

PROGRESS IN NEUROSCIENCE PINS

Seminar Series of the Brain & Mind Research Institute Weill Cornell Medical College (WCMC)



The Graduate Program in Neuroscience of WCMC and Sloan Kettering Institute

Thursday, 3/17/16, 4 PM, coffee at 3:45 PM Room: A-950

"Function and Dysfunction of Cysteine String Protein-a (CSPa): Not Just a Synaptic Chaperone"

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Abstract:

Our lab studies cellular mechanisms that maintain protein homeostasis in neurons, and how failures in proteostasis contribute to neurodegenerative diseases. Adult-onset neuronal ceroid lipofuscinosis (ANCL) is an invariably fatal lysosomal storage disease with no treatment and no known mechanism of pathogenesis. The project to be discussed is aimed at delineating the molecular mechanism of ANCL caused by mutations in Cysteine String Protein-a (CSPa). Recently, several independent studies have found ANCLcausing mutations in the gene encoding cysteine string protein- α (CSP α); yet, a gap persists in our understanding of exactly how ANCL mutations in CSPa lead to lysosomal dysfunction and neuron death. Previously, CSPa was shown to chaperone the synaptic SNARE protein SNAP-25 (Sharma et al. 2011). Now we have found that the SNAP-25 homolog SNAP-23 is also a client of the CSPa/Hsc70/SGT chaperone complex. Importantly, SNAP-23 is a SNARE protein which mediates lysosomal exocytosis, thus offering a direct connection from CSPa dysfunction to lysosomal pathology in ANCL. The presentation will be about progress in this ongoing project.

Recent relevant publications:

- Sharma M*, Burré J, Südhof TC*, CSPα Promotes SNARE-Complex Assembly by chaperoning SNAP-25 during synaptic activity. *Nature Cell Biology*, 2011; 13(1):30-9. [* <u>Corresponding authors</u>; PMID: 21151134; PMCID: N/A]
- Sharma M*, Burré J, Bronk P, Zhang Y, Xu W, Südhof TC*. CSPα knockout causes neurodegeneration by impairing SNAP-25 function. *The EMBO Journal*, 2011; 31(4):829-41. [* *Corresponding authors*; PMID: 22187053; PMCID: PMC3280561]
- 3) Sharma M*, Burré J, Südhof TC*. Proteasome inhibition alleviates SNARE-dependent neurodegeneration. Science Translational Medicine, 2012; 4(147):ra113. [* <u>Corresponding authors</u>; PMID: 22896677; PMCID: N/A]



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