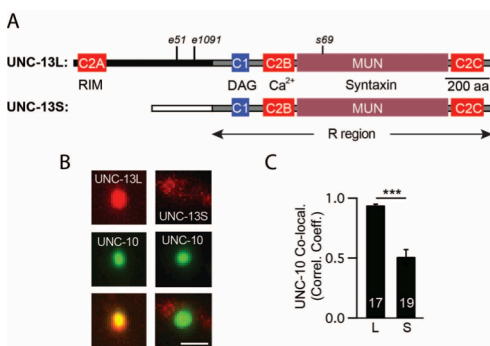


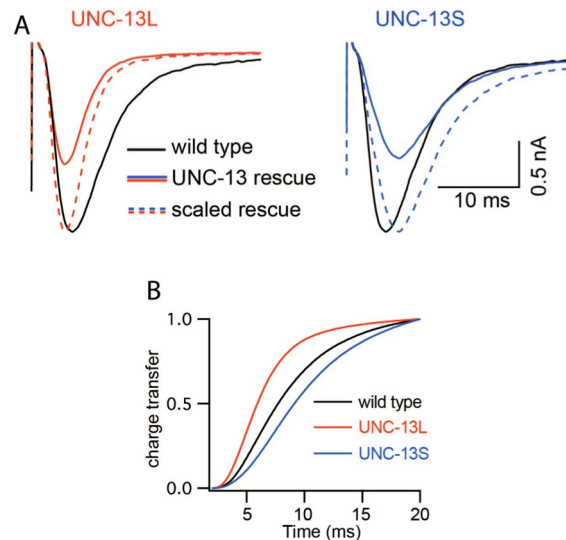
## Tuning the kinetics of neurotransmitter release

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Our behaviors and our thoughts are encoded by the temporal pattern of activity in the brain. Consequently, factors that alter the kinetics of synaptic responses are likely to play a pivotal role in shaping behavior and cognition. In this project, we are investigating the cell biological mechanisms that dictate the kinetics of neurotransmitter release. Synaptic transmission consists of fast and slow components of neurotransmitter release. We recently showed that these components are mediated by distinct exocytic proteins. The *C. elegans unc-13* gene is required for SV exocytosis, and encodes long and short isoforms (UNC-13L and S). Fast release was mediated by UNC-13L whereas slow release required both UNC-13 proteins and was inhibited by Tomosyn. The spatial location of each protein correlated with its effect. Proteins adjacent to active zones mediated fast release while those controlling slow release were more distal or diffuse. These results suggest that UNC-13L, UNC-13S, and Tomosyn form a molecular code that dictates the timing of neurotransmitter release. Current projects aim to define biochemical mechanisms that account for differences in UNC-13L and S exocytosis kinetics.



**Fig. 1. UNC-13L and S have distinct subsynaptic locations.** (A) Diagram illustrating domain structures of UNC-13 isoforms. (B) Distribution of UNC-13 isoforms at active zones (labeled with UNC-10/RIM). (C) Summary data showing the UNC-13L is significantly more co-localized with UNC-10/RIM than UNC-13S.



**Fig. 2. UNC-13L and S mediate fast and slow release respectively.** Averaged and peak normalized evoked responses (A) and cumulative charge transfer during evoked responses (B) are shown for the indicated genotypes. UNC-13L mediated responses have faster activation and decay kinetics. UNC-13S responses exhibit slower kinetics.