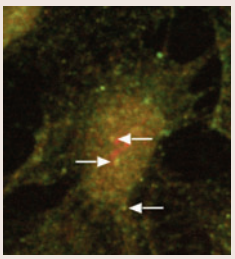
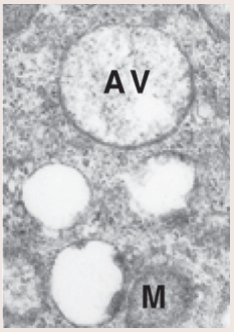
# In this issue



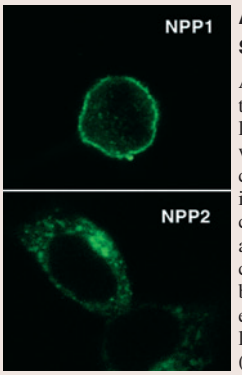
## Wnt pathway takes a Hint

Wnt (aka Wingless) signalling plays crucial roles in developmental processes and control of cell proliferation in adult organisms. In the canonical pathway, binding of Wnt to Frizzled receptors leads to the release of β-catenin from a cytoplasmic degradation complex. β-catenin can then translocate to the nucleus, where it cooperates with LEF1/TCF transcription factors to regulate gene expression. Jörg Weiske and Otmar Huber now identify a novel Wnt pathway regulator, the tumour suppressor Hint1 (p. 3117). The authors show that Hint1 binds to pontin and reptin, two proteins that modulate β-catenin/TCF transcriptional activity. They have mapped the residues responsible and demonstrate that Hint1 associates with the LEF-1/TCF–β-catenin transcription complex through pontin/reptin. Significantly, they go on to demonstrate that Hint1 can negatively regulate β-catenin/TCF transcriptional activity and thereby inhibits expression of the cell-cycle regulator cyclin D1. In addition, Weiske and Huber present evidence that Hint1 acts by disrupting the pontin-reptin complex. They conclude that Hint1 is an important regulator of canonical Wnt signalling. Since this is deregulated in numerous cancers, their findings reveal the basis for the protein's tumour suppressor activity.



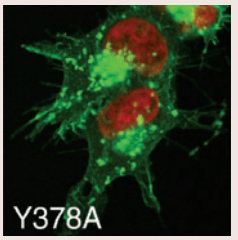

## Repro-grammed cell death

Programmed cell death (PCD) is usually thought to occur by one of two mechanisms. Type I PCD (apoptosis) involves the enzymes caspases and is characterized by chromatin condensation and nuclear fragmentation. Type II is instead characterized by accumulation of autophagic vacuoles, which sequester cytosol and organelles during autophagy (a survival response used to combat nutrient deprivation). But how distinct are type I and type II PCD and what is the real relationship between type II PCD and autophagy? Guido Kroemer and co-workers have examined PCD in nutrient-deprived cells lacking the lysosomal protein LAMP2. These have increased numbers of autophagic vacuoles, because fusion of these vacuoles with lysosomes is inhibited (see p. 3091). The authors find that, despite accumulation of autophagic vacuoles, the PCD that occurs displays numerous hallmarks of apoptosis, such as loss of mitochondrial potential, caspase activation and chromatin condensation. Moreover, they can block it with caspase inhibitors and agents that stabilize mitochondria. The authors conclude that cells that accumulate autophagic vacuoles can progress to apoptosis. They therefore argue that the two types of PCD are not as distinct as many thought.



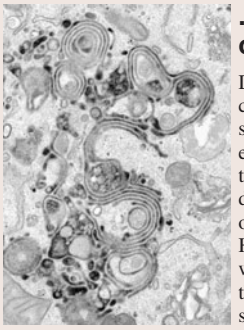

## Autotaxin's secret life

Autotaxin (NPP2) is a tumour-associated lysophospholipase whose upregulation correlates with invasiveness of cancer cells. It is an attractive target for cancer therapy because it generates extracellular lysophosphatidic acid (LPA), which promotes metastasis at several levels – LPA stimulates cell proliferation, survival, migration and angiogenesis. Autotaxin was thought, like its close relative NPP1, to be a transmembrane protein. Mathieu Bollen and co-workers now show that it is instead secreted, and this has important implications (see p. 3081). The authors observe autotaxin in the Golgi apparatus of HEK293 cells and find that the vast majority ends up in the culture medium. They have used domain swapping and mutagenesis to define the signal peptide that directs it into the secretory pathway. Moreover, they demonstrate that the protein is synthesised as a pre-pro-enzyme, in which the N-terminal signal peptide is followed by an octapeptide that is subsequently cleaved by proprotein convertases such as furin. The processed enzyme is more active than its precursor. Bollen and co-workers therefore suggest that anticancer therapies that target autotaxin could be directed against its synthesis, processing or enzymatic activity.




## Endocytic motif defies consensus...

Proteins internalized at the cell surface by clathrin-mediated endocytosis contain specific sorting sequences that bind to the internalization machinery. The best characterized of these is the tyrosine-based YXXΦ motif (in which X is any residue and Φ is a bulky, hydrophobic residue). This binds to a specific region in the μ2 subunit of the AP2 clathrin adaptor protein, and structural studies have shown that the spacing between the Y and Φ residues is crucial. Ruth Murrell and co-workers now unveil a novel type of tyrosine-based endocytic motif (p. 3073). They have used site-directed mutagenesis and CD8-based chimeras to analyse endocytosis of P2X4 receptors, ATP-gated cation channels that rapidly cycle off the plasma membrane. These receptors possess consensus YXXΦ motifs, but surprisingly these are inaccessible to AP2 and not needed for endocytosis. Instead, the authors show, a downstream YXXGΦ motif is required. Determining the structure of a YXXGΦ–μ2 complex, they demonstrate that the motif recognizes the same region of μ2 but accommodates the extra G residue by altering its backbone configuration. These findings thus define a second type of AP2-binding tyrosine motif, extending the range of sequences that could drive internalization.



## ...endosomes out of sorts

During endocytosis, cargo receptors are sorted in early endosomes according to whether they are destined for recycling or degradation. However, it is unclear whether cargos move through predetermined structures or whether cargo selection underpins endosomal morphology. Phillip Woodman and colleagues now provide evidence for the latter scenario by examining endosomes after inhibiting the sorting of epidermal growth factor receptor (EGFR) by depleting cells of tumour susceptibility gene 101 (TSG101; see p. 3003). TSG101, a ubiquitin-binding protein required for EGFR sorting, is the mammalian orthologue of a subunit of the yeast ESCRT-1 complex, which mediates ubiquitin-dependent sorting in early endosomes as they mature into multivesicular bodies. The authors show that knocking down TSG101 yields multicisternal early endosomes that have multiple sorting defects and closely resemble the defective endosomes seen in yeast mutants lacking functional ESCRT-1. Thus, they suggest, if ESCRT-1 complexes cannot form, ubiquitylated cargos are not recruited to the appropriate regions of early endosomes and, consequently, the membrane reorganisations needed to form normal endosomal vacuoles and tubules go awry.

## *Development* in press

### Eyes wide open

During mammalian development, eyelid growth, fusion and subsequent reopening involve cell proliferation, shape changes, migration and death. In a paper published in *Development*, Tao et al. report that fibroblast growth factor 10 (FGF10) controls the proliferation and coordinated migration of epithelial cells during eyelid development. The researchers investigate eyelid development in *Fgf10*-deficient mice, which are born with open instead of shut eyelids. They show that activin βB and transforming growth factor α, both of which are critical for eyelid development, are downregulated in the leading epithelial edge of the developing mutant eyelid, but are upregulated in explanted cultures of normal eyelid primordia after FGF10 treatment. Overall, their results indicate that FGF10 signalling is required early in eyelid development for cell shape changes and proliferation of the prospective eyelid epithelium, and later for the changes underlying epithelial cell migration during eyelid closure, a process that resembles wound healing.

**Tao, H., Shimizu, M., Kusumoto, R., Ono, K., Noji, S. and Ohuchi, H.** (2005). A dual role of FGF10 in proliferation and coordinated migration of epithelial leading edge cells during mouse eyelid development. *Development* **132**, 3217-3230.