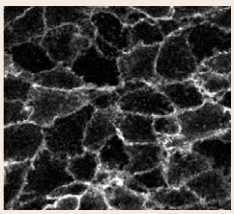
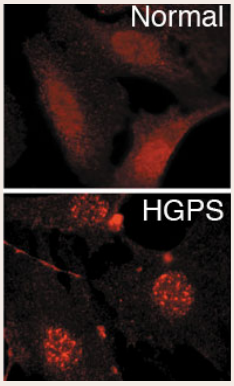
In this issue

by Jane Bradbury



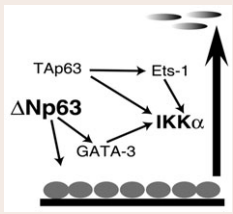
Prion protein mans the barrier

Prion diseases such as Creutzfeld-Jacob disease involve the conversion of prion protein (PrP^{C}) to its pathogenic isoform PrP^{Sc}. PrP^{C} – a glycosylphosphatidylinositol-anchored protein – is highly expressed in brain and several other tissues, but its physiological function is unclear. Now, Sylvie Cazaubon and co-authors report that PrP^{C} localizes to intercellular junctions between brain endothelial cells and regulates the trans-endothelial migration of immune cells (see p. 4632). Brain endothelial cells form the blood-brain barrier, which stops circulating immune cells and pathogens entering the brain. The authors show that PrP^{C} is expressed by vascular endothelium in the brain and is present in lipid raft microdomains at endothelial cell-cell junctions in brain endothelial cells from several species. This localization, they report, probably depends on homophilic interactions between PrP^{C} molecules on adjacent cells. They also reveal that antibodies to PrP^{C} block the migration of monocytes through human brain endothelial cells in vitro. Thus, the authors conclude, a previously unsuspected physiological role for PrP^{C} could be to modulate immune responses in the brain by controlling monocyte entry.



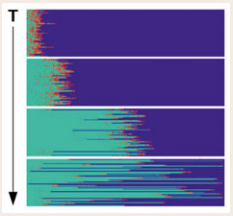
Checkpoints signal premature ageing

Patients with Hutchinson-Gilford progeria syndrome (HGPS) and restrictive dermopathy (RD) age extremely quickly. In both diseases, processing of farnesylated prelamin A into lamin A (a component of the nuclear lamina that supports the nucleus and organizes chromatin) is defective, but why this accelerates aging is unclear. Now, Yue Zou and colleagues report that DNA damage checkpoints are constantly activated in HGPS and RD cells (as they are in normally aged cells) because of DNA damage caused by accumulated prelamin A (see p. 4644). The authors show that the checkpoint kinases ATM (ataxia-telangiectasia-mutated) and ATR (ATM- and Rad3-related) and their downstream effectors are activated in HGPS and RD fibroblasts. Inactivation of ATM and ATR partly overcomes the resultant replication arrest, but treatment with a farnesyltransferase inhibitor (which corrects the aberrant nuclear morphology of these cells) does not reduce DNA damage or checkpoint signalling. Thus, suggest the authors, prelamin A accumulation causes DNA damage and abnormal nuclear morphology by distinct mechanisms, and treatments for HGPS and RD will need to target both phenotypes.



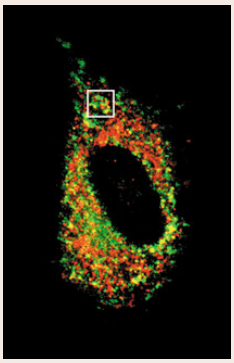
p63 and IKKα: a skin-deep pathway

The epidermis – the skin's outer layer – is a stratified epithelium that provides the body with an essential waterproof and bug-proof covering. Its development requires the activity of the p53-related transcription factor p63 and IκB kinase α (IKKα) – a kinase that regulates the transcription factor NF-κB but also has kinase-independent activities. On p. 4617, Eleonora Candi, Gerry Melino and co-authors report that p63 acts upstream of IKKα in epidermis formation. p63 exists as two major isoforms: TAp63, which contains an N-terminal transactivation domain; and ΔNp63, which lacks this domain. The authors show that TAp63 (but not ΔNp63) directly induces IKKα expression by targeting p53-like responsive elements in the *IKKα* promoter. They also show that p63 drives IKKα expression indirectly by regulating the expression of two other transcription factors that bind to the *IKKα* promoter: Tap63 drives Ets-1 expression and both isoforms drive GATA-3 expression. Finally, the authors show that genetic complementation with TAp63 and ΔNp63 rescues IKKα expression in $p63^{-/-}$ mice This demonstration that p63 acts upstream of IKKα in epithelial development may have clinical implications – for example, in the treatment of severe burns.



MAPless microtubule dynamics

Microtubules – polymers of tubulin – are important components of the cytoskeleton. They constantly cycle between periods of growth and shrinkage; this 'dynamic instability' is critical for many of their cellular roles, but what determines this behaviour? On p. 4781, Holly Goodson and colleagues use computer modelling to show that several cellular phenomena previously thought to require complex regulatory machinery are actually predictable outcomes of interactions between a system of dynamic microtubules and the physical environment. For example, the authors show that the persistent growth of microtubules does not require the activity of microtubule-associated proteins (MAPs) but is an inevitable consequence of a nucleated system of dynamic microtubules polymerizing in a constrained space in which tubulin is limiting. Overall, the authors' findings provide a foundation for a better understanding of microtubule dynamics. In addition, they reveal how, during evolution, complex cellular behaviours might have arisen from simple interactions without the need for the intricate regulatory machinery, which may have evolved later to modulate them.



GRIFter implicated in receptor trafficking

Endosome-to-lysosome trafficking of internalized cell-surface receptors is critical for the control of cell signalling. However, the molecular mechanisms that control endosomal sorting are poorly understood. On p. 4689, Lian Li and colleagues identify GRIF1 – γ-amino-*n*-butyric acid A ($GABA_A$) receptor interacting factor 1 – as a new regulator of this process. A key protein in the control of endosomal trafficking is hepatocyte-growth-factor-regulated tyrosine kinase substrate (Hrs). To understand more about this protein's function, the authors used yeast two-hybrid screening to identify its binding partners. They report that GRIF1 interacts with Hrs and that the two proteins colocalize on early endosomes. Overexpression of GRIF1 and knocking it down by RNAi both inhibit the degradation of internalized epidermal growth factor receptors by blocking their trafficking from endosomes to lysosomes. Interestingly, the authors find that GRIF1 also regulates the movement of early endosomes along microtubules through its interaction with the kinesin motor protein. They suggest, therefore, that GRIF1 modulates endosome transport by acting as an adaptor protein that links Hrs-containing early endosomes to kinesin.

Development in press

A new twist to asymmetry

The establishment of the embryonic axes is a crucial developmental event. Anteroposterior and dorsoventral axis determination is reasonably well understood, but in some organisms the earliest steps of left-right (LR) axis formation remain unclear. Now, in a paper appearing in *Development*, Danilchik and co-workers describe an intrinsic chirality in the cortex of *Xenopus* eggs that might predetermine this animal's LR asymmetry. They report that one-cell *Xenopus* embryos and parthenogenetically activated eggs undergo a twisting motion in which the animal pole rotates counterclockwise past the vegetal cortex after treatment with 2,3-butanedione monoxime (BDM), which disrupts actin-myosin interactions. BDM treatment, they report, induces a shear zone parallel to the egg's equator in which long actin fibres develop in a microtubule-independent manner, and randomizes the LR orientation of visceral organs in affected tadpoles. The researchers suggest that the consistent chirality of the BDM-induced twisting movement reveals a cryptic asymmetry in the egg's cortical actin cytoskeleton that could play an early role in LR axis determination.

Danilchik, M. V., Brown, E. E. and Riegert, K. (2006). Intrinsic chiral properties of the Xenopus egg cortex: an early indicator of left-right asymmetry? *Development* **133**, 4619-4630.