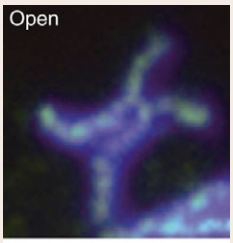
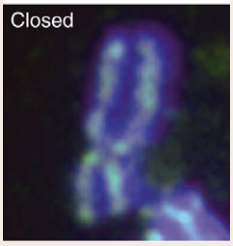
In this issue

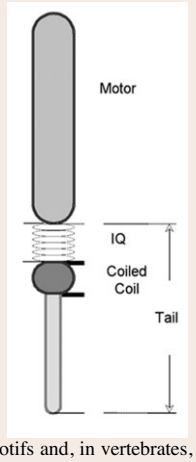
by Jane Bradbury





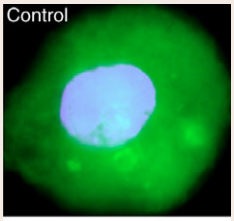
Separase loosens cohesin arm lock

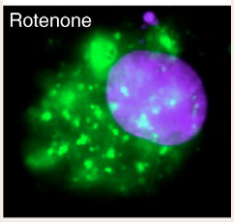
Sister chromatid cohesion, which ensures faithful chromosome segregation during cell division, is mediated by cohesin. This multi-subunit complex is dismantled in two phases. The prophase pathway is thought to remove most of the cohesin from chromosome arms. Then, at anaphase, separase removes cohesin from centromeres (where the shugoshin protein Sgo1 protects it from the prophase pathway) by cleaving the cohesin subunit Scc1. Now, on p. 4188, Toru Hirota and co-workers report that the complete removal of cohesin from chromosome arms actually requires separase. Cohesion between chromosome arms is preserved if mitosis is arrested with a proteasome inhibitor (separase is activated at anaphase when its inhibitor securin is targeted for degradation by the proteasome), they report, but this cohesion is lost in Sgo1-depleted cells. They also present results that suggest that some separase activity might be present before anaphase. Overall, the authors conclude that the separase pathway dismantles a subset of cohesin complexes on the chromosome arms that, like those at the centromeres, are protected from the prophase pathway by Sgo1.



Myosin motor caught necking

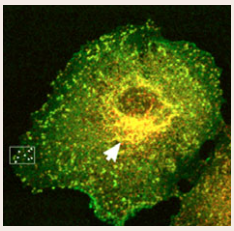
Type V myosins – dimeric, actin-associated motors – actively move organelles and molecules around cells. They contain a motor domain, a long neck region, a coiled-coil dimerization domain and a globular tail to which cargo binds. The neck region normally contains six calmodulin-binding IQ motifs and, in vertebrates, seems to control how fast myosin V moves around the cell. Surprisingly, on p. 4093, Daniel Mulvihill and colleagues report that the in vivo movement of the fission yeast type V myosin Myo52 is independent of its neck domain. The authors use live-cell imaging to follow the intracellular movements of Myo52 and mutants that lack the coiled-coil domain (Myo52 CC) or the entire neck region (Myo52 IQ). Myo52, they report, moves long distances along actin filaments in an ATP-dependent manner but Myo52 CC fails to form motile foci, which indicates that dimerization is required for Myo52 movement. By contrast, Myo52 IQ moves normally in the cell. Thus, the authors suggest, the role of the neck region of myosin V proteins might vary significantly between organisms.





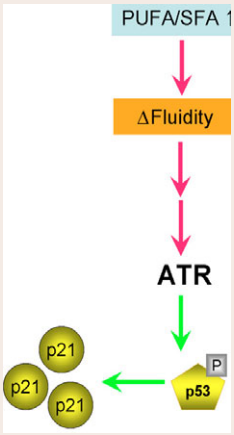
Cancer cells die of consumption

During starvation, cells use autophagy (self-digestion) to generate nutrients essential for cell survival. However, autophagy can also promote cell death. Spencer Gibson and colleagues now reveal that the induction of this form of death in cancer cells involves the accumulation of reactive oxygen species (ROS) in mitochondria (see p. 4155). Inhibitors of the mitochondrial electron transport chain (mETC) complexes I and II [rotenone and thenoyl trifluoroacetone (TTFA), respectively] induce cell death and autophagy in U87 cells (a glioma cell line derived from astrocytes) and other transformed cells, they report, but not in primary mouse astrocytes. Rotenone and TTFA both induce ROS production and the authors show that the ROS scavenger tiron decreases the autophagy and cell death induced by these inhibitors. Knocking down the antioxidant enzyme manganese-superoxide dismutase (SOD2) by RNAi has the opposite effect. Because the autophagy-induced death only occurs in cancer cells, the authors suggest that prolonged activation of autophagy with mETC inhibitors could provide a strategy for the treatment of apoptosis-resistant cancers.



Cells drink dynamin-ically

The large GTPase dynamin 2 (Dyn2) helps cells internalize material by clathrin- and caveolae-mediated endocytosis. Its role in other internalization mechanisms is controversial, however. Now, Mark McNiven and colleagues report that Dyn2 drives fluid-phase micropinocytosis (internalization of small amounts of extracellular fluid), one of several mechanisms that cells use to sample their external environment (see p. 4167). Inhibition of all four Dyn2 splice variants by anti-dynamin antibodies or RNAi, the authors report, reduces the uptake of the fluid markers dextran and horseradish peroxidase in serum-starved epithelial cells. Dyn2 inhibition has no effect, however, on the uptake of these markers in serum- or EGF-stimulated cells, which suggests that Dyn2 is required for fluid-phase micropinocytosis but not for stimulated fluid uptake via macropinocytosis. The authors also report that cells expressing dominant-negative mutants of two specific Dyn2 variants – Dyn2(ba) and Dyn2(bb) – endocytose less dextran than cells expressing wild-type Dyn2. This suggests that different Dyn2 splice variants have different endocytic functions.



p53 applies brakes fluidly

For years, researchers have concentrated on the role of p53 in genomic stability, but this tumour suppressor has other important functions. For example, the p53-p21 checkpoint can be activated and cells arrested in G1 phase of the cell cycle by perturbation of phospholipid homeostasis. Now, Zhongmin Ma and co-workers reveal more about how this occurs (see p. 4134). Blocking the group VIA Ca^{2+}-independent-phospholipase A2 ($iPLA_2$), a protein that helps to regulate rapid phospholipid turnover during G1, induces cell-cycle arrest. The authors show that inhibition of $iPLA_2$ induces the phosphorylation of p53 at Ser15 by the DNA checkpoint kinase ATR in the absence of DNA damage. In addition, they report that $iPLA_2$ inhibition increases the ratio of polyunsaturated- to saturated-fatty-acid-containing phosphatidylcholines (PCs) in cellular membranes. The authors propose that $iPLA_2$ normally regulates cell membrane fluidity and function by controlling the ratio of polyunsaturated to saturated fatty acids in PCs and suggest that any increase in this ratio activates ATR to postpone cell division until the problem is rectified.

Development in press

GSCs and the Argonautes

Germline stem cells (GSCs) in the *Drosophila* ovary are an excellent model system for studies of mechanisms that regulate stem cell maintenance and differentiation. In a paper published in *Development*, Yang and co-workers report that Argonaute 1 (AGO1), a protein involved in RNA silencing, controls the fate of *Drosophila* GSCs. Piwi, another Argonaute protein, helps to maintain GSCs by silencing *bag of marbles* (*bam*), a gene that is required for GSC differentiation, but do other Argonaute proteins play similar roles? The researchers report that the overexpression of *Ago1* leads to GSC overproliferation, whereas its loss causes a reduction in GSC number. This result, together with an analysis of the fate of germline clones that lack a functional *Ago1* gene, suggests that an AGO1-dependent miRNA pathway plays an instructive role repressing GSC differentiation. Finally, the researchers show that some GSCs partly differentiate in *Ago1 bam* double mutants, which suggests that AGO1 (unlike Piwi) might regulate GSC fate in a *bam*-independent manner.

Yang, L., Chen, D., Duan, R., Xia, L., Wang, J., Qurashi, A., Jin, P. and Chen, D. (2007). Argonaute 1 regulates the fate of germline stem cells in *Drosophila*. *Development* **134**, 4265-2472.