SYNAPTIC PLASTICITY

Myosin Vb:
delivery on demand

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Long-term potentiation (LTP) induction and the concomitant rise in Ca^{2+} that occurs through NMDAR (*N*-methyl-D-aspartate receptor) activation leads to LTP expression through postsynaptic insertion of AMPARs (α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors) and dendritic spine growth. However, the mechanistic link between the induction and the expression of LTP is unclear. Wang *et al.* now show that myosin Vb (MyoVb) undergoes a Ca^{2+} -dependent conformational change that facilitates its interaction with and the subsequent membrane fusion of AMPAR-containing recycling endosomes (REs) in dendritic spines.

Class V myosins are motor proteins that transport cargo along

F-actin. MyoVb associates with the GTPase Rab11 through its effector, Rab11-FIP2, which resides on REs. The authors found that labelled MyoVb molecules and REs co-trafficked within spines in hippocampal cultures. On LTP induction, MyoVb associated with a population of REs that localized at the base of the spines and then trafficked with the REs into the spine head.

What links LTP induction to the association of MyoVb and REs? Myosin Va has previously been shown to undergo Ca^{2+} -dependent conformational changes. To test whether MyoVb is similarly regulated, the authors created two MyoVb mutants: MyoVb-CCtr, which favours an open, cargo-binding conformation, and MyoVb- Δ RBD, which cannot bind the Rab11-Rab11-FIP2 complex. *In vitro* binding studies with purified forms of these mutants, wild-type MyoVb and Rab11-FIP2 indeed showed that the interaction of wild-type MyoVb with Rab11-FIP2 is Ca^{2+} -dependent; conversely, MyoVb-CCtr bound to Rab11-FIP2 without Ca^{2+} , indicating that a Ca^{2+} -dependent conformational change in MyoVb is necessary for binding. In hippocampal neurons, MyoVb-CCtr colocalized with REs in dendritic spines and shafts even under basal conditions, whereas MyoVb- Δ RBD localized almost exclusively to spines and did not colocalize with Rab11-FIP2. During LTP induction, wild-type MyoVb but not MyoVb- Δ RBD mobilized REs to the spine heads, whereas MyoVb-CCtr caused them to accumulate in spines independent of the LTP stimulus. These findings show that a Ca^{2+} -dependent conformational change in

MyoVb is required for its interaction with REs through Rab11-FIP2 and for the subsequent mobilization of REs.

Next the authors knocked down MyoVb expression using RNA interference (RNAi) and found that this abolished LTP-induced mobilization of REs into spines and their subsequent exocytosis. This effect could be reversed by expressing RNAi-resistant forms of wild-type MyoVb or MyoVb-CCtr, with the latter producing the greatest rescue, but not by expressing RNAi-resistant MyoVb- Δ RBD, indicating that binding of Rab11-FIP2 by MyoVb is required for the mobilization and exocytosis of REs. Similar results were obtained when the authors monitored spine growth and the insertion of the AMPAR subunit GluR1 into dendritic spines.

Finally, the authors studied transgenic mice expressing a sensitized mutant form of MyoVb (MyoVb-Y119G) that is susceptible to inhibition by the artificial ADP analogue PE-ADP. Introduction of PE-ADP through a patch pipette into CA1 neurons in hippocampal slices acutely blocked LTP.

These findings demonstrate that on LTP induction MyoVb associates in a Ca^{2+} -dependent manner with REs through the Rab11-Rab11-FIP2 complex, and that this association is required for both the insertion of AMPARs into the postsynaptic membrane and spine growth.

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ORIGINAL RESEARCH PAPER Wang, Z. *et al.* Myosin Vb mobilizes recycling endosomes and AMPA receptors for postsynaptic plasticity. *Cell* **135**, 535–548 (2008)