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Insights into neurotransmitter release from the structure of Munc13-1 C1C2BMUN

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Munc13-1 acts as a master regulator of neurotransmitter release, mediating docking-priming of synaptic vesicles and diverse presynaptic plasticity processes. It is unclear how the functions of the multiple domains of Munc13-1 are coordinated. The crystal structure of a Munc13-1 fragment including its C1, C2B and MUN domains (C1C2BMUN) reveals a 195 Å-long multi-helical structure with the C1 and C2B domains packed at one end. The similar orientations of the respective diacyglycerol- and Ca2+-binding sites of the C1 and C2B domains suggest that the two domains cooperate in plasma-membrane binding and that activation of Munc13-1 by Ca2+ and diacylglycerol during short-term presynaptic plasticity are closely interrelated. Electrophysiological experiments in mouse neurons support the functional importance of the domain interfaces observed in C1C2BMUN. The structure imposes key constraints for models of neurotransmitter release and suggests that Munc13-1 bridges the vesicle and plasma membranes from the periphery of the membrane-membrane interface. Details of the hurdles faced during the challenging structure determination will also be provided, which included high crystal non-isomorphism, severe data anisotropy and low resolution.

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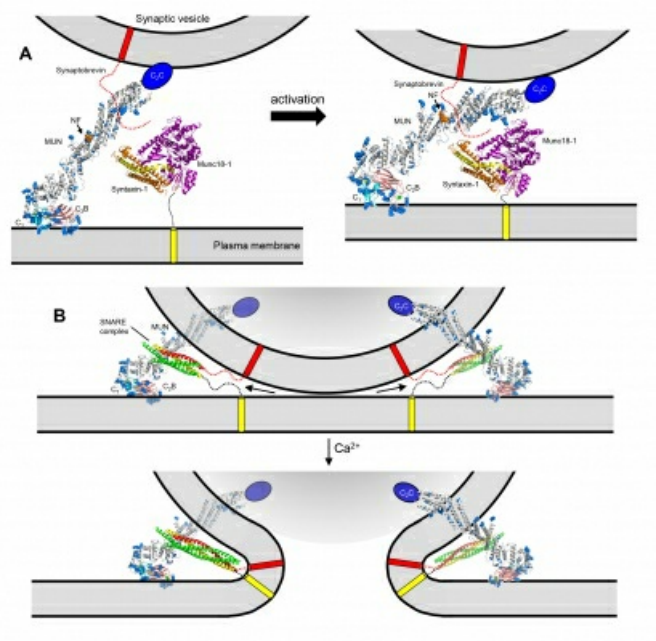

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