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TEMASEK LIFESCIENCES LABORATORY

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Hosted by: Dr Koh Tong-Wey

Physiological Functions of Synucleins

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Dr. Sreeganga Chandra is an Associate Professor at Yale University. After completing her undergraduate degree in India, she received her Ph.D. from Purdue University. She did her postdoctoral studies in the lab of Dr. Thomas Südhof, then at UT Southwestern Medical Center at Dallas, where she characterized the structure and function of α-synuclein. In 2007, she started her independent lab at Yale University. The central theme of her research is synaptic dysfunction in Parkinson's disease. Her lab is actively investigating the normal physiological functions of the synuclein protein family. Another area of research is the intersection between Parkinson's disease and lysosomal storage diseases, most notably Gaucher's disease and neuronal ceroid lipofuscinosis.

α-Synuclein is a member of a family of three abundant, presynaptic proteins that includes β- and γ-synuclein. To delineate the physiological functions of synucleins, we have taken a loss-of-function approach and have generated αβγ-synuclein triple KO mice. Our analysis revealed that deletion of synucleins results in age-dependent neuronal dysfunction. This suggests that synucleins are important for long-term neuronal health and has major implications for the development of α-synuclein targeted therapeutics for PD.

To obtain insight into the molecular functions of synucleins, we implemented several parallel approaches. We have compared the entire synaptic proteome of wildtype and synuclein null mice. These experiments showed a select upregulation of proteins that bend membranes such as endophilin A1. We then tested if synucleins also share this property and found for the first time that all synucleins can robustly generate membrane curvature. Since our original publication, several groups have shown that synucleins can sense and generate membrane curvature. These properties suggests that synucleins function either at the exo- or endocytic steps of the synaptic vesicle (SV) cycle, two steps that require membrane bending. We monitored SV cycling in wildtype and αβγ-Syn$^{-/-}$ neuronal cultures using pHlourin imaging, and observed a striking endocytic phenotype in αβγ-synuclein triple KO neurons. We confirmed our result showing slowed endocytosis in αβγ-Syn$^{-/-}$ neurons using electron microscopy and slice electrophysiology. We are presently using in vitro endocytic reconstitution assays to precisely define the endocytic step where synucleins act. Our progress has established that synucleins regulate the kinetics of SV endocytosis by acting at early during membrane bending and cargo selection. This is the first description of a conserved function for the synuclein protein family, since the discovery of these proteins over two decades ago.

Recent Publications:

1. Vargas, K.J., Makhani, S., Davis, T., Westphal, C., Castillo, P.E., and **Chandra, S.S**. (2014). Synucleins regulate the kinetics of synaptic vesicle endocytosis. J. Neuroscience. 34, 9364-9376. PMID: 25009269
2. Westphal, C. and **Chandra, S.S.** (2013). Monomeric synucleins generate membrane curvature. J. Biol. Chem. 288, 1829-1840. PMID: 23184946; PMC3548493.
3. Greten-Harrison, B., Polydoro, M., Tomita, M.M, Diao, L., Williams, A., Nie, E.H, Makani, S., Tian, N., Castillo, P.E., Buchman, V.L., and **Chandra, S.** (2010). Characterization of αβγ -synuclein triple knockout mice reveals age-dependent neuronal dysfunction. Proc. Natl. Acad. Sci. U S A. 107, 19573-19578. PMID: 20974939; PMC2984188.