Epitranscriptomic and epigenetic dysfunctions in neurodegenerative diseases FTD and ALS

Shuying Sun, Ph.D.

Department of Physiology, Brain Science Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Dysfunction of RNA metabolism has emerged to play crucial roles in multiple neurodegenerative diseases, including frontal temporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). The most common genetic cause of FTD and ALS is hexanucleotide repeat expansion in the first intron of the *C9ORF72* gene. RNA-mediated toxicity is implicated in the pathogenicity. N^6-methyladenosine (m^6A) is the most prevalent internal RNA modification. We identified that the global m^6A is downregulated in C9ORF72- FTD/ALS patient-derived induced pluripotent stem cell (iPSC)-differentiated neurons (iPSNs) and postmortem brain tissues. This leads to transcriptome-wide mRNA stability changes, especially the neuronal genes with inferred association to ALS. Recently, we also found that m^6A regulates chromatin-associated RNAs (caRNAs) in C9ORF72-FTD/ALS. We show that m^6A hypomethylation increases the caRNA level, associated with chromatin accessibility changes. Reduction of caRNAs alleviates chromatin abnormalities in patient-derived neurons. We provide evidence in support of a new pathogenic mechanism involving epitranscriptome-epigenome mediated dysregulation of gene networks in FTD/ALS.

Sponsored By: NIH RF1NS127925 and R01AG078948

Presenter Name and contact information:
Shuying Sun, Ph.D., Associate Professor
Department of Physiology
Johns Hopkins University School of Medicine
Baltimore, Maryland, USA
Email: shuying.sun@jhmi.edu