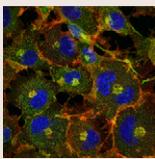
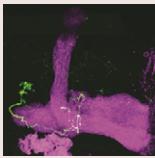


# In this issue



## Rab35 and Arf6: a balancing act

The levels of integrins and cadherins at the plasma membrane need to be carefully balanced by the cell during cell migration and adhesion, but how the trafficking events that coordinate these levels are regulated is unknown. On page 722, Peter McPherson and colleagues examine the interdependence of two small GTPases, Rab35 and Arf6, on the recycling of adhesion molecules, cell-cell interactions and cell migration. They show that *Rab35* knockdown enhances the intracellular accumulation of cadherins, correlating with reduced cell-cell adhesion. The loss of Rab35 also increases recycling of  $\beta 1$  integrin and epidermal growth factor receptor, and signalling to focal adhesion kinase, correlating with enhanced cell migration. Rab35 is known to recruit the Arf6 GTPase-activating protein (GAP) ACAP2 to inactivate Arf6, whereas Arf6 recruits Rab35 GAPs to inactivate Rab35; the authors show, however, that *Rab35* knockdown significantly enhances endogenous Arf6 activity, providing direct evidence that Rab35 is a negative regulator of Arf6. In addition, simultaneous knockdown of Rab35 and Arf6 reverses the enhanced cell migration induced by *Rab35* knockdown, indicating that Rab35 suppresses Arf6 to limit cell migration. Interestingly, the authors find that *Rab35* mRNA levels are suppressed in certain tumour cells, which could explain the hyperactivity of Arf6 in many tumours. These data therefore identify a key molecular mechanism for coordinating the antagonistic functions of cell migration and differentiation.



## Molecular chaperones protecting the brain

Axon degeneration is a key event that is observed in the early stages of many neurodegenerative conditions, but the mechanism by which it is induced is not well understood. Julian Ng and colleagues have previously shown that inactivating the c-Jun N-terminal kinase (JNK) pathway leads to axon degeneration in *Drosophila melanogaster* mushroom body (MB) neurons; here (p. 838), Ng and his team seek to understand this process. They find that inactivating JNK causes an age-dependent axonal degeneration in MB neurons. Screening candidate suppressor genes revealed that Wallerian degeneration slow (*Wld<sup>S</sup>*) protein blocks JNK-mediated axonal degeneration. Different portions of *Wld<sup>S</sup>* are thought to confer neuroprotective function, and the authors show that the nicotinamide mononucleotide adenyltransferase 1 (*Nmnat1*) portion is required, whereas the nicotinamide adenine dinucleotide enzyme activity, as well as the N-terminus (N70), of *Wld<sup>S</sup>* are not; this is in contrast to axotomy models of neurodegeneration. Furthermore, ectopically expressed molecular chaperones heat shock protein 26 (*Hsp26*) and *Hsp70* also protect against the axonal-degeneration phenotype induced by the loss of JNK and *Nmnat*. The authors propose, therefore, that non-enzyme *Nmnat* and chaperone functions are key interactors with the JNK pathway in controlling axonal stability.

## Upcoming Commentaries and Cell Science at a Glance posters

### Cell Science at a Glance posters

- Interactions and functions of the adenomatous polyposis coli (APC) protein at a glance *Inke S. Näthke*
- Virus entry at a glance *Ari Helenius*

### Commentaries

- Modulation of T-cell signaling by the actin cytoskeleton *Jay T. Groves*
- Autophagy and microtubules *Patrice Codogno & Christian Poüs*



## Armed to the teeth with $\alpha\beta 6$ integrin

Tooth enamel is the hardest mineralised tissue in the body and is produced by cells called ameloblasts. During the secretory stage of amelogenesis, enamel proteins such as amelogenin are secreted into the enamel matrix, which is in direct contact with the ameloblast plasma membrane. In most cell types, integrins mediate cell-matrix adhesion and signalling, but the receptors that mediate ameloblast adhesion and matrix production are not well characterised. Hannu Larjava and colleagues (p. 732) hypothesised that integrin  $\alpha\beta 6$ , which might have a role in protection from periodontal disease, is expressed in ameloblasts where it regulates biominerallisation of enamel. The authors show that both human and mouse ameloblasts express  $\beta 6$  integrin mRNA and protein. In mice deficient in  $\alpha\beta 6$  integrin (*Igfb6<sup>-/-</sup>*), they found chalky rounded incisors, with a significantly reduced mineral-to-protein ratio, whereas the molars of these mice show reduced mineralisation and severe attrition. These phenotypes are rescued by the expression of *Igfb6* under the control of the K14 promoter using a transgenic mouse approach. Interestingly, the abnormal accumulation of amelogenin-rich extracellular matrix the authors see in *Igfb6<sup>-/-</sup>* teeth is primarily due to increased amelogenin synthesis rather than reduced removal of the matrix proteins. Larjava et al. conclude that integrin  $\alpha\beta 6$  does indeed have a crucial role in regulating the deposition of amelogenin and subsequent enamel biominerallisation.

## From Disease Models & Mechanisms Deafness in distal renal tubular acidosis

Mutations in *ATP6V0A4*, which encodes a subunit of the H<sup>+</sup>-ATPase proton pump, underlie distal renal tubular acidosis (dRTA), a condition that often involves deafness in addition to kidney-related problems. In *Disease Models & Mechanisms*, Karen P. Steel and colleagues now examine the auditory system in *Atpv60a4*-knockout mice, which recapitulate the human renal dRTA phenotype and have impaired hearing. The authors report that the endolymphatic compartments in these mice are expanded, whereas hair-cell development in the cochlea (which is crucial for normal hearing) is unaffected. Notably, *Atpv60a4*-knockout mice lack an endocochlear potential (the voltage that is needed to make hair cells more sensitive to sound), although the K<sup>+</sup> channels that normally help to generate this potential are strongly expressed. Together, these results establish *Atpv60a4*-knockout mice as a model for dRTA-associated hearing loss.

Lorente-Cánovas, B., Ingham, N., Norgett, E. E., Golder, Z. J., Karet Frankl, F. E. and Steel, K. P. (2013). Mice deficient in H<sup>+</sup>-ATPase a4 subunit have severe hearing impairment associated with enlarged endolymphatic compartments within the inner ear. *Dis. Model. Mech.* **6**, 434-442.

## From Development Tumour suppression trafficked by Atg6

Autophagy is a conserved catabolic process that degrades the cell's own components, through the lysosomal machinery, in response to cell stress. Atg6/beclin 1 is a core component of the vacuolar protein sorting 34 (Vps34) complex that is required for autophagy. It is also a tumour suppressor, a function that has been attributed to its role in autophagy. But could the potential function of Atg6/beclin 1 in other vesicle-trafficking pathways be involved in tumour development? In *Development*, Eric Baehrecke and co-workers generate *Atg6*-mutant *Drosophila melanogaster* and show that *Atg6* is essential for autophagy, endocytosis and protein secretion. By contrast, the core autophagy gene *Atg1* is required for autophagy and protein secretion only. Consistent with the tumour suppressor role of beclin 1, loss of *Atg6* causes over-production of blood cells and the formation of melanotic blood cell masses. Together, these results suggest that the involvement of Atg6/beclin 1 in multiple vesicle trafficking pathways underlies its role as a tumour suppressor.

Shravage, B. V., Hill, J. H., Powers, C. M., Wu, L. and Baehrecke, E. H. (2013). *Atg6* is required for multiple vesicle trafficking pathways and hematopoiesis in *Drosophila*. *Development* **140**, 1321-1329.