Title: “Regulation of a DLK-1 and p38 MAP kinase pathway by the ubiquitin ligase RPM-1 is required for presynaptic development”

Summary:
Synapses display a stereotyped ultrastructural organization, commonly containing a single electron-dense presynaptic density surrounded by a cluster of synaptic vesicles. The mechanism controlling subsynaptic proportion is not understood. Loss of function in the C. elegans rpm-1 gene, a putative RING finger/E3 ubiquitin ligase, causes disorganized presynaptic cytoarchitecture. RPM-1 is localized to the presynaptic periactive zone. We report that RPM-1 negatively regulates a p38 MAP kinase pathway composed of the dual leucine zipper-bearing MAPKKK DLK-1, the MAPKK MKK-4, and the p38 MAP kinase PMK-3. Inactivation of this pathway suppresses rpm-1 loss of function phenotypes, whereas overexpression or constitutive activation of this pathway causes synaptic defects resembling rpm-1(lf) mutants. DLK-1, like RPM-1, is localized to the periactive zone. DLK-1 protein levels are elevated in rpm-1 mutants. The RPM-1 RING finger can stimulate ubiquitination of DLK-1. Our data reveal a presynaptic role of a previously unknown p38 MAP kinase cascade.