Submitter (PI) Name: Jian Feng

Submitted (PI) email: feng@bio.fsu.edu

Neuron subtype specific role of DNA methylcytosine dioxygenase TET1 in cocaine addiction

Haiyang Xu, Graham Kaplan, Yuxiang Li, Nick Waddell, Amber Brown, Rachel Hedinger, and Jian Feng

Department of Biological Science and Program in Neuroscience, Florida State University

The role of DNA epigenetic modifications, such as DNA methylation, has been increasingly appreciated in drug addiction. Recently, TET enzymes were recognized to oxidize methylated DNA cytosine into 5-hydroxymethylcytosine, and additional forms of modification, which may lead to DNA demethylation. However, the function of TET enzymes and their associated DNA methylation turnover in drug addiction is still elusive. Previously, we found that TET1 in the nucleus accumbens is implicated in cocaine action. We therefore hypothesize it may carry neuron-subtype specific roles in the two types of accumbal medium spiny neurons, dopamine D1 receptor-expressing medium spiny neurons (D1-MSN) or dopamine D2 receptor-expressing MSNs (D2-MSN). In the present study, we investigated the impact of *Tet1* deletion in either D1-MSN or D2-MSN on behavioral responses to cocaine in reward- and addiction-related behavioral paradigms. We found that *Tet1* knockout in D1-MSN of male mice or D2-MSN of female mice enhances the rewarding value of cocaine, potentiates the vulnerability to cocaine binge, and amplifies the incentive motivation for taking cocaine. However, Tet1 knockout in D2-MSN of male mice or D1-MSN of female mice has the opposite effects. We are in process to characterize the TET1 mediated DNA methylation changes in these two neuron-subtypes of both males and females. Our work-in-progress findings suggest the DNA epigenetic modification's role in addiction can be both cell-type and sex specific.