Role of Novel Long Non-Coding RNAs in Neuroinflammation and Neurodegenerative diseases

Ashcharya Rishi, Avishankar Chini, Prarthana Guha and **Subharangsu Mandal***

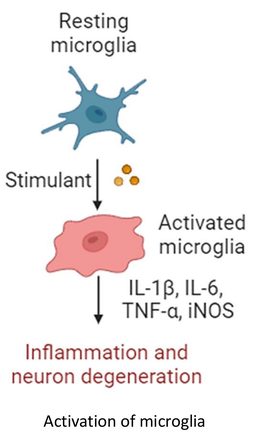
Department of Chemistry and Biochemistry, University of Texas at Arlington, Arlington, TX

Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder affecting nearly 7 million Americans and 50 million people worldwide. Characterized by amyloid-beta (Aβ) plaques, tau hyperphosphorylation, and cognitive decline, AD is increasingly linked to neuroinflammation mediated by microglia, the brain's resident immune cells. A key factor in maintaining synaptic plasticity and cognitive health, brain-derived neurotrophic factor (BDNF) has been found to decrease in neurodegenerative diseases like AD, impacting neuron survival and function. Recent studies, including our own, suggest that BDNF expression is regulated by the long non-coding RNA (LncRNA) HOTAIR, emphasizing a role for LncRNAs in brain health and disease. Our research aims to identify novel LncRNAs associated with Aβ-induced neuroinflammation and microglial activation in AD. We have observed that Aβ-induced neuroinflammation downregulates BDNF in microglia, suggesting that LncRNAs may play key regulatory players in neuroinflammatory pathways. In parallel, our studies in human THP1-derived macrophages (THP1-Mϕ) have revealed novel LncRNAs involved in inflammatory responses, some potentially also involved in Aβ induced neuroinflammation. This work will focus on elucidating the mechanisms by which these novel LncRNAs modulate Aβ-induced neuroinflammation and contribute to AD progression. Furthermore, this research could uncover potential diagnostic and therapeutic targets for Alzheimer's disease.

Introduction

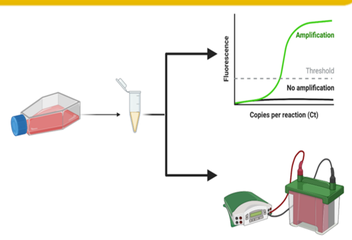
- Neuroinflammation, particularly microglial activation, plays a critical role in neurodegenerative diseases.
- Microglia, the resident immune cells in the brain, respond to a stimulant such as Aβ by releasing pro-inflammatory cytokines, chemokines, and reactive oxygen species, which contribute to neuronal damage and cognitive decline.
- Long non-coding RNAs (LncRNAs) have been found to play an important role in the regulation of neuroinflammation.



- In this study we aim explore the role of inflammation associated LncRNAs under Aβ induced inflammation

Methodology

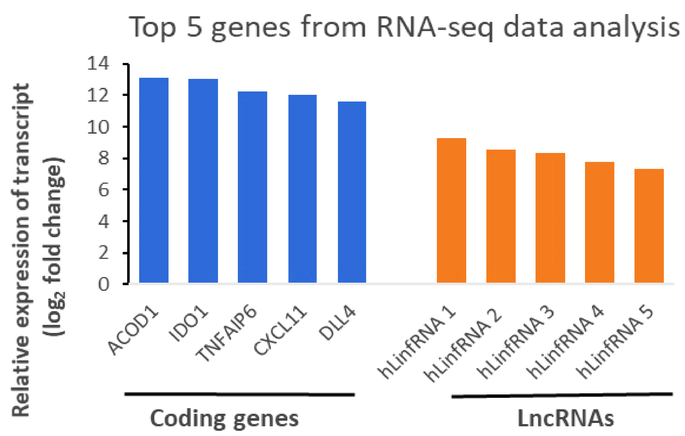
- Microglial cells were cultured and induced by Aβ peptide
- Quantitative PCR and Western blotting techniques were utilized for mRNA and protein analysis



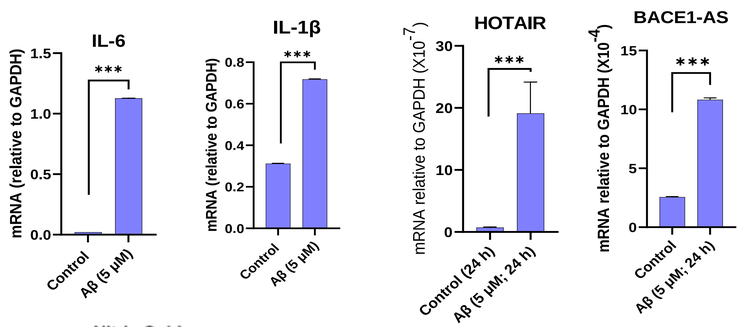
Discussion

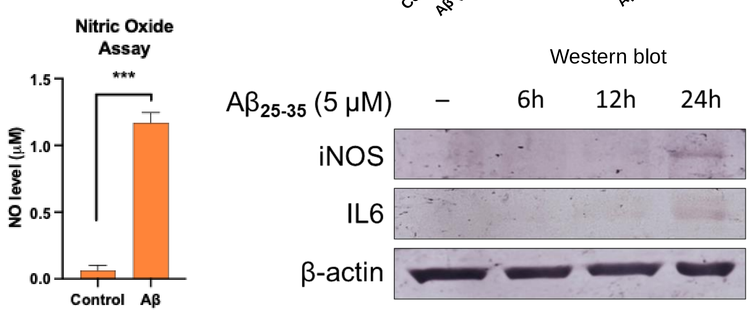
- Recently long noncoding RNAs have been identified as key players in cell signaling and inflammation
- By identifying novel LncRNAs associated with Aβ-induced neuroinflammation and microglial activation, we have uncovered potential key players in the mechanisms underlying AD progression.
- The discovery of a panel of LncRNAs involved in inflammation, opens new avenues for targeted therapeutic interventions.

RNA-seq reveals novel long non-coding RNAs potentially associated with inflammation and macrophage activation in human

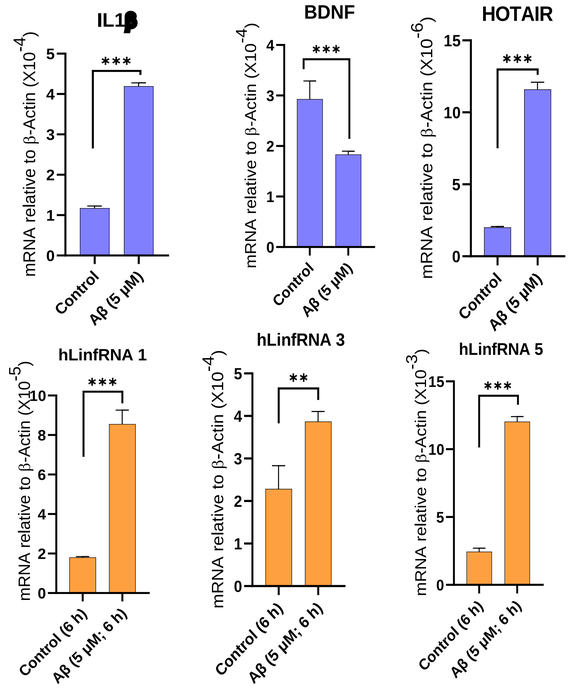


Aβ stimulation upregulates proinflammatory cytokines, nitric oxide and lncRNAs in mouse and rat microglia respectively





Aβ induces hLinfRNAs in human microglia (HMC3)



References

- Chini *et. al.,* Novel Human Long-noncoding RNAs associated with Inflammation and Macrophage Activation. Sci Rep 13, 4036 (2023).
- Obaid *et. al.*, LncRNA HOTAIR regulates lipopolysaccharide-induced cytokine expression and inflammatory response in macrophages. Sci Rep 8, 15670 (2018).
- Deb P *et. al.*, Dynamic regulation of BDNF gene expression by estradiol and lncRNA HOTAIR, Gene, 2024.

Acknowledgement

Collaborators

Prof. Young-Tae Kim
Department of Bioengineering, University of Texas, Arlington

Prof. James Simpkins
Department of Neuroscience, West Virginia University

Mandal lab members

National Institutes of Health
Turning Discovery Into Health

1 R15 HL170257-01