genetic risk factors for sporadic AD, particularly the apolipoprotein E ε4 (APOE4) allele, confer risk through mechanisms extending beyond amyloid processing [6]; and (iv) the molecular changes underlying early-stage vulnerability remain incompletely characterized, particularly regarding epigenetic alterations that may precede protein aggregation [7].

The tau propagation hypothesis, while providing an elegant explanation for the stereotypical progression of neurofibrillary pathology through connected brain networks [8], similarly fails to account for the earliest molecular events that render specific neuronal populations vulnerable to degeneration. Moreover, neither framework adequately explains why aging represents the strongest risk factor for AD, nor how environmental and lifestyle factors interact with genetic predisposition to determine disease trajectory.

Recent advances in epigenomics have revealed that transposable elements (TEs), particularly long interspersed nuclear element-1 (LINE-1), become derepressed in aging and AD brains, contributing to genomic instability, neuroinflammation, and neuronal dysfunction [9, 10]. These findings suggest that epigenetic derepression of TEs represents an early and potentially causative event in AD pathogenesis, occurring upstream of or in parallel with classical proteinopathy. The piRNA pathway, originally characterized as a germline defense mechanism against TEs, has emerged as a critical guardian of somatic genome integrity in post-mitotic neurons, providing a mechanistic link between aging, epigenetic vulnerability, and neurodegeneration.

PIWI-interacting RNAs (piRNAs) constitute the largest class of small non-coding RNAs in animals, typically 24–32 nucleotides in length, that associate with PIWI clade Argonaute proteins to regulate transposable elements and modulate gene expression [11]. First discovered in Drosophila germline cells [12], piRNAs were long considered restricted to germline tissues where they silence TEs through transcriptional and post-transcriptional mechanisms, preserving genome integrity across generations. However, landmark studies beginning in 2012 demonstrated robust piRNA expression in mammalian somatic tissues, particularly neurons [13].

Rajasethupathy and colleagues identified abundant piRNAs in the adult Aplysia nervous system and demonstrated their essential role in memory-related synaptic plasticity, establishing a somatic function for this pathway beyond TE silencing [13]. Subsequent studies revealed that piRNAs are dynamically expressed throughout mammalian brain development, with distinct patterns in neural progenitor cells, mature neurons, and glial populations [14].

The neuronal piRNA pathway exhibits several distinctive features that underscore its functional importance. First, piRNA expression in neurons far exceeds that observed in other somatic tissues, with certain neuronal piRNA clusters producing thousands of unique small RNA species [15]. Second, neuronal piRNAs display remarkable diversity in their genomic origins, arising not only from canonical piRNA clusters but also from protein-coding gene transcripts, long intergenic non-coding RNAs, and transposable element sequences [16]. Third, the pathway demonstrates dynamic regulation by neuronal activity, with piRNA expression and PIWI protein localization rapidly responding to synaptic stimulation and learning paradigms [17]. Critically, the neuronal piRNA pathway functions as a multifunctional regulator of cellular homeostasis. Beyond canonical TE silencing, neuronal piRNAs modulate mRNA stability and translation [18], regulate alternative splicing [19], influence DNA methylation patterns at specific loci [20], and contribute to DNA repair mechanisms [21]. These diverse functions position piRNAs as central integrators of epigenetic information in post-mitotic neurons, whose long lifespan and non-dividing nature render them particularly dependent on robust genome maintenance mechanisms.

Several converging lines of evidence support the hypothesis that piRNA dysregulation con- tributes to AD pathogenesis. First, post-mitotic neurons are uniquely vulnerable to TE activation due to their extended lifespan, high metabolic activity, and dependence on epigenetic maintenance mechanisms that may decline with age [22]. The piRNA pathway represents a critical defense against such activation, and its compromise would be predicted to have severe consequences for neuronal survival.

Second, recent transcriptomic analyses have identified widespread dysregulation of piRNA expression in human AD brains. A landmark study by Qiu and colleagues detected 9,453 piRNAs in AD brain tissue, with 103 piRNAs showing significant differential expression between AD and control samples [23]. Notably, these changes included both upregulation and downregulation of specific piRNA species, suggesting complex pathway remodeling rather than simple loss of function. Subsequent studies have confirmed piRNA alterations in AD cerebrospinal fluid (CSF) and plasma, highlighting their potential as minimally invasive biomarkers [24].

Third, seminal work by Sun et al. demonstrated that pathogenic tau directly causes piRNA depletion through nuclear exclusion of PIWI proteins, leading to LINE-1 derepression, DNA damage, and neuronal death in tauopathy models [25]. This study provided the first mechanistic link between tau pathology and piRNA pathway dysfunction, establishing a feedforward loop wherein tau aggregation compromises genome defense, leading to further cellular damage. Fourth, Aβ oligomers induce oxidative stress and impair mitochondrial function [26], conditions known to disrupt piRNA biogenesis factors including mitochondrial-associated proteins essential for primary piRNA production [27]. Aβ-induced cellular stress may therefore compromise piRNA pathway function independently of tau pathology, or synergistically with it, creating multiple entry points for piRNA dysregulation in AD.

Finally, the downstream consequences of piRNA loss, TE activation, genomic instability, neuroinflammation via cytosolic DNA sensing pathways, and dysregulated gene expression, converge on established mechanisms of AD pathogenesis, suggesting that piRNA dysregulation may represent a unifying upstream event that amplifies classical proteinopathy-driven damage. The landscape of non-coding RNA (ncRNA) research in AD has been dominated by microRNAs (miRNAs) and, more recently, long non-coding RNAs (lncRNAs). Hundreds of miRNAs have been implicated in regulating APP processing, tau phosphorylation, and neuroinflammation [28], while lncRNAs such as BACE1-AS have been shown to modulate Aβ production through diverse mechanisms [29]. These discoveries have advanced our understanding of post-transcriptional gene regulation in AD and identified promising therapeutic targets.

This review synthesizes current evidence for piRNA dysregulation in AD across multiple levels: molecular mechanisms of piRNA biogenesis and function in neurons; transcriptomic evidence from human AD tissues and biofluids; mechanistic links to Aβ toxicity and tau pathology; down- stream consequences for neuroinflammation and intercellular communication; and therapeutic strategies targeting the piRNA pathway. By positioning piRNAs within an integrated model of AD pathogenesis, we aim to illuminate novel therapeutic targets and biomarker opportunities that may complement existing approaches focused on protein clearance.

2. Biogenesis and Canonical Functions of piRNAs in Neural Homeostasis

2.1. Genomic Organization: piRNA Clusters, Ping-Pong Cycle, and PIWI Clade Proteins (PIWIL1–4 in Humans)

piRNA biogenesis represents a complex, multi-step process involving coordinated action of numerous nuclear and cytoplasmic factors. In humans, four PIWI proteins, PIWIL1 (HIWI), PIWIL2 (HILI), PIWIL3, and PIWIL4 (HIWI2), serve as the effector molecules that bind piRNAs and execute their regulatory functions [31]. These proteins exhibit distinct expression patterns, subcellular localizations, and functional specializations that together enable the diverse roles of the piRNA pathway.

Genomic Architecture of piRNA Loci. piRNAs are predominantly generated from ge- nomic regions termed piRNA clusters, which span tens to hundreds of kilobases and are enriched in transposable element fragments and repetitive sequences [32]. The human genome contains ap- proximately 200 such clusters, many located on autosomes but with significant representation on sex chromosomes, particularly the Y chromosome [33]. These clusters are transcribed as long single-stranded precursors by RNA polymerase II, generating transcripts that are subsequently processed into mature piRNAs. piRNA clusters are classified into two major categories based on their genomic organization and processing mechanisms. Unidirectional clusters contain TE sequences oriented in one di- rection and produce primary piRNAs exclusively from the same genomic strand. In contrast, bidirectional clusters contain TE sequences in both orientations, enabling the production of both sense and antisense piRNAs that can engage in the ping-pong amplification cycle [34].

Primary piRNA Biogenesis. Primary piRNA production initiates with the transcription of cluster-derived long precursor RNAs, which are exported to the cytoplasm where they associate with mitochondrial membranes [35]. Here, the endonuclease PLD6 (also known as Zucchini or MitoPLD) cleaves these precursors to generate piRNA intermediates with 5' uridine preferences [36]. The fragments are then loaded onto PIWI proteins, with PIWIL2 and PIWIL4 primarily receiving primary piRNAs in humans [37]. Following loading, the 3' ends of piRNA intermediates undergo trimming by exonucleases, including PARN and TDRD9, followed by 2'-O-methylation at the 3' terminal nucleotide catalyzed by HENMT1 [38] (Figure 1). This methylation confers stability by protecting piRNAs from exonucleolytic degradation and distinguishes them functionally from miRNAs. The mature piRNA-PIWI complexes then traffic between cytoplasmic processing bodies and the nucleus, where they execute their regulatory functions [37, 39].

The Ping-Pong Cycle. A defining feature of piRNA biogenesis is the amplification loop known as the ping-pong cycle, which dramatically increases piRNA abundance while enriching for sequences targeting active transposable elements [39]. This cycle operates as follows: a primary piRNA loaded onto PIWIL2 (or PIWIL4) recognizes and cleaves complementary target transcripts, including active TE mRNAs, generating new 5' ends precisely 10 nucleotides down- stream of the original piRNA's 5' end. These cleavage products are loaded onto PIWIL1 (or PIWIL3), forming the opposite strand of secondary piRNAs [40].

The secondary piRNAs, in turn, target antisense TE transcripts or cluster-derived precursors, generating additional primary piRNAs and completing the amplification loop. This cycle preferentially amplifies piRNAs targeting active TEs, providing an adaptive defense mechanism that responds to TE threat [40]. Notably, the ping-pong cycle generates characteristic signatures, 10-nucleotide overlaps between sense and antisense piRNAs, that can be detected in deep sequencing data, providing evidence for active amplification [41]. Neuronal Specificities. While the core piRNA biogenesis machinery is conserved across tissues, neurons exhibit several distinctive features. First, neuronal piRNA populations include numerous species derived from non-cluster genomic regions, including protein-coding gene 3' UTRs and intergenic sequences, suggesting expanded targeting capabilities beyond TE control [41]. Second, neuronal piRNA expression changes dynamically throughout development, with distinct populations emerging during neurogenesis, synaptogenesis, and aging [42]. Third, PIWI protein subcellular localization in neurons is activity-dependent, with nuclear-to-cytoplasmic shuttling regulated by synaptic stimulation [43].

2.2. Non-Canonical Roles: Epigenetic Silencing, mRNA Stability, and Translation Regulation

While TE silencing represents the canonical function of piRNAs, accumulating evidence reveals diverse non-canonical roles in gene regulation that are particularly relevant to neuronal function and may be compromised in neurodegenerative disease. Transcriptional Silencing via DNA Methylation and Heterochromatin Formation. Nuclear PIWI-piRNA complexes can direct transcriptionally silencing of target loci through recruitment of epigenetic repressive machinery [42, 44].

In Drosophila, Piwi-mediated silencing involves interaction with heterochromatin protein 1 (HP1) and the histone methyltransferase Su(var), leading to H3K9me3 deposition and heterochromatin formation at TE loci [44]. Mammalian PIWIL proteins similarly associate with DNA methyltransferases (DNMT3A/3B) and histone methyltransferases (SUV39H1), enabling DNA methylation and repressive histone modifications at target sequences [45].

This transcriptional silencing mechanism extends beyond TEs to regulate protein-coding genes. Studies in neuronal cells demonstrate that PIWIL2 can localize to gene promoters and influence their expression through epigenetic modifications [46]. The ability to direct locus-specific epigenetic changes positions piRNAs as potential regulators of gene expression programs under- lying neuronal plasticity and memory formation. Post-Transcriptional Regulation of mRNA Stability and Translation. Cytoplasmic piRNA-PIWI complexes can regulate mRNA fate through multiple mechanisms. Direct base-pairing between piRNAs and complementary sequences in mRNA 3' UTRs can trigger translational repression or mRNA destabilization, similar to miRNA-mediated regulation but often with greater specificity due to longer complementarity [47].

Additionally, PIWI proteins interact with translation machinery components, including eIF4E and poly(A)-binding proteins, suggesting direct modulation of protein synthesis [48]. In Aplysia neurons, specific piRNAs have been shown to regulate local protein synthesis at synapses, a process essential for memory consolidation [13]. This capability for local, activity-dependent translational control may be particularly important in neurons with extended processes where nuclear- encoded regulation is insufficiently rapid. Alternative Splicing Regulation. Emerging evidence indicates that piRNAs can influence alternative splicing decisions. PIWIL1 has been detected in nuclear speckles, subnuclear domains enriched in splicing factors, and piRNA depletion alters splicing patterns for genes involved in synaptic function and neurodevelopment. The mechanistic basis for this regulation remains incompletely understood but may involve piRNA-guided recruitment of splicing factors to pre-mRNA or modulation of chromatin marks that influence splice site selection [45, 49].

DNA Repair and Genome Maintenance. Recent studies implicate the piRNA path- way in DNA repair mechanisms. PIWIL2 interacts with RAD [51], a key component of homologous recombination, and piRNA-depleted cells show increased sensitivity to DNA double- strand breaks [50]. Given that DNA damage accumulates in aging neurons and contributes to AD pathogenesis [51], this function may be particularly relevant to neurodegenerative vulnerability.

2.3. Unique Features in Post-Mitotic Neurons: piRNA Expression Dynamics During Aging and Stress

Post-mitotic neurons present unique challenges for genome maintenance that may heighten their dependence on piRNA-mediated defenses. Unlike dividing cells, which can dilute accumulated damage through cell division, neurons must maintain genomic integrity throughout the organ- ism's lifetime [51]. This extended lifespan renders neurons particularly vulnerable to the cumulative effects of TE activation, DNA damage, and epigenetic drift. Aging-Related Changes in piRNA Expression. Multiple studies document age-dependent alterations in piRNA expression profiles. In Drosophila, piRNA abundance declines with age in brain tissue, correlating with increased TE expression [52]. Similar patterns have been observed in mammalian systems, with reduced expression of specific piRNA clusters and PIWI proteins in aged mouse and human brain tissue [53]. These aging-related changes are not uniform across all piRNA species. Certain piRNAs targeting evolutionarily recent TE families show the most pronounced decline, potentially reflecting the adaptive nature of the piRNA response [54]. The mechanisms underlying age-related piRNA loss remain incompletely characterized but may include reduced expression of biogenesis factors, impaired PIWI protein stability, and altered subcellular localization.

Stress-Induced piRNA Alterations. Neuronal piRNA expression responds dynamically to cellular stressors relevant to AD pathogenesis. Oxidative stress, a hallmark of AD brain tissue, alters piRNA biogenesis through multiple mechanisms. First, oxidative damage to piRNA precursors or PIWI proteins may impair their function [55]. Second, oxidative stress-induced mitochondrial dysfunction compromises the biogenesis machinery that depends on mitochondrial membranes. Third, stress signaling pathways may directly regulate piRNA cluster transcription or PIWI protein expression [56]. Heat shock and other proteotoxic stressors also modulate piRNA pathway components. The heat shock protein HSP90 interacts with PIWI proteins and is required for their stability and function [57]. Under conditions of proteotoxic stress, such as those induced by Aβ oligomers or aggregated tau, competition for HSP90 may compromise piRNA pathway integrity while also affecting other HSP90 clients including kinases involved in tau phosphorylation [55, 57].

Activity-Dependent Regulation. Neuronal activity dynamically regulates piRNA ex- pression and PIWI protein localization. Electrical stimulation of hippocampal neurons induces rapid changes in nuclear PIWIL1 levels [43] (Figure 1), while learning paradigms alter expression of specific piRNA populations in the hippocampus and cortex. This activity-dependence suggests that piRNAs may participate in activity-dependent gene expression programs underlying synaptic plasticity and memory formation [58]. The mechanisms linking neuronal activity to piRNA regulation are beginning to emerge. Calcium signaling, a central mediator of activity-dependent responses, modulates piRNA bio- genesis factor expression and PIWI protein phosphorylation. Activity-regulated transcription factors may directly activate piRNA cluster transcription, while activity-dependent changes in chromatin accessibility could alter piRNA precursor production from specific genomic loci [59].

3. Evidence of piRNA Dysregulation in AD

3.1. Transcriptomic Profiling Studies in Human AD Brains and CSF: Upregulated vs. Downregulated piRNA Signatures

The application of high-throughput RNA sequencing technologies to AD research has enabled comprehensive characterization of small RNA alterations in disease tissues, revealing substantial piRNA dysregulation across multiple brain regions and biofluids. The first systematic analysis of piRNA alterations in human AD brains was conducted by Qiu and colleagues, who performed small RNA sequencing on hippocampal tissue from AD patients and age-matched controls [23]. This study detected 9,453 distinct piRNAs in brain tissue, with 103 piRNAs showing significant differential expression in AD. Notably, the observed changes were bidirectional: 61 piRNAs were significantly upregulated while 42 were downregulated, suggesting complex pathway remodeling rather than uniform loss of function [23, 58-60].

Subsequent studies have expanded these observations to additional brain regions and larger cohorts. Analysis of the prefrontal cortex from the Religious Orders Study and Rush Memory and Aging Project (ROSMAP) cohort identified over 500 differentially expressed piRNAs, with pathway analysis implicating specific clusters on chromosomes 1, 9, and X [60]. Regional comparisons revealed that the hippocampus and entorhinal cortex, regions showing earliest and most severe pathology, exhibited the most pronounced piRNA alterations, while the cerebellum, relatively spared in AD, showed minimal changes [60].

The majority of differentially expressed piRNAs in AD brains originate from intronic regions of protein-coding genes, raising the possibility that their altered abundance reflects changes in host gene transcription rather than specific piRNA regulation. However, a substantial subset of altered piRNAs derives from intergenic clusters and transposable element sequences, suggesting independent regulation of piRNA biogenesis in disease states [23, 31].

Cerebrospinal Fluid and Blood-Based Studies. The detection of piRNAs in accessible biofluids has significant implications for biomarker development. Recent studies have identified altered piRNA profiles in AD CSF, with specific signatures distinguishing AD from cognitively normal controls and correlating with disease severity [24]. A combined signature of three miRNAs and three piRNAs demonstrated high diagnostic accuracy for AD, with area under the receiver operating characteristic curve (AUC) exceeding 0.85 [61]. Plasma piRNA profiles have also shown promise for AD detection. Xin and colleagues identified over 1,000 differentially expressed piRNAs in plasma from AD patients compared to controls, with enrichment for piRNAs targeting neuroinflammation-related genes. Notably, some plasma piRNA alterations mirrored those observed in brain tissue, suggesting that peripheral piRNA changes may reflect central nervous system pathology [62].

Correlations with Molecular Pathology. piRNA alterations in AD brain tissue correlate with established measures of disease pathology. In hippocampal samples, expression levels of specific piRNAs targeting LINE-1 elements show inverse correlation with LINE-1 mRNA and protein abundance, consistent with loss of TE silencing as a consequence of piRNA reduction. Additionally, piRNA changes correlate with markers of DNA damage, including γH2AX foci and 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels,63 supporting a mechanistic link between piRNA loss and genomic instability [25, 26].

3.2. Correlation with Braak Staging, Amyloid PET, and Tau PET Biomarkers

The relationship between piRNA alterations and established AD biomarkers provides insight into the temporal dynamics of piRNA dysregulation during disease progression. Braak Stage Correlations. Analysis of piRNA expression across different Braak stages reveals progressive changes that parallel neurofibrillary pathology.

Early Braak stages (I–II), characterized by limited entorhinal cortex involvement, show relatively modest piRNA alterations. However, by Braak stages III–IV, when pathology extends to limbic regions, substantial piRNA dysregulation becomes evident, with further progression at stages V–VI [62-64].

This staging-dependent pattern suggests that piRNA alterations may accelerate with disease progression, potentially creating a feedforward loop wherein accumulated pathology drives further epigenetic dysregulation. Alternatively, certain piRNA changes may represent protective responses that become overwhelmed as disease advances. Correlation with Amyloid and Tau PET. In vivo imaging biomarkers enable correlation of molecular piRNA changes with regional Aβ and tau burden [62, 63]. Studies combining PET imaging with subsequent tissue analysis demonstrate that brain regions with high amyloid or tau tracer uptake exhibit the most pronounced piRNA alterations. Specific piRNAs show particularly strong correlations with tau PET signals, consistent with the demonstrated effect of tau pathology on PIWI protein localization [25, 65].

Notably, some piRNA alterations appear to precede detectable PET signal changes, suggesting potential utility as early biomarkers. Preclinical AD cases with abnormal CSF Aβ42 but normal amyloid PET show intermediate piRNA expression patterns between normal controls and overt AD, supporting the hypothesis that piRNA changes occur during preclinical disease stages [65, 66].

3.3. Cell-Type Specificity: Microglial, Astrocytic, and Neuronal piRNA Changes in AD Models

The cellular specificity of piRNA alterations in AD has important implications for understanding disease mechanisms and developing targeted interventions. Recent advances in single-cell and single-nucleus RNA sequencing have begun to resolve cell-type-specific piRNA changes.

Neuronal piRNA Alterations. Neurons show the most pronounced piRNA dysregulation in AD brain tissue, consistent with their high baseline piRNA expression and vulnerability to degeneration. Both excitatory and inhibitory neurons exhibit piRNA changes, though distinct patterns emerge between subtypes. Excitatory neurons of the hippocampal CA1 region, which are particularly vulnerable in AD, show downregulation of piRNAs targeting evolutionarily young LINE-1 subfamilies, potentially explaining the observed activation of these elements in vulnerable neuronal populations [66-68]. GABAergic interneurons also exhibit piRNA alterations, though the pattern differs from principal neurons. Parvalbumin-positive interneurons show preserved or even increased expression of specific piRNA clusters, potentially reflecting compensatory responses or differential vulnerability to disease processes [68].

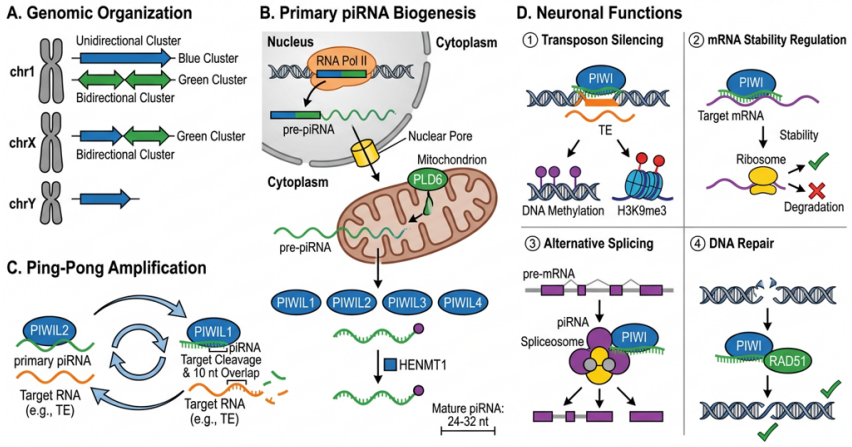


Figure 1: piRNA Biogenesis Pathway and Neuronal Functions. (A) Genomic organization of piRNA clusters on human chromosomes, with enrichment on sex chromosomes. Unidirectional clusters produce primary piRNAs from one strand, while bidirectional clusters enable ping- pong amplification. (B) Primary piRNA biogenesis involves transcription by RNA polymerase II, export to cytoplasm, and cleavage by PLD6 at mitochondrial membranes. Mature piRNAs (24–32 nt) are loaded onto PIWI proteins (PIWIL1–4) with 3' end methylation by HENMT1. (C) The ping-pong amplification cycle: PIWIL2-bound primary piRNAs cleave complementary transcripts, generating secondary piRNAs loaded onto PIWIL1, which in turn generate additional primary piRNAs. (D) Neuronal functions of piRNAs include transposon silencing via DNA methylation and H3K9me3 deposition, post-transcriptional regulation of mRNA stability and translation, alternative splicing modulation, and DNA repair facilitation.

Microglia and astrocytes, while expressing lower baseline piRNA levels than neurons, also show disease-associated alterations. Microglia from AD brains exhibit downregulation of piRNAs targeting inflammatory pathway components, potentially contributing to the sustained neuroinflammatory state characteristic of AD. Astrocytic piRNA changes include upregulation of species targeting glutamate transporter mRNAs, which may impair glutamate clearance and contribute to excitotoxicity [69, 70]. The cell-type specificity of piRNA alterations suggests that therapeutic strategies targeting the piRNA pathway may need to consider cell-type-specific delivery or mechanism of action. Neuronal-focused interventions may prioritize restoration of TE silencing and genome integrity, while microglial targeting might emphasize anti-inflammatory effects [70].

4. Mechanistic Links Between piRNA Dysregulation and Amyloid- beta Toxicity

4.1. Aβ-Induced Oxidative Stress and piRNA Processing Enzyme Dysfunction

Amyloid-beta oligomers, the neurotoxic species thought to drive synaptic dysfunction and neuronal death in AD, induce multiple cellular stress responses that converge on piRNA pathway disruption. Oxidative Stress and Mitochondrial Dysfunction. Aβ oligomers generate reactive oxygen species (ROS) through multiple mechanisms, including direct interaction with transition metals, activation of NADPH oxidase, and impairment of mitochondrial electron transport chain function. This oxidative stress has profound consequences for piRNA biogenesis, as multiple pathway components are sensitive to oxidative damage [71].

The endonuclease PLD6, essential for primary piRNA production, requires an intact catalytic site with conserved cysteine residues that are susceptible to oxidation [72]. Oxidative modification of PLD6 impairs its endonuclease activity, reducing the generation of piRNA intermediates from cluster transcripts. Similarly, the methyltransferase HENMT1, responsible for stabilizing mature piRNAs, shows reduced activity under oxidative conditions [73]. Mitochondrial dysfunction induced by Aβ may further impair piRNA biogenesis through disruption of the mitochondrial membrane platform where PLD6 operates. As mitochondrial dynamics and membrane integrity deteriorate in response to Aβ toxicity, the spatial organization of piRNA processing may be compromised, effectively decoupling precursor transcription from downstream processing steps [74].

PIWI Protein Stability and Localization. Aβ-induced cellular stress affects PIWI protein stability through multiple mechanisms. The chaperone HSP90, which stabilizes PIWIL2 and PIWIL4, becomes sequestered by misfolded proteins and aggregated species in stressed neurons. Competition for limited HSP90 capacity may therefore compromise PIWI protein folding and stability, reducing functional piRNA-PIWI complex formation [57, 71]. Additionally, Aβ exposure alters PIWI protein subcellular localization. In cultured neurons treated with Aβ oligomers, PIWIL1 shows reduced nuclear localization and accumulation in cytoplasmic aggregates, potentially impairing its transcriptional regulatory functions while also sequestering associated piRNAs away from their nuclear targets [75].

4.2. Permissive Retrotransposon Activity: LINE-1 Derepression as a Mediator of Aβ-Driven DNA Double-Strand Breaks

The consequences of piRNA pathway disruption extend to activation of transposable elements, particularly LINE-1, with profound implications for neuronal genome integrity. LINE-1 Activation in AD. Multiple independent studies have documented LINE-1 activation in AD brains. LINE-1 mRNA and the encoded ORF1p protein are elevated in hippocampal and cortical tissue from AD patients compared to age-matched controls [76]. Single-cell analyses reveal that LINE-1 activation occurs predominantly in neurons, with the highest expression observed in cells exhibiting AD-related transcriptional signatures [77].

The mechanism linking piRNA loss to LINE-1 activation involves derepression of transcriptional silencing. In healthy neurons, piRNA-directed DNA methylation and H3K9me3 deposition maintain LINE-1 promoters in a heterochromatic state. When piRNA levels decline, these re- pressive marks are lost, enabling RNA polymerase II access and transcriptional activation. Once expressed, LINE-1 mRNA is exported to the cytoplasm where it is translated into ORF1p and ORF2p proteins that enable retrotransposition [77, 78].

DNA Double-Strand Break Formation. LINE-1 retrotransposition involves reverse transcription of LINE-1 mRNA and integration of the resulting cDNA into the genome, a process mediated by ORF2p endonuclease activity that creates DNA double-strand breaks (DSBs) at target sites [79] (Figure 2). Even in the absence of productive retrotransposition, LINE-1 ORF2p expression generates DSBs through its endonuclease activity, overwhelming cellular DNA repair capacity [80].

Aβ-induced piRNA depletion may therefore create a permissive environment for LINE-1- mediated DNA damage. Neurons exposed to Aβ oligomers show increased LINE-1 expression, elevated DSB markers (including γH2AX and 53BP1 foci), and impaired DNA repair responses. These effects are attenuated by LINE-1 knockdown or overexpression of specific piRNAs targeting LINE-1 sequences, establishing a causal link between piRNA loss, LINE-1 activation, and genomic instability [80-82].

4.3. Feedforward Loop: Aβ Oligomers, piRNA Loss, Genomic Instability, Increased BACE1 Expression, and APP Processing

The relationship between Aβ toxicity and piRNA dysregulation may form a self-amplifying feedforward loop that accelerates disease progression. Genomic Instability and APP Processing. DNA damage activates cellular stress responses that can influence amyloidogenic APP processing. The DNA damage response (DDR) kinase ATM phosphorylates multiple substrates involved in APP metabolism, including FE65, a nuclear adaptor protein that influences APP transcriptional regulation [83]. Additionally, DDR activation increases BACE1 expression through p53-dependent transcriptional mechanisms, potentially increasing Aβ production [84].

LINE-1-mediated DNA damage may therefore amplify amyloidogenic processing through DDR activation. Neurons with elevated LINE-1 activity show increased BACE1 expression and Aβ production [85], while genetic or pharmacological inhibition of LINE-1 reduces amyloid burden in AD mouse models. Closing the Loop. The feedforward loop operates as follows: (i) Aβ oligomers induce oxidative stress and impair mitochondrial function; (ii) these stressors compromise piRNA biogenesis and PIWI protein stability; (iii) piRNA depletion permits LINE-1 derepression (Table 1); (iv) LINE-1 activity generates DNA DSBs and activates the DDR; (v) DDR signaling increases BACE1 expression and Aβ production (Figure 2); (vi) increased Aβ further stresses neurons and perpetuates the cycle [84-87].

This model suggests that piRNA dysregulation may not merely accompany AD pathology but actively drive disease progression by amplifying the amyloidogenic cascade. Interventions that restore piRNA function or inhibit LINE-1 activity could potentially break this feedforward loop, offering disease-modifying effects independent of direct Aβ clearance [86, 87].

Table 1. Integrated Pathological Cascade Linking Aβ-Induced Oxidative Stress, piRNA Pathway Dysfunction, and LINE-1 Derepression to Genomic Instability, DNA Double-Strand Breaks, and Feed-Forward Amplification of BACE1/APP Processing.

Pathological Node	Primary Trigger / Event	Molecular Consequence	Downstream Effector	Feedback Loop Target	Resulting Cellular Phenotype
Aβ Oligomer Accumulation	Extracellular and intraneuronal Aβ42 oligomers	ROS burst (•OH, H_2O_2, $ONOO^-$), lipid peroxidation (4-HNE adducts)	Oxidative inactivation of piRNA processing enzymes (e.g., PIWIL1, DDX4, TUT4/7)	Impaired piRNA biogenesis → loss of transposon silencing	Proteostatic stress, synaptic dysfunction, initiation of oxidative cascade [25, 57, 71, 85]
piRNA Processing Enzyme Dysfunction	4-HNE modification and carbonylation of PIWI-clade proteins	Reduced ping-pong cycle activity, defective piRNA 3′ end methylation (HENMT1 inactivation)	Global reduction in piRNA repertoire, particularly those targeting LINE-1 ORF1/ ORF2	LINE-1 promoter hypomethylation (secondary to piRNA loss)	Retrotransposon derepression, loss of small RNA-mediated genome defense [38, 73]

LINE-1 Derepression	Loss of piRNA-mediated silencing + oxidative demethylation of LINE-1 5′UTR	Increased L1 ORF1p (RNA chaperone) and ORF2p (endonuclease/ RT) expression	L1 RNP formation, reverse transcription in the nucleus	Direct nicking of genomic DNA at TTAAAA consensus sites	DNA single-strand nicks, replication fork stalling [74-78, 84-88]
DNA Double-Strand Breaks (DSBs)	Stalled replication forks at L1 insertion sites, ORF2p endonuclease activity, abortive reverse transcription	γH2AX focus formation, ATM/ ATR pathway activation, p53 phosphorylation	Chronic DDR signaling, non-homologous end joining (NHEJ) errors	Genomic rearrangements at the *BACE1* and *APP* loci	Chromosomal translocations, copy number variations, cellular senescence [79-43]
Genomic Instability-Induced BACE1 Upregulation	DSB-driven enhancer–promoter rewiring, loss of miR-29a/b binding sites in *BACE1* 3′UTR	Increased BACE1 transcription (≥5-fold), reduced lysosomal degradation of BACE1	Elevated β-secretase activity, increased sAPPβ and C99 fragments	Further Aβ42 generation via amyloidogenic pathway	Feed-forward loop: more Aβ → more oxidative stress → more piRNA loss → more L1 activity → more DSBs → more BACE1 [84-87]
Aberrant APP Processing	BACE1 overexpression + γ-secretase modulation by lipid peroxidation products	Shift from α- to β-cleavage, increased Aβ42/ Aβ40 ratio	Intracellular Aβ oligomer accumulation, mitochondrial Aβ import	ROS amplification (via mitochondrial Aβ + mPTP opening)	Self-sustaining cycle of oxidative stress, genomic damage, and proteotoxicity [84, 86-89]

4.4. Emerging Evidence from piRNA Knockdown in APP/PS1 Neuronal Cultures

Experimental manipulation of piRNA levels in AD model systems provides direct evidence for the pathway's contribution to Aβ-related pathology. piRNA Knockdown Phenotypes. Acute knockdown of individual PIWI proteins or piRNA biogenesis factors in primary neurons induces phenotypes relevant to AD pathogenesis. PIWIL2 knockdown increases LINE-1 expression, activates the cGAS-STING pathway, and sensitizes neurons to Aβ-induced toxicity. These effects are attenuated by concurrent LINE-1 suppression, confirming that LINE-1 derepression mediates downstream consequences of piRNA loss [86, 87].

4.4. Emerging Evidence from piRNA Knockdown in APP/PS1 Neuronal Cultures

In APP/PS1 transgenic mouse neurons, piRNA pathway inhibition exacerbates Aβ-induced synaptic dysfunction, impairing long-term potentiation and reducing dendritic spine density be- yond the effects of Aβ alone [88]. Conversely, supplementation with synthetic piRNAs targeting LINE-1 sequences partially rescues synaptic deficits in these cultures, demonstrating therapeutic potential [89]. CRISPR Activation of piRNA Clusters. Recent studies have employed CRISPR activation (CRISPRa) to upregulate endogenous piRNA cluster expression in neurons. Targeted activation of the human 12q24.31 piRNA cluster, which produces LINE-1-targeting piRNAs, reduces LINE-1 expression and protects against Aβ-induced neurotoxicity. These proof-of- concept experiments validate the therapeutic hypothesis that restoring piRNA expression can mitigate AD-related pathology [90].

5. Crossroads of piRNA Dysregulation and Tau Pathology

5.1. Tau Hyperphosphorylation and PIWI-piRNA Complex Mislocalization from Nucleus to Cytoplasm

The landmark study by Sun et al. established a direct mechanistic link between tau pathology and piRNA dysregulation, demonstrating that pathogenic tau induces piRNA depletion through disruption of PIWI protein nuclear localization. Tau-Mediated Nuclear Export of PIWI Proteins. Under normal conditions, PIWIL1 and PIWIL2 shuttle between the nucleus and cytoplasm, with nuclear localization required for their transcriptional regulatory functions. In tauopathy models, hyperphosphorylated and aggregated tau accumulates in the nucleus, where it interacts directly with PIWI proteins and promotes their export to the cytoplasm [25].

This interaction is mediated by the proline-rich region of tau and the PAZ domain of PIWI proteins. Pathogenic tau mutations (including P301L and R406W) associated with familial frontotemporal dementia enhance this interaction, explaining the more severe piRNA depletion observed in these genetic forms. Once exported, PIWI proteins accumulate in cytoplasmic aggregates containing phosphorylated tau, effectively sequestering them away from their nuclear targets [91].

Consequences for piRNA Function. Nuclear PIWI depletion has profound consequences for piRNA-mediated transcriptional silencing. Without nuclear PIWI proteins, piRNAs cannot direct heterochromatin formation or DNA methylation at TE loci, leading to derepression. Consistent with this mechanism, tau transgenic mice and human tauopathy brains show reduced nuclear PIWIL1 staining that correlates with LINE-1 expression levels and neurofibrillary pathology burden [25, 29]. The cytoplasmic sequestration of PIWI proteins also impairs their post-transcriptional regulatory functions. piRNAs retained in cytoplasmic aggregates cannot access their mRNA targets, disrupt translational regulation and potentially contribute to synaptic dysfunction [92].

5.2. piRNA Targetome Analysis: Predicted Binding to Tau mRNA 3'UTR and Alternative Splicing Alterations

Beyond the indirect effects of PIWI mislocalization, specific piRNAs may directly regulate tau expression and processing through post-transcriptional mechanisms. Tau mRNA as a piRNA Target. Bioinformatic analysis identifies multiple piRNA binding sites within the 3' UTR of human MAPT mRNA encoding tau protein [93]. These sites exhibit strong complementarity to piRNAs expressed in human brain tissue, suggesting potential for direct regulation. Experimental validation using reporter assays confirms that specific piRNAs can suppress tau mRNA translation through 3' UTR binding, providing an endogenous mechanism for tau regulation [94].

Notably, the 3' UTR of MAPT contains multiple genetic variants associated with AD risk, including the rs242557 variant in the MAPT H1 haplotype. These variants alter piRNA binding site accessibility, potentially modulating tau expression levels and disease risk through piRNA- mediated regulation. Individuals carrying risk variants that disrupt piRNA binding show elevated tau expression in brain tissue, supporting functional relevance [95, 96]. Alternative Splicing Regulation. MAPT undergoes complex alternative splicing to generate six major tau isoforms in the adult human brain, with the 3R:4R isoform ratio critical for normal function and disease pathogenesis. piRNAs have been implicated in splicing regulation through interactions with spliceosome components and modulation of chromatin marks influencing exon inclusion [96, 97]. Specific piRNAs show differential expression between brain regions with distinct tau isoform profiles, and piRNA depletion alters MAPT splicing patterns in neuronal cultures. These findings suggest that piRNA dysregulation may contribute to abnormal tau splicing in AD, potentially increasing production of aggregation-prone isoforms or disrupting the normal 3R:4R balance [98, 99].

5.3. Neurofibrillary Tangle-Associated piRNAs: Potential Role in Microtubule Stability via HSP70/90 Modulation

Neurofibrillary tangles (NFTs), the hallmark intracellular inclusions of AD, contain hyperphosphorylated tau along with numerous associated proteins and nucleic acids. Recent analyses have identified piRNA enrichment within NFT fractions isolated from AD brain tissue. piRNA Sequestration in Tangles [100]. The mechanism of piRNA incorporation into NFTs remains incompletely understood but likely involves binding to tau-associated proteins with nucleic acid binding capacity, including heterogeneous nuclear ribonucleoproteins (hnRNPs) and TAR DNA-binding protein 43 (TDP-43) [101]. Once incorporated, piRNAs may be unavailable for their normal regulatory functions, effectively producing a functional depletion even if total cellular piRNA levels appear preserved. The specific piRNA species enriched in NFTs differ from those depleted in soluble fractions, suggesting selective sequestration based on sequence features or associated proteins. NFT-associated piRNAs show enrichment for sequences targeting cytoskeletal and synaptic genes, potentially explaining the selective vulnerability of these cellular compartments in AD [101, 102].

Effects on Chaperone Function. The heat shock proteins HSP70 and HSP90 play critical roles in tau biology, with HSP70 promoting tau clearance and HSP90 stabilizing pathogenic conformations [103]. PIWI proteins interact with both HSP70 and HSP90, and piRNAs modulate these interactions through allosteric effects on PIWI protein conformation. piRNA depletion or sequestration may therefore alter chaperone function in AD neurons. Reduced piRNA availability could impair HSP70-mediated tau clearance while enhancing HSP90-dependent stabilization of toxic tau species, shifting the balance toward aggregation and neurodegeneration [104]. Consistent with this model, HSP90 inhibitors, which disrupt PIWI-chaperone interactions, reduce tau pathology in transgenic mice while also restoring piRNA pathway function [57, 105].

5.4. Synergistic Effect: Combined piRNA Loss and Tau Seeding Exacerbate Synaptic Failure in 3D Culture Models

The convergence of piRNA dysregulation and tau pathology produces synergistic effects on neuronal function that exceed the additive contributions of each insult alone. 3D Culture Models. Human induced pluripotent stem cell (iPSC)-derived 3D neural culture systems enable modeling of AD pathogenesis in a more physiologically relevant context than traditional 2D cultures. These models support formation of synaptically connected neuronal net- works and can recapitulate key AD features including Aβ aggregation and tau propagation when seeded with patient-derived brain extracts [106].

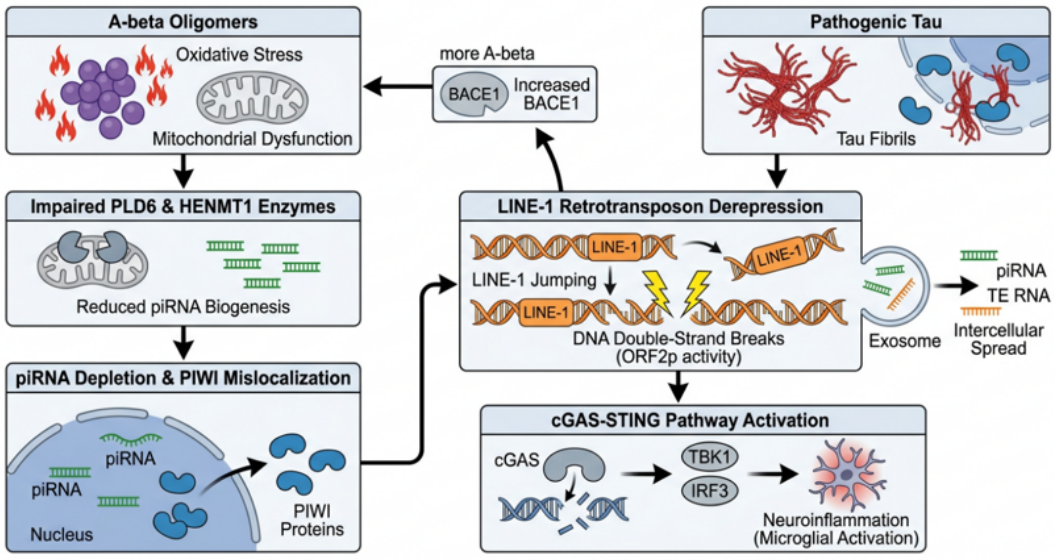


Figure 2: Mechanistic Links Between piRNA Dysregulation and AD Pathology. (A) Amyloid-beta toxicity induces oxidative stress and mitochondrial dysfunction, impairing PLD6 and HENMT1 function to reduce piRNA biogenesis. (B) piRNA depletion permits LINE-1 retrotransposon derepression; ORF2p-mediated DNA cleavage generates double-strand breaks (DSBs). (C) DNA damage activates DDR pathways, increasing BACE1 expression and Aβ pro- duction, creating a feedforward loop. (D) Pathogenic tau sequesters PIWI proteins in cytoplasmic aggregates, preventing nuclear translocation and transcriptional silencing. (E) Convergent activation of cGAS-STING pathway by cytosolic LINE-1 DNA and mitochondrial DNA triggers neuroinflammation. (F) Exosomal release of piRNAs and transposable element RNA enables intercellular propagation of epigenetic vulnerability.

In 3D cultures, combined manipulation of piRNA levels and tau seeding produces more severe synaptic dysfunction than either manipulation alone. PIWIL2 knockdown cultures seeded with AD-derived tau show accelerated tau aggregation, reduced synaptic puncta, and impaired network activity compared to control cultures with equivalent tau seeding [107]. Conversely, piRNA supplementation delays tau seeding and preserves synaptic function, supporting a protective role for the pathway [108]. The synergistic interaction between piRNA loss and tau pathology likely reflects convergence on common downstream pathways. Both insults activate the cGAS-STING pathway, induce DNA damage, and disrupt synaptic homeostasis, such that combined exposure exceeds cellular resilience thresholds. Additionally, piRNA loss may impair cellular defenses against proteotoxic stress, rendering neurons more vulnerable to tau aggregation [109].

6. Common Downstream Pathways: Neuroinflammation, Exosome Communication, and Epigenetic Memory

6.1. piRNA Dysregulation as a Trigger for cGAS-STING Activation via Cytosolic Retroelement DNA

The cGAS-STING pathway represents a critical innate immune surveillance mechanism that detects cytosolic DNA and initiates inflammatory responses. In AD, aberrant cGAS-STING activation contributes to neuroinflammation and neuronal death, and piRNA dysregulation may serve as an upstream trigger for this pathway [110].

Sources of Cytosolic DNA. Multiple DNA species accumulate in the cytosol of stressed and aging neurons, including mitochondrial DNA (mtDNA) released during mitochondrial dysfunction [111], and retroelement DNA generated by LINE-1 reverse transcription [112]. Under normal conditions, these DNA species are efficiently cleared or compartmentalized, preventing immune recognition. piRNA depletion permits LINE-1 activation and the accumulation of reverse transcription intermediates in the cytoplasm. These DNA species can bind and activate cGAS, generating the second messenger cyclic GMP-AMP (cGAMP) that activates STING [113]. Additionally, LINE-1 ORF2p-mediated DNA damage may generate micronuclei or DNA fragments that escape nuclear containment and activate cytosolic sensors [114].

STING activation induces type I interferon responses and inflammatory cytokine production through TBK1 and IRF3 signaling. In AD brain tissue, elevated levels of phosphorylated TBK1 and IRF3 correlate with piRNA depletion and LINE-1 expression, suggesting pathway activation downstream of piRNA pathway compromise [115, 116]. Pharmacological inhibition of STING reduces neuroinflammation and improves cognitive function in AD mouse models, demonstrating functional importance. Importantly, the beneficial effects of STING inhibition are attenuated in mice with genetic LINE-1 suppression, supporting the mechanistic link between LINE-1 derepression (secondary to piRNA loss) and cGAS-STING activation [117, 118].

6.2. Exosomal piRNA Signatures: Intercellular Spread of Epigenetic Vulnerability from Neuron to Glia

Extracellular vesicles (EVs), including exosomes, mediate intercellular communication in the nervous system and may propagate pathogenic factors between cells. Recent studies have identified piRNAs as cargo within neuronal-derived EVs, raising the possibility that piRNA dysregulation spreads between cells. piRNA Packaging into EVs [119]. piRNAs are selectively packaged into exosomes through interactions with RNA-binding proteins including hnRNPA2/B1 and Argonaute proteins. The sorting mechanism appears sequence-specific, with certain piRNA species showing preferential enrichment in EV fractions compared to cellular contents [120, 121].

In AD, the EV piRNA profile differs significantly from that of healthy controls [121]. Specific piRNAs targeting neuroprotective genes are depleted from EVs, while others targeting inflammatory mediators are enriched [122], potentially reflecting disease-associated alterations in sorting mechanisms or cellular piRNA content. Functional Transfer Between Cells. EVs isolated from AD brain tissue or CSF can transfer piRNAs to recipient cells in culture, altering their gene expression profiles [123]. Neurons treated with EVs from piRNA-depleted cells show reduced piRNA levels and increased LINE-1 expression, suggesting that EV-mediated transfer can propagate epigenetic vulnerability. This mechanism may explain the spread of pathology between brain regions in AD [124]. Neurons in early-affected regions experiencing piRNA depletion could release EVs containing reduced piRNA levels or altered piRNA profiles, transmitting epigenetic dysfunction to connected neurons in a prion-like manner [123-125].

Microglial Uptake and Activation. Microglia efficiently internalize neuronal-derived EVs and respond to their cargo [126]. EVs from AD neurons induce microglial activation and inflammatory cytokine production [127], effects that are attenuated by RNase treatment or specific piRNA depletion [128], implicating RNA cargo in microglial response. piRNA-containing EVs may therefore serve as mediators of neuron-glia communication in AD, transmitting signals of neuronal stress or damage that trigger reactive microglial states. The specific piRNA content of EVs could determine the nature of the microglial response, with certain piRNA profiles promoting phagocytic clearance and others driving inflammatory damage [128, 129].

6.3. Transgenerational Epigenetic Inheritance of piRNA Defects: Relevance to Sporadic AD

While most discussion of piRNA function focuses on somatic cells, the germline functions of piRNAs raise intriguing questions about transgenerational inheritance of epigenetic states relevant to AD risk. piRNA-Mediated Transgenerational Inheritance. In model organisms, piRNAs can transmit epigenetic information across generations, silencing TEs and regulating gene expression in offspring. This inheritance occurs through deposition of piRNAs in gametes, where they can direct epigenetic modifications in the early embryo [129].

Evidence for similar transgenerational inheritance in mammals has emerged, with paternal piRNA populations influencing offspring phenotypes. While the extent and mechanisms of such inheritance in humans remain unclear, the possibility that parental piRNA profiles could influence offspring AD risk deserves consideration [130]. Relevance to Sporadic AD. Sporadic AD accounts for over 95% of cases and cannot be explained by known genetic variants alone. Epigenetic factors, potentially including piRNA- mediated effects, may contribute to the "missing heritability" of AD. Parental age, a known risk factor for AD in offspring, correlates with increased TE activity and altered piRNA expression in gametes, suggesting a potential mechanism linking parental age to offspring disease risk [131, 132].

While speculative, this framework highlights the need for longitudinal studies examining piRNA profiles across generations in families with AD. If transgenerational inheritance of piRNA states occurs in humans, it could inform risk stratification and preventive strategies.

7. Therapeutic Implications: Restoring piRNA Function in AD

7.1. Synthetic piRNA Mimics and PIWI Protein Stabilizers: Proof-of-Concept in Drosophila and Mouse Tauopathy Models

The demonstration that piRNA loss contributes to neurodegeneration suggests that restoring piRNA function could have therapeutic benefit in AD. Multiple strategies are under investigation to achieve this goal. Synthetic piRNA Mimics. Chemically modified oligonucleotides designed to mimic endogenous piRNAs can be delivered to cells to restore specific piRNA functions. These mimics typically incorporate 2'-O-methyl or locked nucleic acid (LNA) modifications to enhance stability and binding affinity, along with conjugation to cell-penetrating peptides or cholesterol to facilitate cellular uptake [132, 133].

In Drosophila models of tauopathy, systemic administration of synthetic piRNAs targeting LINE-1 elements reduces brain LINE-1 expression, attenuates neurodegeneration, and improves lifespan [134]. Similar effects are observed in mouse tauopathy models, where intracerebroventricular delivery of LINE-1-targeting piRNA mimics reduces tau pathology and preserves cognitive function [135]. The specificity of piRNA targeting presents both opportunities and challenges. Highly specific piRNAs can selectively silence particular TE families without affecting host gene expression, but the vast diversity of piRNA targets requires careful selection of sequences that maximize therapeutic benefit while minimizing off-target effects [135]. PIWI Protein Stabilizers. Small molecules that stabilize PIWI proteins or enhance their interaction with piRNAs represent an alternative therapeutic strategy. HSP90 inhibitors, paradoxically, can stabilize certain PIWI protein conformations and restore piRNA pathway function despite their general destabilizing effects on HSP90 client proteins [57].

Screening campaigns have identified additional PIWI stabilizers that enhance piRNA loading and nuclear localization. These compounds show protective effects in cellular models of oxidative stress and Aβ toxicity, warranting further development for in vivo applications [135-137].

7.2. CRISPR Activation (CRISPRa) of Silenced piRNA Clusters on the Y Chromosome and Autosomes

Rather than delivering exogenous piRNAs, therapeutic approaches could aim to restore endogenous piRNA production through activation of silenced piRNA clusters. CRISPRa Technology. CRISPR activation (CRISPRa) uses catalytically inactive Cas9 (dCas9) fused to transcriptional activation domains to upregulate target gene expression without permanent genomic modification. This technology can be directed to piRNA cluster promoters to enhance their transcription and increase piRNA production [138].

The Y chromosome harbors numerous piRNA clusters that are active in testis but silenced in somatic tissues [139]. CRISPRa targeting of these clusters in neurons can reactivate their transcription, generating novel piRNA populations that target TEs and provide genome defense. Proof-of-concept studies demonstrate that Y chromosome cluster activation reduces LINE-1 expression and protects neurons from oxidative stress [140, 141]. Autosomal piRNA clusters can similarly be targeted for activation. Cluster-selective CRISPRa enables tailored piRNA production to address specific therapeutic needs, such as targeting particular TE families overrepresented in AD brain tissue [142].

Delivery Challenges. CRISPRa delivery to the central nervous system remains challenging. Adeno-associated virus (AAV) vectors can efficiently transduce neurons but have limited packaging capacity for the large dCas9-activator fusion proteins [142, 143]. Splitintein approaches that deliver dCas9 and activator domains in separate vectors enable co-expression and functional reconstitution in target cells. Alternative delivery strategies include lipid nanoparticles encapsulating Cas9 mRNA and guide RNAs, and engineered exosomes targeted to neurons [144, 146].

7.3. Small Molecule Enhancers of piRNA Biogenesis

Pharmacological enhancement of endogenous piRNA production represents a potentially tractable therapeutic strategy that avoids the delivery challenges of nucleic acid-based approaches. Targeting piRNA Biogenesis Factors. The enzymatic machinery of piRNA biogenesis offers multiple targets for small molecule modulation. PLD6, the mitochondrial endonuclease essential for primary piRNA production, can be activated by small molecules that promote its mitochondrial membrane association or enhance catalytic activity. Screening campaigns have identified PLD6 activators that increase piRNA levels in cellular models, though their blood-brain barrier penetration requires optimization [145-147].

The RNA helicase DDX4 (also known as VASA) plays essential roles in piRNA precursor processing and PIWI protein loading [148]. DDX4 inhibitors have been developed for cancer indications, but DDX4 activators could potentially enhance piRNA biogenesis. Structure-based drug design efforts are underway to identify allosteric activators of DDX4 helicase activity [149]. MOV10L1, an RNA helicase required for primary piRNA biogenesis, represents another promising target. MOV10L1 knockout mice show complete loss of testicular piRNAs and male infertility, highlighting its essential function. Small molecules that enhance MOV10L1 activity or stability could boost piRNA production in somatic tissues [149, 150].

Epigenetic Modulators. piRNA cluster transcription is regulated by epigenetic marks including DNA methylation and histone modifications. DNA methyltransferase inhibitors (DN- MTis) such as 5-azacytidine can derepress silenced piRNA clusters, increasing piRNA production [151]. However, global hypomethylation may have undesirable effects including TE activation at non- target loci. More selective approaches target chromatin modifiers that specifically regulate piRNA clusters. The histone demethylase KDM1A (LSD1) is recruited to piRNA clusters and represses their transcription; LSD1 inhibitors can therefore increase piRNA production from specific clusters. Clinical-grade LSD1 inhibitors are in development for cancer indications and could be repurposed for AD if CNS penetration is achieved [152].

7.4. Challenges: piRNA Redundancy, Off-Target Transposon Silencing, and Delivery Across the Blood–Brain Barrier

Despite promising preclinical results, several challenges must be addressed to translate piRNA- based therapies to clinical applications. piRNA Redundancy and Specificity. The piRNA pathway exhibits substantial functional redundancy, with multiple piRNAs targeting the same TE families and overlapping functions among PIWI proteins. While this redundancy provides robust genome defense under normal conditions, it may limit the efficacy of therapies targeting individual piRNAs or PIWI proteins [153].

Conversely, restoring or enhancing piRNA function risks excessive silencing of TEs that may have beneficial functions. Certain TEs contribute to neuronal gene expression programs and neural plasticity [154]; their inappropriate silencing could have unintended consequences. Therapeutic strategies must therefore balance restoration of genome defense against pathological TE activation with preservation of physiologically important TE functions. Off-Target Effects [155]. piRNAs can bind imperfectly complementary targets in addition to their primary TE targets, potentially regulating host gene expression in unpredictable ways. Synthetic piRNA mimics must be carefully designed and validated to minimize off-target binding while maintaining on-target efficacy [154-156].

CRISPRa-mediated cluster activation similarly risks generating piRNAs with unintended targets (Figure 3). The diversity of piRNA species produced from activated clusters makes predicting off- target effects challenging [156]. Targeted activation of well-characterized clusters with defined piRNA repertoires may mitigate this risk. Blood-Brain Barrier Penetration. Effective delivery of piRNA-based therapeutics to the brain remains a significant hurdle. Small molecule approaches offer the simplest path to CNS penetration but may lack specificity [157]. Nucleic acid-based therapies require specialized delivery vehicles; current AAV vectors face limitations in packaging capacity and immunogenicity, while lipid nanoparticles and exosome-based approaches are still in early development [155, 157]. Intranasal administration offers a non-invasive route for CNS delivery that bypasses the blood-brain barrier. Proof-of-concept studies demonstrate that synthetic piRNA mimics can reach the brain following intranasal delivery in mouse models, supporting further development of this approach [157].

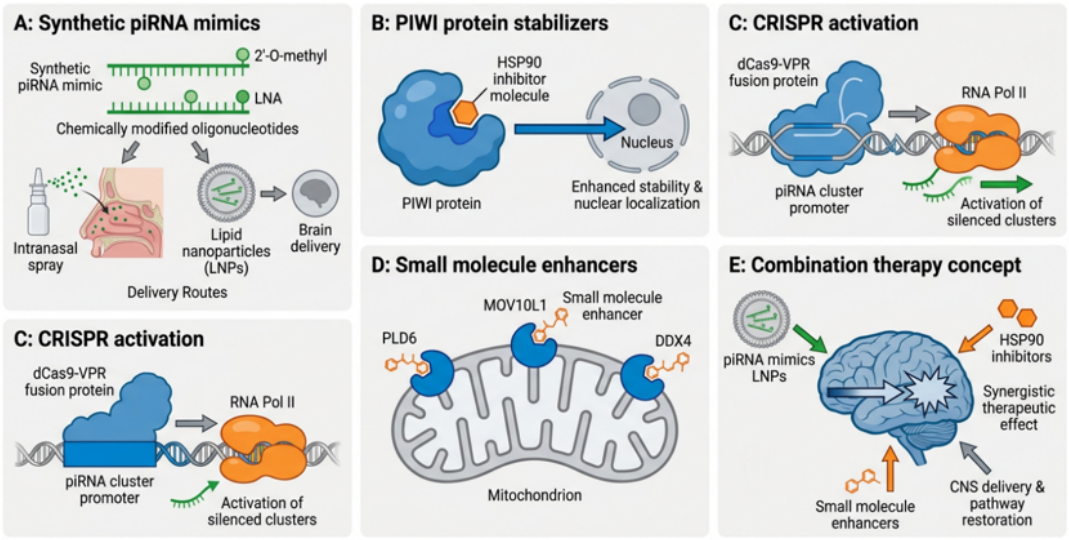


Figure 3: Therapeutic Strategies Targeting the piRNA Pathway in AD. (A) Synthetic piRNA mimics with chemical modifications (2'-O-methyl, LNA, phosphorothioate) can be delivered via intranasal administration or nanoparticle carriers to restore specific piRNA species. (B) PIWI protein stabilizers including HSP90 inhibitors and allosteric modulators enhance piRNA loading and nuclear translocation. (C) CRISPR activation (CRISPRa) of silenced piRNA clus- ters using dCas9-VPR recruits transcriptional machinery to increase endogenous piRNA produc- tion. (D) Small molecule enhancers of piRNA biogenesis target PLD6, MOV10L1, and DDX4 to increase processing of piRNA precursors. (E) Combination approaches targeting multiple nodes of the pathway may provide synergistic therapeutic effects.

8. Conclusion

This review has synthesized evidence positioning piRNA dysregulation as a convergent mechanism linking amyloid-beta toxicity, tau pathology, and downstream neurodegeneration in Alzheimer's disease. The piRNA pathway, initially characterized as a germline defense against transposable elements, has emerged as a critical guardian of neuronal genome integrity, with diverse functions extending to epigenetic regulation, mRNA stability control, and DNA repair. Multiple lines of evidence support the pathogenic relevance of piRNA alterations in AD: (i) human AD brains show significant piRNA dysregulation correlating with disease stage and biomarker changes; (ii) Aβ-induced oxidative stress compromises piRNA biogenesis machinery; (iii) tau pathology sequesters PIWI proteins in cytoplasmic aggregates; (iv) piRNA depletion permits LINE-1 retrotransposon activation, leading to DNA damage and cGAS-STING-mediated neuroinflammation; and (v) experimental restoration of piRNA function protects against AD- related pathology in model systems.

The feedforward loop connecting piRNA loss to genomic instability and enhanced amyloidogenic processing suggests that piRNA dysregulation may not merely accompany AD but actively drive disease progression. This mechanistic insight opens novel therapeutic avenues targeting the piRNA pathway, including synthetic piRNA mimics, PIWI stabilizers, CRISPR-mediated cluster activation, and small molecule enhancers of biogenesis. Several critical questions remain for future investigation. Single-cell and spatial analyses will resolve the cellular and regional specificity of piRNA alterations. Human organoid models with inducible piRNA manipulation will clarify the temporal dynamics of pathway dysfunction. The potential role of piRNAs in microglial phagocytosis and the intersection with APOE4 genotype warrant particular attention given their therapeutic implications.

As the field moves toward clinical translation, challenges including piRNA redundancy, off- target effects, and blood-brain barrier penetration must be addressed. Nevertheless, the con- vergence of genetic, molecular, and pathological evidence positions piRNA pathway restoration as a promising strategy for disease modification in Alzheimer's disease, complementing existing approaches focused on protein clearance with interventions targeting the epigenetic foundations of neuronal vulnerability.

Conflict of Interest

The authors declare no competing interests that may have influenced in this manuscript.

Generative AI statement

The authors declare that Gen AI and large language models (LLMs) were used in the creation of this manuscript. Generative AI items like instatext, wordvice, and DeepL were used for structural editing and improve handwriting of the text.

Author Agreement

This paper is submitted with the agreement of all its co-authors and the author list has been approved by all authors.

Acknowledgments

Not applicable.

Author Contribution

We agree that the author list and order is correct and complete. We understand that any changes to the author list (additions, deletions, order changes) after submission will require a formal request to the editor signed by all authors. Order list include:

ST: Conceptualization, Visualization, Writing - Original Draft, Supervision, Project Administration; **ZS:** Conceptualization, Writing - Original Draft; **PA:** Conceptualization, Writing - Original Draft.

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