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piRNAs in neurodegenerative diseases: Mechanisms of pathogenesis and therapeutic potential

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Abstract

Introduction: Neurodegenerative disorders (NDs), such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), and tauopathies are highly prevalent and cause significant public health concerns globally. Although research has focused on pathological proteins such as β-amyloid, the growing interest in non-coding RNAs, including piRNAs, is shifting the understanding of neurodegenerative disorder mechanisms.

Objective: This review aims to summarize the evidence of the role of piRNAs in neurodegenerative disorder pathogenesis and their potential as diagnostic biomarkers.

Materials and methods: A systematic review was conducted following PRISMA guidelines. We included randomized controlled trials, cohort studies, and case-control studies focusing on piRNAs in neurodegenerative disorders. Data were extracted from PubMed and ScienceDirect using search terms related to piRNAs and neurodegenerative diseases published between 2009 and 2024.

Results: Eleven studies met the inclusion criteria. These studies highlighted the dysregulation of piRNAs in diseases such as Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis, suggesting that piRNAs influence disease mechanisms by maintaining genomic stability, regulating transposable elements, and participating in protein degradation. Several piRNAs, including piR-hsa-92056, emerged as potential biomarkers with diagnostic accuracy.

Discussion: The evidence underscores the crucial role of piRNAs in neurodegeneration. Mechanistic studies reveal that piRNA dysfunction may trigger cascades of genomic instability leading to neuronal death. piRNAs are emerging as valuable therapeutic targets and biomarkers in neurodegenerative disorders.

Conclusions: piRNAs hold potential as innovative therapeutic and diagnostic tools in NDs. Future research should focus on developing piRNA-based interventions to prevent neurodegeneration.

Keywords: IpiRNAs, Neurodegenerative diseases, Pathogenesis, Biomarkers, Alzheimer's disease, Parkinson's disease, Therapeutic targets.

piRNAs en enfermedades neurodegenerativas: mecanismos de patogénesis y potencial terapéutico

Resumen

Introducción: las enfermedades neurodegenerativas, como la enfermedad de Alzheimer, el Parkinson y la esclerosis lateral amiotrófica, son una preocupación de salud pública a nivel mundial. A pesar de los avances en la comprensión de estas patologías, los mecanismos moleculares subyacentes siguen siendo en gran parte desconocidos.

Objetivo: esta revisión sistemática busca resumir las evidencias sobre el papel de los piRNAs en la patogénesis de las enfermedades neurodegenerativas y su potencial como biomarcadores diagnósticos y terapéuticos.

Materiales y métodos: se realizó una revisión sistemática siguiendo las guías PRISMA. Se incluyeron ensayos clínicos controlados aleatorios, estudios de cohortes y de casos y controles que se centraran en piRNAs en enfermedades neurodegenerativas. Se extrajeron datos de PubMed y ScienceDirect entre los años 2009 y 2024.

Resultados: once estudios cumplieron con los criterios de inclusión. Estos estudios subrayan la desregulación de los piRNAs en enfermedades como Alzheimer, Parkinson y esclerosis lateral amiotrófica, sugiriendo que los piRNAs influyen en los mecanismos de la enfermedad a través del mantenimiento de la estabilidad genómica, la regulación de elementos transponibles y la degradación de proteínas. Varios piRNAs, como piR-hsa-92056, surgieron como biomarcadores con precisión diagnóstica.

Discusión: la evidencia destaca el papel crucial de los piRNAs en la neurodegeneración. Estudios mecanísticos revelan que la disfunción de los piRNAs puede desencadenar cascadas de inestabilidad genómica que culminan en la muerte neuronal. Los piRNAs emergen como valiosos objetivos terapéuticos y biomarcadores en enfermedades neurodegenerativas.

Conclusiones: los piRNAs tienen el potencial de ser herramientas terapéuticas y diagnósticas innovadoras en las enfermedades neurodegenerativas. Se debe priorizar el desarrollo de intervenciones basadas en piRNAs para prevenir la neurodegeneración.

Palabras clave: piRNAs, enfermedades neurodegenerativas, patogénesis, biomarcadores, enfermedad de Alzheimer, enfermedad de Parkinson, objetivos terapéuticos.

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Introduction

Neurodegenerative disorders (NDs), such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), and tauopathies represent a significant public health burden both in Colombia and globally due to their high prevalence and the progressive neurological decline they cause (1–6). Despite advances in understanding these diseases, the molecular mechanisms underlying their pathogenesis remain largely unknown, limiting the development of effective treatments and early diagnostic tools (7). Traditionally, neurodegeneration research has focused on pathological proteins such as β-amyloid, hyperphosphorylated tau, and α-synuclein (3, 8). However, the growing interest in non-coding RNAs, such as microRNAs (miRNAs) and PIWI-interacting RNAs (piRNAs), has opened new avenues of research with the potential to revolutionize our understanding of these diseases (9–13).

piRNAs, a class of small non-coding RNAs, were initially discovered in germ cells, where they play a fundamental role in maintaining genomic stability by silencing transposable elements (14–17). piRNAs interact with PIWI-like proteins, forming complexes that not only regulate genome stability but also participate in gene expression regulation and epigenetic modulation at a multisystemic level, including the central nervous system (CNS) (7, 8, 11, 18, 19, 20).

Non-regulation of piRNAs has been reported in transcriptomic studies of human brains and animal models of diseases such as AD and PD, and it has been proposed that the loss of functional piRNAs may contribute to neurodegeneration through the activation of transposable elements, alteration of protein degradation, and failure in the regulation of key epigenetic pathways (9, 10, 19, 20). Furthermore, PIWI-like proteins and piRNAs have begun to be considered as potential biomarkers for early diagnosis of these diseases and new therapeutic targets.

In this context, this systematic review seeks to gather and examine the existing evidence on the role of piRNAs in neurodegenerative diseases, along with the molecular mechanisms by which they contribute to the pathogenesis of conditions like AD, PD, ALS, and tauopathies, aiming also to assess their potential as diagnostic and therapeutic biomarkers.

Methods

This systematic review aimed to assess an up-to-date overview of the piRNA role in neurodegenerative diseases. Adhering to PRISMA (21–22) guidelines, the review followed a structured approach:

Eligibility criteria

- **Types of studies:** This systematic review will include cohort studies, Randomized Controlled Trials (RCTs), and case-control studies.
- **Participants:** The study will focus on patients diagnosed with neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and Huntington's disease.
- **Interventions:** Interventions can include experimental or therapeutic approaches targeting piRNAs and PIWI-like proteins aimed at understanding their role in neurodegenerative diseases. This may involve pharmacological treatments, gene therapy, and molecular modulation techniques.
- **Comparators:** Various treatment approaches will be compared, including interventions targeting piRNAs/PIWI-like proteins versus standard care or placebo.
- **Outcomes:**
- **Primary outcomes:** Disease progression, cognitive and motor function, and biomarkers of neurodegeneration.
- **Secondary outcomes:** Survival rates, incidence of adverse effects, and improvement in quality of life.

Inclusion criteria

1. Original research articles and clinical trials.
2. Studies involving human patients or animal models.
3. Focus on piRNAs' role in neurodegenerative disease pathogenesis or therapy.
4. Outcome measures include disease mechanisms, therapeutic targets, and clinical implications.
5. Studies published in the last 15 years.
6. Studies published in English.

Exclusion criteria

1. Reviews, case reports, meta-analyses, editorials, and letters to the editor.
2. Studies not involving neurodegenerative diseases or piRNAs in pathogenesis or therapy.
3. Studies lacking clear outcome measures related to disease mechanisms or therapeutic targets.
4. Studies published more than 15 years ago.
5. Non-English studies.

Search strategy: ("piRNAs" OR "piwi-interacting RNAs") AND ("Neurodegenerative Diseases"[Mesh] OR "Alzheimer Disease"[Mesh] OR "Parkinson Disease"[Mesh]) AND ("Pathogenesis" OR "Therapy"[Mesh] OR "Therapeutic Targets") AND ("Outcome Measures" OR "Clinical Implications") AND (2009/01/01[PDAT]: 2024/12/31[PDAT]) AND (english[Language]).

Information sources and search strategy: The search started in September 2024 utilizing PubMed and ScienceDirect with terms related to piRNA in ND. The search was refined to include relevant results from 2009 to 2024. Google Scholar was used to identify any additional relevant articles and grey literature.

Selection process: The process consisted of three stages: identification, screening, and inclusion. Titles and abstracts were reviewed in Rayyan23, applying the inclusion and exclusion criteria. Any discrepancies were resolved by the review authors. Following the screening (n=47), 36 articles were excluded, resulting in 11 articles that met the inclusion criteria.

Data collection and quality assessment: The methodological quality of the included studies was assessed using tools appropriate for each study design. Non-randomized studies were evaluated with the Newcastle-Ottawa Scale (Table 1) (23). The quality assessment aimed to determine risk of bias, study validity, and the overall reliability of the findings.

Results

We conducted a literature search in two databases (PubMed and ScienceDirect) and identified 47 relevant papers. After confirming no duplicates (n = 0), we screened titles and abstracts (n = 47) and excluded review articles and unrelated studies (n = 36). Ultimately, 11 studies were included in this systematic review (Figure 1).

Our research analyzed 11 articles that demonstrate the relation between piRNAs with the neurodegenerative diseases (Table 2).

Huang et al. (1) revealed dysregulation of piRNAs in Caenorhabditis elegans models of Lewy body disease. Using transgenic strains overexpressing α-synuclein and a combination of α-synuclein and β-amyloid, they observed that the elimination of piRNA biogenesis genes, such as tofu-1, significantly improved motor behavior in these models. These findings suggest that piRNAs may be related to the regulation of protein degradation, a crucial process in the progression of neurodegenerative diseases. Moreover, studies in human brain samples from patients with advanced Parkinson's disease showed overexpression of piRNAs, suggesting an association between piRNA dysfunction and Lewy body-related disorders and PD (Figure 2) (1, 8, 11).

The transcriptomic analysis by Zhang and Wong (2) on Parkinson's disease revealed that somatic piRNAs are dysregulated in different Parkinson's subtypes and in varied Parkinson's-related diseases, such as Parkinson's disease dementia (PDD), and across different stages of the disease, from premotor to motor stages. They identified 902 somatic piRNAs, 527 of which were present in the brain, suggesting a relevant role for these piRNAs in the nervous system. Specific piRNAs, such as piR-has-92056 and piR-hsa-1909905, were highlighted as diagnostic biomarkers with high accuracy (AUC = 0.89), reinforcing their potential for early diagnosis of PD (2, 7).

Using Drosophila melanogaster and postmortem human brain samples from Alzheimer's and progressive supranuclear palsy (PSP) patients, Sun et al. (3) explored the interaction between piRNAs and transposable elements in tauopathies. Their results showed that piRNA depletion promotes the dysregulation of transposable elements, contributing to neuronal death. The loss of piRNAs in these diseases is associated with heterochromatin decondensation, which allows the activation of transposable elements, implicating piRNAs in maintaining genomic stability in neurons affected by tauopathies.

Qiu et al. (7) conducted a transcriptomic profile of human brains from Alzheimer's patients, identifying over 9,400 piRNAs in the brain, 103 of which were expressed between AD cases and controls. These

Table 1. Newcastle-Ottawa Scale

Author	Year	Selection (4)	Comparability (2)	Outcome (3)	Total Score (9)
Huang X (1)	2023	3/4 - Good experimental design, adequate control, but lacks human validation.	1/2 - Well-defined animal model, but no multiple control groups.	2/3 - Coherent results but needs replication in other models.	6
Zhang T (2)	2022	4/4 - Strong selection, human data analysis using GEO.	2/2 - High comparability, multiple PD subtypes evaluated.	3/3 - High accuracy in results, validated biomarkers replicated in human cohorts.	9
Sun W (3)	2018	3/4 - Good use of animal models and human samples but lacks prospective validation.	1/2 - Limited comparability, no other tauopathy models included.	2/3 - Promising results but not replicated in larger cohorts.	6
Belkozhayev A (4)	2022	3/4 - Solid selection, but analysis based on bioinformatic predictions.	1/2 - Limited comparability, lacks in vivo experimental validation.	2/3 - Theoretical results are solid but require empirical validation.	6
Abdelhamid RF (5)	2022	4/4 - Good experimental design, validation in human and animal models.	2/2 - Adequate comparability between ALS and controls.	3/3 - Solid results, replicated in different models and validated molecularly.	9
Simoes FA (6)	2022	4/4 - Well-defined patient selection with PSP, serum and CSF analysis.	2/2 - Adequate comparability between PSP patients and healthy controls.	3/3 - Validated in cohorts, well-defined biomarkers.	9
Qiu W (7)	2017	4/4 - Good use of human samples, comprehensive transcriptomic analysis.	1/2 - Limited comparability in terms of AD subtypes diversity.	2/3 - Interesting results but require further validation in independent cohorts.	7
Jain G (8)	2019	4/4 - Well-selected cohort of AD and MCI patients.	2/2 - Adequate comparability between study groups.	3/3 - High diagnostic accuracy, biomarker validation in independent cohorts.	9
Schulze M (9)	2018	3/4 - Good experimental design but limited to sporadic Parkinson's patients.	1/2 - Limited comparability among groups, lacks analysis in other PD subtypes.	2/3 - Promising results but requires validation in larger cohorts.	6
Roy R (10)	2020	3/4 - Good experimental models but lacks human validation.	1/2 - Limited comparability, lacks replication in other neuropathological models.	2/3 - Promising results, but no replication in larger human cohorts.	6
Roy J (11)	2017	4/4 - Comprehensive transcriptomic analysis in human AD brains.	1/2 - Limited comparability in terms of cohort diversity.	2/3 - Solid results but need validation in independent cohorts.	7

Source: Own elaboration based on (23).

piRNAs were correlated with previously identified genetic risk SNPs for Alzheimer's, suggesting that piRNAs are directly involved in regulating pathogenic pathways in AD (7, 9). The study also highlighted the abundance of piRNAs in the human brain, suggesting their role in neurodegeneration could be broader than previously thought.

Jain et al. (8) expanded the understanding of piRNAs in AD by discovering a combined signature of three piRNAs and three miRNAs that was capable of detecting AD pathology with significant accuracy (AUC = 0.83). Additionally, their analysis predicted the conversion of patients with mild cognitive impairment to Alzheimer's dementia with even higher accuracy (AUC

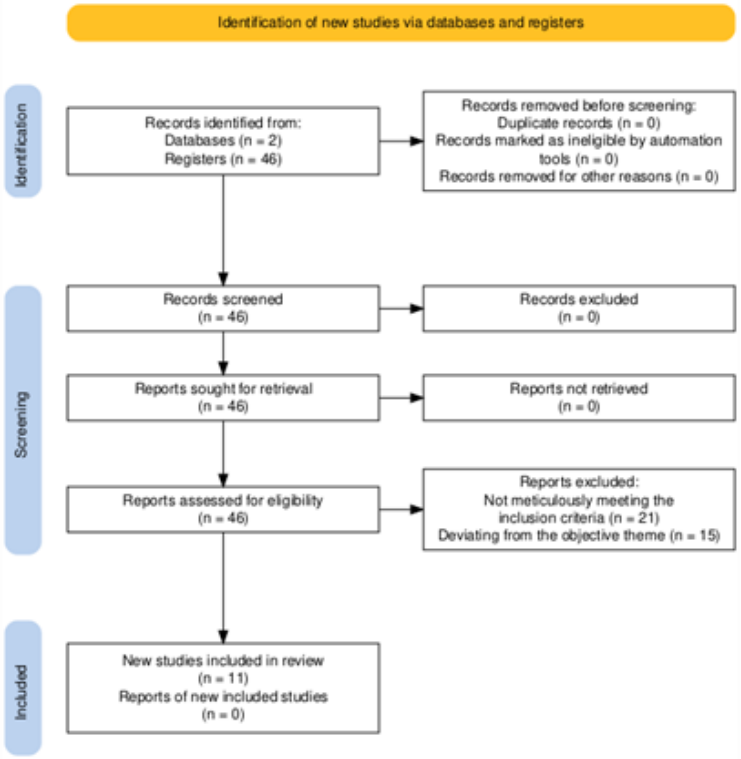

Figure 1. PRISMA flow chart

Source: Own elaboration based on (21, 22).

= 0.86). These findings suggest that piRNAs are not only involved in AD pathogenesis but also hold significant potential as biomarkers for early diagnosis and disease progression monitoring (8, 12).

Regarding amyotrophic lateral sclerosis (ALS), Abdelhamid et al. (5) reported that piRNA dysfunction is linked to TDP-43 pathology in ALS patients (5, 13, 14). They identified that PIWI-like proteins 1 and 4 (PIWIL1 and PIWIL4), which are involved in piRNA biogenesis, were dysregulated in motor neurons affected by ALS. This suggests that piRNA dysfunction may contribute to the neurodegenerative process in ALS, marking a new potential therapeutic target for this devastating disease.

Simoes et al. (6) focused on progressive supranuclear palsy, where they found significant dysregulation of the piRNA hsa-piR-31068 in both serum and cerebrospinal fluid (CSF) of PSP patients (6, 9, 14). This dysregulation could serve as a distinctive disease marker, suggesting that piRNAs have the potential to be used as biomarkers in biofluids, facilitating earlier and more precise diagnosis of PSP.

In the context of Alzheimer's disease pathogenesis, Schulze et al. (9) documented that differentiated neuronal cells derived from patients with sporadic Parkinson's disease showed abundant piRNA dysregulation. These results provide further evidence that piRNAs are important regulators of neuronal homeostasis and that their dysfunction may be central to neurodegeneration in various diseases, including Parkinson's and Alzheimer's (9).

Finally, Roy et al. (10) proposed that PIWI proteins, which interact with piRNAs, could act as a molecular bridge between the blood-brain barrier and neuropathological conditions (10, 18). They suggest that piRNAs and PIWI proteins are involved in regulating neuronal homeostasis, and their dysfunction may precede the onset of neurodegenerative diseases.

Table 2. Characteristics of the reviewed studies

Author	Year	Topic	Main Result
Huang X (1)	2023	PIWI-interacting RNA expression in Lewy body disease model.	Dysregulated piRNAs were observed in a C. elegans model of Lewy body disease, showing improved motor function after piRNA biogenesis genes knockdown.
Zhang T (2)	2022	Dysregulation of somatic piRNA expression in Parkinson's disease.	Somatic piRNAs were significantly deregulated in different subtypes and stages of Parkinson's disease, identified as potential biomarkers with high diagnostic accuracy.
Sun W (3)	2018	piRNA depletion in tauopathies and its effect on transposable elements.	piRNA depletion promotes neuronal death in tauopathies through dysregulation of transposable elements.
Belkozhayev A (4)	2022	Interaction of miRNAs and piRNAs with human genes containing di- and trinucleotide repeats.	Predicted associations between miRNAs/piRNAs and mRNAs with di- and trinucleotide repeats in neurodegenerative and oncological diseases.
Abdelhamid RF (5)	2022	piRNA/PIWI protein complex as a biomarker in ALS.	Dysregulation of PIWI-like proteins and piRNAs was linked to ALS, associated with TDP-43 pathology, highlighting them as potential biomarkers.
Simoes FA (6)	2022	Potential of piRNAs as biomarkers in progressive supranuclear palsy.	Identified piRNAs as potential biomarkers in PSP, with significant changes in piRNA expression in serum and CSF samples.
Qiu W (7)	2017	Transcriptome-wide piRNA profiling in Alzheimer's disease.	Identified more than 9,400 piRNAs in the brain, with 103 differentially expressed in Alzheimer's disease, suggesting their role in neurodegeneration.
Jain G (8)	2019	miRNA and piRNA signature in Alzheimer's disease detection.	A combined signature of three miRNAs and three piRNAs was identified as a biomarker for Alzheimer's disease, with high diagnostic accuracy.
Schulze M (9)	2018	piRNA deregulation in sporadic Parkinson's disease.	Differentiated neuronal cells derived from sporadic Parkinson's disease patients showed abundant deregulation of piRNAs, suggesting their involvement in neurodegeneration.
Roy R (10)	2020	PIWI protein as a molecular bridge in neuropathological conditions.	PIWI-like proteins may have a potential role in neuroprotection, linking the blood-brain barrier and neuropathological conditions.
Roy J (11)	2017	Dysregulated piRNAs in Alzheimer's disease and their role in pathogenesis.	Identified dysregulated piRNAs in Alzheimer's disease, associated with neuronal death through the activation of transposable elements.

Source: Own elaboration.

Discussion

The accumulated evidence across these studies underscores the central relevance of piRNAs in various neurodegenerative diseases. Mechanistically, piRNAs appear to play a multifaceted role in neuronal homeostasis, acting as regulators of gene expression, genomic stability, and protection against transposable elements. The dysfunction of piRNAs observed in diseases such as Alzheimer's, Parkinson's, and tauopathies highlights a pathogenic convergence point: the loss of control over transposable elements and the dysregulation of RNA processing (Figure 3) (7–9).

Huang et al. (1) demonstrated that piRNA dysfunction in Lewy body disease models is not only correlated with the disease but that manipulation of piRNA biogenesis genes has protective effects on motor behavior, pointing to a potential therapeutic approach (1, 21–22). In this regard, the findings by Zhang and Wong (2) in Parkinson's disease also highlight the role of piRNAs as diagnostic biomarkers, suggesting that piRNAs could be used to identify subtypes and related diseases, and monitor its progression (2, 23, 24).

Research on tauopathies (3) and AD (7, 8) reinforces the idea that piRNAs are essential for genomic

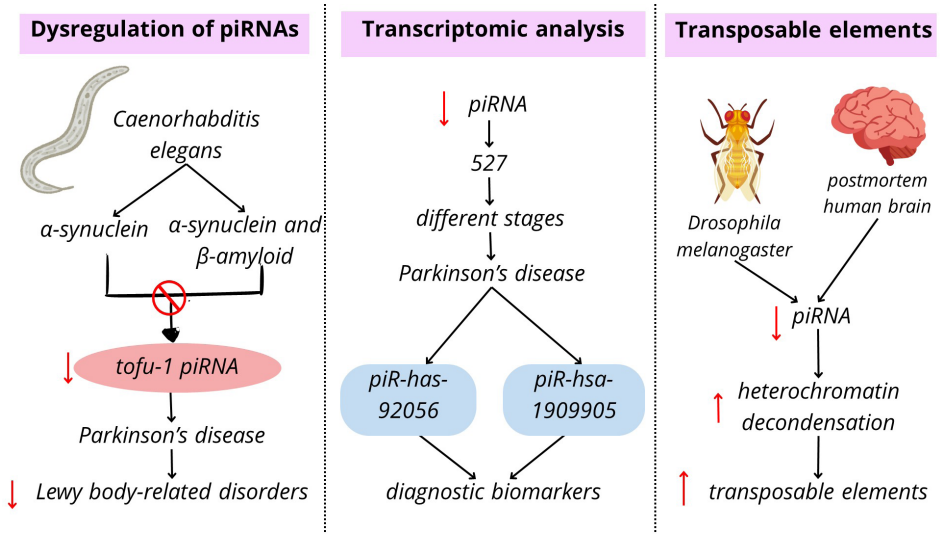

Figure 2. In vivo models for detection of dysregulation of piRNAs

Source: (1-3).

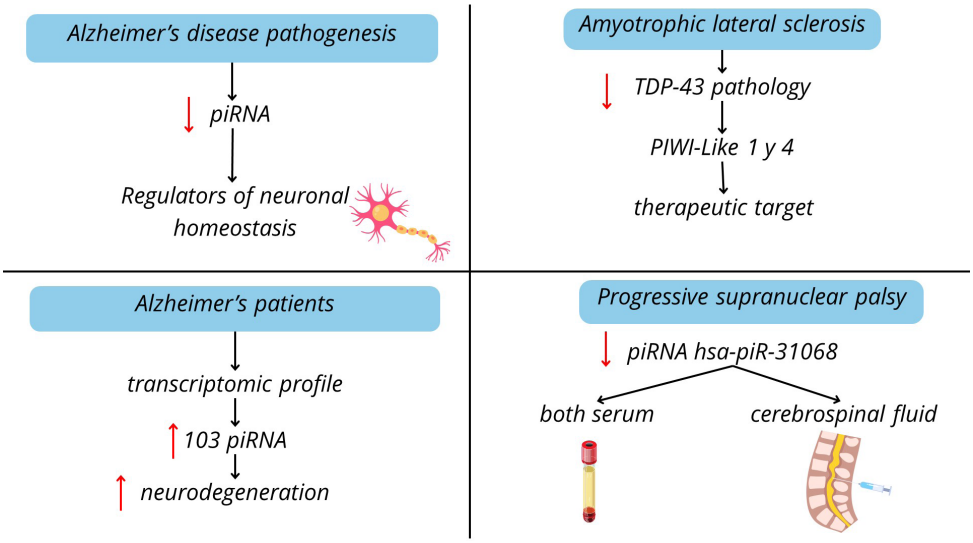

Figure 3. piRNA association with neurodegenerative diseases

Source: (7-9).

integrity in neurons and that their dysfunction can trigger pathogenic cascades culminating in neuronal death. The observation that piRNAs are involved in transposable element dysregulation suggests that these small RNAs could be a viable therapeutic target for preventing or delaying neurodegeneration (3, 7, 8, 25, 26).

The discovery of piRNA dysfunction in ALS (5) and PSP (6) expands the spectrum of neurodegenerative diseases where piRNAs could serve as biomarkers or therapeutic targets. Studies in ALS highlight that PIWI protein dysregulation is correlated with TDP-43 pathology, a key marker of ALS. This finding opens new avenues for the exploration of piRNA- and PIWI-targeted therapies in ALS (7, 8, 27–30).

In the Colombian context, the implementation of piRNA-based therapies for neurodegenerative diseases faces certain challenges regarding feasibility and coverage. Introducing these innovative therapies would require advanced infrastructure and trained personnel, which may be limited in the short term. However, collaborations with international institutions could facilitate clinical trials within the country, creating a pathway for eventual integration into specialized centers. Although initial costs could limit access in early stages, it is essential to explore strategies to ensure equitable access within the healthcare system. Finally, while piRNA-based therapies hold great potential, they should not replace the importance of preventive interventions. Ideally, piRNA therapies could complement preventive strategies, working together to reduce the burden of neurodegenerative diseases across the population.

Conclusions

piRNAs have emerged as essential regulators in neurodegeneration, playing a complex role in preserving neuronal homeostasis by modulating transposable elements, protein degradation, and genomic stability. The reviewed studies indicate that piRNA dysfunction is a common characteristic across various neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), progressive supranuclear palsy (PSP), and tauopathies. As research continues to elucidate the molecular mechanisms by which piRNAs contribute to these pathologies, the potential for developing piRNA-based diagnostic tools and therapeutic approaches is expanding.

The identification of specific piRNA signatures in neurodegenerative diseases marks a significant step towards precision medicine, offering the possibility of earlier and more accurate diagnoses. Additionally, the modulation of piRNA and PIWI protein activity presents a novel and promising therapeutic approach that could transform the management of neurodegenerative disorders. Targeting piRNA pathways to restore neuronal homeostasis or prevent neurodegeneration opens new avenues for treatment, especially in diseases for which no curative therapies currently exist.

As the understanding of piRNAs continues to evolve, these small non-coding RNAs hold the potential to reshape both the diagnostic landscape and therapeutic strategies for neurodegenerative diseases, providing new hope for patients affected by these devastating conditions. It is crucial to strengthen both innovative therapies and preventive strategies within the Colombian context, particularly for neurodegenerative diseases. While piRNA therapies are promising, they should be viewed as complementary to established preventive interventions, ensuring comprehensive and equitable care throughout the country.

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