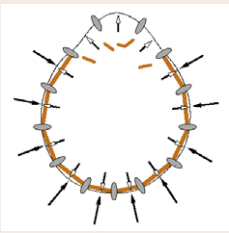
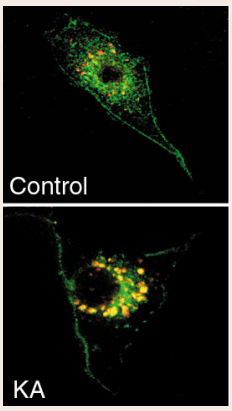
In this issue

by Jane Bradbury



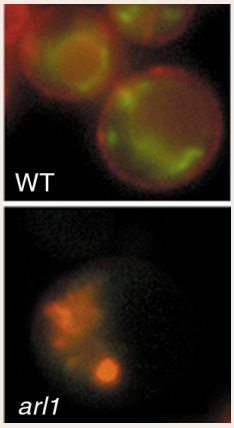
Blebs do the locomotion

During amoeboid locomotion, which many metazoan cells use to migrate through tissues, actin polymerization is thought to generate filopodia and lamellipodia at the leading edge, which move the cell forward. However, this model does not fully explain amoeboid movement – for example, why do some cells glide and others move jerkily? On p. 3833, Kunito Yoshida and Thierry Soldati propose that the focal production of blebs – transparent, spherical cell-surface protrusions – is also important for amoeboid locomotion. Blebs 'blow' out from the cell surface when myosin-II-driven contraction of the back of the cell increases the cytoplasmic fluid pressure. By visualizing the dynamics of F-actin, the authors show that migrating *Dictyostelium* cells continuously produce these blebs at the leading edge. Pseudopodia extension, cell-body retraction and the speed of cell locomotion are all reduced in myosin-II-null cells, cells treated with the myosin II inhibitor blebbistatin, and cells at high osmolarity – none of which can form blebs. Thus, suggest the authors, efficient amoeboid movement involves formation of blebs and filopodia/lamellipodia, which are produced by two mechanically distinct processes.



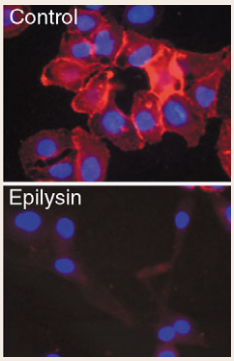
Syntaxin 1A: sorting out neuro-transmitters

Glutamate transporters, including excitatory amino-acid carrier 1 (EAAC1), prevent the overstimulation of nerve cells by mediating the reuptake of excitatory neurotransmitters at synapses. Because EAAC1 is also involved in the synthesis of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) at presynaptic terminals, it helps to maintain the balance between glutamate and GABA in the synaptic cleft. Since neurotransmitter imbalances cause epilepsy, establishing how EAAC1 activity is regulated is an important goal. On p. 3776, Lan Bao, Gang Pei and colleagues reveal that syntaxin 1A, a SNARE protein involved in membrane trafficking and neurotransmitter release, is involved in this regulation. They show that EAAC1 is endocytosed through the clathrin-mediated pathway and that syntaxin 1A potentiates its internalization. In addition, they find that knocking down endogenous syntaxin 1A by RNAi blocks endocytosis and degradation of EAAC1 induced by kainic acid (KA), which triggers epilepsy in rodents. Their results thus indicate that syntaxin 1A might be involved in epileptogenesis and identify the endocytic pathway in which it functions as a potential target for new treatment strategies.



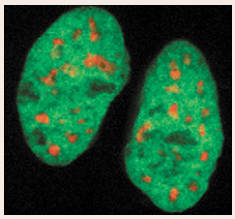
Arl1p drops GPI anchor at the membrane

Glycosylphosphatidyl-inositol (GPI) anchors tether various proteins to the plasma membrane. How such proteins are delivered from the trans-Golgi network (TGN) to the cell periphery is unclear. On p. 3845, Fang-Jen Lee and co-authors implicate the small Arf-like GTPase Arl1p in the process. Arl1p functions in the regulation of Golgi structure and in membrane trafficking at the TGN, but until now no Arl1p-regulated cargo had been identified. The authors show that the GPI-anchored yeast protein Gas1p, which normally resides at the cell surface, accumulates in internal structures in an *arl1* mutant rather than moving to the plasma membrane. By contrast, they find that several cell-wall-localized GPI-anchored proteins and a non-GPI-anchored plasma membrane protein are transported normally in the *arl1* mutant. Additional experiments indicate that the Arl1p regulators Sys1p and Arl3p, and its effector Imh1p, are also involved in Gas1p transport. Thus, the authors suggest, the Sys1p–Arl3p–Arl1p–Imh1p signalling cascade facilitates the transport of a subgroup of GPI-anchored proteins from the TGN to the plasma membrane.



Epilysin spurs epithelial transition

An important step in carcinogenesis is the conversion of polarized epithelial cells to migrating mesenchymal cells. Several matrix metalloproteinases (MMPs) – proteases that remodel the extracellular matrix – have been implicated in such epithelial-to-mesenchymal transitions (EMTs). Now, Jouko Lohi and colleagues report that epilysin (MMP28), the newest member of this protein family, induces TGF-β-dependent EMT in human A549 lung adenocarcinoma cells (see p. 3856). Stable expression of catalytically active epilysin in A549 cells, they report, results in EMT, loss of the cell-cell adhesion molecule E-cadherin from the surface, and proteolytic processing of latent TGF-β complexes in the extracellular matrix. Although the EMT is irreversible, the authors show that an MMP inhibitor and TGF-β-neutralizing antibodies prevent its onset. They also reveal that epilysin is attached to the surface of epithelial cells through its hemopexin domain but released after EMT by MT1-MMP, which is upregulated by epilysin. The authors suggest, therefore, that transient epilysin activity helps to regulate the phenotype of epithelial cells and may help to induce cell invasion during carcinogenesis.



Transcription sites: pair and pair alike

Transcription by RNA polymerase II occurs in discrete transcription sites scattered throughout the nucleus. Recent work indicates that coordinately regulated genes are recruited to the same transcription sites, but what controls their recruitment to these sites? Alexandra Binnie, Nicholas Proudfoot and co-authors have used the transcription domains (TDs) formed when transiently transfected plasmids are transcribed as a model system to study this process (see p. 3876). By co-transfecting plasmid pairs into HeLa cells, they show that plasmids containing homologous transcribed sequences form shared TDs. By contrast, those containing non-homologous transcribed sequences enter separate TDs, even if they have homologous backbone or promoter sequences. They also find that a low copy number promotes formation of TDs, but high concentrations of one plasmid do not inhibit formation of TDs by a non-homologous, low-copy-number plasmid. The authors therefore propose that homology between transcribed sequences drives recruitment of genes into TDs; a similar mechanism might recruit coordinately regulated endogenous genes to shared transcription sites.

Development in press

CDC42 takes a PARtner

The establishment of polarity is an important developmental event. In nematodes, the segregation of different PAR proteins into anterior and posterior cortical domains establishes anteroposterior polarity in the one-cell embryo. The segregation of these polarity proteins is coupled to rearrangements of the actomyosin cytoskeleton. In a paper published in *Development*, Schonegg and Hyman now reveal that the Rho family GTPases CDC42 and RHO-1 coordinate actomyosin contractility and PAR protein localization during polarity establishment in these embryos. Using live imaging of GFP-tagged PAR proteins and RNAi-mediated depletion of the two GTPases, the researchers show that RHO-1 activity helps to localize CDC42 to the anterior of the embryo by regulating the early organization of myosin. CDC42 then stabilizes the actomyosin network and localizes PAR-6 to the anterior cortex. These results are at odds with previous data suggesting that CDC42 helps to maintain but not establish polarity and provide important new insights into how RHO-1 and CDC42 might interact during developmental cell polarization events.

Schonegg, S. and Hyman, A. A. (2006). CDC-42 and RHO-1 coordinate acto-myosin contractility and PAR protein localization during polarity establishment in *C. elegans* embryos. *Development* **133**, 3507-3516.