Name: Huiping Zhang Email: huipingz@bu.edu

Effects of Chronic Intermittent Ethanol (CIE) Exposure on Global m6A RNA Methylation and m6A Regulatory Gene Expression in Mouse Liver

Ji Sun Koo[1,2], Christine M. Side[3], Jacqueline M. Barker[3], Huiping Zhang[1,2]

[1]Department of Psychiatry, Boston University Chobanian and Avedisian School of Medicine, Boston MA02118, USA;
[2]Department of Medicine (Biomedical Genetics), Boston University Chobanian and Avedisian School of Medicine, Boston MA02118, USA;
[3]Department of Pharmacology & Physiology, College of Medicine, Drexel University, Philadelphia, PA 19102, USA

Background: Chronic ethanol consumption can lead to alcohol use disorder and liver disease through epigenetic changes at both transcriptional and post-transcriptional levels. We hypothesize that chronic ethanol exposure alters RNA methylation profiles and m6A regulatory gene expression in the liver.

Methods: The study included three groups of C57BL/6J mice: (1) naïve; (2) self-administration (SA, or low-dose ethanol intake); and (3) SA followed by chronic intermittent ethanol (CIE) exposure (high-dose ethanol intake). Global m6A RNA methylation levels were measured using an m6A ELISA assay. Ethanol-induced expression changes of five m6A writer genes (Mettl3, Mettl4, Mettl14, Kiaa1429, and Wtap), two m6A eraser genes (Fto and Alkbh5), and five m6A reader genes (Ythdc1, Ythdc2, Ythdf1, Ythdf2, and Ythdf3) in mouse livers were quantified using RT-qPCR.

Results: No significant differences in global m6A RNA methylation were observed among the three groups of mice. However, in male mice with high-dose ethanol intake, global m6A RNA methylation levels were positively correlated with blood ethanol concentrations (BECs). Additionally, high-dose ethanol intake led to decreased expression of m6A writer, eraser, and reader genes.

Discussion: High-dose ethanol intake appears to impact global m6A RNA methylation, particularly in male livers. The observed downregulation of both m6A "writer" (methylase) and "eraser" (demethylase) genes may act as a balancing mechanism to maintain an overall stable m6A methylation profile in the liver. In future studies, we plan to investigate transcriptome-wide, ethanol-induced m6A RNA methylation changes at individual genes, with a specific focus on those involved in alcohol addiction.