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ROLE OF CIRCRNAS IN PSYCHIATRIC AND FETAL ALCOHOL SPECTRUM SYNDROME DISORDERS

Jason P. Weick[1], Amber J. Zimmerman[1], Kristen J. Brennand[2], Stephen J. Haggarty[3], Vince D. Calhoun[4,1,5], Jingyu Liu[4], Kevin K Caldwell[1], Nora Perrone-Bizzozero[1], Jonathan L. Brigman[1], Nikolaos Mellios[1]*

1 Department of Neurosciences, University of New Mexico School of Medicine, Albuquerque, NM.
2 Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY.
3 Center for Genomic Medicine, Chemical Neurobiology Laboratory, Departments of Neurology and Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA.
4 The Mind Research Network, Albuquerque, NM, USA.
5 Department of Electrical and Computer Engineering, University of New Mexico, Albuquerque, NM

Although circular RNAs (circRNAs) are a subtype of non-coding RNAs enriched in the mammalian brain, nothing is known about their potential involvement in psychiatric and neurodevelopmental disorders. Here, we first show that *circHomer*1, a circRNA derived from Homer protein homolog 1 (HOMER1), is reduced in the orbitofrontal cortex (OFC) and in stem cell-derived neuronal cultures from patients with schizophrenia (SCZ) and bipolar disorder and is inversely correlated to the relative abundance of *HOMER1B mRNA* isoform. Using *in vivo* knockdown of *circHomer*1 in mouse OFC, we show that it modulates the synaptic localization of Homer1b and is necessary for OFC-mediated reversal learning. Moreover, we demonstrate that *circHomer*1 inhibits synaptic transmission and binds to an RNA-binding protein that can increase its synaptic localization. Lastly, a SCZ-linked single nucleotide polymorphism is associated with reduced OFC *circHomer*1 expression and altered local functional connectivity. Collectively, these data introduce a novel psychiatric disease-associated circRNA that regulates synaptic gene expression, neuronal function, and cognitive flexibility. In parallel, we show data of altered circRNA expression in fetal brains of an animal model of Fetal Alcohol Syndrome Spectrum Disorders. Ongoing experiments are aiming at examining the effects of ethanol-induced circRNAs on neuronal development and synaptic plasticity in mouse brain and human pluripotent stem cell-derived neuronal cultures.

Biography

Nikolaos Mellios has completed his MD at the University of Athens, School of Medicine, Greece (1996-2002) and his PhD from the University of Massachusetts, School of Medicine (2004-2009) with a focus on Neurosciences. He continued his Post-doctoral studies at the Picower Institute for Learning and Memory at MIT (2009-2015) and since August 2015, he has started his own lab at the Department of Neurosciences at the University of New Mexico, School of Medicine. He has published numerous papers in high impact journals on the role of non-coding RNAs in neurodevelopmental and psychiatric disorders.

NMellios@salud.unm.edu