In This Issue

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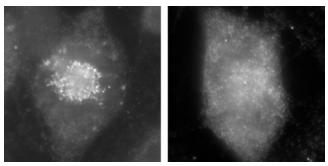
Spindly gets a lipid link to kinetochores



Spindly is recruited to mitotic kinetochores in the absence (left) but not the presence (right) of a farnesyl transferase inhibitor.

The mitotic checkpoint protein hSpindly must be farnesylated at its C terminus in order to be recruited to kinetochores, Moudgil et al. reveal.

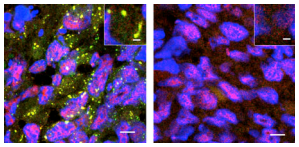
Mitotic checkpoint proteins assemble on kinetochores and prevent chromosomes from segregating until they are properly attached to the mitotic spindle. Spindly helps recruit the motor protein dynein to kinetochores so that, once chromosomes are correctly attached, checkpoint proteins can be transported away from the kinetochores and mitosis can proceed. Spindly itself is recruited to kinetochores by the RZZ complex, but the details of this interaction are unknown.

Moudgil et al. found that the C terminus of human Spindly (hSpindly) is farnesylated in vivo. This lipid modification usually promotes proteins' associations with cell membranes, but mutating hSpindly's farnesylation site or inhibiting the enzyme farnesyl transferase disrupted hSpindly's interaction with the RZZ complex and blocked the protein's recruitment to mitotic kinetochores.

Farnesyl transferase inhibitors (FTIs) were originally developed to impair the function of oncogenic Ras, but they are now thought to inhibit cell division by reducing the farnesylation of one or more mitotic proteins. Two other farnesylated kinetochore proteins, CENP-E and CENP-F, still localized to kinetochores in the presence of FTIs, and knocking down hSpindly produced a prometaphase delay similar to that seen in FTI-treated cells. hSpindly is therefore likely to be the major mitotic target of FTIs. Senior author Gordon Chan now wants to investigate how farnesylation promotes hSpindly's association with the RZZ complex. The lipid group might induce a conformational change in hSpindly, or it could interact directly with an RZZ subunit. ***BS***

Moudgil, D., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201412085.

Stress granules ease the way for metastasis



Fewer stress granules (yellow) occur in osteosarcoma cells lacking G3BP1 (right) than in controls (left). Nuclei are labeled blue.

Tumors that produce more stress granules are more likely to metastasize, Somasekharan et al. reveal.

When cells are under duress, they curtail almost all protein synthesis and stash their mRNAs in stress granules. The structures help healthy cells, but they also allow tumor cells to survive harsh conditions. The protein YB-1, which is overexpressed in many types of cancer cells, accumulates in stress granules, but researchers don't know how YB-1 affects these particles.

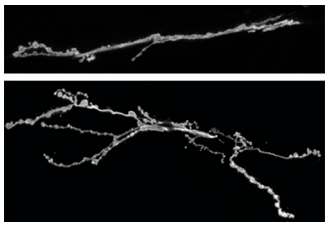
Somasekharan et al. found that stressed-out sarcoma cells need YB-1 to assemble stress granules. Knocking down YB-1 decreased levels of one stress granule protein, G3BP1. The team determined that YB-1 attaches to the mRNA for G3BP1 and stimulates its translation.

To determine the effects of YB-1 in vivo, the researchers implanted mice with sarcomas that either made or lacked the protein. A month later, cells in the control tumors carried more stress granules than did the tumor cells missing YB-1. Somasekharan et al. then implanted mice with tumors that either produced or lacked G3BP1. The control tumors harbored more stress granules than did the G3BP1-deficient tumors, and only the control tumors metastasized.

The researchers aren't sure how the reduction in stress granules curbs metastatic spread. The structures might lock away mRNAs for proteins that prevent cells from moving. The results suggest that drugs to inhibit stress granule formation might rein in cancer metastasis. ***ML***

Somasekharan, S.P., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201411047.

A POSH accent for synaptic growth



Compared with wild-type synapses (top), neuromuscular junctions are overgrown in a *Rab8* mutant fly (bottom).

Defects in endosomal trafficking that result in neurodegeneration stimulate synaptic growth, West et al. reveal.

Mutations in the gene encoding the ESCRT-III subunit CHMP2B have been linked to both frontotemporal dementia and amyotrophic lateral sclerosis. The ESCRT-III complex regulates the formation of endosomal multivesicular bodies, and disruptions to this process affect numerous trafficking and signaling pathways. To investigate which of these pathways contribute to neurodegeneration, West et al. screened for mutations that enhance the death of *Drosophila* eye cells expressing a disease-associated dominant mutant version of CHMP2B.

Mutations in the gene encoding the small GTPase Rab8 enhanced mutant CHMP2B-induced cell death, the researchers found. Motor neurons lacking *Rab8* function formed extra-large synapses with muscle cells due to an increase in JNK and TGF-β signaling. Rab8 localized to recycling endosomes, and markers for these organelles were reduced in *Rab8* mutant flies. Additionally, a protein called POSH accumulated on late endosomes. POSH scaffolds an upstream activator of the JNK pathway called TAK1 and is also an E3 ubiquitin ligase that promotes the destruction of the TGF-β regulator HRS. Removing POSH from *Rab8* mutant flies reduced the activity of both signaling pathways and restored synaptic growth to normal levels.

Dominant CHMP2B also induced POSH accumulation in mammalian neurons and synaptic overgrowth in *Drosophila* larvae, a phenotype suppressed by overexpressing wild-type Rab8. Thus, disruptions to multivesicular bodies or recycling endosomes cause POSH to accumulate and activate signaling pathways that stimulate synaptic growth. The same pathways could also promote neurodegeneration, so senior author Sean Sweeney now wants to identify additional genes involved in the process. ***BS***

West, R.J.H., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201404066.