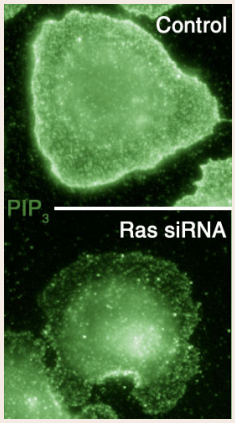
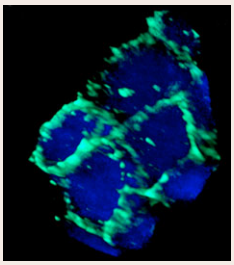
In this issue

by Jane Bradbury



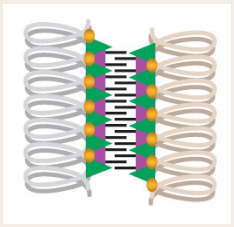
Moving performance by Rac-Ras double act

Cell migration involves extension of actin-rich protrusions (lamellipodia) at the cell's leading edge, which depends on the signal transducer phosphoinositide 3-kinase (PI3K). Ras and Rac GTPases can both activate PI3K but what are their relative contributions during migration? On p. 3138, Jonathan Backer and co-workers reveal distinct roles for these two proteins in PI3K-dependent extension of lamellipodia in rat adenocarcinoma cells stimulated with epidermal growth factor (EGF). They show that the activation kinetics of Ras but not Rac match the production of phosphatidylinositol (3,4,5)-trisphosphate [PtdIns(3,4,5)P_3], a measure of PI3K activation, at the leading edge. Knocking down K-Ras by RNAi, they report, abolishes PtdIns(3,4,5)P_3 production at the leading edge and inhibits EGF-stimulated protrusion. By contrast, knocking down Rac1 has no effect on PtdIns(3,4,5)P_3 levels or EGF-stimulated protrusion but nevertheless inhibits cell migration. It does this, report Backer and colleagues, by inhibiting the formation of focal complexes, which anchor cells to the substrate and thus provide traction. The authors propose, therefore, that Ras and Rac play distinct but coordinated roles during the movement of these cells.



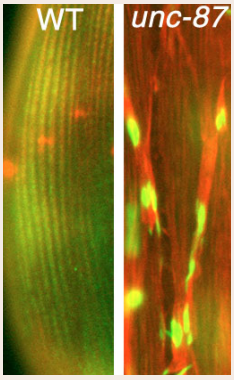
Ninein motions for microtubule reorganisation

During epithelial cell differentiation, a radial microtubule array anchored at the centrosome reorganises into an apico-basal array anchored at apical non-centrosomal sites. This major reorganisation involves the release/relocation of microtubule-anchoring proteins such as the centrosomal protein ninein, but this process has not been studied in detail. Now, on p. 3064, Mette Mogensen and co-authors report that ninein is released from the centrosome and transported along microtubules to apical non-centrosomal anchoring sites during epithelial cell differentiation. They show that it is present at the centrosome and in cytoplasmic speckles in cultured epithelial cells and use fluorescence recovery after photobleaching (FRAP) to reveal dynamic exchange between these ninein pools. They use immunolocalisation and live-cell imaging in situ (in the inner ear) and in culture, respectively, to demonstrate that ninein speckles are released from the centrosome and relocate to apical non-centrosomal anchoring sites in a microtubule-dependent manner during epithelial differentiation. Finally, the authors provide evidence that the apical non-centrosomal microtubule-anchoring sites are associated with adherens junctions in polarised epithelial cells.



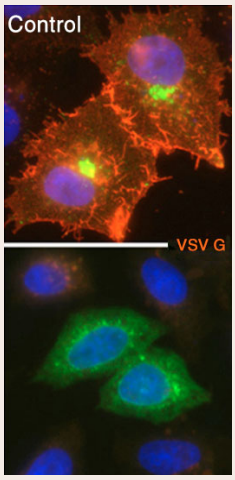
Meiotic cohesion: a very ORDinary mechanism

Cohesin complexes hold sister chromatids together during meiosis and mitosis but relatively little is known about the meiotic form of cohesin. Radhika Khetani and Sharon Bickel remedy this on p. 3123 by describing the localisation and dynamics of the cohesin subunits SMC1 and SMC3 during *Drosophila* oogenesis. They show that the SMCs colocalise with Orientation Disruptor (ORD), a protein needed for meiotic cohesion, at centromeres and along the arms of meiotic chromosomes during pachytene, where they form part of the chromosome cores (structures needed for homologous recombination at meiosis). In *ord* mutants, the SMCs do not accumulate at centromeres in oocytes but localise normally along chromosome cores during early meiosis, although the chromosome cores subsequently disassemble. The authors also show that chromosome core assembly but not recruitment of SMCs to the centromeres requires C(2)M, a meiosis-specific protein. Their data thus indicate that cohesin loading is regulated differently at centromeres and chromosome arms during meiosis.



UNC-87 stabilises actin with a CLIK

Actin filaments are intrinsically dynamic but their stabilisation is essential for actomyosin-based contractility and for maintaining stable cell structures. Tropomyosin stabilises actin filaments by preventing binding of the actin-depolymerising factor cofilin. But, report Shoichiro Ono and colleagues, the nematode protein UNC-87 also antagonises the effects of cofilin (see p. 3022). UNC-87 contains seven calponin-like (CLIK), actin-binding repeats. The authors show that UNC-87 competes with UNC-60B (a muscle-specific form of nematode cofilin) for binding to actin filaments in vitro and inhibits cofilin-dependent actin severing and depolymerisation. In vivo, actin filament stability in the *C. elegans* body wall muscle is reduced in *unc-87* mutants; this disorganised actin phenotype is suppressed in *unc-87 unc-60B* double mutants. Other results indicate that UNC-87 has a more potent antagonistic effect on cofilin activity than tropomyosin and that the functions of the two actin-stabilising proteins are not identical in vivo. The authors propose, therefore, that tropomyosin and UNC-87 have distinct cellular roles in regulation of actin dynamics.



GAPs in Golgi formation

Rab GTPases control transport between the ER and the Golgi complex and, consequently, are important for maintenance of the Golgi. GTPase-activating proteins (GAPs) inactivate GTP-bound Rab proteins; so to discover which human Rab proteins are needed to maintain an active Golgi complex, Francis Barr and colleagues have screened a host of human Rab GAPs for the ability to disrupt the Golgi and ER-to-Golgi protein transport in human cells (see p. 2997). They find that only two GAPS (RN-tre and TBC1D20, GAPS for Rab43 and Rab1, respectively) disrupt both these processes. TBC1D20, the authors show, is localised to the ER by a transmembrane anchor and its overexpression blocks ER-to-Golgi transport and causes loss of the Golgi. Knocking down Rab1 by RNAi produces a similar phenotype, they report, whereas expression of the TBC1D20-binding partner reticulon antagonises the effects of TBC1D20 overexpression. The authors therefore conclude that Rab1 and Rab43 are required for the biogenesis and maintenance of human Golgi complexes.

Development in press

Disease role for cohesin

The cohesin complex ensures accurate sister chromatid segregation during cell division but it also seems to play an important role in development. Indeed, mutations in several cohesin components are associated with the human developmental disorder Cornelia de Lange syndrome (CdLS). Until now, there has been no animal model for this syndrome but, in a paper published in *Development*, Zhang and co-workers report that mice lacking the cohesin regulatory protein PDS5B are born with developmental abnormalities reminiscent of CdLS. The *Pds5B*-deficient mice, like people with CdLS, exhibit abnormal skeletal patterning, heart defects and cleft palates. Unexpectedly, however, the researchers did not find any chromosome cohesion defects in *Pds5B*$^{-/-}$ cells. Furthermore, they detected high levels of PDS5B in post-mitotic neurons of wild-type mice, identified a DNA-binding domain in the protein and showed that it localizes to the nucleolus. PDS5B and the cohesin complex may therefore control organogenesis by regulating developmental gene expression rather than chromosome dynamics.

Zhang, B., Jain, S., Song, H., Fu, M., Heuckeroth, R. O., Erlich, J. M., Jay, P. Y. and Milbrandt, J. (2007). Mice lacking sister chromatid cohesion protein PDS5B exhibit developmental abnormalities reminiscent of Cornelia de Lange syndrome. *Development* **134**, 3191-3201.