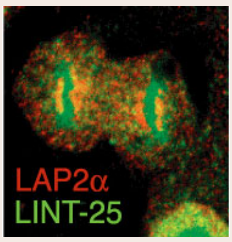
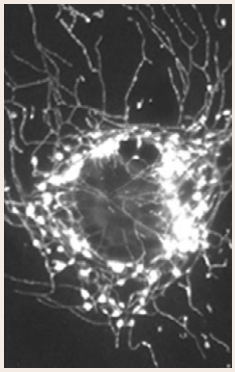
In this issue



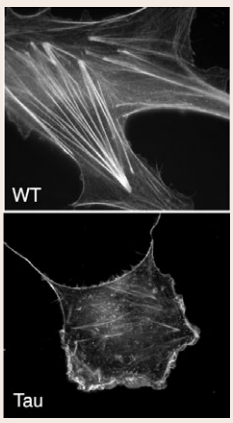
New LAP dog for nuclear lamins

The nuclear protein lamina-associated polypeptide 2α (LAP2α) plays a key role in chromatin organisation, cell cycle regulation and differentiation. These functions are, in part, regulated by its interactions with the A-type lamins that reside in the nuclear compartment and the tumour suppressor pRb. To investigate the mechanisms of LAP2α function in chromatin organisation and cell cycle control, Nana Naetar and co-workers (p. 737) used a yeast two-hybrid approach to identify a novel LAP2α binding partner, LAP2α-interactor-25 (LINT-25). The authors confirmed the direct interaction between LINT-25 and the LAP2α C-terminus with additional in vitro binding assays. LINT-25 protein is upregulated and relocalises to heterochromatin foci when cells exit the cell cycle, and its upregulation is tightly coupled with the downregulation and proteasomal degradation of LAP2α. Furthermore, the authors demonstrate that LINT-25 upregulation is not dependent on LAP2α but that LINT-25 acts upstream of LAP2α to regulate its cell cycle function. The authors propose a model whereby LINT-25 causes loss of LAP2α by affecting its stability, thus contributing to the proper timing of cell cycle exit.



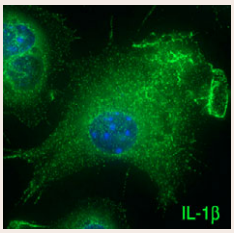
Mitochondrial networking

Mitochondria form discrete organelles or connected networks; yet it remains unclear how this structure affects mitochondrial function. On p. 838 Giovanni Benard and co-authors report that mitochondrial-network organisation and bioenergetics are intricately linked. To investigate the importance of mitochondrial fission on energy production the authors suppressed dynamin-related protein-1 (Drp1), a key mediator of this process, using RNAi. This revealed a dramatic reduction in energy production as a result of alterations in mitochondrial membrane fluidity. They assessed the impact that inhibition of oxidative phosphorylation has on mitochondrial-network organisation and demonstrated that inhibition of respiratory chain complex I using rotenone causes gross structural perturbations to the mitochondrial reticulum. Furthermore, using fibroblasts from patients with mitochondrial disease and human cells treated with modulators of oxidative phosphorylation, the authors were able to conclude that the rate of ATP production probably dictates mitochondrial morphology. They propose that the flux-force relationship of mitochondrial oxidative phosphorylation is the major factor determining mitochondrial shape and network organisation.



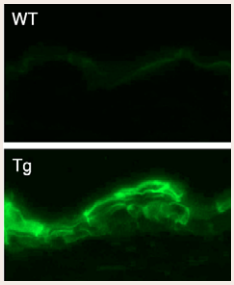
Tau: actin' on a kinase

Tau proteins interact with tubulin to stabilise and promote microtubule assembly and are implicated in multiple neurodegenerative tauopathies, including Alzheimer's disease; however, little is known about other cellular functions of tau. On p. 748, Vandana Sharma and colleagues explore its interaction with Src family kinases (SFKs). They show that tau potentiates activation of SFKs (Src and Fyn) both in vitro and in vivo, which alters actin organisation in response to growth factor stimulation. This effect on actin organisation is mediated, at least in part, by Src and does not require association of tau with microtubules. They conclude that the interaction between Src and tau allows tau to participate in growth-factor-induced actin remodelling and establish a cell biological function for tau beyond its role in microtubule assembly and stabilisation. The authors go on to speculate that mutant or hyperphosphorylated forms of tau that show increased association with and activation of SFKs could impact actin dynamics and cell proliferation in neurodegenerative tauopathies.



IL-defined processing

The pro-inflammatory cytokine interleukin-1β (IL-1β) is implicated in acute and chronic inflammatory diseases. However, despite its biological importance, the mechanisms involved in its processing and trafficking are poorly defined. On p. 772, David Brough and Nancy Rothwell define the cellular mechanisms involved in IL-1β post-translational processing and provide insight into the atypical pathway by which IL-1β is generated. The authors demonstrate that cleavage of the precursor polypeptide Pro-IL-1β by caspase-1 occurs predominantly in the cytosol following activation of the proinflammatory purinergic receptor P2X7 by ATP and suggest a lack of lysosomal involvement. Structural changes to the cell, following caspase-1 activation, promote the cellular release of IL-1β, which itself precedes cell death. The authors propose that IL-1β processing occurs in the cytosol by a mechanism that resembles the programmed cell death process, pyroptosis, which requires caspase-1. Understanding mechanisms of bioactive IL-1β generation may help identify new targets for anti-IL-1β therapies and improve our understanding of inflammatory processes during disease.



Desmosomal cadherin's dark side

The desmosomal proteins that underpin desmosomes have been linked to various aspects of epithelial morphogenesis and the establishment of tissue architecture particularly in stratified epithelia. Now Donna Brennan and colleagues investigate the isoform-specific functions of desmosomal cadherin desmoglein 2 (Dsg2) in epidermal biology (see p. 758). The authors generated transgenic mice expressing Dsg2 under the control of the involucrin promoter, which restricts expression to the differentiating cell layers of the skin. These mice exhibit extensive epidermal hyperplasia associated with increased proliferation of the basal and suprabasal epithelial layers. Increased epidermal proliferation is coupled with increased activation of the PI3K/Akt, MAPK, STAT3 and NFκB signalling pathways, which are often associated with increased growth rate. In addition Dsg2 expression confers resistance to anoikis through NFκB activation. Furthermore the authors show that the Dsg2 transgenic mice develop papilloma-like lesions and are more susceptible to chemical carcinogenesis. This study highlights an unrecognised aspect of Dsg2 function in epidermal biology and supports a role for the protein in epithelial malignant transformation

Development in press

Notch: an angiogenesis off switch

Notch signalling through the ligand Delta-like 4 (Dll4) is essential for normal vascular development, but which aspect of endothelial cell behaviour does this signalling pathway control? In an article that appears in the journal *Development,* Leslie et al. show for the first time that, in zebrafish embryos, Dll4-Notch signalling tells endothelial cells to stop migrating and proliferating (behaviours that form new sprouts on existing vessels) once a vascular circuit has been completed. The researchers report that, although blood vessel formation starts normally in embryos in which Dll4 production has been blocked with a morpholino antisense oligonucleotide, the embryos develop a network of aberrant interconnected branches unless vascular endothelial growth factor (VEGF) signalling is also blocked. Ectopic activation of Notch, by contrast, prevents endothelial sprouts forming. The researchers conclude that Notch signalling acts as an angiogenic 'off' switch in endothelial cells exposed to VEGF. Thus, given the recent demonstration that Dll4 blockade decreases tumour growth in mice by promoting non-productive angiogenesis, targeting Dll4 could provide a new way to treat cancer.

Leslie, J. D., Ariza-McNaughton, L., Bermange, A. L., McAdow, R., Johnson, S. L. and Lewis, J. (2007). Endothelial signalling by the Notch ligand Delta-like 4 restricts angiogenesis. *Development* **134**, 839-844.