Munc13-1 at the Heart of Synaptic Transmission: Novel Layers of Regulatory Mechanisms and Structural Insights

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Munc13-1 serves as a master regulator of synaptic vesicle priming and neurotransmitter release, with its activity precisely controlled by diverse regulatory mechanisms to meet the demands of neuronal communication. Recent studies have revealed novel layers of Munc13-1 regulation that extend beyond its established role in SNARE complex assembly. Our recent works demonstrate that Munc13-1 function is modulated through multiple pathways: (i) EphB2-mediated phosphorylation of Doc2 relieves Doc2's inhibitory blockade on Munc13-1, thereby facilitating SNARE complex assembly and enhancing spontaneous release and synaptic augmentation; (ii) an evolutionarily conserved polyglutamate (polyE) sequence in Munc13-1's N-terminus forms an autoinhibitory conformation by binding to the MUN domain through charge-charge interactions, which can be relieved by physiological Ca^{2+} concentrations or potential phosphorylation events; (iii) Munc13-1 is efficiently recruited to RIM/RBP-mediated liquid-liquid phase separated condensates at active zones, creating specialized microdomains that maximize vesicle priming efficiency. Complementing these functional insights, we have determined the cryo-EM structure of a key intermediate complex containing Munc13-1 and the SNARE proteins, providing unprecedented molecular details of how Munc13-1 orchestrates SNARE assembly during vesicle priming. Collectively, these findings position Munc13-1 as a central signaling hub that integrates diverse regulatory inputs—including postsynaptic retrograde signals, intracellular Ca^{2+} dynamics, post-translational modifications, and biomolecular condensation—to precisely control the probability and plasticity of neurotransmitter release, with implications for understanding synaptic dysfunction in neurological disorders.