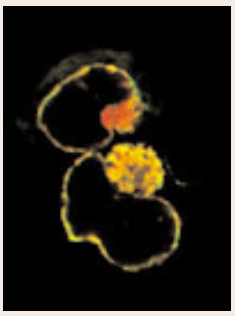
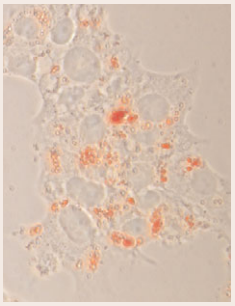
In this issue



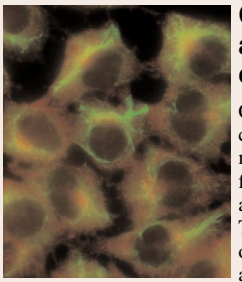
Histone code written on nuclear envelope

The positioning of chromatin within the nucleus plays an important role in gene regulation. The underlying mechanisms are poorly understood, but recent evidence indicates that architectural features such as the nuclear envelope (NE) can control gene expression by defining specific repressive environments. On p. 4017, Gideon Rechavi and co-workers define the role of a key NE protein, LAP2β, in this process. They find that LAP-2β acts as a general repressor that can inhibit various transcription factors (e.g. NF-κB, p53 and E2F proteins) in luciferase reporter assays. They also observe that it interacts and colocalizes at the NE with HDAC-3, one of a group of histone deacetylases known to repress transcription by modifying histones. By contrast, LAP-2β does not interact with the related enzyme HDAC1. The authors go on to demonstrate that the HDAC inhibitor trichostatin A blocks the repressive effect of LAP-2β and that LAP2β can induce deacetylation of histone H4 both in vitro and in vivo. Their findings provide valuable insight into the role of the NE in epigenetics and could be particularly significant given the various severe laminopathies that arise from disruption of NE protein function.



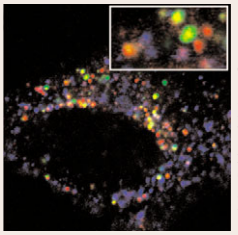
SREBP stressed out by glucose

In type II diabetes, high levels of blood glucose and lipids are thought to lead to reduced insulin secretion and the destruction of pancreatic β-cells. The molecular basis for this glucolipotoxicity is obscure, but it might involve transcription factors that regulate lipid metabolism. Haiyan Wang and co-workers have therefore examined the role of steroid-response-element-binding protein (SREBP), a lipogenic transcription factor induced in many animal models of diabetes (p. 3905). They demonstrate that treatment with high levels of glucose and expression of SREBP-1c have markedly similar affects on INS-1 insulinoma cells: both lead to lipid accumulation and apoptosis, and they produce similar gene expression profiles. By generating a stable cell line expressing a dominant negative mutant of SREBP-1c, the authors are able to show that the transcription factor is required for the glucolipotoxic effects of high glucose levels. Significantly, they also find that high glucose levels in INS-1 cells cause ER stress. Since this phenomenon has a well-established role in proteolytic activation of SREBP, a pathway in which hyperglycaemia and hyperlipidaemia induce ER stress and consequent SREBP activation could be critical feature of the pathogenesis of type II diabetes.



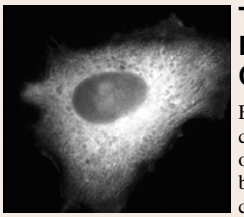
Cadherins at a crossroads…

Cadherins are cell-cell adhesion molecules essential for tissue integrity and development. They form two types of junction: at adherens junctions, classical cadherins, such as N-cadherin, are linked to actin through β- and α-catenin; at desmosomes, desmosomal cadherins are instead linked to intermediate filaments, such as vimentin. On p. 3883, Karen Knudsen and co-workers reveal that things are not so simple. They have developed a novel assay for cadherin function in which a steroid activates an N-cadherin mutant fused to a modified oestrogen receptor. Addition of 4-hydroxytamoxifen (4OHT) to fibroblasts expressing the mutant causes them to form tightly compacted aggregates through cadherin-mediated cell-cell adhesion. The authors observe that this is associated with increased interaction of N-cadherin with the cytoskeleton. Surprisingly, however, they find that this does not involve actin but vimentin. Vimentin becomes more organized at the cell periphery and can be coimmunoprecipitated with N-cadherin. More importantly, Knudsen and co-workers can block compaction of the cells by knocking down vimentin by RNAi. Their findings indicate that N-cadherin-mediated adhesion can involve intermediate filaments not just the actin cytoskeleton and thus blur the lines between the well-defined junctional complexes.



…FGF receptors at a fork

Many growth factors bind to a host of related receptors. This allows them to have distinct outputs in different circumstances, but how the signalling mechanisms differ is hard to establish – particularly if the receptors are very similar. Fibroblast growth factor receptors (FGFRs) are a case in point. Jørgen Wesche and co-workers have therefore examined whether differences in trafficking of these receptors after they internalize might affect their output (p. 3869). Expressing FGFR1–FGFR4 in HeLa cells that lack endogenous FGFRs, the authors track their movements following FGF treatment by costaining for markers of specific sorting routes. They find that, after internalization, all four receptors enter endosomes. Thereafter the receptors paths diverge: FGFR1–FGFR3 tend to be sorted to lysosomes for degradation (they colocalize with EGF), whereas FGFR4 is recycled (it colocalizes with transferrin). Noting that FGFR4 lacks several lysine residues conserved in FGFR1–FGFR3, Wesche and co-workers speculate that these are potential ubiquitylation sites and indeed show that FGFR4 is less ubiquitylated than its siblings. FGFR4 thus seems to escape ubiquitin-directed destruction. Its recycling could prolong FGF signalling, explaining why it alone promotes progression of some tumors.



Traffic police: PC TAIRE and COPII

Export of secretory cargo from the ER occurs in vesicles bearing the COPII coat complex. Increasing evidence indicates that the process is regulated by phosphorylation. However, the protein kinases involved have remained unclear. Now, on p. 3839, David Stephens and colleagues report that PCTAIREs – a branch of the cyclin-dependent kinase family – interact directly with COPII and modulate cargo transport. To identify regulators of COPII function, they used two-hybrid screening with the human COPII subunit Sec23 as bait. One positive clone encoded a fragment of PCTAIRE-3, one of three PCTAIRE isoforms. The authors then used co-immunoprecipitation studies in cell lysates to show that recombinant PCTAIRE-1 and PCTAIRE-3 can both interact with Sec23. Finally, they demonstrate that specifically inhibiting PCTAIRE kinase activity causes gross changes in the organization and function of the early secretory pathway. Stephens and colleagues therefore conclude that PCTAIRE plays a role in this pathway by regulating COPII function.

Development in press

The dynamics of PcG repression

During development, Polycomb group (PcG) proteins maintain patterns of gene repression that are mediated by homeobox-containing proteins. These PcG chromatin-binding proteins form several multicomponent complexes, but how these repress transcription in vivo is unknown. In a paper published in *Development*, Ficz and colleagues now report that PcG protein complexes exchange rapidly, most within two minutes, in living *Drosophila* embryos, which suggests that PcG repression occurs through dynamic competition with other chromatin-binding proteins. By using fluorescence recovery after photobleaching (FRAP) microscopy, the researchers determined the kinetic properties of two PcG-GFP fusion proteins in whole *Drosophila* embryos, wing imaginal discs and salivary glands. They show that PcG complexes are rapidly exchanged throughout development and that complexes at different chromosomal sites have different exchange rates. Thus, PcG complexes maintain the long-term repression of developmental regulatory genes dynamically rather than by statically limiting the access of transcriptional activators to chromatin.

Ficz, G., Heintzmann, R. and Arndt-Jovin, D. J. (2005). Polycomb group protein complexes exchange rapidly in living *Drosophila*. *Development* **132**, 3963-3976.