N6-methyladenosine and Epitranscriptomic Regulation of Learning and Responses to Cocaine

Meera Patel1, Zhuoyue Shi1, Jessica Koranda1, Chuan He2, and Xiaoxi Zhuang1,

1Department of Neurobiology and 2Department of Chemistry, the University of Chicago

N6-methyladenosine (m6A) profoundly regulates mRNA metabolism and protein synthesis. Recent data suggest that m6A deficiency in the brain have significant functional consequences on development, synaptic plasticity and learning. We deleted Mettl14, an essential component of the m6A methyltransferase complex, in different brain regions and cell types. We also generated or obtained mice with constitutive or cell type specific genetic deletion of various m6A reader proteins (RNA binding proteins that recognize m6A and mediate downstream functional consequences). Mettl14 deletion reduced striatal m6A levels without altering cell numbers or morphology. Transcriptome-wide profiling of m6A-modified mRNAs in Mettl14-deleted striatum revealed downregulation of striatal mRNAs encoding neuron- and synapse-specific proteins in both D1 and D2 neurons, but D1 and D2 neuron identity genes were uniquely downregulated in each respective cell type. These changes increased neuronal excitability, reduced spike frequency adaptation and profoundly impaired striatal-mediated behaviors. In the dorsal striatum, they severely impaired motor learning whereas in the nucleus accumbens they severely impaired appetitive Pavlovian learning without affecting motor learning. Mettl14 deletion in D1 neurons severely impaired responses to cocaine whereas Mettl14 deletion in D2 neurons or in dopamine neurons significantly enhanced responses to cocaine. One of the m6A reader proteins, YTHDF1, seems to mediate many of the above phenotypes. How exactly YTHDF1 responds to challenges, affects downstream targets, cellular properties, circuit functions and behaviors is under investigation.