Project Title: Dissecting the Role of Ral GTPase and Exocyst in Synaptic Plasticity and Regeneration

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Summary: (1000 characters)
Defects in synaptic morphology and activity-dependent plasticity are a hallmark of neurodevelopmental and neurodegenerative disorders[1]. We identified a novel pathway that regulates neuronal morphology in response to activity through the engagement of RalGTPase and the exocyst complex in the regulation of postsynaptic membrane growth at the synapse[2]. Additionally, we now show that activity-dependent formation of new presynaptic boutons is compromised in Ral and exocyst mutants, suggesting that this pathway plays a central role in synaptic plasticity (unpublished). Ral GTPase is a small GTPase from the Ras superfamily and the exocyst is a conserved protein complex that is an effector for several GTPases, which, collectively might serve to control where, when and how, are vesicles targeted to a specific exocytic place. Ral and the exocyst interact and are known to be involved in many cellular processes including regulation of exocytosis, neuronal development, and cancer growth and metastasis[2,3]. By being able to receive regulatory information from different pathways, the exocyst and Ral can serve as a hub to precisely regulate where, when and how are vesicles targeted to an exocytic place in order to mediate synaptic growth. Our goal is to dissect the mechanism by which the Ral/exocyst pathway regulates the formation of new synaptic structures in response to synaptic activity. Given the mechanistic similarities between synaptic plasticity and neuronal regeneration, we will explore whether this pathway plays a role in axonal regeneration, using a well-established nerve-crush assay, *in vivo*[4].

Our strategy is to use the relatively simple nervous system of *Drosophila*[5]. We will use the *Drosophila* neuromuscular junction (NMJ) as a model because it is a highly plastic glutamatergic synapse, with stereotypical morphology that is genetically determined, but that can be remodeled by synaptic activity. In addition to the powerful genetics and other available tools for the study of *Drosophila* synapses, 75% of all human disease genes have related sequences in *Drosophila* and nearly a third are predicted to have functionally equivalent counterparts, making *Drosophila* an excellent model to study these questions. Dissecting the signaling cascade triggered by the Ral/Exocyst pathway will be key to understand how intracellular trafficking participates in structural plasticity and in regeneration.

Bibliographic references:

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