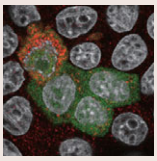
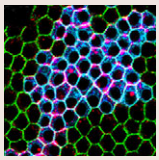
In this issue



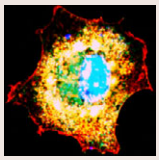
Competition as a tumour suppressor?

In *Drosophila*, normal and transformed cells do not always sit comfortably side-by-side. Instead, they compete for survival in a process referred to as 'cell competition'. The events that occur at the interface of normal and transformed cells could have important implications for carcinogenesis, but so far it has been unclear whether a similar process occurs in mammals. On page 59, Yasuyuki Fujita and colleagues now suggest that cell competition is evolutionarily conserved by showing that loss of the tumour suppressor Scribble induces this process in MDCK cells. The authors find that, in the presence of normal cells, Scribble-knockdown cells undergo apoptosis and are extruded from the monolayer. Cell death does not occur, however, when cells lacking Scribble are cultured alone. Furthermore, caspase-3 is activated independently of cell extrusion, which indicates that cells do not die as a result of anoikis. Studies in *Drosophila* have implicated JNK with a role in mediating competition-induced cell death. By contrast, here, the researchers find that p38 MAPK (MAPK14) is required for the induction of apoptosis in mammalian cells lacking Scribble. These observations not only contribute to the understanding of how the cell environment can influence cell death but, importantly, also highlight that cell competition could act as an alternative tumour suppressor pathway in mammals.



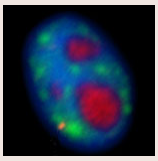
α-Catenin function stays at the junction

Adherens junctions mediate cell–cell adhesion in epithelia and are important for development, tissue homeostasis and cell polarity. α-Catenin provides the link between junctional cadherins and actin through its ability to associate with β-catenin – which can bind to the cytoplasmic tail of cadherins – as well as F-actin and F-actin-binding proteins. Controversy remains, however, about how α-catenin forms this link: one model proposes that it acts as a physical linker that remains associated with the cadherin–β-catenin complex, whereas another model suggests that α-catenin acts through an allosteric mechanism whereby it dissociates from β-catenin to subsequently form a homodimer that can interact with F-actin. In addition, recent evidence has suggested adhesion-independent cytoplasmic roles for α-catenin. Ulrich Tepass and colleagues (p. 233) now generate *Drosophila α-Catenin* (*α-Cat*) mutants to investigate which of the models represents cellular events in vivo. The *α-Cat* mutants exhibit developmental defects that are consistent with a loss of cadherin function, and DE-cadherin and Armadillo (β-catenin) are lost from cell contacts. Interestingly, the *α-Cat* mutant phenotype can be rescued by expressing a DE-cadherin::α-Catenin fusion protein, which suggests that – at least in the tissues tested – α-Catenin acts in association with DE-cadherin and does not have cadherin-independent cytoplasmic functions.



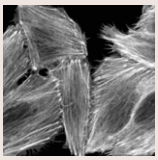
New way to stop N-WASP

Members of the Wiscott–Aldrich syndrome protein (WASP) family bind to and subsequently activate the actin-related protein 2 and 3 (Arp2/3) complex and, together, these proteins are key mediators of actin polymerisation. Neural-WASP (N-WASP) activity is regulated by a number of different mechanisms, including through its interaction with phosphoinositides and small GTPases, tyrosine phosphorylation and an intramolecular interaction between its GTPase-binding (GBD), and verprolin, cofilin and acidic (VPA) domains. Kwang Chul Chung and co-workers (p. 67) now report an additional N-WASP regulatory mechanism that involves the proline-directed serine/threonine kinase DYRK1A (dual-specificity tyrosine-phosphorylation-regulated kinase 1A). They show that DYRK1A interacts with N-WASP and phosphorylates three threonine residues (Thr196, Thr202 and Thr259) in the DYRK1A GBD. This phosphorylation strengthens the interaction between the GBD and the VCA domain and locks N-WASP in an autoinhibited conformation that inhibits Arp2/3-mediated actin polymerisation. The overexpression of phosphomimetic N-WASP mutants inhibits the formation of filopodia and dendritic spines in COS-7 cells and primary hippocampal neurons, respectively. The authors conclude that, through phosphorylating N-WASP, DYRK1A contributes to the regulation of actin-based cellular processes.



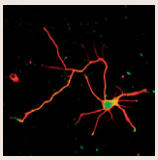
Cajal bodies: no integrity without integrator

The eukaryotic nucleus is compartmentalised into a number of functional domains, including chromosome territories and nuclear bodies. The Cajal body is one of the most prominent nuclear bodies and is thought to be the site for formation of small nuclear and small nucleolar ribonucleoprotein particles (snRNPs and snoRNPs, respectively). Although it is known that Cajal bodies contain a number of proteins, such as coilin, fibrillarin, dyskerin and Nopp140, in addition to snRNPs and snoRNPs, the mechanism underlying their formation remained unclear so far. Here, Hideaka Takata, Kei-ichi Shibahara and colleagues (p. 166) shed light on the biogenesis of these snRNA-related suborganelles by highlighting a role for the integrator complex in establishing Cajal bodies. They show that RNAi-mediated depletion of two integrator subunits (INTS4 and INTS11) results in the relocalisation of coilin to the nucleolus instead of to Cajal bodies. In addition, the Cajal body component survival of motor neuron protein (SMN) and Sm proteins localise to the cytoplasm, where they form prominent cytoplasmic granules. The authors also find that cells lacking INTS4 accumulate premature U2 snRNAs in the nucleus and conclude that the 3′-end processing activity of snRNAs by the integrator complex is crucial for the formation of completely functional Cajal bodies.



Liprin-α and actin remodelling

Temporal and spatial remodelling of the actin cytoskeleton is important for cell morphology and migration. The mammalian homologue of Diaphanous (mDia) – an actin nucleator that forms unbranched actin filaments – is an effector of the small GTPase RhoA, which itself is a key regulator of actin remodelling. But how is mDia activity regulated in cells? To answer this question, Shuh Narumiya and colleagues (p. 108) have been looking for mDia-binding proteins in mouse brain lysates using an N-terminal mDia1 fragment as bait. mDia is autoregulated through an intra-molecular interaction between an N-terminal Dia-inhibitory domain (DID) and a C-terminal Dia autoregulatory domain (DAD). Binding of GTP-bound RhoA to mDia disrupts this intra-molecular interaction and activates mDia. In their pull-down assay, the authors identify Liprin-α (an interacting protein of the leukocyte common antigen-related family of receptor protein tyrosine phosphatases) as an mDia-binding protein. Liprin-α, they report, binds to the active form of mDia through the DID and negatively regulates the localization of mDia to the plasma membrane and the formation of actin stress fibres. Thus, they conclude, Liprin-α is a negative regulator of mDia, and further studies on this function of Liprin-α could shed new light onto the regulation of mDia-mediated actin remodelling in cells. (written by Jane Bradbury)



ADCY5 acts as neuronal signal coordinator

Purinergic receptors are widely expressed in the central nervous system, where they stimulate processes such as inflammation and neurotransmission. Little is known, however, about their involvement in mediating axon elongation during development and following injury. On page 176, Juan José Garrido and co-workers now shed light on the mechanisms that coordinate axon elongation downstream of purinergic receptors. They reported previously, that inhibition of the ionotropic, ATP-operated P2X7 receptor promotes axon growth. Using a combination of pharmacological and molecular biological approaches, they now show that the activation of the metabotropic P2Y13 receptor by ADP also has a negative effect on axonal elongation, whereas the metabotropic P2Y1 receptor has the opposing effect and stimulates axon growth. Whereas P2Y13 (through G_i) and P2X7 (through Ca^{2+}) inhibit adenylate cyclase 5 (ADCY5), P2Y1 (through G_q) activates this enzyme. Changes in ADCY5 activity alter cAMP levels and protein kinase A activity, which subsequently leads to changes in signalling through the PI3K–Akt–GSK3 pathway. Through a carefully orchestrated interplay between the different types of receptors that converges on the same signalling module, neurons are thus able to precisely regulate the extent of axon growth in response to specific external stimuli.