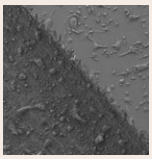
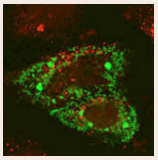
In this issue



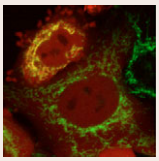
Topography tunes osteoclast activity

The behaviour of many cell types is influenced by the characteristics of the underlying adhesive substrate. For example, deposition and resorption of bone by osteoblasts and osteoclasts, respectively, are influenced by the roughness of the bone to which the cells adhere. Using calcite crystals of varying roughness to simulate the natural diversity of bone surfaces, Benjamin Geiger and colleagues (p. 1503) now examine more closely how substrate nano-topography influences osteoclast activity. Osteoclasts resorb bone by forming a 'ring' of actin-rich podosomes known as a sealing zone: here, the authors show that osteoclasts form large, long-lasting sealing zones when cultured on rough calcite but form only small, short-lived sealing zones on smooth calcite. Furthermore, the amount of actin at sealing zones is fourfold higher in cells adhering to rough surfaces compared with those adhering to smooth surfaces. Accordingly, the rate of resorption seems to be greater on rough surfaces. Surprisingly, however, there is no difference in the levels of vitronectin bound to the two surfaces, suggesting that differences in sealing-zone organisation occur independently of the local concentration of adhesive proteins and are instead influenced mainly by surface topography. These findings provide new insight into the mechanisms of bone remodelling.



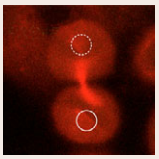
Revisiting roles of Rab7b in transport

Rab7b was recently identified as a small GTPase that shares ~50% identity with Rab7. Previous work suggested that, similar to Rab7, Rab7b regulates transport from early endosomes to late endosomes and/or lysosomes. However, Cecilia Bucci and colleagues (p. 1480) now report that Rab7b is not directly involved in endocytic transport and instead has a distinct role in mediating transport from endosomes to the Golgi and/or trans-Golgi network (TGN). They first show that Rab7b localises to the Golgi and TGN, as well as to late endosomes and lysosomes, in many cell types. Second, unlike Rab7, Rab7b is not involved in the degradation of EGF or EGFR. Third, Rab7b is involved in the transport of lysosomal enzymes: inhibiting Rab7b expression or function causes a block in the transport of the lysosomal enzyme hexosaminidase. Fourth, the same treatment also impairs cathepsin-D maturation, suggesting that normal transport of this protease from the TGN to lysosomes via endosomes is disrupted in the absence of Rab7b. Fifth, Rab7b is required for transport of the TGN protein TGN46 as well as for the proper transport and subcellular localisation of the late endosomal marker CI-MPR. Finally, the authors show that Rab7b is required for retrograde transport of the cholera toxin B subunit from endosomes to the Golgi. Together, these data clarify the unique roles of Rab7b in pathways of intracellular transport.



CK2: uncoupling apoptotic events

Death ligands such as TRAIL and TNFα trigger apoptosis through the mitochondrial (type II) pathway, involving caspase-8-mediated cleavage of the proapoptotic substrate Bid, which induces mitochondrial-outer-membrane permeabilisation (MOMP). On page 1401, Markus Rehm and colleagues now investigate the observation that Bid cleavage is temporally separated from caspase-8 activation, hinting that regulatory factors might control this step in the pathway. Previous population-based studies suggested that the protein kinase CK2 might play a regulatory role in the mitochondrial apoptotic pathway. Here, the authors use FRET and time-lapse imaging to analyse caspase-8-mediated substrate cleavage at the single-cell level, and show that inhibition of CK2 activity eliminates the lag time between TRAIL-induced caspase-8 activation and Bid cleavage, probably by modulating the phosphorylation status of CK2 substrates. The authors conclude that CK2 activity provides 'transient tolerance' to caspase-8 activity by delaying Bid cleavage. These data uncover an additional regulatory step in the mitochondrial apoptotic pathway and caution that the extent of Bid cleavage cannot be determined experimentally on the basis of caspase-8 activity.



Ruling out BRCA2 in cytokinesis

Heterozygous germline mutations in *BRCA2* are associated with an increased risk of developing breast and ovarian cancers. BRCA2 is thought to be important for genome stability owing to its involvement in DNA-repair pathways; in addition, previous work has suggested that BRCA2 might regulate cytokinesis, the final step of cell division. Mark Petronczki and colleagues now provide data that disprove this latter hypothesis (p. 1395). Using time-lapse imaging of HeLa cells, the authors show that depletion of BRCA2 abrogates its function in DNA repair but has no effect on cytokinesis. In addition, a diffusion-based assay that precisely discerns the timing of abscission and cell separation shows that BRCA2 does not have a role in these final stages of cytokinesis. Furthermore, DLD1 colon cancer cells in which both *BRCA2* alleles are disrupted successfully complete cytokinesis. Finally, the authors show that, in contrast to results from a previous study, BRCA2 does not localise to the spindle midzone or midbody, two structures of the mitotic spindle that play important roles during cytokinesis. Together, these data indicate that BRCA2 does not regulate cytokinesis in human cells, which is a finding of crucial importance for understanding cancers with which *BRCA2* mutations are associated.

Assessing centriolar ancestry

Centrioles are highly conserved eukaryotic organelles that have evolved multiple cellular functions in higher organisms. Two reports in this issue now investigate the evolution of centrioles through bioinformatic and experimental approaches. Keith Gull and colleagues (p. 1407) evaluate the distribution of 53 proteins from 45 eukaryotic species to define which centriolar proteins were present in the common eukaryotic ancestor. Among many interesting conclusions, their analyses reveal that ancestral centriolar proteins include a set of 14 core components. In addition, analysis of proteins associated with ciliopathies (which present with the eye disease retinitis pigmentosa) also sheds light on eye evolution. Mónica Bettencourt-Dias and colleagues (p. 1414) use comparative genomics to investigate the evolution of centriole-assembly mechanisms. They search 26 eukaryotic species for orthologues of six human proteins known to be involved in centriole assembly, and experimentally test their predictions. Together, these two reports indicate a stepwise evolution of centriole structure and function: the core assembly machinery that enables centrioles to nucleate cilia and flagella is ancestral, whereas centrosomes evolved more recently (as centrosomal components are found mainly in Holozoa). Overall, these analyses provide insight into how the evolution of centriolar components has enabled adaptation of this structure to new cellular functions.

Development in press

p63 function: a hairy tale

The transcription factor p63 is required for the development of the stratified skin epithelium and of hair follicles. However, although its role in early skin development is well understood, little is known about how p63 directs hair-follicle morphogenesis. In a study published in *Development*, Satrajit Sinha and colleagues now report that ΔNp63α, the major p63 isoform expressed in skin, suppresses hair-follicle differentiation in mice. ΔNp63α, they report, is expressed in the developing hair placode but its expression is restricted to the outer root sheath (ORS; matrix cells and stem cells of the hair-follicle bulge in mature hair). They show that targeted ΔNp63α overexpression in the ORS leads to dramatic defects in hair-follicle development and hair cycling, and causes follicular keratinocytes to adopt an interfollicular cell fate. Global profiling and other experiments suggest that the loss of crucial signalling molecules, including Wnt and β-catenin, causes the hair-follicle defects. Together, these results reveal the in vivo function of a specific p63 isoform and provide new insights into hair development.

Romano, R.-A., Smalley, K., Liu, S. and Sinha, S. (2010). Abnormal hair follicle development and altered cell fate of follicular keratinocytes in transgenic mice expressing ΔNp63α. *Development* **137**, 1431-1439.