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Commentary

# Comment on "Hsa_Circ_0105596/FTO inhibits progression of Parkinson's disease by sponging miR-187-3p and regulating eEF2"

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## Introduction

Parkinson's disease (PD), a progressive neurodegenerative disorder, characterized by clinical features such as bradykinesia and resting tremor. It is characterized by specific neuropathological changes. These changes include the degeneration of dopaminergic neurons in the substantia nigra (SN) pars compacta. Additionally, PD is marked by the presence of Lewy bodies, which are aggregates of misfolded proteins. However, understanding the pathogenesis of PD was not completely clear. In this study, we focused on circRNAs and miRNAs as the core to study Parkinson's disease and proved that circFTO can adsorb miR-187-3p to regulate the core protein eEF2. This process was proved by bioinformatics and experimental verification methods, and it was found that this regulation can also affect inflammation, oxidative stress, and apoptosis. Our study posited that circFTO, through its interaction with miR-187-3p, modulated the expression of eEF2, a protein implicated in the pathogenesis of PD.

## Summary

The study of methodology employed had a certain coherence due to its integrative approach, combining bioinformatics analysis with experimental validation. We utilized transcriptome sequencing data from the SN and striatum, employing WGCNA to identify PD-related modules and pivot genes. Furthermore, our study utilized molecular biology techniques to validate interactions. These techniques included RNA binding protein immunoprecipitation assays and dual luciferase reporter assays for circFTO, miR-187-3p, and eEF2. We found that circFTO was upregulated in the SN of PD patients, and this upregulation was associated with a downregulation of miR-187-3p and a subsequent increase in eEF2 expression. Our findings were consistent with the hypothesis that circFTO sponged miR-187-3p, leading to the derepression of eEF2 and contributing to PD pathogenesis. We also demonstrated that modulating circFTO levels could influence oxidative stress and inflammation in PD models, suggesting a potential therapeutic avenue for targeting this axis. Below, we discussed the main highlights of this article:

### Transcriptomic and proteomic insights into PD

The striatum is involved in the control of movement and was characterized by the degeneration of dopaminergic neurons in the SN. The loss of these neurons led to a reduction in dopamine levels, which is a hallmark of PD [1]. The study presented a thorough transcriptomic analysis comparing the gene expression profiles of PD and normal controls in both the striatum and SN. A substantial

number of upregulated and downregulated genes were identified, with notable genes such as TIMP3, SLC18A2, and S100A12 emerging as potential biomarkers for PD. This gene expression pattern reflected the dysregulation of several key cellular processes in PD, including neurotransmitter regulation, inflammation, and cell survival. In addition, KEGG pathway analysis further highlighted the involvement of critical signaling pathways in PD, such as PI3K-Akt, MAPK, NF-κB, and HIF-1, in the upregulated genes. The downregulated genes were predominantly enriched in pathways related to neurodegeneration, including Huntington's disease, Alzheimer's disease, and PD pathways. These findings emphasized the convergence of multiple neurodegenerative pathways in PD, suggesting a complex and multifactorial disease process that required further exploration.

**The circFTO-miR-187-3p-eEF2 axis: A novel therapeutic target**

One of the most innovative aspects of our study was the identification of the circFTO-miR-187-3p-eEF2 axis as a key regulator in PD progression. This axis represented a previously underexplored mechanism in PD pathology, and our study's findings suggested that it may play a critical role in disease development and progression. CircFTO, which was upregulated in the SN of PD patients, could sponge miR-187-3p, thereby disrupting the regulatory mechanism by which miR-187-3p controlled eEF2 expression. Therefore, the circFTO we studied can be used as an ideal candidate for PD liquid biopsy biomarkers. In addition to this, targeting circFTO-miR-187-3p-eEF2 Axis may potentially alleviate PD symptoms and slow disease progression. MiRNAs are small non-coding RNAs that post-transcriptionally regulate gene expression by binding to complementary sequences in target mRNAs, leading to mRNA degradation or translational repression [2]. MiR-187-3p had been implicated in various biological processes, including neuronal development and function [3]. Our study suggested that miR-187-3p may be a key player in PD pathogenesis by regulating eEF2, a protein involved in protein synthesis and synaptic plasticity. EEF2 was a rate-limiting factor in the elongation phase of protein synthesis, and its dysregulation had been linked to neurodegenerative diseases, including PD [4].

**Multi-omics approach and network analysis**

The multi-omics approach employed was a significant strength of our study. By integrating bioinformatics, transcriptome analysis, and experimental validation, we provided a robust framework for our findings. The use of WGCNA and protein-protein interaction analysis to identify PD-related modules added another layer of depth to the study. WGCNA is a systems biology method that allows for the identification of gene co-expression networks, which can reveal the functional relationships between genes and their roles in disease pathology [5]. The identification of modules enriched in PD-related pathways suggested that these networks may be dysregulated in the disease, providing potential targets for therapeutic intervention.

**The role of eEF2 and eEF2K in neurodegeneration**

A significant focus of the study was the differential expression of eEF2 and eEF2K, which were found to be significantly upregulated in neurons in the PD group compared to controls**.** Elevated eEF2 expression in neurons correlated with an increase in protein synthesis, which is often associated with cellular stress and apoptosis. The study also demonstrated that interference with eEF2 could partially alleviate PD-related neuronal damage. Interestingly, eEF2K, which plays a role in regulating eEF2 activity, was also found to be upregulated in PD neurons, further highlighting its involvement in the neurodegenerative process. This was consistent with previous research suggesting that eEF2 may play a role in neurodegenerative processes [6]. EEF2K, which regulates eEF2 activity, was also found to be upregulated in PD neurons, further highlighting its involvement in the neurodegenerative process.

**Nevertheless, there were several limitations that deserved attention as follow:**

Firstly, the study primarily utilized the SH-SY5Y cell line, which, despite its widespread use in PD research, may not fully recapitulate the complexity of human PD. Future studies could benefit from incorporating patient-derived iPSC models, which offer a more accurate representation of the human disease state in PD pathology. Secondly, the study's focus on short-term effects of interventions was a noted limitation. Given the chronic nature of PD, long-term tracking of intervention effects was crucial for evaluating their potential therapeutic efficacy and understanding the disease's progression over time. Thirdly, the correlation between circFTO, miR-187-3p, and eEF2 did not necessarily imply causation, and the specific mechanisms by which these molecules influenced PD pathology required further elucidation, including inflammation and oxidative stress involved in this study. The study's focus on eEF2 as a downstream target of miR-187-3p was a significant contribution, but the broader implications of this regulation in the context of PD's complex pathology were not fully explored. Additionally, the study could be further expanded through gene knockout or CRISPR-Cas9 gene editing technology, offering more definitive evidence of gene function and its role in PD pathogenesis. Lastly, PD involved not only neurons but also glial cells and other cell types, and understanding the interactions within this microenvironment was crucial for developing effective treatments. Future studies should consider these interactions and their impact on disease progression, potentially leading to novel therapeutic strategies that target the complex interplay between different cell types in the brain.

## Conclusion

In conclusion, our study represented that excessive circFTO sequesters miR-187-3p, impairing its ability to regulate eEF2 expression. It an advancement of the molecular mechanisms underlying PD, particularly in the context of the circFTO-miR-187-3p-eEF2 axis. The research provided valuable insights into potential biomarkers and therapeutic targets, contributing to the growing body of literature on ncRNAs in neurodegenerative diseases. While the study had its limitations, it laid the groundwork for future research that could build upon these findings and address the noted shortcomings. Future directions could include the use of more representative disease models, long-term tracking of intervention effects, and the integration of multi-omics data to provide a more comprehensive understanding of PD. Additionally, expanding the functional validation of genes and considering the disease microenvironment could lead to the development of novel therapeutic strategies that target the complex interplay of factors in PD pathology. Additionally, it will be crucial to validate the findings in larger cohorts and to explore the potential of targeting the circFTO-miR-187-3p-eEF2 axis in clinical trials.

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