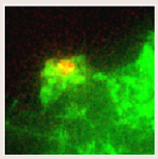
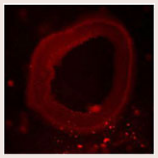
In this issue



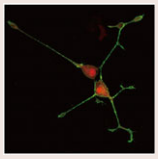
Dimension counts when migrating

Cell migration involves the coordinated action of numerous proteins in response to a variety of soluble and physical guidance queues. Changes in extracellular matrix (ECM) topography can affect cell migration. Cancer cells, for example, are able to migrate more efficiently along fibril-like ECM structures. Andrew Doyle, Ken Yamada and colleagues have previously shown that this effect can be mimicked by migration on one-dimensional fibrillar substrates in vitro. On page 2244, they now address the question of how the fibrillar topography enhances migration efficiency. They find that the protrusion–retraction cycle frequency is higher on one- compared with two-dimensional substrates, which enhances cell protrusion and migration rates. Furthermore, the microenvironment affects the stability of cell adhesions: cells on one-dimensional fibrils exhibit primarily mature adhesions and virtually no nascent adhesions. The analysis of a number of adhesion proteins confirms that the adhesions at the leading edge of a cell on one-dimensional substrates are more stable, and paxillin, vinculin and actin are more strongly associated with these adhesions. Importantly, myosin IIA is crucial for stabilising adhesions during one-dimensional migration, and loss of the contractile force inhibits the increase in migration rate on fibrillar substrates.



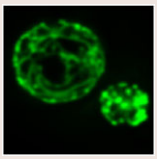
S(1P)topping angiogenesis

Angiogenesis is a tightly controlled process with important roles in various pathological and physiological conditions. Following myocardial infarction, for example, hypoxia-induced vascular growth factor (VEGF) expression stimulates angiogenesis, which contributes to the reperfusion of damaged tissue. Sphingosine-1-phosphate (S1P) levels are also elevated at the site of infarction, but its role in angiogenesis has remained unclear. Here, Graeme Nixon and co-workers (p. 2267) show that S1P inhibits angiogenesis and they delineate the molecular pathway underlying this process. To do so, they developed an in vitro angiogenesis model that involves the co-culture of human coronary artery endothelial and smooth muscle cells (ECs and SMCs, respectively) and human fibroblasts. Using this system, they show that S1P inhibits tubule formation, but only when SMCs are present. This effect is mediated by the S1P-induced activation of the RhoA–Rho kinase pathway in SMCs and the subsequent release of tissue inhibitor of metalloproteinase-2 (TIMP-2) from these cells. TIMP-2 release, in turn, prevents the proper formation of endothelial–endothelial cell junctions. Together, these results not only demonstrate a role for SMCs in the regulation of angiogenesis, but also highlight that the angiostatic effects of S1P are highly dependent on the cellular environment.



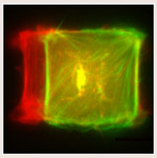
Rab35, Arf6 and the missing link

The Rab and Arf small GTPases coordinate numerous membrane trafficking routes. However, little is known about the functional crosstalk between Rab- and Arf-mediated signals. By examining the role of Rab35 and Arf6 in neurite outgrowth, Hotaka Kobayashi and Mitsunori Fukuda (p. 2235) now uncover a signalling cascade that involves the coordinated activity of both small GTPases. They show that Rab35 as well as the Rab35-binding protein centaurin-β2 (also known as ACAP2) are required for neurite outgrowth. Both of these proteins colocalise with Arf6 on pericentrosomal endosomes in PC12 cells, and Rab35 is required for the recruitment of centaurin-β2 to this location. Furthermore, knockdown and rescue experiments reveal that this sequential recruitment is required for neurite outgrowth in response to nerve growth factor (NGF) stimulation. Centaurin-β2 is a known Arf6 GTPase-activating protein (GAP), which led the authors to probe the role of Arf6 in NGF-induced neurite outgrowth. They report that knockdown of Arf6 reduces neurite length, whereas the expression of a constitutively active Arf6 mutant inhibits NGF-induced neurite outgrowth. Thus, Rab35-mediated recruitment of centaurin-β2 to Arf6-positive endosomes in response to NGF stimulation is essential for inactivating Arf6 to allow proper neurite outgrowth to take place.



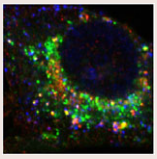
Cofilin moves on from actin

The small actin-binding protein cofilin is a member of the ADF/cofilin protein family and has important roles in regulating actin dynamics. Recent studies have also implicated cofilin in the induction of apoptosis. On page 2288, Campbell Gourlay and colleagues now identify additional functions for the actin modulator in the regulation of mitochondrial function. To examine the roles of cofilin, they make use of a library of *S. cerevisiae* strains expressing mutant forms of cofilin 1. These strains reveal a role for cofilin in the regulation of mitochondrial functions, including oxidative respiration and the production of reactive oxygen species (ROS), and in controlling organelle morphology and biogenesis. Specifically, mutations in cofilin that stabilise F-actin result in the hyperactivation of Ras and an associated increase in ROS production. Cofilin mutations that do not alter actin dynamics result in the upregulation of genes encoding ATP-binding cassette (ABC) transporters, which subsequently confer multi-drug resistance. The authors conclude that cofilin has a crucial role in regulating diverse cellular processes by affecting mitochondrial function. Furthermore, they propose that cofilin acts as a biosensor that allows cells to respond to specific external stimuli by connecting environmental changes to both the cytoskeleton and mitochondria.



Micropatterns go dynamic

Micropatterned substrates can be used to study the processes involved in cell adhesion and spreading. In addition, this approach has provided insight into the role of the spatial arrangement of cell–matrix adhesions with regards to numerous cellular functions, including migration, division and differentiation. However, one of the drawbacks of fixed micropatterned substrates is that they do not allow the study of the cellular changes in response to the remodelling of the extracellular environment. To overcome this problem, Manuel Théry and colleagues (p. 2134) have developed a new laser-based technique that makes it possible to study cytoskeletal modifications in real time in response to changes in the micropattern. Using a tightly focused pulsed laser, they ablate the polyethylene glycol coating near a cell that has adhered to a specific micropattern. The subsequent adsorption of adhesive proteins to the ablated spots creates additional adhesion sites for the cells. To test this system, the researchers investigate the distances between individual adhesion sites that are required for cell extension or contraction and show that this technique can be used to dynamically remodel the actin cytoskeleton. They conclude that this approach offers a versatile way to study how small-scale changes in the micro-environment affect cellular responses.



A new (V)ANGL-e on migration and polarity

In migrating cells, the establishment of planar cell polarity (PCP) must be synchronised with the remodelling of the extracellular matrix (ECM). Indeed, previous studies have shown that PCP is linked with dynamic ECM modifications. But do proteins that are involved in establishing PCP in migrating cells have an active in role in ECM degradation and remodelling? On page 2141, Jason Jessen and colleagues now provide an answer by highlighting a role for the PCP protein Vang-like 2 (VANGL2) in the trafficking of membrane type-1 matrix metalloproteinase (MMP14 or MT1-MMP). Biotinylation and antibody-uptake assays reveal that siRNA-mediated knockdown of VANGL2 impairs MMP14 endocytosis and increases the levels of the protease on the cell surface. Furthermore, focal adhesion kinase (FAK) acts downstream of VANGL2 in the regulation of MMP14 endocytosis. Using *trilobite/vangl2* zebrafish mutants, the researchers confirm that Vangl2 controls Mmp14 activity at the cell surface by regulating endocytosis of the enzyme. Loss of Vangl2 leads to increased ECM degradation and a strong convergence and extension phenotype during gastrulation. The authors propose a model whereby asymmetrical Vangl2 distribution in polarised cells promotes Mmp14 activity on specific cell surfaces to allow localised ECM degradation and targeted migration.