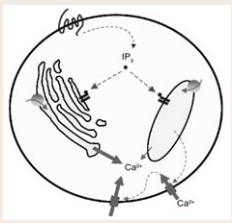
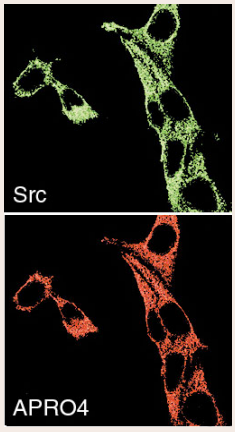
In this issue

by Jane Bradbury



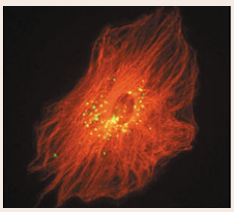
Skin-deep Ca^{2+} signalling from the Golgi

The differentiation, adhesion and motility of keratinocytes – as in many cells – are controlled by intracellular Ca^{2+}. Most non-excitable cells release Ca^{2+} from the endoplasmic reticulum (ER) to mediate Ca^{2+} signalling, but Alain Hovnanian, Theodora Mauro and colleagues now report that keratinocytes are unique in using Ca^{2+} stored in the Golgi (see p. 671). The skin disorder Darier disease is caused by mutations in *ATP2A2*, which encodes the Ca^{2+} ATPase SERCA2 that sequesters Ca^{2+} in the ER. The authors describe how keratinocytes from Darier disease patients respond normally to increases in extracellular Ca^{2+} levels (which provoke intracellular Ca^{2+} release) despite impaired ER Ca^{2+} stores. This normal response results from upregulation of the Golgi Ca^{2+} ATPase hSPCA1. Furthermore, inactivation of the gene encoding hSPCA1 – *ATP2C1*, mutations in which cause the skin disorder Hailey-Hailey disease – diminishes the viability of Darier disease keratinocytes. The authors therefore conclude that the Golgi Ca^{2+} ATPase plays an essential role in Ca^{2+} signalling in the keratinocyte.



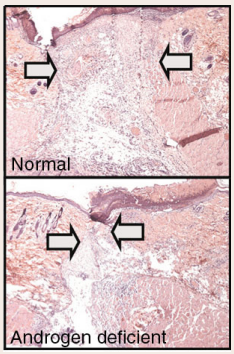
Reining in Src

The nonreceptor tyrosine kinase Src is involved in multiple signal transduction pathways that control proliferation and differentiation. Its activity is tightly controlled by intramolecular interactions that involve its Src-homology (SH) domains. Several proteins upregulate Src activity by disrupting these interactions but few proteins are known to downregulate Src activity. Now, on p. 646, Zohra Rahmani identifies APRO4 as a negative regulator of Src-mediated signalling. Rahmani shows that APRO4 – a member of an 'antiproliferative gene' family – interacts with the Src SH2 and SH3 domains through its C-terminal proline-rich domain and downregulates Src kinase activity in vitro. In addition, the author shows that overexpression of APRO4 in PC12 cells inhibits neurite formation and Ras/MAP kinase signalling; by contrast, antisense-RNA-mediated downregulation of endogenous APRO4 expression induces Src activation and spontaneous neurite formation. Finally, Rahmani observes that, in PC12 cells stimulated to form neurites by treatment with FGF, the kinetics of endogenous Src inactivation correlate with increased co-immunoprecipitation with APRO4. Thus, Rahmani concludes, APRO4 plays an important role in the negative regulation of Src signalling by controlling the basal threshold for Src activation.



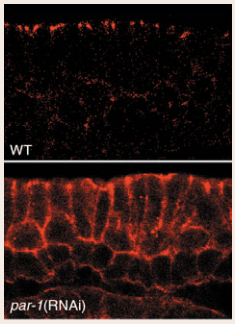
A peroxisomal traffic jam

Peroxisomes are essential organelles that rid cells of toxic substances such as hydrogen peroxide. Peroxisomal disorders are characterized by widespread organ pathology, including neurodegeneration. The genetic basis of many of these is known, but how the various mutations cause disease remains unclear. Denis Crane and co-workers have been investigating Zellweger syndrome (ZS) and D-bifunctional protein (D-BP) deficiency, two peroxisomal disorders characterized by formation of small numbers of over-sized peroxisomes. They report that these characteristics, and also altered cytoplasmic peroxisomal distribution, reflect defects at different stages of microtubule-mediated peroxisome division and trafficking (see p. 636). The authors have examined peroxisomes and microtubules in fibroblasts from patients with ZS or D-BP deficiency and studied the effects of overexpression of PEX11β, a peroxisomal membrane protein implicated in peroxisome proliferation and division. Overexpression of PEX11β restores the abundance, cytoplasmic distribution and alignment of the peroxisomes along microtubules. This suggests that peroxisome proliferation and division, and binding of peroxisomes to microtubules are mechanistically linked processes. The researchers speculate that oxidative damage caused by regional loss of peroxisomes may be responsible for the neurodegeneration seen in ZS and D-BP deficiency.



Wound healing: lost in the male

With age, cuts and grazes take longer to heal, particularly in men. Differences in circulating levels of sex steroids might underlie age- and gender-related variations in wound healing: oestrogens accelerate wound repair by dampening local inflammation; androgens have the opposite effect. Gillian Ashcroft and co-workers now provide new insights into how androgens modulate the inflammatory response during acute wound healing (see p. 722). Castration promotes wound healing in male rats. The authors show that treatment of unneutered male rats with an inhibitor of 5α-reductase, which converts testosterone to 5α-dihydrotestosterone (DHT), mimics this effect, suggesting that DHT is a major inhibitor of wound repair. Other experiments in *Smad3*$^{-/-}$ mice indicate that the transforming growth factor (TGF) β signalling intermediate Smad3 mediates the pro-inflammatory effects of androgens. The authors suggest that inhibition of DHT production could speed wound healing in elderly males and speculate that measurements of circulating DHT might identify elderly male patients at most risk of developing chronic non-healing ulcers.



PARsing polarity

The establishment of cell polarity is crucial for building and maintaining multicellular organisms. In *Drosophila*, the protein kinase Par-1 is thought to be critically involved in establishing polarity but, because *par-1* mutants die early in development, the function of the kinase is poorly characterized. Now, on p. 711, Richard Carthew and colleagues use RNAi to characterize the role of Par-1 in *Drosophila* embryos and eye imaginal discs. By depleting maternal and zygotic Par-1, they discover that it restricts the adherens junctions that link neighbouring cells to an apical position within blastoderm cells, thus revealing a role for it in establishment of cell polarity. Other RNAi experiments indicate that Par-1 is not essential for maintaining epithelial cell polarity once it is established. However, since Par-1 overexpression disrupts polarity, Par-1 must play some role in maintenance of polarity. Finally, the authors use immunostaining and epistasis analysis to uncover a novel role for Par-1: it regulates Notch signalling during embryonic neurogenesis and retina determination, possibly by ensuring that the Notch ligand Delta is correctly localized.

Development in press

Neural cell lineages: time for change?

The spinal cord is a valuable model system for understanding how neural cells diversify. But the lineage relationships between the neural stem cells (NSCs) and their descendents – motoneurons, oligodendrocytes and astrocytes – are still unclear. In a paper appearing in *Development*, Capecchi and colleagues report how they have used conditional cell ablation to shed light on this. A long-held model proposes that both motoneurons and oligodendrocytes arise from a common precursor that expresses oligodendrocyte transcription factor (Olig) proteins. The authors tested this by deleting Olig1-expressing NSCs, conditionally expressing diphtheria toxin under the control of the Olig1 promoter. As expected, they saw an absence of both motoneurons and oligodentrocytes in this system, but they also saw the continuous generation (and death) of their precursor cells and observed that oligodendrocyte precursors were generated for much longer than motoneuron precursors. This refutes the idea that motoneurons and oligodendrocytes come from a single precursor cell type; instead the authors propose a new 'sequential model' to explain their findings.

Wu, S., Wu, Y. and Capecchi, M. R. (2006). Motoneurons and oligodendrocytes are sequentially generated from neural stem cells but do not appear to share common lineage-restricted progenitors in vivo. *Development* **133**, 581-590.