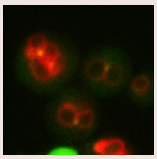
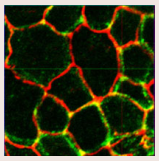
In this issue

By Jane Bradbury



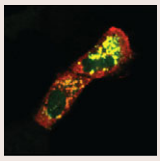
Atg8: new function in vacuolar fusion

Autophagy is a highly conserved, eukaryotic protein-degradation pathway during which double-membrane structures called autophagosomes are formed that sequester intracellular proteins and organelles. The autophagosomes are then transported into the vacuole (in yeast) or into the lysosome (in mammalian cells) for complete degradation. The ubiquitin-like protein autophagy-related protein 8 (Atg8) is required, along with a lipidation system that links it to phosphatidylethanolamine, for autophagy in all eukaryotic cells, but is Atg8 involved in any other biological processes? On page 4107, Yasuyoshi Sakai and colleagues reveal a novel role for Atg8 in vacuolar membrane dynamics in the methylotrophic yeast *Pichia pastoris*. When grown on glucose, the authors report, *P. pastoris* cells contain 2–4 clustered vacuoles; during adaptation to methanol medium and hypotonic conditions, and during organelle inheritance, these vacuoles undergo a major shape change through homotypic fusion. The authors show that Atg8 depletion impairs this response and that vacuole fusion requires C-terminal processing of Atg8. Surprisingly, however, fusion does not require Atg8 lipidation. These results provide the first description of a lipidation-independent function for an Atg8 protein family member.



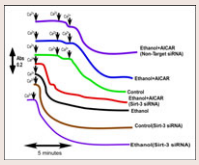
Barriers to gut inflammation

In intestinal epithelia, tight junctions (TJs) normally block paracellular transport (movement between cells) of antigens and solutes from the intestinal lumen to the mucosal layer. In inflammatory bowel disease (IBD), TJ perturbation means that antigens come into contact with immune system cells in the mucosal layer, which causes inflammation and diarrhoea. Now, on page 4145, Jörg-Dieter Schulzke and colleagues provide new insights into intestinal TJ regulation, and suggest a new therapeutic approach for IBD. The authors investigate the effect of TNFα (a cytokine that has pro-inflammatory effects on transepithelial resistance and TJs) and berberine (a herbal antidiarrhoeal agent) on human intestinal cell monolayers and rat colon preparations. TNFα reduces the paracellular resistance of intestinal cell layers and increases their paracellular permeability, the authors report, but does not affect their transcellular resistance. Furthermore, TNFα removes claudin-1 (a TJ tightening protein) from the TJs and increases the expression of claudin-2 (a pore-forming protein). Notably, berberine completely antagonises TNFα-induced barrier changes in both models, its effects being mediated through tyrosine kinase, Akt and NFκB signalling. Together, these results provide an explanation for berberine's antidiarrhoeal action that could aid the design of new IBD therapeutics.



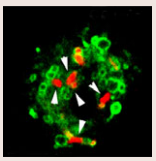
KazrinA, partner for ARVCF-catenin

Catenins, which were originally defined as proteins that bind cadherins at adherens junctions, have numerous cellular roles. ARVCF-catenin, for example, modulates cadherin stability at cell–cell junctions and regulates Rho-family GTPases. But does this p120-catenin subfamily member have any other functional roles? Pierre McCrea and colleagues (p. 4128) now identify *Xenopus* KazrinA (xKazrinA), a widely expressed and conserved protein with little homology to established protein families, as a direct binding partner of *Xenopus* ARVCF (xARVCF). Surprisingly, the xARVCF–xKazrinA complex binds spectrin in the spectrin–actin cytoskeleton and, the authors report, xKazrinA depletion in *Xenopus* embryos produces ectodermal shedding, an effect that is partly rescued by exogenous xARVCF. xKazrinA knockdown also alters RhoA activity, microfilament organisation, cadherin levels and cell adhesion, all outcomes consistent with ectodermal shedding. Finally, the authors show that xKazrinA binds Xp190B RhoGAP. They propose, therefore, that xKazrinA facilitates the association of Xp190B RhoGap and xARVCF with the spectrin–actin network. Here, they suggest, the xARVCF–xKazrinA–Xp190B complex contributes to cytoskeletal organisation, cell adhesion and ectodermal integrity by modulating RhoA activity.



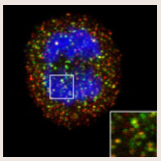
Ethanol's sirtuin route to cell death

Exposure to ethanol causes many changes in cellular physiology and mitochondrial function. These changes lead to steatosis (abnormal lipid retention in cells) and, eventually, the development of alcoholic steatohepatitis and cirrhosis. Now, on page 4117, Nataly Shulga and John Pastorino reveal new details about how ethanol affects mitochondrial function in liver cells. Ethanol sensitises mitochondria to the permeability transition – the opening of a protein pore [the mitochondrial permeability transition (MPT) pore] in the mitochondrial membrane that increases mitochondrial permeability and leads to TNF-induced cell death. The authors show that ethanol has this effect on mitochondria in part by increasing the acetylation and activity of cyclophilin D, a peptidyl-prolyl *cis-trans* isomerase that promotes MPT pore opening. Moreover, the effect of ethanol on cyclophilin D is mediated by inhibition of sirtuin-3, an NAD^+-dependent deacetylase that, like cyclophilin D, is localised to the mitochondrial matrix. Finally, the authors report that activation of AMP-activated protein kinase (AMPK), a modulator of sirtuin activity, prevents the ethanol-induced suppression of sirtuin-3 and the MPT. Together, these findings provide important new insights into how ethanol causes cell death.



Legionella infection modelled

Professional phagocytes ingest and kill many pathogens, but some (e.g. *Legionella pneumophila*) exploit phagocytosis to enter eukaryotic cells and proliferate intracellularly. Here (p. 4039), Salvatore Bozzaro and colleagues use *Dictyostelium discoideum*, a soil amoeba that feeds on bacteria, to investigate how *L. pneumophila* invades eukaryotic cells. Membrane phosphoinositides, which recruit the cytosolic proteins that regulate phagocytosis, macropinocytosis and endolysosomal vesicle maturation, are modified by phosphoinositide 3-kinases (PI3Ks), the phosphatase PTEN and phosphatidylinositol phospholipase C (PI-PLC). The authors report that *Legionella* uptake is sensitive to inhibition of all three modifiers, whereas *Escherichia coli* uptake is sensitive to PI-PLC inhibition only. Combined with other assays, this result suggests that *Dictyostelium* engulfs *Legionella* by macropinocytosis rather than by phagocytosis. The authors also show that *Legionella* proliferates intracellularly in *Dictyostelium*, but that constitutive expression of Nramp1, an endolysosomal iron transporter that confers resistance against invasive bacteria in mice, blocks its proliferation; PI3K inhibition suppresses the protective effect of Nramp1 overexpression. Given these results, the authors propose a model to explain how *Legionella* escapes fusion with acidic vesicles and Nramp1-induced resistance to pathogens in its host cells.



Sec16A restarts secretion post mitosis

Precise inheritance of organelles during mitosis ensures the proper organisation and function of daughter cells. Inheritance of the Golgi complex, a single copy organelle, requires its disassembly before mitosis; Golgi disassembly is driven by mitotic inhibition of COPII-dependent export of proteins from endoplasmic reticulum exit sites (ERESs) to the Golgi. Helen Hughes and David Stephens have been investigating how ERESs are restored at the end of mitosis and, on page 4032, they report that Sec16A – the major human orthologue of Sec16, which defines the site of COPII vesicle budding in yeast – defines the site at which COPII-dependent budding reinitiates after mitosis. Using quantitative 4D imaging of HeLa cells stably expressing fluorescently labelled Sec16A, the authors show that, unlike all other COPII components, Sec16A remains associated with ERESs throughout mitosis. Moreover, Sec16A localisation is coincident with the reappearance of COPII puncta on mitotic exit. Hughes and Stephens suggest, therefore, that Sec16A provides a template for the assembly of functional export domains in anaphase, thus ensuring that the internal architecture of the cell is restored quickly and effectively on exit from mitosis.