Abstract

Munc13 is a deeply conserved synaptic hub protein that coordinates nearly every aspect of neurotransmitter release, although we still lack a complete mechanistic understanding of its actions at the synapse. Using a forward genetic screen in *C. elegans*, we identified and characterized a unique C-terminal domain that is critical for maintaining the pool of fusion-competent vesicles at the synapse (the docking/priming function of Munc13). We also determined that a neighboring protein module comprising a C1-C2 tandem domain mediates an autoinhibitory function that is critical for proper regulation of synaptic transmission. A human point mutation in this site leads to severe neurological dysfunction due to a gain of Munc13 activity. Together with recent structural work on Munc13, our biochemical, genetic, and physiological data suggest a principal organizational role for Munc13 in controlling vesicle docking, SNARE assembly, and membrane fusion.