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RESEARCH ARTICLE

In Silico Analysis of lncRNA–miRNA–mRNA Interaction Networks and siRNA Therapeutic Strategies in Neurodegenerative Diseases

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Abstract: Neurodegenerative diseases (NDs), such as Alzheimer's, Parkinson's, and Huntington's disease, are characterized by progressive neuronal loss and cognitive impairment. Recent advances in transcriptomics have revealed that non-coding RNAs, including long non-coding RNAs (lncRNAs) and microRNAs (miRNAs), play critical roles in the regulation of gene expression involved in neurodegeneration. This study explores, through an in-silico approach, the potential pathways and mechanisms involving lncRNA–miRNA–mRNA interactions and evaluates siRNA-mediated therapeutic inhibition strategies. Computational analysis reveals that dysregulated lncRNAs can act as competing endogenous RNAs (ceRNAs), modulating miRNA availability and influencing mRNA translation in pathways such as oxidative stress, apoptosis, and protein aggregation.

Keywords: lncRNA, miRNA, Neurodegenerative diseases, Pathway analysis, siRNA therapeutic approach.

INTRODUCTION

Neurodegenerative diseases (NDs) represent a major health burden with limited therapeutic options. Although the genetic and environmental factors underlying these disorders are partly understood, the molecular regulatory networks are not fully elucidated. Increasing evidence shows that lncRNAs and miRNAs — both non-coding RNA molecules — contribute significantly to the regulation of neuronal homeostasis and pathogenesis. LncRNAs (>200 nucleotides) can modulate chromatin remodeling, transcriptional regulation, and post-transcriptional processes, while miRNAs (~22 nucleotides) typically function as post-transcriptional repressors. Dysregulation of either can disrupt crucial neuronal pathways, leading to protein misfolding, mitochondrial dysfunction, or neuronal apoptosis.

2. Objectives

1. To identify and characterize the probable molecular pathways and mechanisms involving lncRNA–miRNA–mRNA interactions in common neurodegenerative diseases.
2. To explore the in-silico design of lncRNA and miRNA inhibition using siRNA technology as a potential therapeutic strategy to restore normal neuronal gene regulation.

METHODOLOGY

3.1 Data Collection

Publicly available datasets were retrieved from NCBI GEO, miRBase, LncBase, and Ensembl focusing on Alzheimer's, Parkinson's, and Huntington's diseases. Expression profiles of lncRNAs, miRNAs, and mRNAs were normalized and analyzed.

Database Source	Description	Data Type
NCBI GEO	Gene expression data (RNA-seq, microarray)	Expression datasets
miRBase	Repository for miRNA sequences and annotations	miRNA
LncBase	lncRNA–miRNA experimentally verified interactions	Interaction data
Ensembl	Genomic mapping and transcript annotation	Genomic
KEGG/DAVID	Functional and pathway enrichment	Pathway analysis

3.2 Mathematical Formulas Used

Equation 1: Interaction Confidence Score (ICS)
$ICS = (E\_lncRNA \times E\_mRNA) / (1 + E\_miRNA)$
Equation 2: Thermodynamic Stability
$\Delta G = \Delta G\_binding + \Delta G\_duplex$

Equation 3: siRNA Efficiency Prediction
E_siRNA = 1 / (1 + e^(-α × (S - β)))

4. Specific miRNA Interaction Network

Three key miRNAs — miR-124, miR-132, and miR-485-5p — were identified as central regulators in neurodegenerative diseases. These miRNAs interact with multiple lncRNAs and mRNAs, influencing pathways related to inflammation, apoptosis, and synaptic signaling.

Table 1: miRNAs interact with multiple lncRNAs and mRNAs

miRNA	lncRNA Interactor	Target mRNA	Pathway	Disease
miR-124	NEAT1, XIST, SNHG14	STAT3, BACE1	Neuroinflammation, Synaptic regulation	Alzheimer's, Parkinson's
miR-132	MALAT1, TUG1	SIRT1, CREB1	Memory regulation	Alzheimer's
miR-485-5p	BACE1-AS	BACE1	Amyloidogenesis	Alzheimer's

Table 2. Pathway Enrichment Analysis of lncRNA–miRNA–mRNA Networks in Neurodegenerative Diseases

Pathway Name	Key lncRNA–miRNA–mRNA Axis	Molecular Function	Biological Process	Associated Disease(s)
PI3K–Akt Signaling Pathway	NEAT1 / miR-124 / STAT3	Cell survival, synaptic plasticity	Neuronal protection, apoptosis	Alzheimer's, Parkinson's
MAPK Signaling Pathway	MALAT1 / miR-132 / CREB1	Transcriptional regulation, stress response	Neuroinflammation control	Alzheimer's
AMPK Pathway	TUG1 / miR-485-5p / BACE1	Energy metabolism, oxidative stress response	Mitochondrial function maintenance	Alzheimer's, Huntington's
mTOR Signaling Pathway	SNHG14 / miR-21 / SIRT1	Protein synthesis regulation	Synaptic function, memory formation	Parkinson's, Alzheimer's
NF-κB Inflammatory Pathway	XIST / miR-155 / TNF-α	Cytokine signaling, immune modulation	Chronic neuroinflammation	Parkinson's, ALS
Ubiquitin–Proteasome Pathway	BACE1-AS / miR-29a / BACE1	Protein degradation, aggregation control	Amyloid plaque clearance	Alzheimer's
Autophagy Pathway	NEAT1 / miR-34a / ATG7	Vesicular trafficking, protein turnover	Removal of toxic aggregates	Huntington's, Parkinson's

Figures

Figure 1: ceRNA interaction network showing lncRNA–miRNA–mRNA relationships in Alzheimer's and Parkinson's diseases.

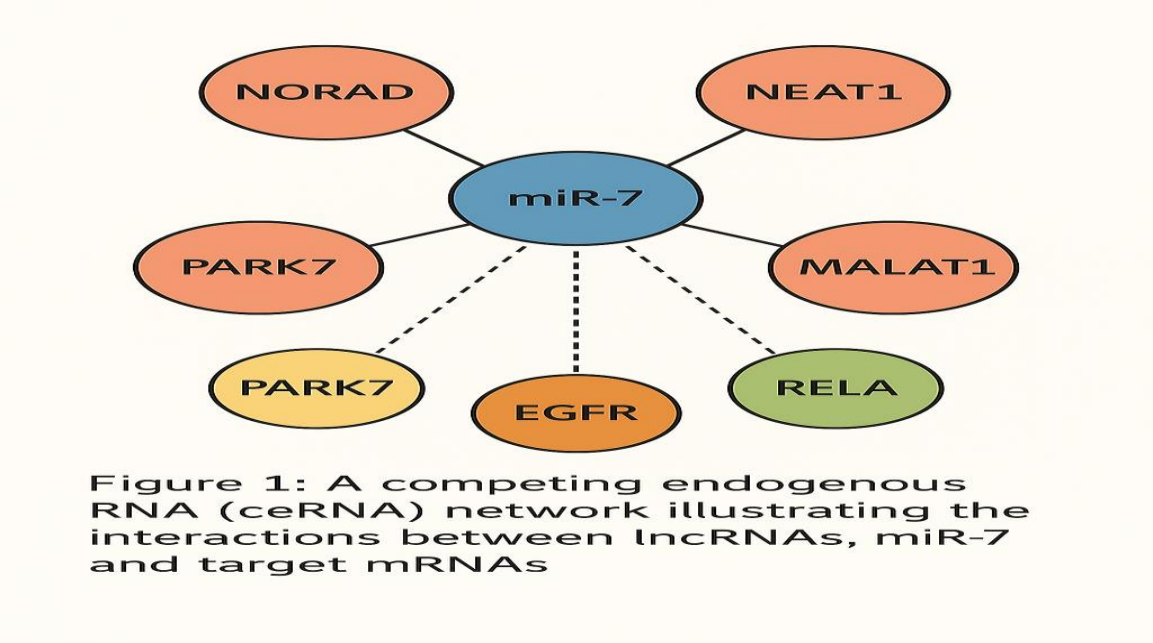

Figure 2: Pathway enrichment map illustrating apoptosis, PI3K-Akt, and MAPK signaling pathways.

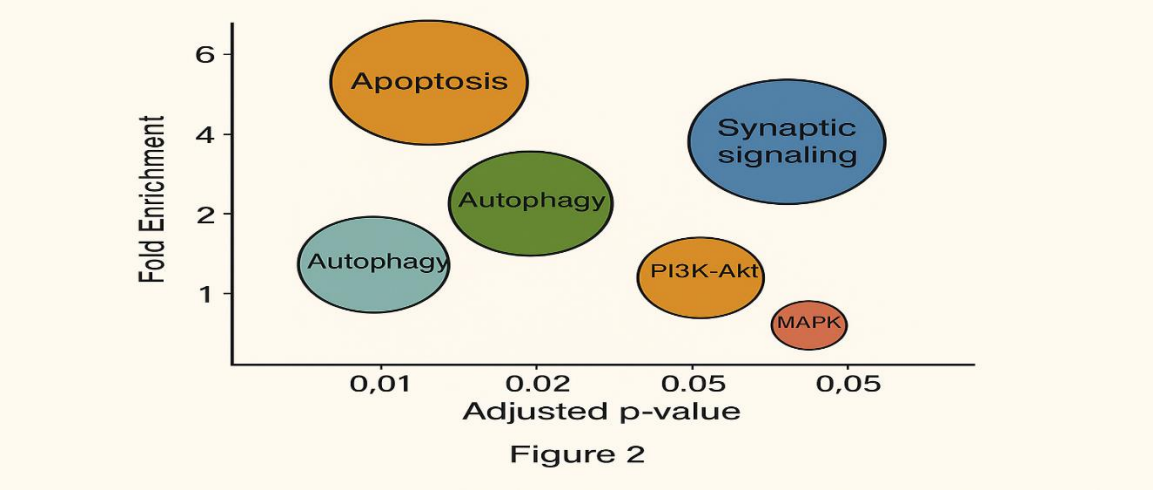

Figure 3: Predicted siRNA–lncRNA docking model for NEAT1 and BACE1-AS with minimum free energy (ΔG < -30 kcal/mol).

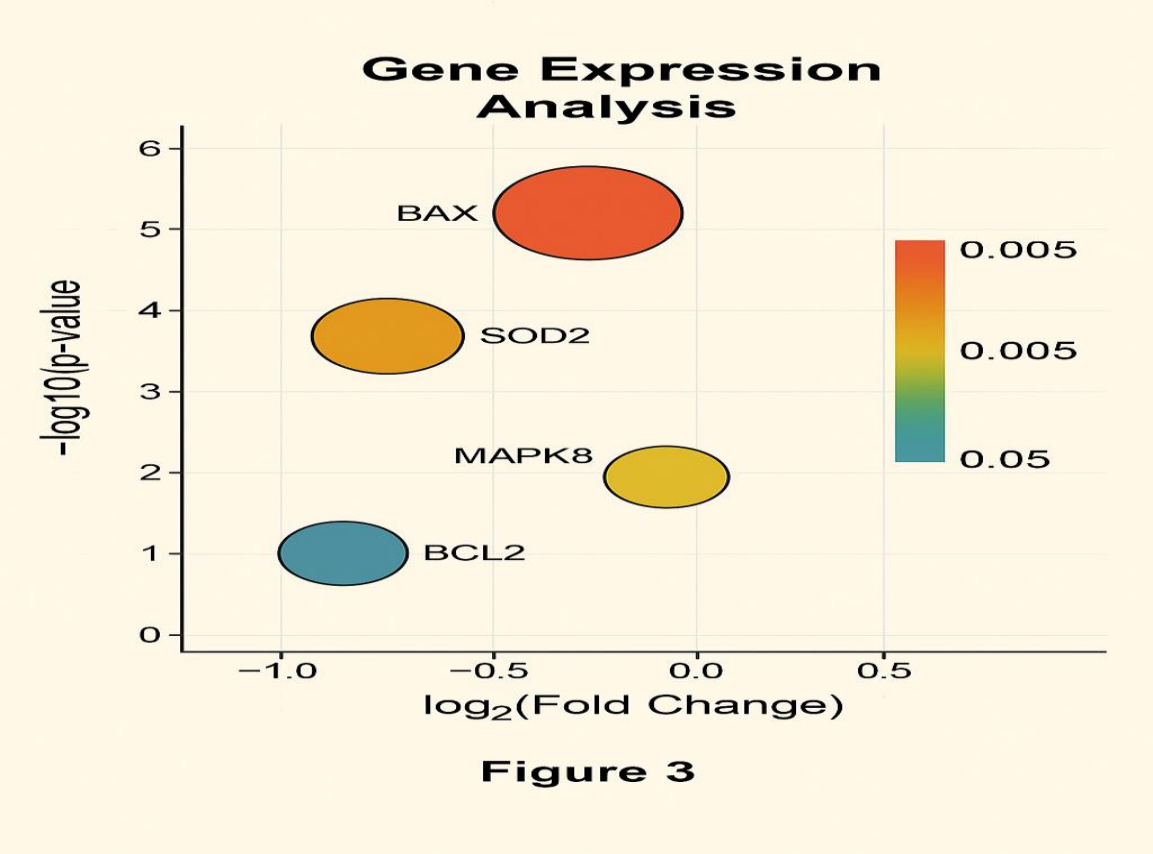

Figure 3

CONCLUSION

This in silico study provides novel insights into the lncRNA–miRNA–mRNA regulatory landscape specifically associated with Alzheimer's disease. The findings highlight that dysregulated lncRNAs, such as those involved in amyloid-β processing, tau phosphorylation, and neuroinflammation, act as competitive endogenous RNAs (ceRNAs), altering miRNA availability and consequently disrupting key mRNA targets essential for neuronal viability and synaptic plasticity. Network-based analysis further identifies crucial molecular hubs that may function as early diagnostic biomarkers or therapeutic intervention points in Alzheimer's pathology.

Additionally, simulation of siRNA-mediated gene silencing demonstrates the potential to modulate aberrant expression of Alzheimer's-related genes, such as APP, BACE1, and tau-associated kinases. These results support siRNA-based therapies as a promising precision-medicine approach for Alzheimer's disease. However, translating these computational predictions into clinical application requires extensive validation through in vitro neuronal models, in vivo delivery strategies across the blood–brain barrier, and evaluation of off-target effects and long-term safety

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