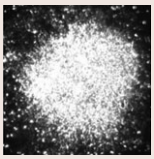
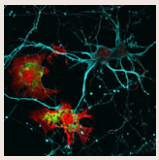
# In this issue

By Jane Bradbury



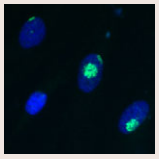
## MicroRNA-managing ovarian cancer

The expression of microRNAs (miRNAs) – small noncoding RNAs that regulate gene expression by binding to the 3′-untranslated region (3′UTR) of target mRNAs – is frequently deregulated in ovarian cancer, but the role of miRNAs in this form of cancer is poorly understood. One possibility is that miRNAs regulate the expression of the serine/threonine kinase activin receptor-like kinase 7 (ALK7), through which the growth factor Nodal acts to induce apoptosis in ovarian cancer cells. On page 359, Chun Peng and colleagues test this possibility by analysing the interaction between miRNAs and the 3′UTR of *ALK7* mRNA. Using human ovarian cancer cell lines, they show that miR-376c targets ALK7, and that ectopic expression of miR-376c increases cell proliferation and survival, blocks Nodal-induced apoptosis and blocks cisplatin-induced cell death. Moreover, ALK7 expression is weak and miR-376c levels are high in cancer cells from patients who respond poorly to chemotherapy, whereas the converse is true in samples from patients who respond well to chemotherapy. The authors conclude, therefore, that cisplatin-induced death of ovarian cancer cells involves the Nodal–ALK7 pathway, and that miR-376c helps to promote the survival, proliferation and chemoresistance of ovarian cancer cells by targeting ALK7.



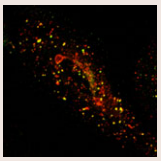
## Exosome uptake: silencing autoantigens

The transfer of antigens from oligodendrocytes to immune cells in the central nervous system (CNS) is a crucial step in the induction of the autoimmune response against myelin that occurs in multiple sclerosis, but how is this transfer accomplished? On page 447, Mareike Schnaars, Mikael Simons and colleagues suggest that some autoantigens in the CNS are selectively transferred from oligodendrocytes to microglia (macrophage-like cells that are resident in the brain and spinal cord) by exosomes (small membrane vesicles that originate in the endosomal system). The authors show that oligodendrocytes release exosomes that are specifically and efficiently taken up by microglia in vitro and in vivo. Internalisation of the exosomes, they report, occurs by a macropinocytotic mechanism that does not induce an inflammatory response. Notably, although stimulation of microglia with interferon-γ induces upregulation of MHC class II molecules in a subset of microglia, the one that internalises exosomes does not seem to have antigen-presenting capacity. The authors propose, therefore, that constitutive macropinocytotic clearance of exosomes is an important mechanism through which a subset of microglia participates in the degradation of oligodendrocyte membranes in an immunologically silent manner.



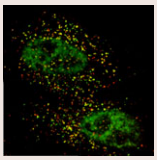
## Mind the gap: DDR in non-cycling cells

Eukaryotic cells protect themselves against potentially deadly genotoxic insults with a network of DNA damage response (DDR) mechanisms, which are initiated by specific sensors that detect DNA damage or chromosome alterations. Signal transduction pathways that involve the ATR kinase and other phosphoinositol-3-kinase-like kinases then activate cell cycle checkpoints and other protective pathways to ensure that DNA lesions are fully repaired before cell division occurs. Here, Leon Mullenders and colleagues (p. 435) investigate how UV-induced DNA lesions activate the DDR in non-cycling human cells. They show that, in non-cycling cells proficient in nucleotide excision repair (NER; a repair pathway that removes UV-induced DNA lesions), DNA damage signalling is rapid and transient. By contrast, in non-cycling NER-deficient cells, DNA damage signalling is delayed and persistent, and UV-induced checkpoint activation coincides with the formation of single-stranded DNA breaks. Finally, the authors report that checkpoint activation in both NER-proficient and NER-deficient cells involves ATR-kinase-dependent signalling. Thus, in non-dividing mammalian cells, DNA damage signalling, which ultimately prevents the transition from G1 to S phase, involves both NER-dependent and NER-independent processing of UV-induced lesions.



## Peering into mucolipidosis type IV

Mucolipidosis type IV (MLIV) is an inherited lysosomal storage disease that is characterised by severe neurological and ophthalmologic abnormalities. It is caused by loss-of-function mutations in mucolipin 1 (MCOLN1), a lysosomal ion channel protein that belongs to the transient receptor potential superfamily. But why do mutations in this protein cause MLIV? To find out more about the function of MCOLN1, Rosa Puertollano and colleagues (p. 459) use a yeast two-hybrid screen to identify two lysosome-associated protein transmembrane (LAPTM) family members as new interaction partners of MCOLN1. The authors confirm this interaction by co-immunoprecipitation, and show that MCOLN1 and LAPTMs colocalise at late endosomes and lysosomes. Notably, overexpression of LAPTMs causes lysosome enlargement and defective lysosomal degradation, whereas depletion of endogenous LAPTMs induces the accumulation of concentric multi-lamellar structures and electron-dense inclusions that closely resemble the structures that are seen in the cells of patients with MLIV. Overall, these data suggest that MCOLN1 regulates LAPTMs and that LAPTMs are involved in the regulation of lysosomal function. The identification and development of compounds that modulate LAPTM function might, therefore, provide a treatment for MLIV.



## SNAREd into autophagy

Autophagy is a conserved, intracellular bulk degradation process that mediates the turnover of organelles and long-lived proteins. During autophagy, cytoplasmic components and organelles are sequestered in a double-membrane vesicle (the autophagosome) that fuses with the lysosome, thereby delivering its contents for lysosomal degradation. Deregulated autophagy is implicated in cancer and in some myopathies and neurodegenerative diseases. Now, on page 469, David Rubinsztein and colleagues report that the syntaxin-5 soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex is required for autophagy in human cells. SNAREs have pivotal roles in membrane fusion, and autophagy involves several membrane fusion events. Using genetic knockdown, the authors show that the syntaxin-5 SNARE complex regulates the later stages of autophagy. They report that this SNARE complex affects autophagy by regulating ER-to-Golgi transport of lysosomal proteases, which are essential for lysosomal function. Depletion of individual components of the syntaxin-5 SNARE complex results in accumulation of autophagosomes because of lysosomal dysfunction and decreases the degradation of autophagic substrates. Together, these results reveal a new link between the early secretory pathway and the autophagy–lysosomal-degradation pathway.

## *Development* in press

### Wnt/PCP signalling, microtubules and gastrulation

During vertebrate gastrulation, convergence and extension (C&E) movements shape the germ layers to form the anterioposteriorly elongated body axis of vertebrate embryos. Non-canonical Wnt/planar cell polarity (Wnt/PCP) signalling regulates C&E by polarising the morphology and behaviour of cells, which suggests that the Wnt/PCP pathway influences the microtubule cytoskeleton. In an article published in *Development*, Lila Solnica-Krezel and co-workers investigate this possibility by assessing the position of the centrosome microtubule organising centre (MTOC) relative to the cell nucleus and the body axes during zebrafish gastrulation. They report that MTOCs occupy a polarised position within the plane of the ectoderm and mesoderm, becoming biased to the posterior and dorsal/medial side of the cell between mid and late gastrulation. This polarisation, they report, depends on intact Wnt/PCP signalling. Conversely, microtubule disruption experiments show that microtubules are required to initiate the anterior localisation of Prickle, a core PCP signalling component. These and other results suggest that reciprocal interactions between Wnt/PCP signalling and the microtubule cytoskeleton are required during C&E gastrulation movements.

**Sepich, D. S., Usmani, M., Pawlicki, S. and Solnica-Krezel, L.** (2011). Wnt/PCP signaling controls intracellular position of MTOCs during gastrulation convergence and extension movements. *Development* **138**, 543-552.