Synaptic and extra-synaptic functions of a vesicle associated co-chaperone

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Nerve terminals are able to maintain the continuous release of neurotransmitters during extended periods of time at locations far away from the cell soma. For example, presynaptic terminals from tonic motorneurons receive from 300.000 to 500.000 action potentials per day (Hennig and Lomo, *Nature* 1985) imposing on SNARE complexes a heavy-duty cycling of protein folding and unfolding reactions. Cysteine String Protein-alpha (CSP-alpha) is a synaptic vesicle protein that, together with Hsc-70 and SGT (small glutamine-rich protein), forms a chaperone complex essential to maintain a functional pool of SNAP25 and to promote SNARE complex assembly (Chandra et al., Cell 2005; Sharma et al. *Nat. Cell Biol.* 2011). In humans, mutations in the DNAJC5 gene, that codes CSP-alpha, cause autosomal-dominant adult onset neuronal ceroid lipofuscinosis, that leads to seizures and early death in young adults (Noskovà et al. *Am J Hum Genet* 2011; Benitez at al. PLoS One 2011). Interestingly knock-out mice lacking CSP-alpha suffer from early lethality due to presynaptic degeneration (Fernández-Chacón et.al., *Neuron* 2004). We have found that motorneurons require CSP-alpha to maintain the readily releasable vesicular pool and synaptic vesicle recycling (Rozas., et al., *Neuron* 2012). Interestingly, in central neurons, we have shown that CSP-alpha prevents activity-dependent degeneration of GABAergic synapses in high firing rate parvalbumin-positive neurons, indicating that high-neural activity increases synapse vulnerability and CSP-alpha is essential to maintain presynaptic function under a physiologically high-activity regime (García-Junco-Clemente et al., *JNeurosci.* 2010). In my talk I will discuss recent unexpected findings that uncover unanticipated functions of CSP-alpha beyond the maintenance of synaptic vesicle trafficking at the nerve terminals.

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