A critical role of an exon junction complex (EJC) factor in regulation of embryonic neurodevelopment and implications in neurodevelopmental disorders

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Nonsense-mediated mRNA decay (NMD) is RNA surveillance mechanism that degrades mRNAs carrying premature termination codons (PTCs). This mechanism requires several key EJC factors to distinguish PTC from the normal stop codon. But how this mechanism modulates the embryonic neurodevelopment and behaviors is largely unknown. In this study, we demonstrated that RBM8a plays a key role in neural progenitor proliferation and differentiation. First, RBM8a is highly expressed in the sub-ventricular zone of early embryonic cortex suggesting that RBM8a may play a role in regulating neural progenitor cells (NPCs). To test this hypothesis, we used in utero electroporation to overexpress or knock down RBM8a in mouse brain at E14. RBM8a stimulates embryonic neural progenitor proliferation and suppresses neuronal differentiation indicating that RBM8a positively regulates NPC proliferation. Conversely, knockdown of RBM8a in the neocortex reduces NPC proliferation and promote premature neuronal differentiation. Consistently, Nes-cre; RBM8af1/+ mice show severe developmental defects including microcephaly and postnatal lethality. When RBM8a is overexpressed in the dentate gyrus of adult brain using stereotactic viral injection, mice showed altered anxiety and depressive-like behaviors. To uncover the underlying mechanisms, genome-wide RNAseq identifies potential substrates of RBM8a in the brain which have been implicated in neurogenesis and plasticity. Interestingly, autism and schizophrenia-risk genes are highly representative in RBM8a associate transcripts. Taken together; we identify a novel role of RBM8a in regulation of neurodevelopment and behaviors. Our studies provide a deeper insight on causes of mental illnesses and will facilitate the development of new therapeutic strategies for neurodevelopmental illnesses.

Biography

Yingwei Mao has completed his PhD at University of Michigan School of Medicine and Postdoctoral studies from MIT Picower Institute of Learning and Memory. He is the Assistant Professor of Penn State University. His lab studies are on the molecular mechanism of neurodevelopment and the relationship to psychiatric disorders. He has published more than 25 papers in reputed journals.

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