Name: Luana Carvalho
PI Name: Amy Lasek
Email: Luana.MartinsdeCarvalho@vcuhealth.org
PI Email: Amy.Lasek@vcuhealth.org

PCBP1-Mediated Alternative Splicing in the Hippocampus During Alcohol Withdrawal

Luana Carvalho, Jonathas Almeida, Hu Chen, and Amy W. Lasek

Department of Pharmacology and Toxicology, Virginia Commonwealth University

Alternative splicing is highly prevalent in the brain and tightly regulated by RNA-binding proteins (RBPs). Disruptions in this regulation have been associated with psychiatric disorders. PCBP1 is a multifunctional RBP that acts as a splicing factor by regulating exon retention and exclusion. We observed an increase in Pcbp1 expression in the rat hippocampus during alcohol withdrawal, a model that induces anxiety- and depressive-like behaviors. We showed that PCBP1 drives Hapln2 alternative splicing, leading to either nonsense-mediated decay of its transcript or the production of a non-functional protein. The Hapln2 gene encodes an extracellular matrix protein involved in nerve conduction velocity, and its altered splicing could impair neurotransmission, offering a potential mechanism for withdrawal-induced emotional and cognitive dysfunctions. Beyond Hapln2, we hypothesize that PCBP1 regulates a broader network of genes, possibly contributing to behavioral outcomes such as anxiety and depression during withdrawal. Using RNA Immunoprecipitation Sequencing (RIP-Seq), we aimed to profile PCBP1-regulated transcripts in the hippocampus of rats during alcohol withdrawal to better understand splicing mechanisms in this context. We observed increased PCBP1 binding to introns and exons during alcohol withdrawal, suggesting that it does play a genome-wide role in splicing regulation. KEGG pathway analysis revealed that PCBP1-associated transcripts are enriched in pathways related to neurodegeneration and axonal guidance, implicating PCBP1 in processes such as progressive neuronal loss, neuroinflammation, and synaptic or axonal dysfunction. These mechanisms are known to contribute to emotional and cognitive impairments, suggesting a broader role for PCBP1 in alcohol-induced neurodegeneration and white matter integrity.