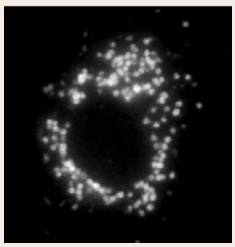
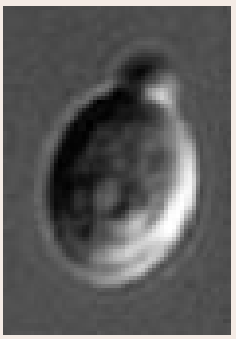
In this issue

by Jane Bradbury



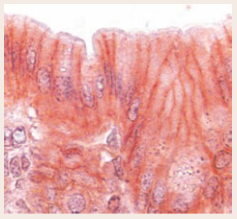
Mitochondria: controlling the fission reaction

Mammalian mitochondria, for mysterious but apparently essential reasons, frequently change shape through fission and fusion. Mitochondrial fission, which is also involved in apoptosis, requires at least two proteins: the cytosolic dynamin-like protein DLP1/Drp1 and the mitochondrial outer membrane protein hFis1, which seems to recruit DLP1 to mitochondria. On p. 4141, Yisang Yoon and colleagues provide new insights into how hFis1 regulates mitochondrial fission by identifying two regions of the protein that are required for this process. The N-terminal region of hFis1 forms six α-helices; among these, α2-α3 and α4-α5 form two tetratricopeptide repeat (TPR) folds that mediate protein-protein interactions. By examining deletion mutants of hFis1, the authors show that the TPR region mediates binding of hFIS1 to DLP1 and that the α1 helix regulates this interaction. They suggest that hFis1 is the main regulator of mitochondrial fission and propose that it acts in a two-step process: recruitment of DLP1 by the TPR motif is followed by α1-mediated release of DLP1 assemblies, which then bind to the mitochondrial surface and mediate membrane fission.



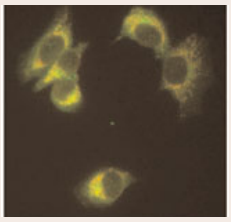
Budding role for PKC

In eukaryotes, protein kinase C (PKC) is implicated in the regulation of many important cellular processes, including proliferation and polarized growth. In budding yeast, a single PKC (Pkc1p) activates the Mpk1p MAP kinase pathway that is essential for cell-wall construction and bud emergence. However, little is known about its other functions. Now, Masaki Mizunuma and colleagues report that Pkc1p maintains polarized bud growth in an Mpk1p-independent manner (see p. 4219). The authors describe how yeast cells carrying *pkc1-834*, a novel mutant allele of *PKC1*, establish polarity normally but do not maintain polarized growth during cell budding. Maintenance of Ca^{2+}-induced F-actin polarization is defective in these mutant yeast cells, and this phenotype is apparently caused by decreased expression of the G1 cyclin Cln2p. The authors propose that this novel Mpk1p-independent role for Pkc1p and its previously described Mpk1p-dependent role are important for the coordinated regulation of polar bud growth and the cell cycle.



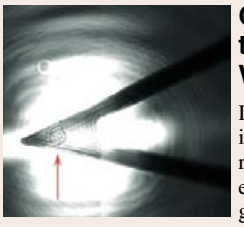
Channelled treatment for cystic fibrosis

In cystic fibrosis, the loss-of-function of CFTR, a membrane protein that allows apical efflux of Cl^- from secretory epithelial cells, causes the mucus obstruction characteristic of the disease. The Cl^- channel CIC-2 might function as an alternative route for Cl^- efflux that, if pharmacologically activated, would compensate for CFTR deficiency, but its cellular localization is controversial. On p. 4243, Francisco Sepúlveda and co-workers use immunocytochemistry to show that CIC-2 localizes exclusively to the basolateral membranes of absorptive intestinal epithelial cells in vivo. Then, in transfection assays, they demonstrate that CIC-2 sorts to the basolateral membrane of several epithelial cell lines; this sorting is dependent on the AP-1B clathrin adaptor complex and on a di-leucine motif in a C-terminal crystathione beta synthase domain (CBS-2) of CIC-2. Drugs that modulate the function of the CBS-2 domain might therefore allow CIC-2 to compensate for loss of CFTR in cystic fibrosis by altering its targeting.



RBP3 muscles in on Pol II

Transcription by RNA polymerase II (Pol II) is dynamically regulated by assembly of the core enzyme with mediator proteins, transcription factors and other auxiliary factors. Several core subunits are involved in tissue-specific transcription, including RPB3, which directly contacts the myogenic transcription factor myogenin and the transcription factor ATF4. Expression of RBP3 is tightly regulated during muscle differentiation. Now Claudio Passananti and colleagues report that its subcellular localization is also regulated during this process (see p. 4253). The authors show that RPB3 accumulates in the cytoplasm of cycling myogenic cells but migrates to the nucleus upon induction of differentiation. They then use two-hybrid analysis, together with coimmunoprecipitation and colocalization experiments in myogenic cells, to identify HCR (a gene product implicated in susceptibility to psoriasis) as the cytoplasmic RPB3-interacting protein. Finally, the authors demonstrate that knocking down HCR by RNAi in cycling myogenic cells results in migration of RBP3 to the nucleus. They therefore conclude that HCR provides a cytoplasmic docking site for RPB3 and suggest that this interaction represents an additional level of tissue-specific transcriptional regulation.



Gastrulation: the pull of Wnt11

During gastrulation, intricate cellular rearrangements establish the three germ layers of the embryo. As part of this process, the progenitor cells of the different layers acquire specific adhesion properties. These properties are thought to be modulated by Wnt signaling. On p. 4199, Pierre-Henri Puech, Carl-Philipp Heisenberg and co-workers provide the first direct evidence for this hypothesis by using atomic force microscopy to measure the strength of the adhesion between individual primary gastrulating zebrafish cells and fibronectin-coated substrates. They show that mesendodermal progenitor cells from zebrafish silberblick mutant embryos, which carry a loss-of-function mutation in the *wnt11* gene, require less force to remove them from a fibronectin-coated substrate than do wild-type cells. Other results indicate that this difference results from the reduced adhesion of the *wnt11* mutant cells through integrins to the fibronectin substrate. Thus, the authors conclude, Wnt11 signaling modulates cell adhesion during gastrulation, possibly by regulating integrin expression/localization in the mesendodermal progenitors.

Development in press

Long live sperm stem cells

Stem cells are believed to possess special machinery that allows them to replicate indefinitely without accumulating defects. However, embryonic stem and embryonic germ cells often acquire chromosomal and imprinting abnormalities in culture. Recent work published in *Development* by Kanatsu-Shinohara and colleagues is therefore somewhat surprising. These authors cultured spermatogonial stem cells, derived from newborn mouse testes, for two years and found them to be remarkably genetically and epigenetically stable over this time. The cells' stability is reflected in their ability to produce normal sperm when transplanted into infertile mice and by the fact that the sperm can generate normal, fertile offspring when used in IVF experiments. The only detectable change, the authors report, is a shortening of the telomeres of the stem cells, but this occurs so slowly that it should not hamper the future use of these cells as a tool for genetic modification.

Kanatsu-Shinohara, M., Ogonuki, N., Iwano, T., Lee, J., Kazuki, Y., Inoue, K., Miki, H., Takehashi, M., Toyokuni, S., Shinkai, Y., Oshimura, M., Ishino, F., Ogura, A. and Shinohara, T. (2005). Genetic and epigenetic properties of mouse male germline stem cells during long-term culture. *Development* **132**, 4155-4163.