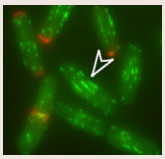
In this issue



Myo52 spells catastrophe for MTs

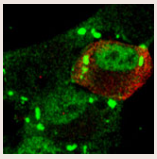
Polarised growth – which determines cell shape – has been closely studied in the fission yeast *Schizosaccharomyces pombe*, in which cell growth occurs exclusively at cell tips and requires the actin cytoskeleton. To switch from monopolar to bipolar growth in preparation for cell division, *S. pombe* cells also require the activity of the microtubule (MT) cytoskeleton – but how do the two cytoskeletal networks interact? On page 3862, Rebeca Martín-García and Daniel Mulvihill identify a role for the actin-associated myosin motor Myo52 in actin-MT interactions. The authors first show that, in yeast lacking fully functional Myo52, MTs that contact the cell end keep growing and curl around the end of the cell; by contrast, MTs in wild-type *S. pombe* undergo catastrophe (a switch from growth to shrinking). Moreover, in *myo52* mutant yeast, the removal of the MT-plus-end-binding protein Tip1 from MT tips at cell ends (an event that is associated with MT catastrophe) is inhibited. The authors next show that Tip1 undergoes ubiquitylation and proteolysis, and that this is regulated by Myo52 and the ubiquitin receptor Dph1, both of which interact with Tip1. They conclude that Myo52 promotes MT catastrophe at cell ends by facilitating Tip1 removal and degradation. These results provide fresh insight into interactions between the MT and actin cytoskeletons.

Sperm-oocyte adhesion: a new player

Before penetrating the oocyte during fertilisation, sperm must bind to the zona pellucida (ZP), the glycoprotein membrane that surrounds the oocyte. The ZP glycoprotein ZP3 is important for sperm binding, but little has been known about which other proteins are involved. Now, Robert Lyng and Barry Shur (p. 3894) report the identification of an additional sperm-adhesion ligand. The research group showed previously that, in addition to ZP3, ovulated mouse oocytes contain a peripherally associated high-molecular-weight glycoprotein with sperm-binding activity; now, they identify this species [which they name oviduct-specific glycoprotein (OGP)] by sequence analysis and purify it under native conditions. Notably, immunodepletion of OGP from oviduct lysates inhibits sperm-oocyte adhesion, and purified OGP also competitively inhibits adhesion. The authors next show that distinct glycoforms of OGP localise to different regions of the oviduct and oocyte; in particular, a relatively scarce glycoform [which was identified on the basis that it binds to peanut agglutinin (PNA)] associates preferentially with the sperm surface and the ZP. Importantly, PNA-binding OGP can induce sperm to bind to two-cell embryos (which do not normally interact with sperm). The authors propose a specific role for PNA-binding OGP in sperm-oocyte adhesion.

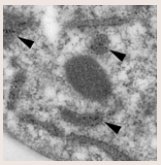
Apoptosis: Nma111p needs the nucleus

Similar to multicellular organisms, the yeast *Saccharomyces cerevisiae* can undergo apoptosis in response to stress. Much of the molecular machinery that executes apoptosis is conserved among yeast and metazoans, but there are some notable differences. For instance, in metazoans the serine protease Omi (also known as HtrA2) is a mitochondrial protein that is released to the cytosol in apoptosis; by contrast, Nma111p (an Htr-like protein that is required for stress-induced apoptosis in *S. cerevisiae*) localises to the nucleus, suggesting that its role in the apoptotic programme is distinct from that of Omi. On page 3931, Birthe Fahrenkrog and colleagues confirm that this is the case. Using heterokaryon assays, they first show that Nma111p does not shuttle between the nucleus and cytoplasm, even under pro-apoptotic conditions. They next identify two clusters of basic residues near the Nma111p N-terminus that form a nuclear localisation sequence (NLS); moreover, mutations in the NLS reduce peroxide-induced apoptosis and lead to enhanced lifespan during chronological ageing. On the basis of these and other data, they conclude that nuclear localisation is a prerequisite for the apoptotic activity of Nma111p. These results underscore the differences between the apoptotic programmes in yeast and metazoans, and emphasise the role of the nucleus in yeast apoptosis.



The push and pull of SG dynamics

Stress granules (SGs) and P-bodies (PBs) are related RNA- and protein-containing foci that store and silence mRNA in the cytoplasm – SGs are induced in response to stress, whereas PBs are constitutively present (but are further induced under stress). Both structures are known to be highly dynamic – but how are RNA and protein components shuttled in and out of the foci? To address this question, Graciela Boccaccio and colleagues (p. 3973) analyse the role of the motors dynein and kinesin in SG and PB dynamics. Using an RNAi approach in cell culture, the authors first show that dynein heavy chain 1 (DHC1) and the dynein adaptor BicD are both required for stress-induced SG formation and PB growth. By contrast, knocking down the kinesin-1 heavy chain KIF5B and kinesin light chain 1 delays the dissolution of SGs. Moreover, simultaneous knockdown of dynein and kinesin reverts the effects of single knockdowns (both on SGs and PBs), indicating that the balance between kinesin- and dynein-driven transport regulates SG and PB growth. Notably, the authors find no evidence that perturbing SG formation and dissolution affects global translational silencing. The finding that dynein and kinesin motors regulate SG and PB assembly in a push-pull manner provides new insight into the dynamics of cytoplasmic granules.



Forming fibrils in the ER

Neurohypophyseal diabetes insipidus (NDI) – which is characterised by excessive thirst and urination – results from mutations in the precursor of vasopressin, an antidiuretic hormone. In individuals with NDI, mutant pro-vasopressin accumulates in the ER of vasopressinergic neurons, causing cell death; however, the basis of this neurotoxicity has remained unclear. Now, Jonas Rutishauser and colleagues (p. 3994) shed light on how mutant pro-vasopressin is packaged in the ER. The authors study several disease-associated dominant mutant forms of pro-vasopressin, and show that the proteins form disulfide-linked homo-oligomeric aggregates both in fibroblasts and a neuronal cell line. The aggregates are visible by immunofluorescence and immunogold EM, and colocalise with the ER chaperone calreticulin. On the basis of mutagenesis experiments, the authors conclude that no specific single cysteine is essential for aggregation in vivo, although the presence of cysteines is required. Notably, the aggregates have a fibrillar substructure, and purified recombinant pro-vasopressin mutants spontaneously form fibrils in vitro. On the basis of these data, the authors propose that autosomal dominant NDI – similar to other neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease – is associated with the formation of fibrillar protein aggregates.

Development in press

Filopodia hold lens and retina together

In the developing mouse eye, the presumptive lens and retinal epithelia stay in close contact while undergoing a coordinated indentation movement known as invagination. The mechanisms that underlie this invagination event have remained mysterious, although cytoplasmic processes between the two epithelia were described as early as 1902. Now, in a paper published in *Development*, Richard Lang and colleagues identify filopodia (extending mainly from the presumptive lens) as the processes that are present between these two epithelia. Filopodium formation, they report, depends on Cdc42, IRSp53 and focal adhesion kinase, three proteins that have been previously implicated in filopodium generation and anchoring. Using pharmacological inhibitors, the authors reveal that the filopodia can contract through the actin-myosin system to regulate the distance between lens and retinal epithelia, as well as the depth of the lens pit. They conclude that the filopodia act as physical tethers that allow lens and retinal invagination to proceed in a coordinated fashion. Future work should address whether this mechanism of invagination occurs elsewhere during vertebrate morphogenesis.

Smith, A. N., Miller, L.-A., Radice, G., Ashery-Padan, R. and Lang, R. A. (2009). Stage-dependent modes of Pax6-Sox2 epistasis regulate lens development and eye morphogenesis. *Development* **136**, 2977-2985.