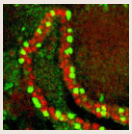
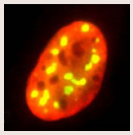
In this issue



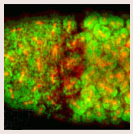
Picking apart the Crumbs complex

The cells of epithelial tissues are polarised into apical and basal membrane regions, which are separated by a region known as the zonula adherens (ZA). Recent studies have shown that the dysfunction of a key regulator of epithelial apicobasal polarity – the Crumbs complex – can lead to various disease states of epithelial tissues, including retinal degeneration and tumorigenesis. Other work has shown that the Crumbs complex has important roles in development. On page 2604, Helen Skaer and colleagues take a closer look at the role of Crumbs (Crb, a key member of the Crumbs complex) during the development of different epithelial tissues in *Drosophila*. Their study shows that Crb is not required during early stages of development in epithelial tissues, but is essential during later stages when the cells begin to reorganise and remodel their junctional contacts. During this later morphogenetic phase, Crb maintains the polarised distribution of polarity proteins (such as Bazooka and Discs large) and thereby maintains the proper formation of ZAs. These ideas are expanded in a Commentary by Natalia Bulgakova and Elisabeth Knust (p. 2587), in which the mechanisms that regulate the Crumbs complex are reviewed. Bulgakova and Knust also discuss how dysfunction of the Crumbs complex contributes to pathophysiology. These articles highlight the importance of the Crumbs complex in maintaining normal apicobasal polarity of epithelial tissues.



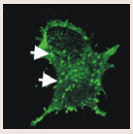
PML-IV puts the brakes on telomerase

Telomerase influences replicative senescence through its capacity to add protective hexameric repeats to the ends of chromosomes, promoting chromosomal stability. Owing to the activity of telomerase in immortalised cells, including some types of stem cells and cancer cells, there is an interest in identifying factors that influence telomerase activity. On page 2613, Jaewhan Song and colleagues now reveal that promyelocytic leukemia (PML) isoform IV (PML-IV) is a negative regulator of telomerase activity. They show that RNAi-mediated inhibition of PML expression suppresses both intrinsic and interferon-α-induced telomerase activity. Furthermore, TERT (the catalytic component of telomerase) is found to localise in the nucleoplasm together with PML in discrete nuclear speckles known as PML nuclear bodies when telomerase activity is induced. Although alternative splicing gives rise to several different isoforms of PML, the authors identify here that the inhibitory effect of PML on telomerase is specifically mediated by isoform IV, probably because of unique sequences in its C-terminal region. Finally, the authors show that long-term stable expression of PML-IV leads to prolonged suppression of telomerase activity and shortened telomeres in the H1299 cell line. Because some of the effects of PML-IV on TERT are shown to be equivalent in several cell types, this might be a conserved means by which telomerase is regulated.



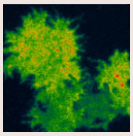
Troponin et al. go nuclear

Troponin I (TnI) and the two tropomyosins Tm1 and Tm2 are part of a complex that has a well-characterised role in regulating muscle sarcomere contraction. Some evidence suggests, however, that these proteins might also have a role in other cell types and processes. Now, Alberto Ferrús and colleagues (p. 2623) provide new evidence that the Tn-Tm complex has important functions in the nucleus during *Drosophila* embryogenesis. The authors first determine that TnI can translocate between the cytoplasm and the nucleus in the S2 cell line, and propose that its subcellular localisation might depend on the physiological state of the cells. They then show that embryos carrying mutations in TnI, Tm1 or Tm2 display nuclear defects at the early pre-cellular stage, such as abnormal localisation of actin, altered tubulin structure and fragmented chromosomes. At the onset of cellularisation, the mutant embryos show a disruption of apicobasal polarity, and mislocalisation of the polarity proteins Dlg and Pins. The authors conclude, therefore, that the Tn-Tm complex is required for proper actin function in the *Drosophila* embryo, and thereby supports proper nuclear divisions and the correct localisation of polarity proteins that are essential during development.



Driving invadopodium dynamics

The degradation of the extracellular matrix (ECM) by invasive tumour cells is mediated in part by protease-rich projections known as invadopodia. The formation of these actin-based structures can be enhanced by different stimuli, including Src tyrosine kinase, which activates several other proteins involved in invadopodium dynamics. On page 2727, Peter Lock and colleagues investigate the role of Tks5, a Src substrate known to be crucial for the invasive capacity of several human tumour cell lines. In this study, they confirm that Tks5 and Src synergise to promote invadopodium formation, and reveal that Tks5 directly associates with the adaptor proteins Nck1 and Nck2; this interaction requires Tks5 phosphorylation at Tyr557 and the Src-homology 2 domain of Nck1/2. Mutation of the Tyr557 residue abolishes colocalisation of Tks5 and Nck1/2 in invadopodia, indicating that Src-mediated phosphorylation of Tks5 at this site serves as a recruitment signal for Nck1/2 to invadopodia. Furthermore, they show that Src promotes the formation of a Tks5–Nck1/2–N-WASP ternary complex. In agreement with the known roles of Nck1/2 and N-WASP in regulating actin dynamics in other settings, the authors conclude that Tks5 cooperates with these proteins to stimulate actin assembly in invadopodia. The mechanism by which this promotes ECM degradation awaits investigation, but might involve increased local expression of proteases.



G-protein dynamics in *Dictyostelium*

Heterotrimeric G proteins enable eukaryotic cells to respond to chemoattractants in their environment. Biochemical studies have established that dissociation of membrane-associated Gα and Gβγ subunits leads to the activation or inhibition of downstream effector molecules, but the membrane dynamics of G-protein subunits in intact cells were relatively uncharacterized. On page 2597, Chris Janetopoulos and colleagues now address this issue by investigating G-protein subunit dynamics in the simple eukaryote *Dictyostelium discoideum*. In this study, the authors combine fluorescence resonance energy transfer (FRET) and total internal reflection fluorescence microscopy (TIRFM) to investigate G-protein-subunit dynamics before and after stimulation with the G-protein coupled receptor ligand cAMP. They show that, in response to cAMP, Gα2 and Gβγ subunits dissociate, and the Gβγ subunit diffuses away from the plasma membrane. Furthermore, photobleaching studies show that the subunits cycle between the cytosol and the plasma membrane, suggesting that chemoattractant receptors and their associated G proteins do not form stable complexes in the absence of signalling. Although the movements of G proteins were thought to be mainly restricted to the plasma membrane, the authors propose on the basis of their data that inactive and active subunits in fact shuttle between the membrane and the cytosol in *Dictyostelium*.

Development in press

Fascin-ating fly blood-cell migration

Remodelling of the actin cytoskeleton is required for the dynamic cell-shape changes that underlie cell migration, which is a pivotal developmental process. But what are the key regulators of actin reorganisation during cell migration? In a study published in *Development*, Serge Plaza and colleagues reveal that the migration of a subpopulation of motile blood cells (macrophage-like plasmatocytes) during *Drosophila* embryogenesis involves the actin-bundling protein Fascin. They show that plasmatocytes express high levels of Fascin, and that Fascin is required for their polarisation and migration during development and during an inflammatory response to epithelial wounding. Fascin, they report, localises to and is essential for the assembly of actin-rich microspikes that extend beyond the leading edge of the migrating plasmatocytes. Finally, they show that Fascin activity is regulated post-translationally by phosphorylation in a tissue-specific manner. In humans, increased Fascin expression is correlated with the invasiveness of various tumours. Thus, these unique insights into Fascin function and regulation during normal development might help to explain how dysregulated Fascin expression contributes to cancer progression.

Zanet, J., Stramer, B., Millard, T., Martin, P., Payre, F. and Plaza, S. (2009). Fascin is required for blood cell migration during *Drosophila* embryogenesis. *Development* **136**, 2557-2565.