PROGRESS IN NEUROSCIENCE PINS

Seminar Series of the
Brain & Mind Neuroscience Institute
Weill Cornell Medical College (WCMC)
&
The Graduate Program in Neuroscience of
WCMC and Sloan Kettering Institute

Thursday, 4/14/16, 3:45 PM
Weill Auditorium

Presentation 1: Loss of *cacna1c* ($Ca_v1.2$) results in social and cognitive deficits and altered protein translation in the prefrontal cortex of mice

Zeeba D Kabir, Ph.D., Laboratory of Dr. Anjali Rajadhyaksha

Genome wide association studies have identified the Ca^{2+} channel gene, *CACNA1C* as a candidate risk gene for developing multiple neuropsychiatric disorders including bipolar disorder, schizophrenia, major depressive disorder and autism. Common to each of these disorders are deficits in social and cognitive functioning. While the current treatments for neuropsychiatric disorders target the mood and emotional symptoms, the core components, they fail to alleviate the social and cognitive deficits. The *CACNA1C* gene encodes for the $Ca_v1.2$ L-type Ca^{2+} channel that is crucial for neuronal development and synaptic plasticity. Using a conditional genetic knockout mouse model of *cacna1c* (Cav1.2) we find that loss of *cacna1c* results in social behavioral deficits in addition to deficits in distinct aspects of learning and memory. At the cellular level, these *cacna1c*-deficient mice have altered excitatory-inhibitory balance in the prefrontal cortex (PFC) that is concurrent with decreased protein translation. Furthermore, viral vector-mediated focal knockdown of *cacna1c* in the prefrontal cortex (PFC) of adult mice is sufficient to recapitulate the deficits in social behavior but not those in learning and memory suggesting a developmental role of *cacna1c* in learning. We are currently working on a pharmacological rescue of these social and cognitive deficits in *cacna1c*-deficient mice. These findings will begin to provide novel insight into the pathophysiology of *CACNA1C*-linked neuropsychiatric disorders and aid towards better treatment strategies to alleviate the social and cognitive deficits observed in these patients.

Recent Publications:

1**)** Kabir ZD, Lee AS, Rajadhyaksha AM (2016). L-type Ca^{2+} channels in mood, cognition and addiction: Integrating human and rodent studies with a focus on behavioral endophenotype. *J Physiol.* 2016 Feb 23. [Epub ahead of print]

Presentation 2: "New insights into Amyotrophic Lateral Sclerosis from studies of FUS aggregates in yeast"

Cornelia Kurischko, PhD, Senior Research Associate. Laboratory of Dr. Gregory Petsko

The focus of my research for the last years has been the nuclear interactions of the yeast RNA-binding protein Ssd1 and their nuclear and cytoplasmic functions. Ssd1 associates with its target mRNAs from "birth" (co-transcriptional binding, splicing, and export from the nucleus) to "death" (polarized transport to the daughter cells for translation or delivery to stress granules and P-bodies for storage or decay). Herein, the N-terminal prion-like domain of Ssd1 has multiple nuclear and cytoplasmic functions.

I am now applying this knowledge of Ssd1 to a human RNA-binding protein, FUS, which in its mutated form is one of the causes for the neurodegenerative disease ALS (Lou Gehrig's disease). Although FUS does not show sequence homology to Ssd1, its domain structure and cellular behavior resembles the yeast protein. Expression of FUS in yeast allows its genetic, molecular-genetic and cell biological investigation. Yeast is a very well established model organism. FUS seems to be specifically recognized by yeast cells. This allows to identify conserved pathways and organelles FUS is related to. These results will serve as a blueprint to investigate FUS in its natural environment, e.g. in neuronal cells.

Recent Publications:

1) Kurischko C., Kuravi V.K., Herbert C.J., Luca F.C. 2011. Nucleocytoplasmic shuttling of Ssd1 defines the destiny of its bound mRNAs. *Mol. Microbiol.* 81, 831-849

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