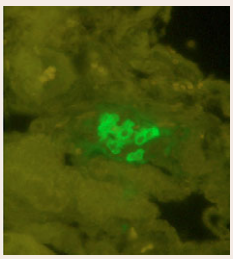
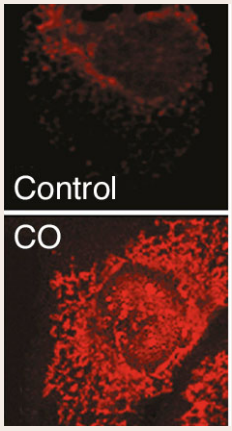
In this issue



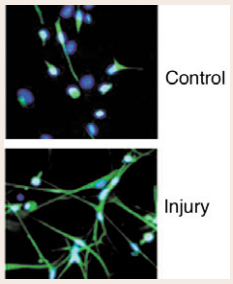
Home for β cells

β cells, the insulin-producing cells lost in type I diabetes, were thought to reside only in the pancreas. Now, during detailed analysis of mouse livers, Dutton et al. (p. 239) have uncovered another source of β cells: the liver. The β cells are located within extra-hepatic bile ducts and have elevated levels of insulin mRNA, the proteolytically cleaved insulin C-peptide and insulin-containing secretory granules characteristic of pancreatic β cells. Furthermore, isolated hepatic ducts containing these β cells can secrete insulin in response to glucose. Using specific genetic markers to identify liver cells, the authors demonstrate that the β cells originate directly from liver epithelium rather than the pancreas. Attempts to replace or increase the number of β cells, in the treatment of type I diabetes have been hindered by the limited supply of pancreatic islets. The identification of this novel source of β cells offers renewed hope for the treatment of diabetes.



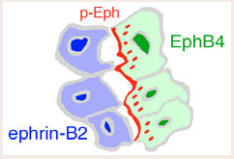
CO-ordinating mitochondrial biogenesis

Carbon monoxide (CO) causes cellular hypoxia and cytotoxicity and functions as a neurotransmitter in the brain by binding to multiple heme proteins. Suliman and colleagues (p. 299) now demonstrate a new physiological role for CO in cardiac mitochondrial biogenesis. Mitochondrial biogenesis is regulated by coordinate expression of specialised transcriptional coactivators and factors, which increases expression of mitochondrial proteins, mitochondrial density and mitochondrial DNA copy number. The authors show that all of this occurs in mouse cardiac tissue following exposure to CO. The effect is independent of both nitric oxide synthase (NOS) and hypoxia, which indicates that it is not a general effect of endogenously formed gases. CO activates two key enzymes involved in mitochondrial biogenesis: guanylate cyclase and PKB. Nitric oxide (NO) also activates the guanylate cyclase pathway whereas PKB is only activated by CO. The authors demonstrate that PKB activation in the heart and cardiomyocytes requires increased mitochondrial H_2O_2 production and release, as a result of CO binding to mitochondrial cytochrome a_3. Their study defines both CO and H_2O_2 as novel activating factors in cardiac mitochondrial biogenesis.



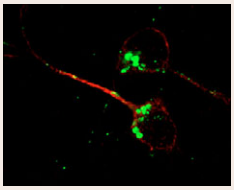
Cdc2 on the move in nerve regeneration

Schwann cells play a major supporting role in peripheral nerve regeneration following injury. They migrate towards the site of injury, where they provide a guide for regenerating axons. However, the molecular events that control their migration are largely unknown. On p. 246, Namgung and colleagues demonstrate that the cyclin-dependent kinase Cdc2, better known for its role controlling cell cycle progression, is necessary for this process. They find that following injury to the sciatic nerve, isolated Schwann cells show elevated Cdc2 expression and enhanced migration. Inhibition of Cdc2 can block this effect, whereas increased Cdc2 expression enhances cell migration. The authors identify caldesmon, an actin-binding protein, as a key Cdc2 kinase substrate. Phosphorylation of caldesmon by Cdc2 alters its subcellular localisation away from the peripheral cytoskeleton to the centre of the cell. They go on to show that inhibition of the Cdc2-caldesmon pathway, using a dominant-negative form of caldesmon, suppresses Schwann cell migration. Their data support an emerging new function of Cdc2 and other Cdk family members in the nervous system and provide insight into the mechanisms of nerve regeneration.



Eph-ective cell repulsion

Eph receptor tyrosine kinases and their membrane-bound ephrin ligands control cell movement in several developing tissues. Activation of Eph receptors (EphBs) through cell-cell contact leads to cell-cell repulsion and separation. Although several pathways have been implicated in this process, the precise mechanisms are poorly defined. Evans et al. (p. 289) establish a role for Ena/VASP – a family of cytoskeletal regulators – proteins downstream of Eph receptor signalling in Eph-mediated cell repulsion. Both soluble and substrate-bound ephrinB2 cause a repulsive response in neural tube explants by destabilising lamellipodia in the neural crest. The authors demonstrate that Ena/VASP proteins contribute to the destabilisation of neural crest lamellipodia and facilitate cell-cell repulsion at sites of ephrin activation. Ena/VASP-deficient fibroblasts display reduced repulsion in response to ephrin ligands. Moreover, Ena/VASP proteins localise to sites of Eph receptor activation and are required for internalisation of receptor-ligand complexes, which is necessary during Eph-mediated cell repulsion. This study provides significant insight into the mechanisms behind repulsive signalling and demonstrates a new link between Ephrin signalling and the Ena/VASP family.



Lamp light for neuronal endosomes

LAMP proteins are involved in lysosomal function and intracellular trafficking. During a bioinformatics-based search for lysosome-associated molecules, Philippe Pierre and co-workers have identified brain-associated LAMP-like molecule (BAD-LAMP), a new member of the LAMP family in mice (p. 353). This unconventional LAMP-like protein defines a new endocytic compartment in specific subsets of cortical projection neurons. Interestingly, its post-natal expression coincides with cortical synaptogenesis, indicating a possible role in this process. Unlike other LAMP family members, BAD-LAMP has a highly restricted localisation: it is enriched in distinct intracellular vesicles in defined zones along the neuronal projections. Although BAD-LAMP is endocytosed, the vesicles in which it accumulates do not contain markers for classical intracellular transport pathways. Further analysis of BAD-LAMP endocytosis in HeLa cells revealed that it constantly recycles to the plasma membrane via a dynamin/AP2-dependent mechanism. The defined expression and distribution patterns of BAD-LAMP demonstrate a role for non-conventional endocytic vesicles and membrane lipids in the maturation or function of specific cortical neurones.

Development in press

A hair-raising choice for Gata3

The hair follicle is composed of the hair shaft and epithelial stem cells, which can repopulate hair follicles if an inductive signal is received from the surrounding dermal papilla. Gata3 is known to be involved in hair follicle and epidermis differentiation, but precisely how remains unclear. Now, Kurek and co-workers reveal that Gata3 integrates different signalling networks and is crucial in regulating the choice between forming the different layers of the hair follicle and maintaining the epidermis. In a paper published in *Development*, the results of a comparative transcriptional assay designed to identify upregulated genes in *Gata3* mutant hair follicles reveal that increases in Notch, Wnt and BMP pathway components occur in the absence of Gata3, while genes associated with cell cycle progression and apoptosis are downregulated. In the absence of Gata3, hyperproliferation occurs in the basal epidermal cells at the expense of correct hair follicle development. The authors propose that Gata3 acts as a moderator between hair follicle development and epithelial cell differentiation.

Kurek, D., Garinis, G. A., van Doorninck, J. H., van der Wees, J. and Grosveld, F. G. (2007). Transcriptome and phenotypic analysis reveals Gata3-dependent signalling pathways in murine hair follicles. *Development* **134**, 261-272.