Analysis of autism-linked mutations in C. elegans

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Recent studies suggest that mutations in 500-1000 genes confer risk for Autism spectrum disorders (ASD). Many of these genes encode synaptic proteins; however, in most cases, little is known about how these mutations alter synaptic transmission. The goal of this project is to analyze autism-linked mutations for changes in synaptic transmission, using the *C. elegans* neuromuscular junction (NMJ) as a model. In a recent study, we showed that mutations in three genes linked to ASD (Neurexin, Neuroligin, and MEF-2) regulate the kinetics of neurotransmitter release (Fig. 1). We showed that post-synaptic Neurexin (NX) and pre-synaptic Neuroligin (NL) mediate a retrograde synaptic signal that inhibits neurotransmitter release. Retrograde inhibition is induced by mutations inactivating a muscle microRNA (miR-1) and is abolished by mutations inactivating the transcription factor MEF-2, a miR-1 target. NX and NL selectively inhibit fusion of a subpopulation of synaptic vesicles (SVs) that mediate slow release, most likely via changes in Tomosyn, an inhibitor of SV exocytosis. Mouse triple knockouts lacking NL1-3 (2) also have prolonged post-synaptic responses (1). Based on these results, we propose three changes in the kinetics of post-synaptic responses may be cellular mechanism that contributes to the developmental and cognitive defects associated with ASD.

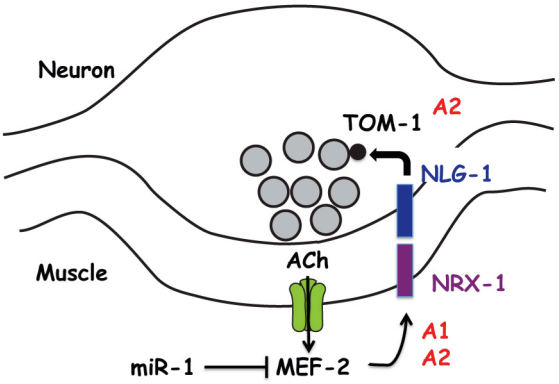

Fig. 1. Autism linked genes mediate retrograde inhibition of ACh release. miR-1 inhibits MEF-2 expression in muscles. MEF-2 activity is regulated by muscle depolarization, and indirectly controls NRX-1 levels. NRX-1 and NLG-1 inhibits slow ACh release, most likely by increasing the activity of TOM-1/Tomosyn. Model based on data published in Simon et al. (2008) and Hu et al. (2012).

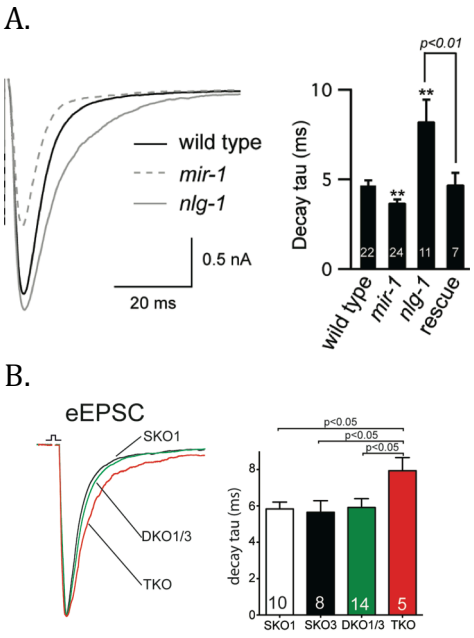

Fig. 2. Autism linked mutations alter kinetics of post-synaptic responses. (A) Evoked post-synaptic currents decay more slowly in mutants lacking NLG-1. (B) Similar changes in evoked EPSC decay kinetics are observed in mouse NL1/2/3 triple knockouts (TKO). Figures taken from Hu et al. (2012).