SYNAPTOGENESIS

Spinster directs the traffic

How is the growth of a synaptic arborization controlled? This question has important implications for the function of neural circuits, because the shape and size of the arborization strongly influences the number and strength of connections that a neuron makes with its targets. In a recent paper in *Neuron*, Sweeney and Davis report on the characterization of *spinster* (*spin*), a gene that encodes a negative regulator of synaptic growth, and they provide an intriguing insight into the role of protein trafficking in the control of synaptic morphology.

In *Drosophila*, the *spin* mutation was initially identified for its effects on courtship behaviour. Sweeney and Davis showed that loss of *spin* function also causes synaptic overgrowth at the neuromuscular junction (NMJ), with some axons producing more than double their usual number of boutons. *spin* seems to function both pre- and postsynaptically, as restoring expression at only one of these sites produced only a partial rescue of the overgrowth phenotype.

The explanation for this phenotype came from two seemingly disparate sets of observations. First, the authors found that Spin — a transmembrane protein with sequence homology to monoamine transporters — localizes to the late endosomal/lysosomal compartment in both the neuron and the postsynaptic muscle fibre. These subcellular compartments were enlarged in the *spin* mutant, and they also showed abnormal architecture. In addition, there was evidence for defects in lysosomal clearance.

Second, previous studies have implicated transforming growth factor-β (TGF-β) in the regulation of synaptic growth. In these new experiments, Sweeney and Davis decreased TGF-β signalling with receptor mutations, and they showed that this reduced synaptic overgrowth in the *spin* mutants. They also increased the levels of TGF-β signalling by blocking the activity of the inhibitory molecule Daughters against Dpp (Dad). They found that this manipulation produced a synaptic overgrowth phenotype similar to that seen in the *spin* mutants.

How can these observations be reconciled to produce a model of Spin function? The late endosomal compartment is the site of a crucial protein trafficking decision — whether to recycle internalized receptors back to the cell surface, or send them to the lysosome for degradation. Sweeney and Davis propose that *spin* is necessary for the proper execution of this trafficking decision and that in its absence, there is enhanced signalling, either due to increased sorting of receptors to the cell surface, or inefficient degradation of receptors in the lysosome.

So, this study provides evidence that misregulated growth factor signalling, resulting from defects in endosomal trafficking, can cause synaptic overgrowth. These findings might have implications for lysosomal storage diseases in humans, such as Batten's disease. Neurodegeneration is a frequent characteristic of these diseases, but it has not been clear how this relates to the defects in lysosomal function. The *spin* mutant provides us with new possibilities for exploration.

Heather Wood

References and links

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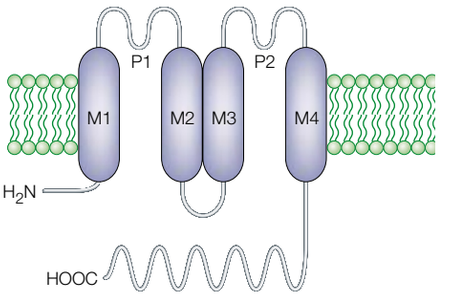
ION CHANNELS

A new TASK for 14-3-3 proteins

14-3-3 proteins regulate several cellular processes, such as the cell cycle, the shuttling of proteins between the nucleus and the cytoplasm, and the transport of proteins into mitochondria and chloroplasts. Although 14-3-3 proteins are abundant in the brain, their function in neurons remains unclear. But new research by Rajan *et al.* gives us a clue to their role by showing that they might promote the membrane expression of KCNK potassium channels.



The main structural peculiarities of KCNK channels are the presence of two pore domains and a relatively long carboxy-terminal tail.

The best-characterized function of KCNK proteins is as 'leak' channels; they are responsible for the background membrane currents that are present at rest and that rise instantly to a new steady level in response to voltage steps. Rajan *et al.* carried out a two-hybrid screen to identify proteins that interact with the carboxyl termini of a series of KCNK channels — TASK-1 (KCNK3), TASK-3 (KCNK9) and TASK-5 (KCNK15) — and isolated several 14-3-3 protein isoforms. The authors identified the specific sequence of the KCNK proteins that interacted with the 14-3-3 isoforms, establishing that the final 40 residues of the channel contributed to this interaction, and that the last five residues were essential for significant binding to the 14-3-3 proteins. Moreover, Rajan *et al.* found that deleting the essential carboxy-terminal domain of the KCNK channels reduced membrane currents in heterologous expression systems, and that mutations in this interacting domain had a similar effect. Importantly, this effect seemed to result from an impairment of the surface expression of KCNK proteins, as the imaging of fluorescently labelled channels showed that most of the mutant protein remained in the cytoplasm.

Although we don't know whether this interaction is relevant *in vivo*, the authors showed that KCNK3 and the 14-3-3ζ isoform could be co-immunoprecipitated from synaptic membrane extracts, indicating that such an interaction might take place *in situ*. The authors speculate that interaction with 14-3-3 proteins might modulate KCNK channel trafficking to the neuronal surface. Establishing the precise mechanism that accounts for this modulation will be an important new direction in this field.

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FURTHER READING Kurachi, Y. & Ishii, M. The 14-3-3 protein as a novel regulator of ion channel localization. *J. Physiol. (Lond.)* 18 October 2002 (doi:10.1113/jphysiol.2002.033886) | Goldstein, S. A. N. *et al.* Potassium leak channels and the KCNK family of two-P-domain subunits. *Nature Rev. Neurosci.* **2**, 175–184 (2001)