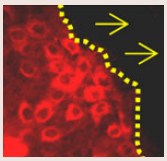
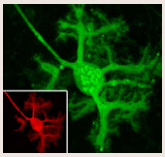
In this issue



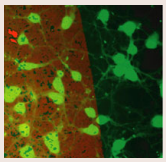
How HIF1 helps healing

The transcription factor hypoxia-inducible factor 1 (HIF1), which regulates oxygen homeostasis, is activated by stabilisation of the HIF1α subunit under low-oxygen conditions. Several studies have hinted that HIF1 might also have a role in cell adhesion and motility; now, Roser Buscà and colleagues (p. 2992) establish that HIF1 is important in keratinocyte migration during wound healing. The authors previously used an in vitro scratch-wound assay to show that several targets of HIF1 were upregulated in keratinocyte sheets in response to wounding, and they now show that HIF1α protein levels increase under the same conditions. Moreover, they demonstrate that HIF1α stabilisation is regulated by the PI3K-Akt pathway and, unusually, occurs under normoxic conditions. When HIF1α is depleted by siRNA, keratinocyte migration is impaired; additionally, HIF1α depletion abolishes the scratch-wound-dependent upregulation of the ECM protein laminin-332 (which is important in wound healing). The authors show that HIF1α binds directly to the promoter region of *LAMA3* (which encodes the α-subunit of laminin-332) and stimulates *LAMA3* transcription. Their results shed light on the mechanism of wound healing and establish a new, hypoxia-independent role for HIF1.



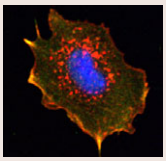
Depressing news for cPLA2α

Cerebellar long-term depression (LTD) – which has been implicated in motor learning – is a form of synaptic plasticity in which transmission through synapses is decreased. LTD is induced when AMPA receptors are continuously removed from the post-synaptic membrane of Purkinje cells – but what are the cellular signals that cause the internalisation and degradation of these receptors? Cytosolic phospholipase A2α (cPLA2α), which produces arachidonic acid (AA), is thought to be important in LTD induction so, on page 3015, Tetsuya Hirabayashi and colleagues explore how this enzyme is activated in Purkinje cells. The authors show that cPLA2α translocates to the Golgi when AMPA receptors are stimulated, and that translocation is Ca^{2+}-dependent. When LTD is chemically induced, they show, cPLA2α becomes phosphorylated and AA is released (the addition of pyrrophenone, a cPLA2α-specific inhibitor, abolishes AA production). The amount of GluR2 (an AMPA-receptor subunit) at the cell surface decreases persistently after the chemical induction of LTD; again, this effect is sensitive to pyrrophenone. The authors conclude that cPLA2α regulates the persistent decrease in surface expression of AMPA receptors; this underscores the role of cPLA2α and AA in cerebellar LTD.



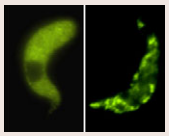
CSPGs show axons the way

During neural development and regeneration, chondroitin sulfate – the glycosaminoglycan (GAG) component of chondroitin sulfate proteoglycans (CSPGs) – has been proposed to guide axonal growth by acting as a chemorepellent. Chondroitin can be sulfated at several sites on its carbohydrate backbone – but can the pattern of CSPG sulfation affect its axon-guiding activity? On page 3083, Herbert Geller and colleagues suggest that it can. The authors show that chondroitin-4-sulfate, but not chondroitin-6-sulfate, repels the growing axons of mouse cerebellar granule neurons; this effect is abolished when chondroitin-4-sulfate is treated with chondro-4-sulfatase. Moreover, reactive astrocytes (which inhibit axonal growth) upregulate CSPG expression and produce more 4-sulfated than 6-sulfated GAG chains. Knocking down endogenous chondroitin-4-O-sulfotransferase 1 (C4ST1) in these astrocytes depletes 4-sulfation and reduces the repellent activity of the conditioned medium; conversely, astrocytes in which C4ST1 is overexpressed have more 4-sulfated GAG chains and are much less permissive to neuronal growth. Importantly, the expression of 4-sulfated GAG chains by reactive astrocytes is acutely increased in a mouse model of spinal injury. Thus, the site of chondroitin sulfation affects its role in axon guidance.



A Crk-Nck switch for Abl?

During cell adhesion and migration, focal adhesions (FAs) form and dissolve, and cytoplasmic actin structures such as filopodia and lamellipodia are dynamically reorganised. These processes must be spatially and temporally coordinated – but how is this controlled? On page 3071, Bruce Mayer and colleagues describe a role for the PxxP motifs of the non-receptor tyrosine kinase Abl – which is known to modulate actin rearrangement – in the coordination of actin dynamics and FA formation. The authors show that the four PxxP motifs (which bind to SH3 domains) are required for the formation of filopodia during cell attachment. Using an SH3-domain phage-display library, they show that the Crk and Nck families of adaptor proteins are preferential binding partners of Abl. Overexpression of Nck proteins increases the number of filopodia per cell and downregulates FAs; by contrast, cells that overexpress Crk proteins have fewer filopodia, spread more quickly and upregulate the formation of FAs and lamellipodia. The authors propose a model in which binding to Abl PxxP motifs downregulates signalling through Crk proteins and stimulates Nck signalling, both of which favour filopodia over lamellipodia. They conclude that, through Crk and Nck, Abl coordinates FA formation and actin reorganisation.



Trypanosomes: turning up the heat

When eukaryotic cells are subjected to stress, they respond by downregulating growth-associated genes and upregulating genes that promote survival. In trypanosomes, gene regulation relies almost entirely on post-transcriptional mechanisms because mRNA is synthesised in multigenic arrays – but how might this affect the stress response? On page 3002, Mark Carrington and colleagues address this question by analysing mRNA dynamics in *Trypanosoma brucei* (which causes African sleeping sickness) after heat shock. The authors show that several aspects of the *T. brucei* heat-shock response are similar to that of mammalian cells; for instance, the number of polysomes per cell decreases rapidly after heat shock, as do the levels of many mRNA species (although some become more prevalent). In addition, processing bodies (P-bodies) increase in number, and cytoplasmic stress-granule-like structures accumulate at the cell periphery. Notably, however, stress granules can form without the site-specific phosphorylation of eIF2α, which is usually a requirement for stress-granule formation in mammalian cells. Moreover, the authors show that the 5′-3′ endonuclease XRNA accumulates rapidly at a focus in the cell posterior after heat shock. These results identify key differences between the mammalian and trypanosomal heat-shock responses.

Development in press

Proneural proteins keep mitotic time

Cell specification and division are precisely coordinated during neurogenesis, but what controls the timing of mitotic entry? In a paper published in *Development*, Pao-Ju Chang and colleagues investigate the timing of mitosis in the neural precursors of the *Drosophila* external sensory organs. The authors show that proneural proteins, such as the transcription factors Achaete (Ac) and Scute (Sc), undergo negative-feedback regulation; this involves their degradation by the Phyl-Sina E3 ubiquitin-ligase complex. In *Drosophila*, sensory-organ precursors (SOPs) undergo asymmetric cell divisions after being specified by Ac and Sc, and the timing of the G2-M transition in SOP divisions controls daughter-cell fate specification. In *phyl* mutants, the researchers report, accumulation of Ac and Sc delays or blocks SOP division at the G2-M transition; a reduction in the *ac* and *sc* gene dose rescues this defect. Other results indicate that the adaptor Phyl links the proneural proteins to the RING protein Sina. Because *phyl* is a transcriptional target of Ac and Sc, the researchers propose that these proneural proteins control the timing of neural-precursor division by initiating their own degradation.

Chang, P.-J., Hsiao, Y.-L., Tien, A.-C., Li, Y.-C. and Pi, H. (2008). Negative-feedback regulation of proneural proteins controls the timing of neural precursor division. *Development* **135**, 3021-3030.