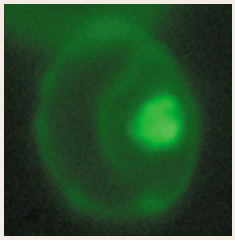
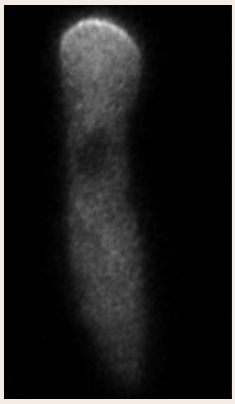
In this issue

by Jane Bradbury



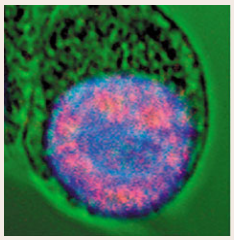
Malaria parasite's acid stomach

Global efforts to control malaria are severely compromised by the spread of resistance to the antimalarial drug chloroquine. The mechanism of resistance is not clear, but chloroquine is known to have its toxic effect in the parasite's digestive vacuole, and in resistant parasites, less of the drug accumulates in this vacuole. One proposal is that pH changes in the vacuole are responsible for chloroquine resistance. On p. 1016, Kiaran Kirk and colleagues argue against this hypothesis, showing no significant difference between the pH of the digestive vacuoles of chloroquine-sensitive and resistant parasites. The authors preloaded erythrocytes with several dextran-linked pH-sensitive dyes and then infected them with chloroquine-sensitive or chloroquine-resistant parasites. The parasites endocytose the dye-loaded erythrocyte cytosol and deposit it into the digestive vacuole, thus allowing the authors to estimate its pH. Their findings indicate that the differences in chloroquine accumulation exhibited by sensitive and resistant parasites are not the result of differences in vacuole pH, and so the search for the origin of chloroquine resistance continues.



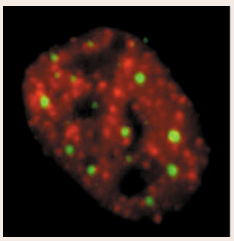
Setting a Crac-king pace

Eukaryotic cells sense chemical gradients during a variety of physiological processes and then move up or down the gradients by extending pseudopods. The molecular mechanisms involved in such chemotaxis are evolutionarily conserved and have been studied extensively in *Dictyostelium*. Pleckstrin homology (PH)-domain proteins bind to phosphatidylinositol 3,4,5-triphosphates [PtdIns(3,4,5)P_3] at the leading edge of chemotaxing *Dictyostelium* cells to regulate pseudopod formation. Now, Masahiro Ueda and co-workers reveal that the steady-state localization of the PH-domain protein Crac at the leading edge pseudopod is maintained by rapid exchange of individual molecules (see p. 1071). The authors track single Crac-GFP molecules and report that most bind very transiently to PtdIns(3,4,5)P_3 at the front of migrating cells; a few bind more stably to adenyl cyclase A (ACA)-dependent sites at the rear of the cells, where they might regulate ACA activity. The authors propose that the dynamic binding behaviour of PH-domain proteins allows *Dictyostelium* to reorientate rapidly in response to directional changes of chemoattractant and suggest that other chemotactic signalling components may exhibit dynamic behaviour similar to that of Crac.



Phospholipid arrested at checkpoint

Checkpoints halt the eukaryotic cell cycle at various points if any of the processes needed to complete cell division (e.g. chromosomal segregation) fail. On p. 1005, Zhongmin Alex Ma and colleagues report that the disruption of phospholipid turnover in G1-phase cells is another factor that induces cell-cycle arrest. The turnover of phosphatidylcholine (the major phospholipid in mammalian membranes) is rapid in G1 phase but stops in S phase to allow cells to make enough membrane for their daughters. Turnover of phosphatidylcholine in G1 phase is regulated by the opposing actions of CTP:phosphocholine cytidyltransferase and the group VIA Ca^{2+}-independent phospholipase A_2 ($iPLA_2$). The authors show that inhibition of $iPLA_2$ arrests cells in G1 phase and induces accumulation of the tumour suppressor p53 and expression of the cyclin-dependent kinase inhibitor $p21^{cip1}$. Additional experiments in p53-deficient and $p21^{cip1}$-deficient cells confirm that inhibition of $iPLA_2$ activates the p53-$p21^{cip1}$ checkpoint. Thus, conclude the authors, $iPLA_2$ and p53 cooperate to monitor the integrity of membrane phospholipids in G1 phase to ensure cells are well prepared for division.



PML's out-of-body experience

Promyelocytic leukaemia (PML) bodies are chromatin-associated sites of DNA metabolism present in the nuclei of mammalian cells. For much of the cell cycle, PML bodies are stable but David Bazett-Jones and his team now describe how they change during early S phase, mitosis and early G1 phase. On p. 1026, the authors show that PML bodies become distorted and undergo fission to form microbodies as cells enter S phase. Noting that PML bodies remain associated with chromatin and double in number during S phase, the authors suggest these alterations in their behaviour reflect changes in the topology of DNA as it replicates. On p. 1034, the authors go on to investigate the biochemical and morphological changes in PML bodies during mitosis. They find that the PML protein that defines these structures is recycled from one cell cycle to the next via chromatin-associated and freely diffusing mitotic accumulations of PML protein (MAPPs) – structures that contain the PML protein but lack several PML body components. The authors propose that, in early G1 phase, chromatin-associated MAPPs provide a seed for the reformation of PML nuclear bodies through the redistribution of PML protein from cytoplasmic MAPPs. They suggest that other nuclear bodies may use a similar mechanism to partition during mitosis.

Chromosome passengers with unequal assignments

During mitosis, the cell nucleus and cytoplasm undergo complex reorganizations. These are triggered in part by Aurora kinase B, which is regulated by the inner centromere protein (Incenp). Both proteins are components of the chromosomal passenger protein complex, which is required for several key mitotic functions, including spindle assembly and cytokinesis. The complex has been studied in detail in vitro but much less in developing organisms in vivo. On p. 1144, Mar Carmena and colleagues report that Incenp is required for cytokinesis and asymmetric cell division during the development of the *Drosophila* nervous system. The authors have isolated a null allele of *Drosophila Incenp*, which is lethal at embryonic stage 13. In embryos homozygous for this allele, histone phosphorylation and cytokinesis are defective in the developing nervous system, which indicates depletion of Aurora kinase B activity. In addition, localization of the cell-fate determinant Prospero is abnormal during asymmetric neuroblast division in these embryos. Thus, as well as regulating mitosis in symmetrically dividing cells, the chromosomal passenger complex also influences the more elaborate process of asymmetric cell division during development.

Development in press

NF-κB: making mice furry

What makes our furry friends furry? Mouse fur actually consists of several hair types – e.g. guard, awl, auchene and downy zigzag hairs – but little is known about the signals that direct their development. Now, in a paper published in *Development*, Schmidt-Ullrich et al. report that the transcription factor NF-κB controls the proliferation (but not the initiation) of guard hair placodes and their growth into the mesoderm to form hair follicles. Mice with suppressed NF-κB activity or defects in ectodysplasin A1 (Eda A1; *tabby* mice) or its receptor (EdaR; *downless* mice) have similar hair defects. By crossing NF-κB reporter mice with *tabby* and *downless* mice, the researchers show that Eda-A1/EdaR signalling activates NF-κB, which then controls guard hair placode down-growth by inducing expression of the signalling molecule sonic hedgehog and cyclin D1. Eda-A1/EdaR/NF-κB signalling also controls the morphology of other hair types, and additional signals regulate NF-κB activity to control follicle growth. The transcription factor is thus central to the molecular mechanisms that regulate hair development.

Schmidt-Ullrich, R., Tobin, D. J., Lenhard, D., Schneider, P., Paus, R. and Scheidereit, C. (2006). NF-κB transmits Eda A1/EdaR signalling to activate Shh and cyclin D1 expression, and controls post-initiation hair placode down growth. *Development* **133**, 1045-1057.