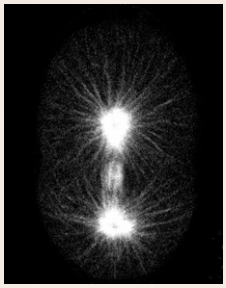
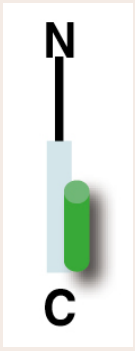
In this issue

by Jenny Bangham



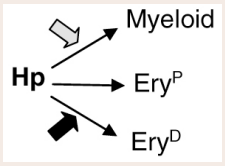
Centralspindlin ploughs the furrow

At the final stage of cell division, an actin-myosin ring forms around the cortex of the cell, which constricts to form a cleavage furrow and pinch the cell in two. What signals initiate and position the cleavage furrow? In nematodes, two signals seem to be important – one from the microtubule asters (the radial arrays of microtubules emanating from the centrosomes), and one from the spindle midzone (where microtubules from opposite poles overlap). On p. 1772, Koen Verbrugghe and John White describe a new model for how the cleavage furrow is positioned. An important player is the centralspindlin complex, which was previously thought not to be needed for furrow formation, only for the completion of cytokinesis. Now, Verbrugghe and White show that centralspindlin localises to the furrow and find that furrowing fails to occur when centralspindlin is missing along with two proteins involved in spindle elongation: PAR-2 and trimeric G-protein Gα. The researchers argue that the stability of the midzone microtubules is crucial for furrow formation. Since PAR-2 is thought to affect microtubule stability at the cortex, they propose that PAR-2 and centralspindlin act redundantly to stabilise microtubules in this region.



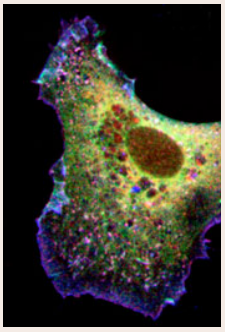
Hsc70 – a place to anchor

Most membrane-associated proteins need sophisticated guidance systems to help them find their way to the right subcellular compartment. The mechanism of post-translational targeting to the endoplasmic reticulum (ER) is particularly elusive; so, to try to identify the components involved, Stephen High and colleagues have been studying tail-anchored (TA) proteins (p. 1743). These are a diverse class of membrane-associated proteins characterised by a hydrophobic C-terminal sequence. The researchers focused on a model ER-associated TA protein, Sec61β, whose targeting to the ER is ATP dependent. Using crosslinking agents, they found that Sec61β binds to the molecular chaperone Hsc70, and that this binding depends on the hydrophobic TA sequence. When the researchers mixed together combinations of purified components normally present in the cytosol, they found that Hsc70 and its co-chaperone Hsp40 are sufficient to target and integrate Sec61β into the ER. The researchers compare the kinetics ofthis system with other pathways of TA-protein biogenesis and conclude that the Hsc70-Hsp40 system is an important mediator of post-translational integration for TA proteins.



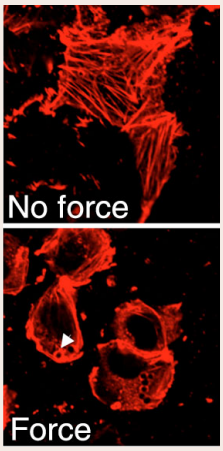
PI3Ks in the blood

Phosphoinositide 3-kinases (PI3Ks) are crucial for cell proliferation and differentiation during early development, which can make their functions in vivo difficult to study. Heather Bone and Melanie Welham are interested in the roles of class I_A PI3Ks during early development of the haematopoietic system and, on p. 1752, describe a study using embryonic stem (ES) cells and embryoid bodies (EBs). The researchers manipulated PI3K activity both pharmacologically (using a general PI3K inhibitor) and genetically (using ES cells lacking 3-phosphoinositide-dependent protein kinase 1, a kinase downstream of PI3K) and found that PI3K signalling is required for cell proliferation during early development in EBs. They also found that PI3Ks are needed during developmental haematopoiesis, although were surprised to find that PI3K signalling was not necessary early on. Specifically, PI3K signalling is required for the expansion of the blast-colony-forming cells (primitive haematopoietic progenitors) and is involved in haematopoietic cell differentiation – both myeloid and erythroid lineages are affected by reduced PI3K activity. The authors conclude that PI3Ks have several different roles at different times during development of the haematopoietic system.



Rivalry at the leading edge

The highly conserved coronins were first identified as actin-binding proteins. But although they are crucial to the dynamics of actin filaments and cell movement, their actin-binding sites have been difficult to pin down. Now, on p. 1779, James Bear and colleagues report a point mutation in a highly conserved region of coronin 1B that prevents its binding to F-actin. They show that the protein has to bind to F-actin at the leading edge in order to affect cell motility, and they go on to describe why. The turnover of actin filaments is regulated by another actin-binding protein, cofilin, which severs and depolymerises filaments. Previous work had suggested that coronin helps cofilin to bind to and sever actin, but Bear et al. find that the binding of cofilin to F-actin is not enhanced by coronin 1A or 1B. In fact, they report that coronin 1B protects actin filaments from being depolymerised by cofilin, and conclude that the two proteins bind antagonistically to actin filaments.



Rho under pressure

High blood pressure and pulse rate cause some dramatic changes to the human heart – cardiac fibroblasts proliferate, cardiomyocytes enlarge and fibroblasts differentiate into myofibroblasts. Myofibroblasts are characterised by their expression of α-smooth muscle actin (SMA), and McCulloch and colleagues are interested in signalling events that lead from haemodynamic stress to SMA expression (see p. 1801). The researchers already knew that mechanical stress causes the small GTPase RhoA to reorganise actin filaments by stimulating phosphorylation of the actin regulators LIM kinase and cofilin. They also knew that actin reorganisation promotes the expression of myocardin-related transcription factor (MRTF), which regulates the SMA promoter. To explore the connection between these pathways, the researchers used collagen-coated magnetic beads to apply stress to fibroblasts in vitro. As expected, force increased RhoA activity in the fibroblasts, causing the phosphorylation of LIM kinase and cofilin, and the polymerization of actin filaments. It also caused the nuclear translocation of an MRTF. But, crucially, using a Rho-kinase inhibitor and actin-polymerization inhibitor, they showed that MRTF translocation requires both Rho kinase and intact actin filaments, demonstrating that force-induced SMA expression occurs through a RhoA–Rho-kinase–LIMK–cofilin pathway.

Development in press

Akts of stem cell self-renewal

The self-renewing ability of stem cells is crucial in many development contexts; however, the mechanisms that regulate the switch between proliferation and differentiation are poorly understood. Spermatogonial stem cells (SSCs) provide an excellent model for studies of self-renewal because large numbers can be expanded in culture, and the markers that characterise these cells are well defined. In a paper published in *Development*, Shinohara and colleagues reveal a crucial role for the phosphoinositide 3-kinase (PI3K)-Akt pathway in mouse SSC self-renewal. Glial-cell-line-derived neurotrophic factor (GDNF) had previously been shown to regulate the process but the downstream signals were not known. Now these authors show that Akt is phosphorylated in the presence of GDNF and that Akt activated this way can maintain SSC self-renewal in culture for several months. Furthermore, they show that the capacity to self-renew can be blocked by an inhibitor of PI3K, thus implicating the PI3K-Akt pathway. The next step will be to determine whether the same applies in other tissue-specific stem cells.

Lee, J., Kanatsu-Shinohara, M., Inoue, K., Ogonuki, N., Miki, H., Toyokuni, S., Kimura, T., Nakano, T., Ogura, A. and Shinohara, T. (2007). Akt mediates self-renewal division of mouse spermatogonial stem cells. *Development* **134**, 1853-1859.