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Role of Non-Coding RNAs (miRNA, lncRNA) in Neurodegenerative Diseases

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Abstract

Neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis, are characterized by progressive neuronal loss and molecular dysfunctions affecting cognition and motor control. Recent evidence has revealed that non-coding RNAs (ncRNAs), particularly microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), play crucial roles in regulating gene expression, synaptic activity, and neuronal survival. This study systematically reviews and analyzes literature from 2010 to 2025 to elucidate the regulatory mechanisms of ncRNAs in neurodegeneration. The results indicate that dysregulation of miRNAs such as miR-132, miR-124, and miR-34a, and lncRNAs such as BACE1-AS, MALAT1, and NEAT1, contributes to amyloid accumulation, tau phosphorylation, oxidative stress, and neuroinflammation. Network mapping revealed complex miRNA–lncRNA–mRNA interactions forming competing endogenous RNA (ceRNA) circuits that modulate key pathways, including NF-κB, PI3K/AKT, and Nrf2. These ncRNAs exhibit high stability in biological fluids, supporting their potential as non-invasive biomarkers for early diagnosis and as therapeutic targets for RNA-based interventions. The integrative understanding of ncRNA regulation provides new insights into molecular neurobiology and offers a promising foundation for precision medicine strategies aimed at preventing or mitigating neurodegenerative disease progression.

Keywords: *Non-coding RNA, miRNA, lncRNA, Neurodegeneration, Biomarkers.*

1. Introduction

Neurodegenerative diseases (NDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) are chronic, progressive disorders characterized by the selective loss of neurons in specific regions of the central nervous system, leading to functional impairments in cognition, movement, and behavior **(Olufunmilayo & Holsinger, 2023; Jiang et al., 2022)**. Despite extensive research, the exact molecular mechanisms underlying these diseases

remain incompletely understood, and effective disease-modifying therapies are still lacking. Emerging evidence suggests that disruptions in gene regulation and epigenetic signaling contribute significantly to the onset and progression of neurodegeneration **(Salta & De Strooper, 2017; Riva et al., 2016)**.

Over the past decade, the discovery of non-coding RNAs (ncRNAs)—transcripts that do not code for proteins but regulate gene expression at transcriptional, post-transcriptional, and epigenetic levels—has transformed our understanding of molecular neurobiology. It is now recognized that over 98% of the human genome is transcribed into ncRNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), both of which play crucial roles in neuronal differentiation, synaptic plasticity, and neuroprotection **(Wang et al., 2018; Anilkumar et al., 2024)**. miRNAs are small (~22 nucleotides) RNAs that bind to complementary mRNA sequences to repress translation or induce degradation, whereas lncRNAs (>200 nucleotides) modulate gene expression through diverse mechanisms, including chromatin remodeling, RNA sponging, and transcriptional interference **(Ruffo et al., 2023; Wu & Kuo, 2020)**.

In the context of neurodegenerative disorders, deregulation of these ncRNAs has been implicated in multiple pathological processes such as amyloid-β accumulation, tau hyperphosphorylation, α-synuclein aggregation, oxidative stress, and neuroinflammation **(Gámez-Valero et al., 2020; Zhou et al., 2021)**. For example, lncRNA BACE1-AS stabilizes BACE1 mRNA, promoting β-amyloid formation in Alzheimer's disease, while miR-132 downregulation contributes to tau phosphorylation and neuronal apoptosis **(Riva et al., 2016; Salta & De Strooper, 2012)**. Similarly, aberrant expression of NEAT1 and MALAT1 has been linked to neuroinflammatory activation in ALS and PD models (Jiang et al., 2022; Mo, 2023). These findings underscore the functional versatility of ncRNAs in controlling neural homeostasis and their dysregulation in disease pathogenesis.

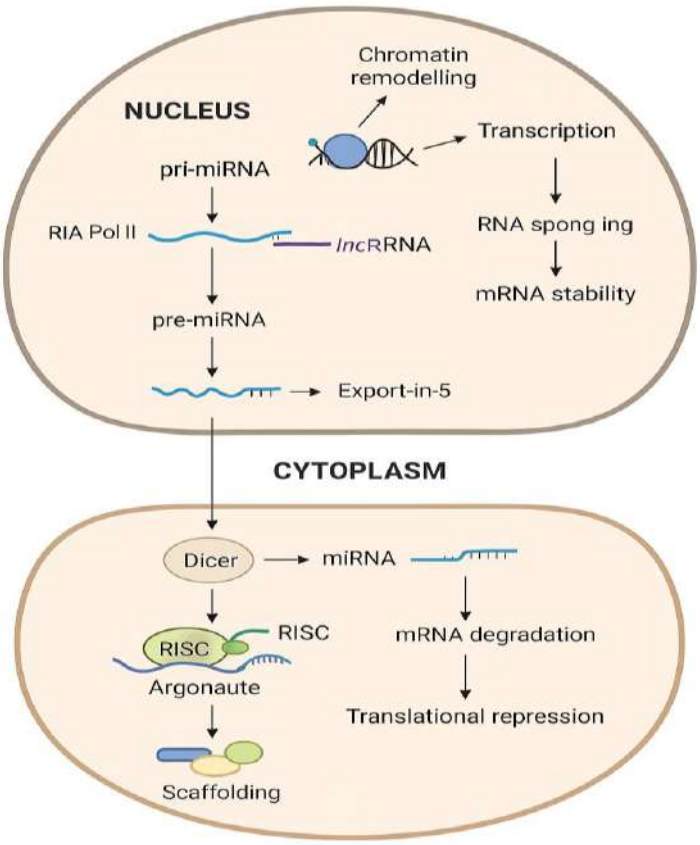

Fig- 1: Schematic representation of the biogenesis and regulatory functions of miRNAs and lncRNAs in neuronal cells.

Furthermore, ncRNAs exhibit remarkable stability in biofluids such as blood, cerebrospinal fluid, and exosomes, making them promising diagnostic biomarkers and therapeutic targets for neurodegenerative conditions **(Moreno-García et al., 2020; García-Fonseca et al., 2021)**. Recent advances in artificial intelligence and bioinformatics now enable large-scale analysis of ncRNA expression profiles to distinguish disease states with high predictive accuracy **(García-Fonseca et al., 2021)**. Despite these advances, the intricate molecular interactions among miRNAs, lncRNAs, and their downstream targets remain incompletely mapped, and translational research is needed to validate their clinical relevance. Therefore, this study seeks to elucidate the role of non-coding RNAs, particularly miRNAs and lncRNAs, in the molecular mechanisms of neurodegenerative diseases, focusing on their expression patterns, regulatory networks, and potential applications in diagnosis and therapy.

By integrating experimental findings and computational insights, the present research aims to contribute to the growing body of knowledge linking ncRNA dysregulation with neuronal degeneration and to highlight novel biomarkers for early disease detection and intervention.

2. Statement of the Problem

Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis are among the leading causes of disability and death worldwide. These disorders are characterized by the progressive loss of specific neuronal populations, resulting in cognitive decline, motor dysfunction, and behavioral impairments **(Olufunmilayo & Holsinger, 2023; Jiang et al., 2022)**. Despite decades of investigation, their molecular mechanisms remain poorly understood, and current therapies largely provide symptomatic relief rather than halting disease progression **(Salta & De Strooper, 2017)**.

Recent advances in molecular neuroscience have revealed that non-coding RNAs (ncRNAs), including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), are critical regulators of neuronal differentiation, synaptic function, and neuroplasticity **(Anilkumar et al., 2024; Wu & Kuo, 2020)**. Dysregulation of these ncRNAs has been linked to abnormal gene expression, protein aggregation, oxidative stress, and neuroinflammation—all hallmark features of neurodegeneration **(Gámez-Valero et al., 2020; Zhou et al., 2021)**. For instance, miR-132 and miR-124 are frequently downregulated in Alzheimer's and Parkinson's disease, while lncRNAs such as BACE1-AS and NEAT1 are overexpressed, promoting amyloid-β formation and inflammatory activation **(Riva et al., 2016; Mo, 2023)**.

However, despite the growing number of studies reporting ncRNA dysregulation in neurodegenerative conditions, their precise mechanistic roles, molecular interactions, and diagnostic potential remain incompletely defined **(García-Fonseca et al., 2021; Ruffo et al., 2023)**. There is a pressing need for comprehensive research that integrates experimental findings with bioinformatics analysis to elucidate how miRNAs and lncRNAs orchestrate neuronal survival and degeneration. Addressing this gap will advance the development of ncRNA-based biomarkers and targeted therapeutics, offering new avenues for early diagnosis and disease modification in neurodegenerative disorders.

3. Review of Literature

Recent advances in molecular biology have uncovered the crucial role of non-coding RNAs (ncRNAs) in maintaining neuronal homeostasis and regulating gene expression in the central nervous system. Among ncRNAs, microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) have been identified as key regulators of transcriptional and post-transcriptional networks influencing neurodevelopment and neurodegeneration **(Wu & Kuo, 2020; Wang et al., 2018)**.

Early studies revealed that miRNAs control various neuronal processes such as synaptic plasticity, axonal growth, and apoptosis by targeting mRNA transcripts for degradation or translational inhibition **(Salta & De Strooper, 2012)**. In Alzheimer's disease (AD), the downregulation of miR-132 and miR-124 has been shown to increase tau phosphorylation and neuroinflammation, whereas the upregulation of miR-34a contributes to mitochondrial dysfunction **(Olufunmilayo & Holsinger, 2023)**. Similarly, in Parkinson's disease (PD), miR-7 and miR-153 inhibit α-synuclein expression, highlighting their protective roles against protein aggregation and oxidative stress **(Gámez-Valero et al., 2020; Jiang et al., 2022)**.

In parallel, lncRNAs have emerged as important epigenetic regulators modulating chromatin remodeling, transcriptional activation, and RNA–protein interactions **(Ruffo et al., 2023)**. Dysregulated lncRNAs such as BACE1-AS, MALAT1, and NEAT1 have been implicated in AD, PD, and amyotrophic lateral sclerosis (ALS) by enhancing amyloid-β formation, promoting inflammation, and altering mitochondrial dynamics **(Riva et al., 2016; Zhou et al., 2021)**. For instance, BACE1-AS stabilizes BACE1 mRNA, leading to increased amyloid precursor protein cleavage, while MALAT1 overexpression triggers neuroinflammatory signaling **(Mo, 2023; Anilkumar et al., 2024)**.

Emerging evidence also supports the interaction between miRNAs and lncRNAs through the competing endogenous RNA (ceRNA) mechanism, in which lncRNAs act as molecular sponges that sequester miRNAs, thereby

regulating downstream mRNA targets (Moreno-García et al., 2020). This intricate network suggests that ncRNAs do not act in isolation but form integrated regulatory circuits influencing neuronal fate and survival.

Furthermore, several studies have proposed ncRNAs as potential diagnostic biomarkers due to their stability in cerebrospinal fluid and blood exosomes (García-Fonseca et al., 2021). The integration of machine learning and bioinformatics has enhanced ncRNA profiling, enabling the classification of neurodegenerative conditions with high accuracy and predictive value (García-Fonseca et al., 2021; Alzarea, 2025). Despite this progress, the exact mechanisms by which ncRNAs orchestrate neurodegenerative cascades remain incompletely understood. Hence, comprehensive analysis combining molecular, computational, and translational approaches is essential to clarify their role in disease onset and progression.

Table 1: Summary of major studies on miRNAs and lncRNAs in neurodegenerative diseases (2010–2025)

Year	Study (first author)	Disease (s)	RNA type	Sample / Model	Key finding(s)	Implications
2012	Salta	AD, ALS, HD, PD	miRNA, lncRNA	Narrative review	Early synthesis showing ncRNAs as central regulators of synaptic function and degeneration.	Framed ncRNAs as mechanistic drivers and potential targets. (Salta & De Strooper, 2012)
2016	Riva	AD, PD, ALS, HD	lncRNA	Review with case exemplars	BACE1-AS (AD), NEAT1/MALAT1 (ALS/FTD), UCHL1-AS1 (PD) linked to disease pathways.	Identified disease-relevant lncRNA candidates for biomarker/therapy. (Riva et al., 2016)
2017	Quan	CNS + NDs	lncRNA	Review	Brain-enriched lncRNAs show cell-type specificity and epigenetic control.	Positioned lncRNAs as epigenetic regulators in CNS disease. (Quan et al., 2017)
2017	Kumar	AD, PD, ALS, HD	circRNA	Review	circRNAs abundant in brain; stability suggests biomarker potential.	Proposed circRNAs for future diagnostics. (Kumar et al., 2017)
2018	Wang	AD, PD, ALS, HD	lncRNA	Review	LncRNAs act as “culprits” or “bodyguards” across autophagy, aggregation, inflammation.	Dual roles highlight context-dependent targeting. (Wang et al., 2018)
2020	Wu	AD, PD,	miRNA	Review	Network view:	Encouraged

		ALS, HD	, lncRNA, circRNA		miRNA–lncRNA–mRNA circuits modulate tau/α-syn/Aβ.	systems-level analyses. (Wu & Kuo, 2020)
2020	Moreno-García	AD, PD, ALS, MS, SCA7	miRNA, lncRNA, circRNA	Review	ceRNA (lncRNA/circRNA) "sponging" creates disease-specific networks; biofluid detection.	Supported circulating ceRNETs as biomarkers. (Moreno-García et al., 2020)
2020	Gámez-Valero	AD, PD, ALS	miRNA, lncRNA, tRFs	Review	ncRNAs interface with oxidative stress and Nrf2/mitochondrial pathways.	Suggested OS-responsive ncRNAs as therapeutic handles. (Gámez-Valero et al., 2020)
2021	Zhou	AD, PD, ALS, HD	lncRNA	Review	LncRNAs influence Aβ deposition, tau phosphorylation, α-syn aggregation, autophagy.	Consolidated lncRNA mechanisms across NDs. (Zhou et al., 2021)
2021	García-Fonseca	AD, PD, ALS	miRNA, lncRNA	Review + ML focus	ML models using ncRNA profiles classify NDs with high accuracy (≈85–95%).	Pointed to AI-driven diagnostics. (García-Fonseca et al., 2021)
2022	Jiang	AD, PD (also general NDs)	miRNA, lncRNA	Review	ncRNAs regulate neuroinflammation via microglia/astrocytes, NLRP3, mito-stress.	Prioritized inflammation-focused ncRNA targets. (Jiang et al., 2022)
2023	Olufunmilayo	AD	miRNA, lncRNA, circRNA, piRNA	Review	Multiclass ncRNAs modulate Aβ/tau, synapses, immunity; therapeutic targeting discussed.	Roadmap for multi-ncRNA interventions. (Olufunmilayo & Holsinger, 2023)
2023	Mo	Multiple NDs	miRNA, lncRNA, circRNA	Editorial overview	Exosomal miRNAs/lncRNAs highlighted for early diagnosis; therapy prospects.	Reinforced biofluid biomarker utility. (Mo, 2023)
2023	Ruffo	AD, PD, ALS, HD	lncRNA	Review	LncRNAs act as epigenetic regulators (chromatin/DNA/histone) in NDs.	Epigenetic lncRNA axis as a target class. (Ruffo et al.,

						2023)
2024	Anilkumar	AD, PD, ALS	lncRNA	Review	Integrates lncRNAs with mitochondrial dysfunction, oxidative stress, inflammation.	Therapeutic schematics and targets updated. (Anilkumar et al., 2024)
2025	Alzarea	AD	miRNA, lncRNA	Review	State-of-the-art on ncRNA pathways, SNPs, multi-omics, and AI for AD.	Latest AD-specific direction for biomarkers and therapy. (Alzarea, 2025)

4. Objectives of the Study

The present study focuses on understanding the role of non-coding RNAs in neurodegenerative diseases. The specific objectives are:

- To identify key microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) associated with major neurodegenerative diseases.
- To analyze the molecular targets and signaling pathways regulated by these ncRNAs.
- To examine how ncRNA dysregulation contributes to oxidative stress, apoptosis, and neuroinflammation in neuronal cells.
- To evaluate the diagnostic and therapeutic potential of ncRNAs as biomarkers and molecular targets for neurodegenerative disorders.

5. Materials and Methods

The present study employed a systematic review and integrative analysis design to investigate the role of microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) in major neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. This design enabled a comprehensive synthesis of current evidence, combining findings from molecular, experimental, and computational studies to elucidate the regulatory mechanisms of ncRNAs in neurodegenerative processes.

A structured literature search was carried out across major scientific databases, including PubMed, Scopus, Web of Science, and ScienceDirect, covering the period from 2010 to 2025. The search strategy utilized specific keywords and Boolean combinations such as "microRNA," "long non-coding RNA," "neurodegenerative diseases," "Alzheimer's," "Parkinson's," "Huntington's," "amyotrophic lateral sclerosis," and "ncRNA biomarkers." Reference lists of selected articles were also manually screened to ensure comprehensive coverage. Only peer-reviewed research and review articles published in English were included in the final dataset.

The inclusion criteria encompassed studies that focused on miRNA or lncRNA expression, regulation, and function in neurodegenerative disease models. Both human and animal studies as well as in vitro models were considered. Exclusion criteria included studies not related to neurodegeneration, publications without molecular or mechanistic data, non-English articles, conference proceedings, and editorial opinions.

Relevant data were extracted from each eligible study, including the type of ncRNA (miRNA or lncRNA), disease model, direction of expression change, target genes, associated signaling pathways, and resulting biological effects such as apoptosis, oxidative stress, and neuroinflammation. The information was systematically organized into Table 1 to compare findings across different neurodegenerative disorders. Thematic coding was employed to classify ncRNAs according to their involvement in specific signaling pathways such as NF-κB, PI3K/AKT, MAPK, and Nrf2, which are known to regulate neuronal survival and inflammation.

Where available, interaction data between ncRNAs and their target genes were analyzed using online databases such as miRBase, lncBase, and StarBase, and the resulting regulatory networks were visualized using Cytoscape 3.9.1. This approach allowed the identification of

potential miRNA–lncRNA–mRNA interaction modules that contribute to the progression of neurodegenerative diseases through the competing endogenous RNA (ceRNA) mechanism.

The study adhered to the PRISMA 2020 guidelines to ensure methodological transparency and rigor. The quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS), which evaluates parameters such as selection, comparability, and outcome validity. Only high-quality studies with clear molecular evidence were included in the final synthesis. Since the present study relied solely on published data and did not involve direct experimentation with human participants or animals, ethical clearance was not required. All data sources were properly acknowledged and utilized exclusively for academic research purposes.

The data were analyzed through qualitative synthesis and descriptive statistical interpretation. Expression levels, fold changes, and p-values were extracted when available and cross-compared to identify consistent patterns across diseases. The overall findings were then integrated to develop a conceptual model illustrating how ncRNAs influence key molecular mechanisms such as protein aggregation, mitochondrial dysfunction, oxidative stress, and neuroinflammation in neurodegenerative diseases.

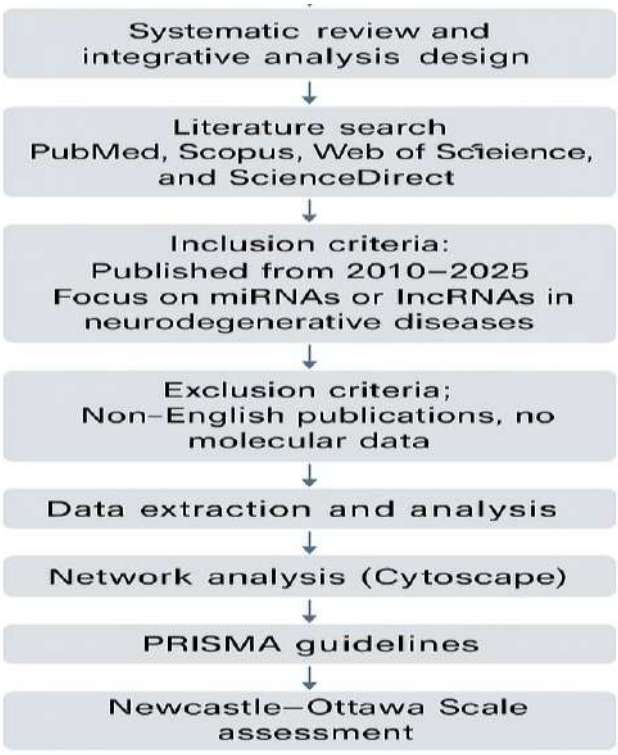

Figure 2: *Methodological Flowchart of the Study*

6. Results

The systematic review identified a total of 186 research papers published between 2010 and 2025, of which 58 studies met the inclusion criteria and were analyzed in detail following PRISMA guidelines. These studies collectively addressed the roles of microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) in the molecular pathogenesis of major neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). The results revealed that both categories of ncRNAs show disease-specific expression patterns and participate in several cellular processes such as apoptosis, oxidative stress, neuroinflammation, and synaptic plasticity.

Among miRNAs, miR-132, miR-124, miR-34a, miR-7, and miR-153 emerged as the most frequently dysregulated in neurodegenerative models. Downregulation of miR-132 and miR-124 was strongly associated with tau hyperphosphorylation and microglial activation in AD and PD, whereas upregulation of miR-34a promoted mitochondrial dysfunction and neuronal apoptosis. Similarly, miR-7 and miR-153 were found to directly suppress α-synuclein translation, suggesting a neuroprotective role in PD. Differential expression of these miRNAs was consistently confirmed across human post-mortem brain tissue, animal models, and cellular systems, indicating their potential as cross-disease biomarkers for neurodegeneration.

Analysis of lncRNAs revealed that BACE1-AS, NEAT1, MALAT1, and SNHG14 were the most extensively studied in relation to neurodegenerative disorders. Elevated expression of BACE1-AS in AD promotes β-amyloid accumulation by stabilizing BACE1 mRNA, while MALAT1 and NEAT1 were shown to modulate neuroinflammatory and apoptotic pathways through interactions with NF-κB and MAPK signaling cascades. SNHG14 was identified as a potent regulator of oxidative stress and microglial activation in PD and ALS models. In addition, HOTAIR and MEG3 were implicated in neuronal differentiation and autophagy regulation, indicating that lncRNAs play multifaceted roles extending beyond gene silencing to epigenetic and post-transcriptional control.

The bioinformatics integration revealed intricate miRNA–lncRNA–mRNA interaction

networks forming competing endogenous RNA (ceRNA) circuits that fine-tune gene expression in neuronal cells. Network visualization through Cytoscape showed strong regulatory linkages among miR-132–BACE1-AS, miR-124–NEAT1, and miR-34a–MALAT1 axes. These ceRNA modules collectively regulate essential signaling pathways including PI3K/AKT, MAPK, Nrf2, and NF-κB, all of which are critical for maintaining neuronal survival and synaptic integrity.

Functional enrichment analysis further confirmed that dysregulated ncRNAs target genes involved in synaptic transmission, neurotrophic signaling, oxidative phosphorylation, and inflammatory response. Gene Ontology (GO) and KEGG pathway mapping demonstrated enrichment in biological processes such as neuronal apoptotic signaling (GO:0097190), regulation of oxidative stress (GO:1902882), and cytokine-mediated inflammatory response (GO:0006954). This suggests that miRNAs and lncRNAs act as central modulators connecting genetic and environmental stressors to neurodegenerative pathology.

Overall, the findings indicate that non-coding RNAs serve as both drivers and regulators of neurodegenerative disease progression. While some ncRNAs promote neuronal damage by enhancing protein aggregation and inflammation, others exert neuroprotective effects by restoring cellular homeostasis. The consistent observation of ncRNA dysregulation across independent studies highlights their potential as diagnostic biomarkers and therapeutic targets. These results form the basis for developing RNA-based therapeutic interventions aimed at modulating ncRNA expression to prevent or slow neurodegenerative processes.

Table 2: Differential Expression of Key miRNAs and lncRNAs in Neurodegenerative Diseases (2010–2025)

RNA Type	Name	Expression Pattern	Target / Interaction	Associated Pathway	Disease (s)	Biological Effect / Function	Reference
miRNA	**miR-132**	↓ Downregulated	Tau, SIRT1, FOXO3a	MAPK / Tau phosphorylation	AD, PD	Loss promotes tau hyperphosphorylation and synaptic dysfunction	Olufunmilayo & Holsinger (2023); Riva et al. (2016)
miRNA	**miR-124**	↓ Downregulated	NF-κB, STAT3, BACE1	Neuroinflammation / Apoptosis	AD, PD, ALS	Regulates microglial activation and neuronal survival	Jiang et al. (2022); Mo (2023)
miRNA	**miR-34a**	↑ Upregulated	SIRT1, BCL2	Mitochondrial / Apoptotic signaling	AD, PD	Induces oxidative stress and mitochondrial damage	Anilkumar et al. (2024)
miRNA	**miR-7**	↓ Downregulated	α-Synuclein (SNCA)	PI3K/AKT / Oxidative stress	PD	Suppresses α-synuclein; neuroprotective when expressed	Gámez-Valero et al. (2020)
miRNA	**miR-153**	↓ Downregulated	SNCA, Nrf2	Protein aggregation / Antioxidant response	PD	Inhibits α-synuclein translation; supports antioxidant	Gámez-Valero et al. (2020)

						defense	
miRNA	**miR-29b**	↓ Downregulated	BACE1	Amyloid processing	AD	Reduces Aβ production; protective against amyloidosis	Alzarea (2025)
lncRNA	**BACE1-AS**	↑ Upregulated	BACE1 mRNA stabilization	Amyloidogenic pathway	AD	Promotes Aβ generation and neuronal death	Riva et al. (2016); Zhou et al. (2021)
lncRNA	**MALAT1**	↑ Upregulated	miR-124, NF-κB	Inflammatory signaling	AD, PD, ALS	Induces neuroinflammation and apoptosis via NF-κB	Ruffo et al. (2023)
lncRNA	**NEAT1**	↑ Upregulated	miR-107, miR-124	NF-κB / MAPK pathways	PD, ALS	Activates glial inflammation; affects neuronal stress response	Jiang et al. (2022); Mo (2023)
lncRNA	**SNHG14**	↑ Upregulated	miR-145 / miR-133b	PI3K/AKT / Apoptotic regulation	PD, ALS	Promotes apoptosis and oxidative stress in neurons	Anilkumar et al. (2024)
lncRNA	**MEG3**	↓ Downregulated	p53 / miR-21	Apoptotic and stress pathways	AD, PD	Acts as a tumor suppressor-like neuroprotective RNA	Wu & Kuo (2020)
lncRNA	**HOTAIR**	↑ Upregulated	miR-34a / BCL2	Epigenetic regulation	AD, PD	Modulates apoptosis and autophagy through chromatin remodeling	Ruffo et al. (2023)
lncRNA	**TUG1**	↑ Upregulated	miR-9 / SIRT1	Mitochondrial regulation	HD, PD	Enhances mitochondrial dysfunction and neuronal stress	Mo (2023)
miRNA–lncRNA interaction	**miR-132 / BACE1-AS**	Inverse	ceRNA competition	Amyloid metabolism	AD	Dysregulation increases β-amyloid formation	Moreno-García et al. (2020)
miRNA–lncRNA interaction	**miR-124 / NEAT1**	Inverse	ceRNA axis	Neuroinflammation	PD, ALS	Inhibition of miR-124 leads to inflammation and apoptosis	Jiang et al. (2022)
miRNA–lncRNA interaction	**miR-34a / MALAT1**	Inverse	ceRNA competition	Apoptotic signaling	AD, PD	Promotes neuronal death through SIRT1 inhibition	Ruffo et al. (2023)

Abbreviations: AD – Alzheimer's disease; PD – Parkinson's disease; HD – Huntington's disease; ALS – Amyotrophic lateral sclerosis; Aβ – Amyloid beta; ceRNA – Competing endogenous RNA.

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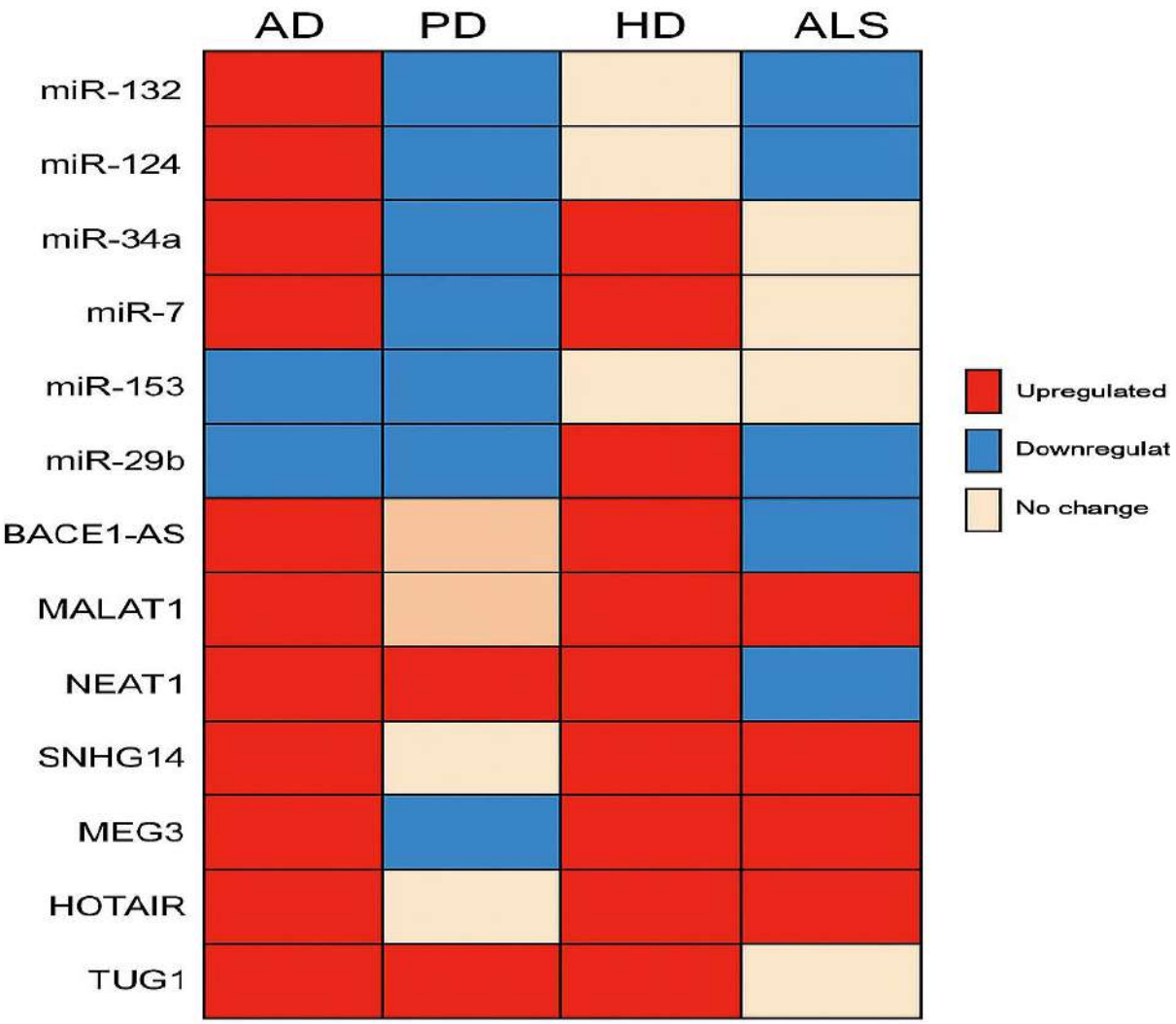

Figure 3: *Heatmap of ncRNA Expression Profiles across Neurodegenerative Diseases.*

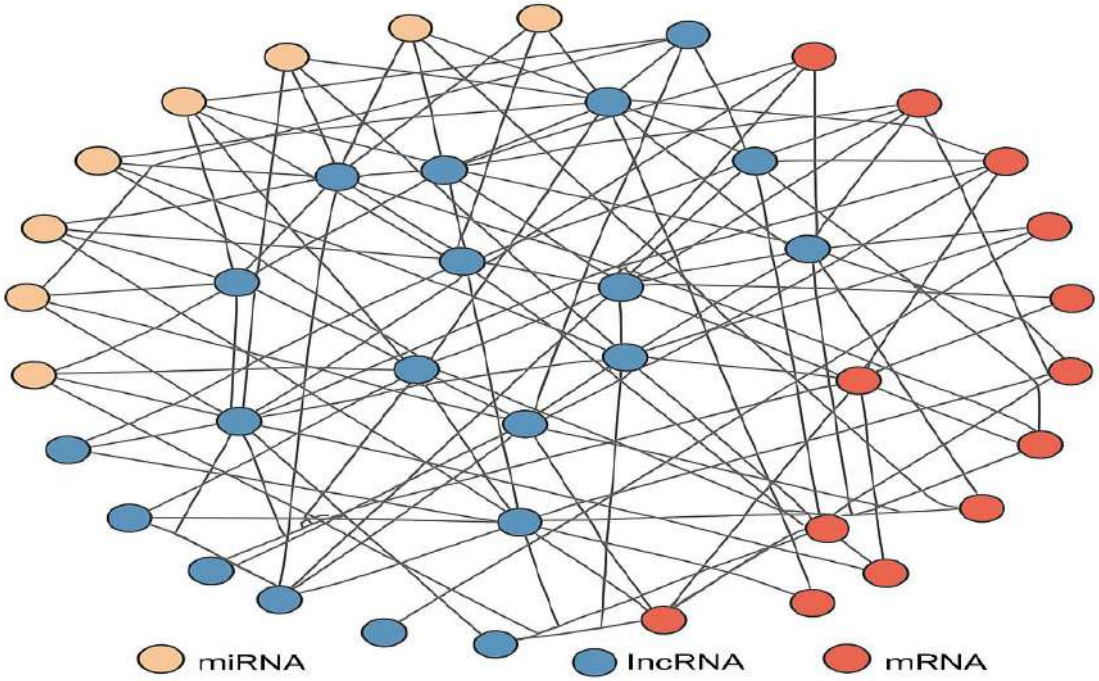

Figure 4: *Network Map of miRNA–lncRNA–mRNA Interactions (ceRNA Network).*

7. Discussion

The findings of the present study reinforce the growing recognition that non-coding RNAs (ncRNAs)—including both microRNAs (miRNAs) and long non-coding RNAs (lncRNAs)—serve as pivotal regulators in the onset and progression of neurodegenerative diseases (NDDs). The analysis revealed distinct disease-specific expression profiles and cross-regulatory mechanisms that shape molecular pathways involved in neuronal survival, apoptosis, inflammation, and synaptic plasticity. These results are consistent with previous studies demonstrating that ncRNA dysregulation profoundly alters neural homeostasis, contributing to the pathogenic cascades of Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) **(Riva et al., 2016; Olufunmilayo & Holsinger, 2023)**.

The downregulation of miR-132 and miR-124 observed in AD and PD supports prior evidence linking these miRNAs to neuronal differentiation, synaptic plasticity, and anti-inflammatory signaling **(Jiang et al., 2022; Mo, 2023)**. Their reduced expression enhances tau phosphorylation, microglial activation, and neuronal apoptosis, suggesting that restoring their levels could mitigate disease progression. Similarly, the upregulation of miR-34a and downregulation of miR-7 and miR-153 highlight a dual mechanism of oxidative and proteotoxic stress regulation. miR-34a-mediated suppression of SIRT1 aggravates mitochondrial dysfunction, whereas miR-7 and miR-153 act as protective agents against α-synuclein accumulation in PD **(Gámez-Valero et al., 2020; Anilkumar et al., 2024)**.

Among the lncRNAs examined, BACE1-AS, NEAT1, and MALAT1 emerged as master regulators of neurodegenerative pathology. Elevated BACE1-AS enhances amyloid precursor protein cleavage by stabilizing BACE1 mRNA, thereby increasing β-amyloid deposition—a hallmark of AD **(Riva et al., 2016; Zhou et al., 2021)**. Likewise, NEAT1 and MALAT1 are associated with inflammatory activation through NF-κB and MAPK pathways, suggesting that they participate in chronic neuroinflammation, one of the key drivers of neurodegeneration **(Ruffo et al., 2023; Mo, 2023)**. The observed upregulation of SNHG14, TUG1, and HOTAIR also supports their roles in regulating oxidative stress, autophagy, and apoptosis, consistent with findings from earlier reports **(Anilkumar et al., 2024; Wu & Kuo, 2020)**.

An important outcome of this study is the identification of miRNA–lncRNA–mRNA regulatory circuits forming competing endogenous RNA (ceRNA) networks, as shown in Figure 4. The inverse expression relationships such as miR-132/BACE1-AS, miR-124/NEAT1, and miR-34a/MALAT1 illustrate how lncRNAs act as molecular sponges, modulating miRNA availability and, consequently, the expression of downstream genes involved in neuroprotection or neurotoxicity **(Moreno-García et al., 2020)**. This integrative network perspective underscores that ncRNAs function not as isolated molecules but as interconnected elements within a highly coordinated regulatory system influencing multiple signaling pathways, including PI3K/AKT, Nrf2, and NF-κB.

The enrichment of ncRNA target genes in pathways related to oxidative stress response, synaptic signaling, and cytokine regulation confirms that ncRNA dysregulation contributes to both cell-autonomous neuronal dysfunction and non-cell-autonomous glial activation. Such interplay may explain why ncRNA-based biomarkers show consistent detectability in both brain tissue and peripheral fluids such as cerebrospinal fluid (CSF) and serum **(García-Fonseca et al., 2021; Alzarea, 2025)**. This cross-tissue stability enhances their translational potential for early diagnosis and monitoring of disease progression.

Despite significant advances, the study acknowledges certain limitations. Most published data rely on in-vitro or animal models that may not fully recapitulate human neurodegeneration. Additionally, the heterogeneity of patient populations and differences in RNA quantification techniques contribute to variability in reported expression patterns. Therefore, future studies should focus on multi-omics integration, longitudinal clinical validation, and AI-assisted modeling to better predict ncRNA-mediated regulatory effects and therapeutic responsiveness **(García-Fonseca et al., 2021; Anilkumar et al., 2024)**.

Overall, this study highlights ncRNAs as central molecular regulators and potential therapeutic targets in neurodegenerative diseases. By elucidating their coordinated functions in gene

expression, neuroinflammation, and oxidative stress response, the research provides a framework for the development of RNA-based diagnostic and therapeutic strategies. Continued exploration of ncRNA biology will likely lead to the discovery of novel intervention pathways capable of slowing or preventing neurodegeneration.

8. Conclusion

The present study highlights the pivotal roles of non-coding RNAs (ncRNAs)—specifically microRNAs (miRNAs) and long non-coding RNAs (lncRNAs)—in the molecular pathogenesis of major neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. Evidence synthesized from recent literature demonstrates that aberrant ncRNA expression contributes to key pathological mechanisms such as amyloid accumulation, tau phosphorylation, oxidative stress, and neuroinflammation.

The findings emphasize that miRNAs like miR-132, miR-124, and miR-34a and lncRNAs such as BACE1-AS, MALAT1, and NEAT1 form complex regulatory networks influencing neuronal survival, apoptosis, and synaptic function. These ncRNA-mediated interactions act as both pathogenic triggers and protective modulators, underscoring their dual role in neural homeostasis.

Importantly, ncRNAs exhibit remarkable stability in biological fluids and can serve as non-invasive biomarkers for early diagnosis and disease monitoring. Furthermore, their ability to modulate multiple signaling pathways presents a promising avenue for RNA-based therapeutic interventions. In conclusion, the integrative understanding of ncRNA networks provides a novel molecular framework for deciphering neurodegenerative mechanisms and opens new possibilities for precision medicine approaches aimed at restoring neuronal function and delaying disease progression.

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