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Mechanisms regulating the assembly and integrity of vertebrate synapses

Abstract:

Synapses are specialized sites of cell-cell contact between neurons designed for the efficient and repetitive release and reception of neurotransmitter substances. Synapse are dynamic signaling machines capable of modulating their activity based on prior experience. During brain development many more synapses are formed than are ultimately need in the adult. The excess are normally removed as neural circuits refine their connection. Intriguingly, synapse formation and removal continues in the adult as part of normal learning and memory mechanisms. In many neurodegenerative disorders, this balance between the formation and elimination of synapses become altered such that large numbers of synapses and ultimately neurons are lost, contributing to the dementia assosciated with these disorder. Using a combination of reverse genetics, live cell imaging and electrophysiology, we have sought to uncover the molecular mechanisms that regulate synapse integrity. Our studies have shown that components of the proteosome, ubiquitin and autophagy systems which regulate protein turnover (proteostasis) are selectively localized at synapses and play fundamental roles in modulate synapse function and integrity. In this presentation, I will discuss how these degradative systems are mechanistically regulated in time and space to tune synaptic transmission as well as synapse integrity.