NEUROTRANSMITTER RECEPTORS

Negotiating the cytoskeletal tracks in neurons

DIGITALVISION

Cell surface GABA type A receptors ($GABA_AR$s) undergo endocytosis and trafficking to lysosomes for degradation; however, the proteins responsible for driving the retrograde transport of these receptors across different cytoskeletal networks remain largely unknown. A new study shows that muskelin has a key role in this process, accompanying $GABA_AR$s along actin filaments and microtubules.

Kneussel and colleagues identified muskelin as a binding partner of $GABA_AR$ α1 subunits in a yeast two-hybrid screen, and showed that the two proteins colocalized in the cell bodies and neurites of cultured hippocampal neurons. The authors knocked out the gene encoding muskelin — *Mkln1* — in mice and found that the absence of this protein was associated with a rise in cell surface expression of $GABA_AR$ α1 subunits, mainly at extrasynaptic sites, and a marked increase in the power of sharp wave-associated ripples, as detected in hippocampal slices.

The authors determined that the rise in cell surface receptor levels was due to a decrease in the $GABA_AR$ internalization rate, suggesting that muskelin is involved in $GABA_AR$ endocytosis. In support of an endocytic role, immunoprecipitation experiments indicated that $GABA_AR$s formed complexes with muskelin and the retrograde-directed F-actin motor myosin VI, which is implicated in the endocytosis of AMPA-type glutamate receptors.

Using time-lapse video microscopy, Kneussel and colleagues further examined the role of muskelin in retrograde trafficking. They detected particles containing both $GABA_AR$ α1 subunits and muskelin that moved in a retrograde direction in neurites. They also observed transport of muskelin with the microtubule-associated motor dynein, and in co-immunoprecipitation experiments, they showed that complexes of muskelin and dynein also contained $GABA_AR$ α1 subunits. Thus, the retrograde transport of $GABA_AR$s downstream of myosin VI-dependent endocytosis involves a microtubule-based mechanism.

Finally, the authors showed that muskelin also participates in the targeting of $GABA_AR$ α1 for degradation. Evidence from sucrose gradient centrifugation and electron microscopy showed that both proteins could be found in early and late endosomes. Moreover, receptor degradation assays indicated that the absence of muskelin impaired the lysosomal breakdown of $GABA_AR$ α1 subunits.

This study demonstrates that muskelin has an important role in $GABA_AR$ intracellular transport, enabling trafficking of these receptors across different cytoskeletal networks. The fact that $Mkln^{-/-}$ mice displayed a high-frequency ripple oscillation phenotype indicates that muskelin is a key regulator of the GABAergic signalling that underlies neuronal network mechanisms.

Darran Yates

ORIGINAL RESEARCH PAPER Heisler, F. F. *et al.* Muskelin regulates actin filament- and microtubule-based $GABA_A$ receptor transport in neurons. *Neuron* **70**, 66–81 (2011)