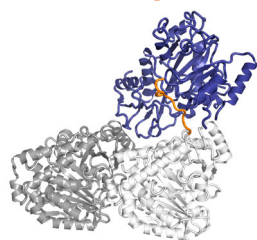


Working at the tail end of tubulin



TTL (blue) binds at the interface of α - (light gray) and β - (dark gray) tubulin, positioning its active site next to α -tubulin's tail (orange).

Prota et al. describe how the enzyme tubulin tyrosine ligase (TTL) specifically recognizes the C terminus of α -tubulin to modulate the behavior of microtubules.

Many enzymes posttranslationally modify the C-terminal tails of the α - and β -tubulin subunits that form microtubules. TTL, for example, adds a tyrosine residue to the C terminus of α -tubulin, resulting in the formation of tyrosinated microtubules that are more dynamic than

detyrosinated filaments in cells. Mice lacking TTL die shortly after birth due to neuronal defects, but how TTL recognizes and modifies α - but not β -tubulin is unclear.

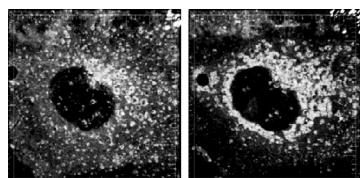
Prota et al. determined the crystal structure of TTL in a

complex with α - and β -tubulin heterodimers. TTL bound at the interface of the α and β subunits and specifically recognized the dimer's curved conformation, explaining why TTL is unable to tyrosinate polymerized microtubules, in which the tubulin subunits adopt a straighter configuration. TTL's tubulin-contacting residues are well conserved, and mutating these amino acids largely abolished TTL's ability to tyrosinate α -tubulin and restrict neurite outgrowth in cultured neurons. This suggests that the neuronal defects of TTL knockout mice are due to the loss of tubulin tyrosination and not because TTL is required to tyrosinate any other substrates.

TTL's orientation on tubulin heterodimers placed its catalytic domain near to α -tubulin's C-terminal tail, which bound to the enzyme's active site through two glutamate residues missing from β -tubulin's C terminus. Senior author Michel Steinmetz now wants to obtain the structures of other tubulin-modifying enzymes bound to their substrates in order to determine how their functions differ from TTL.

Prota, A.E., et al. 2013. *J. Cell Biol.* <http://dx.doi.org/10.1083/jcb.201211017>.

GEFs help Rabs find their target



By mistargeting Rabex-5, Rab5 (white) is redirected from early endosomes (left) to mitochondria (right).

Blümer et al. reveal that Rab GTPases are targeted to the correct intracellular membrane by the guanine nucleotide exchange factors (GEFs) that activate them.

There are over 60 Rabs in human cells that

regulate different vesicle trafficking events by localizing to specific membrane compartments. In their inactive, GDP-bound form, Rabs are maintained in the cytosol by chaperones called GDP dissociation inhibitors (GDIs). When activated by specific GEFs, Rabs dissociate from GDIs and bind to membranes via lipid groups attached to their C termini. But how Rabs localize to particular membranes is unclear.

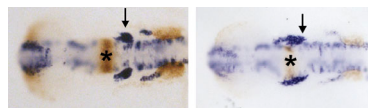
Blümer et al. wondered whether RabGEFs might be important for targeting, as well as activating, the GTPase family.

To test this idea, the researchers devised a way to inducibly mislocalize RabGEFs. When Rabex-5, a GEF that usually activates Rab5 on early endosomes, was redirected to mitochondria, it immediately spurred the recruitment of Rab5—but not other Rab GTPases—to mitochondrial membranes. Rabex-5's GEF domain was sufficient to target Rab5, and Rabex-5 mutants with reduced GEF activity were less efficient at relocating the GTPase.

Blümer et al. showed that two other GEFs—Rabin8 and DrrA—were also capable of recruiting their cognate Rabs to specific membranes. The authors now want to test the targeting function of additional RabGEFs and, because many Rabs don't yet have a known activator, to identify new members of this heterogeneous protein family.

Blümer, J., et al. 2013. *J. Cell Biol.* <http://dx.doi.org/10.1083/jcb.201209113>.

Chemokine turnover keeps neurons on track



Compared with a control embryo (left), TgSNs (blue) fail to accumulate at the ganglion assembly site (arrow) in an embryo lacking Cxcr7b (right).

Changes in a chemoattractant's expression pattern help guide migrating neurons to the right embryonic location, Lewellis et al. reveal.

During zebrafish development, trigeminal sensory neurons (TgSNs) are attracted to a posterior ganglion assembly site by the chemokine SDF1a, which activates a G protein–coupled receptor called Cxcr4b on the neurons. SDF1a is also produced in other parts of the embryonic head, yet TgSNs aren't attracted to these alternative sources of the chemokine.

To find out why, Lewellis et al. examined SDF1a's expression pattern in more detail and found that its mRNA was initially produced in a stripe of cells stretching from the ganglion assembly site to the TgSNs' birthplace. SDF1a expression was then shut

off in more anterior cells as the migrating neurons passed them by en route to their destination.

The researchers discovered that a microRNA, miR-430, was responsible for down-regulating SDF1a mRNA, while a noncanonical chemokine receptor, Cxcr7b, was expressed by nonneuronal cells to scavenge any remaining SDF1a protein. Inhibiting the function of miR-430 or Cxcr7b caused SDF1a levels to persist, resulting in the mislocalization of TgSNs, some of which migrated away from the ganglion assembly site and toward other sources of SDF1a instead.

Lewellis et al. think that, by dynamically refining SDF1a's expression, zebrafish embryos maintain a relatively high concentration of the chemokine on the posterior side of TgSNs, reeling in the neurons to the ganglion assembly site so that they ignore alternative SDF1a sources. The authors now plan to investigate why TgSNs migrate in clusters instead of as individual cells.

Lewellis, S.W., et al. 2013. *J. Cell Biol.* <http://dx.doi.org/10.1083/jcb.201207099>.