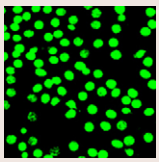
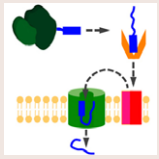
In this issue

By Jane Bradbury



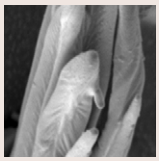
Eyeing up HCEC proliferation

Human corneal endothelial cells (HCECs) form a monolayer of hexagonal cells at the back of the cornea and have a pivotal role in regulating corneal stromal transparency. They are notorious for their limited regenerative capacity in vivo – a characteristic that is caused by contact-induced mitotic arrest. On page 3636, Scheffer Tseng and colleagues report that activating p120-catenin trafficking to the nucleus unlocks this block. They show that the conventional approach taken to achieve HCEC expansion, namely disrupting contact inhibition by treatment with EDTA and basic fibroblast growth factor, activates canonical Wnt signalling and induces endothelial–mesenchymal transition (EMT), especially when transforming growth factor β1 (TGF-β1) is present. By contrast, treatment of HCECs with p120-catenin siRNA promotes HCEC proliferation without inducing EMT. This RNAi activates p120-catenin trafficking to the nucleus, which relieves the repressor activity of the transcription factor Kaiso, activates RhoA–ROCK signalling, and inhibits Hippo signalling without activating canonical Wnt signalling. As a result, the cells proliferate without losing their hexagonal shape or their adherens junctions. This new strategy for unlocking the mitotic block of contact-inhibited HCECs could lead to therapies for corneal blinding diseases that are caused by endothelial dysfunction.



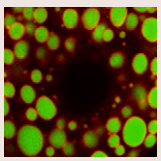
TRC40 routes secretory proteins to the ER

Following synthesis in the cytosol, most eukaryotic proteins must cross one or more membranes to reach their site of function. Proteins that are destined for the secretory pathway are normally targeted to the endoplasmic reticulum (ER) and translocated co-translationally across its membrane. However, some short secretory proteins [such as preprocecropin A (ppcecA), a moth anti-microbial peptide precursor] are post-translationally translocated across the ER membrane in insects and amphibians. Here, Stephen High and co-workers (p. 3612) identify two human secretory proteins – apelin and statherin – as bona fide substrates for post-translational translocation across the ER membrane. They show that ppcecA, apelin and statherin bind to the ATPase TRC40 (also known as ASNA1), which is involved in the post-translational delivery of tail-anchored proteins to the ER membrane, and that this association facilitates their delivery to the ER membrane. ppcecA can also be delivered to the ER by a TRC40-independent pathway. However, on arrival at the ER membrane, all three proteins are transported across the membrane by the Sec61 translocon, irrespective of the delivery route they employed. Thus, the authors speculate, post-translational translocation of secretory proteins in higher eukaryotes might be more prevalent than previously thought.



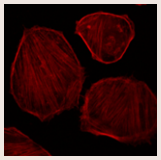
Abp1 sets bristles straight

Changes in cortical actin structures underlie many of the cell shape changes that occur during development, but the mechanisms that are responsible for the fine control of actin dynamics at the cell cortex are still largely unknown. By combining genetic, cell biological and biochemical analyses, Ulrich Thomas, Michael Kessels and colleagues (p. 3578) now show that the lipid- and F-actin-binding protein Abp1 is crucial for actin-driven bristle development in *Drosophila*. The authors report that expression of constitutively membrane-anchored Abp1 leads to a severe split-bristle phenotype. This phenotype is dependent on Scar [also known as Wiskott-Aldrich syndrome protein (WASP) family member, WAVE] – an activator of Arp2/3-mediated actin nucleation – and on the Scar-interacting SH3 domain of Abp1, but not on the actin nucleator WASP. Knockout of *abp1*, they report, leads to defects in both microchaete and macrochaete bristle integrity. Moreover, Arp2- and Scar-deficient flies have similar bristle phenotypes. Finally, the authors show that Abp1 coordinates Scar- and Arp2/3-mediated actin nucleation with phosphoinositide signals that are initiated at the plasma membrane without affecting Scar stability. Taken together, these results add a new layer of complexity to the control of cortical actin nucleation during sensory organ formation in flies.



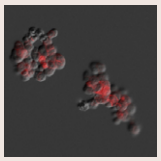
Perilipins: moving fat

Proper lipid storage is vital for maintaining energy homeostasis in eukaryotes. Consequently, understanding the molecular mechanisms of lipid storage regulation is crucial for preventing metabolic disorders such as obesity. Homeostasis of lipid droplets, the main cellular fat storage sites, is regulated by perilipins, which are lipid droplet surface proteins that influence the association of lipases with lipid droplets. Mammalian cells have five perilipin proteins, and the exact function of individual perilipins in vivo has remained elusive. Now, however, Xun Huang and colleagues (p. 3568) report that the two *Drosophila* perilipins, Lsd-1 and Lsd-2 (also known as PLIN1 and PLIN2, respectively), have both opposite and redundant roles in lipid mobilisation. The authors show that, in wild-type larvae, Lsd-1 mainly facilitates fat mobilisation by regulating the lipid droplet surface localisation of dHSL, the *Drosophila* homologue of mammalian hormone-sensitive lipase. dHSL is recruited to the surface of lipid droplets under starvation conditions, and Lsd-1 is necessary for this recruitment. By contrast, analysis of mutant flies lacking both perilipins suggests that Lsd-1 and Lsd-2 have redundant functions in protecting lipid droplets from lipolysis. Taken together, these results provide new information on the in vivo roles of perilipins in the regulation of lipid storage.



Grb2 fills semaphorin (Rho)GAP

The cellular effects of semaphorins – evolutionarily conserved proteins that regulate neuronal development and processes such as tumour metastasis outside the nervous system – are mainly mediated by plexins. Interactions with the tyrosine kinase receptors ErbB-2 and Met modulate signalling through the semaphorin 4D (Sema4D) receptor plexin-B1. Specifically, in cells expressing plexin-B1 and ErbB-2, Sema4D binding activates the small GTPase RhoA and stimulates cellular migration. By contrast, in cells expressing plexin-B1 and Met, Sema4D stimulation results in an association between plexin-B1 and the Rho GTPase activating protein p190 RhoGAP, which inactivates RhoA and inhibits cellular migration. On page 3557, Jakub Swiercz and co-workers now identify growth factor receptor bound-2 (Grb2) as the missing link between plexin-B1 and p190 RhoGAP. The authors show that, in human embryonic kidney and breast cancer cells, activation of plexin-B1 by Sema4D and its subsequent phosphorylation by Met creates a docking site for the Grb2 SH2 domain, thereby recruiting Grb2 to the plexin-B1 receptor complex. This, in turn, allows one of the Grb2 SH3 domains to interact with and activate p190 RhoGAP. Together, these data link the Met-mediated phosphorylation of plexin-B1 with its ability to deactivate RhoA and inhibit cellular migration.



N-cadherin and cell migration

Although cancer cells derived from epithelial tissues usually lose epithelial cell–cell junctions, they are not devoid of cell–cell adhesion proteins. Indeed, a switch from epithelial (E)- to neural (N)-cadherin expression often takes place in aggressive tumours. Wenting Shih and Soichiro Yamada (p. 3661) now report that cohesive cell clusters held together by N-cadherin tend to migrate persistently, rather than by 'random walk', which is often observed in single, isolated cells. MDCK cells treated with hepatocyte growth factor (HGF), the authors show, undergo a complete epithelial-to-mesenchymal transition and E- to N-cadherin switch, and migrate collectively in a three-dimensional matrix. Notably, N-cadherin knockdown prevents the formation of cell–cell junctions between HGF-treated MDCK cells and prevents their migration. Expression of the N-cadherin cytoplasmic or extracellular domain partly rescues this knockdown phenotype. The authors also show that a dynamic N-cadherin–actin linkage is needed for intercellular movement within cell clusters during collective cell migration. These insights into how N-cadherin could promote cancer cell invasion indicate that N-cadherin-targeted therapy might not prevent the invasion of single cancer cells, but could minimise collective cell migration and potentially delay cancer cell dissemination.