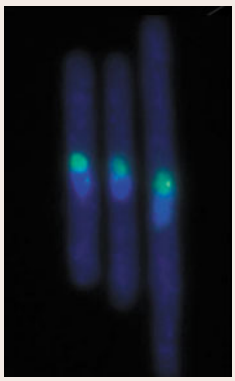
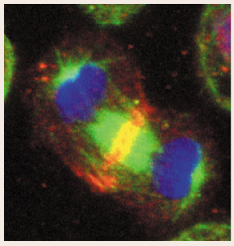
In this issue

by Jane Bradbury



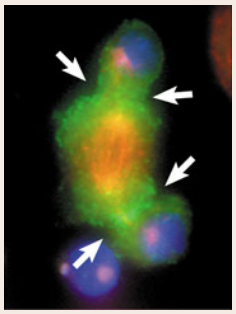
FEARless Cdc14 release in yeast

Cdc14 family phosphatases are highly conserved regulators of cell-cycle progression. Regulated release from the nucleolus partly controls the activity of budding yeast Cdc14p and its fission yeast ortholog Clp1/Flp1. But here, report Dannel McCollum and colleagues, the similarities stop (see p. 4462). In budding yeast, a network of FEAR (for Cdc-fourteen early anaphase release) proteins triggers the release of Cdc14p from the nucleolus in early anaphase. When McCollum and co-authors examine fission yeast mutants lacking FEAR protein orthologs, however, they find that release of Clp1/Flp1 from the nucleolus, which normally occurs upon entry into mitosis in this organism, is unaffected, which indicates that is not triggered by the FEAR network. In addition, they show that, whereas Cdc14p promotes the segregation of nucleolar and telomeric DNA, Clp1p/Flp1 is not required for these processes. Thus, although Cdc14 family phosphatases themselves are highly conserved, their regulation and functions may not be universal. In particular, suggest the authors, several Cdc14 orthologs – including the human form – might be regulated through a conserved FEAR-independent pathway.



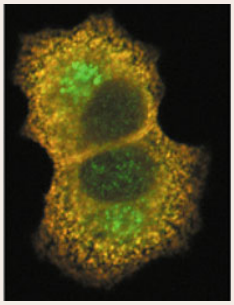
How the spindle is Glue(d) together…

Dynein-dynactin motor complexes are involved in several stages of mitosis. For example, they remove checkpoint proteins from correctly attached kinetochores (the complexes that attach chromosomes to the spindle) by transporting them away along microtubules. Régis Giet and co-authors have now re-investigated the roles of dynein-dynactin complexes in mitosis and cytokinesis by knocking down the dynactin subunit p150^{Glued} by RNAi in *Drosophila* S2 cells (see p. 4431). They show that p150^{Glued} is required for connection of centrosomes to spindle poles, the metaphase-to-anaphase transition, and synchronous chromosome movements during anaphase. Then they show that p150^{Glued} facilitates formation of the central spindle by increasing the efficiency of recruitment of the mitotic kinases Aurora B and polo to the midzone. p150^{Glued} is also needed, the authors report, to recruit Pavarotti-KLP (a component of the centralspindlin complex that is required for cytokinesis) efficiently to the central spindle microtubules. Their results thus confirm the involvement of the dynein-dynactin complex during mitosis and also reveal new roles for it during cytokinesis.



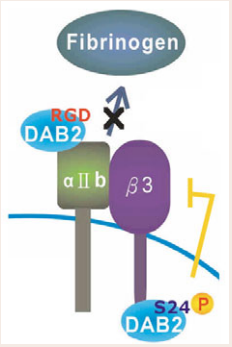
…and produces a GAP in the furrow

During cytokinesis, a cleavage furrow forms at the equator of the cell and partitions its cellular components between its progeny. Spindle microtubules determine the position of the cleavage plane. But do they directly trigger furrow formation or deliver a signal to the cortex to initiate the necessary cytoskeletal rearrangements? On p. 4402, Pier Paolo D'Avino and colleagues provide strong evidence supporting the second possibility by showing that microtubule-mediated delivery of the GTPase-activating protein (GAP) RacGAP50C signals furrow formation during cytokinesis in flies. RacGAP50C and the motor protein Pavarotti are part of the centralspindlin complex necessary for cytokinesis. The authors show that depletion of either component prevents furrowing without affecting the association of spindle microtubules with the cell cortex. They then show that these microtubules deliver the centralspindlin components to the cortex just before furrow formation. Finally, they demonstrate that mislocalization of RacGAP50C causes ectopic furrowing even in the absence of Pavarotti. Thus, the GAP component of centralspindlin appears to be both necessary and sufficient to signal furrow formation during cytokinesis.



Pumping out insulin

The slightly acidic nature of secretory granules is necessary for the efficient processing and subsequent exocytosis of their contents. Vacuolar-type H^+-ATPase (V-ATPase) is thought to acidify many intracellular compartments. Now, on p. 4531, Ge-Hong Sun-Wada and co-authors report that the a3 isoform of this multisubunit enzyme helps to regulate insulin secretion. Mammalian cells express four isoforms of the a subunit of V-ATPase. The authors show that V-ATPase containing the a3 isoform is highly expressed in pancreatic islets and localizes to the membranes of the insulin-containing granules in the β-cells that secrete the hormone. Mice lacking the a3 isoform, they report, have less insulin in their blood than wild-type mice but a near-normal amount of insulin in their islets and a normal insulin-to-proinsulin ratio in their secretory granules. Other experiments reveal that islets isolated from the a3-null mice exhibit impaired insulin secretion in response to glucose. The gene encoding human a3 maps to a chromosome region linked to insulin-dependent diabetes mellitus; so the authors speculate that mutations in it may be involved in diabetes.



DABbling with integrin function

Platelet aggregation plays an important role in blood clotting. When a blood vessel is damaged, platelets are recruited to the injured endothelium, where they release coagulation factors and platelet activation factors from their α and δ granules. Interactions between fibrinogen and integrin αIIbβ3 on the surface of platelets then induce platelet aggregation, which helps to form a clot. On p. 4420, Ching-Ping Tseng and colleagues reveal that the adaptor protein, Disabled-2 (DAB2) negatively regulates these interactions by binding to αIIb integrin on the platelet surface. DAB2 is best known as a cytoplasmic adaptor. The authors now show that it is also present in platelet α granules. During platelet activation, they report, DAB2 is released and binds to the extracellular region of αIIbβ3 integrin. Because this binding involves the part of αIIb integrin that binds to fibrinogen, DAB2 blocks the platelet-fibrinogen interaction and thus inhibits platelet aggregation. The authors propose therefore that DAB2 helps to regulate the size of platelet aggregates, which could prevent excessive clotting.

Development in press

A new player in patterning by proteolysis

The transition from egg to embryo in *nematodes* involves fertilisation, meiosis, exit from meiosis and the establishment of the anteroposterior (AP) axis. These last two processes may be connected: many mutants with meiotic defects, including several that affect ubiquitin-mediated proteolysis, also have polarity defects. Now, in a paper in *Development*, Bruce Bowerman and colleagues report that PAM-1, a puromycin-sensitive aminopeptidase that might act in conjunction with the proteasome to degrade ubiquitin-tagged proteins, is required for both meiotic exit and AP polarity in one-cell worm embryos. The researchers show that meiotic exit is delayed and the AP axis is not specified in *pam-1* mutants. Because inactivation of the B-type cyclin CYB-3 rescues the first (but not the second) of these defects, PAM-1 may regulate CYB-3 during meiotic exit but presumably targets other proteins to regulate polarity. Bowerman and colleagues conclude that PAM-1 contributes to the proteolytic machinery that triggers cell-cycle progression and the establishment of AP polarity in the early worm embryo, and possibly in other embryos.

Lyczak, R., Zweier, L., Group, T., Murrow, M. A., Snyder, C., Kulovitz, L., Beatty, A., Smith, K. and Bowerman, B. (2006). The puromycin-sensitive aminopeptidase PAM-1 is required for meiotic exit and anteroposterior polarity in the one-cell *Caenorhabditis elegans* embryo. *Development* **133**, 4281-4292.