College of Science
Neuroscience Faculty Candidate

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Tuesday, September 29, 2015
310 Kelly Hall
3:00pm – 4:00pm

Alterations of the Neuronal Epigenome in Schizophrenia

Dysregulated neuronal gene expression in the prefrontal cortex (PFC) is a critical building block in the neurobiology of schizophrenia (SCZ). The underlying molecular pathology likely includes broad changes in the transcriptome and epigenome of PFC neurons, and is likely to involve many cis-regulatory elements at gene proximal promoters and distal enhancers, often at sites harboring common polymorphisms implicated in heritable liability for SCZ and directly affecting gene expression. Surprisingly, however, to date there is very little knowledge on the therapeutic potential of transcriptional regulators associated with chromatin aberrations in SCZ.

At base pair resolution on a genome-wide scale, open chromatin-associated histone methylation landscapes and transcription factor signatures in prefrontal cortex (PFC) neurons of subjects diagnosed with schizophrenia and controls were compared. Hypermethylated nucleosomes in diseased neurons were enriched for *myocyte-specific enhancer factor 2C, MEF2C*, recognition sites, including promoters and broad stretches of enhancer chromatin ('super-enhancers') tethered into chromosomal loopings governing the regulation of MEF2C-sensitive genes critical for neuronal signaling. Localized MEF2C chromatin occupancies were linked *in vivo* to transcriptional regulation in adult PFC via methyl-adenine footprinting of neuronal nuclei. Furthermore, short-term (days) and long-term (weeks) neuronal *Mef2c* expression up-regulation in juvenile and adult mouse PFC enhanced cognitive performance at baseline and under a pharmacological challenge with NMDA receptor antagonist drugs.

MEF2C carries strong therapeutic potential for treating neuronal dysfunction and cognitive disorders.

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