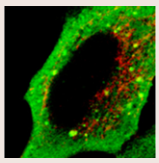
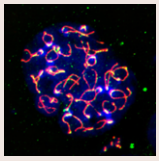
In this issue

By Jane Bradbury



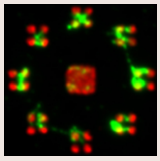
Optineurin minds Rab8′s GAP

Rab GTPases are key components of membrane-trafficking pathways. Each Rab exists in two states in the cell: a GTP-bound active state and a GDP-bound inactive state. Guanine nucleotide exchange factors, which activate Rabs, and GTPase activating proteins (GAPs), which inactive Rabs, regulate Rab cycling and thus membrane trafficking. To date, more than 40 Rab GAPs have been identified, but the mechanisms that target Rabs to their GAPs are unclear. Now, on page 5026, Ghanshyam Swarup and co-workers report that the effector protein optineurin mediates the interaction between Rab8 (which controls several trafficking pathways including endocytic trafficking of the transferrin receptor) with the Rab GAP TBC1D17. The authors show that optineurin, which interacts preferentially with activated Rab8, binds directly to a non-catalytic region of TBC1D17, that Rab8 is linked to TBC1D17 through optineurin, and that this interaction leads to the inactivation of Rab8. Overexpression of TBC1D17 in HeLa cells, they report, reduces recruitment of Rab8 to tubules emanating from the endocytic recycling compartment, and inhibits trafficking of the transferrin receptor. Conversely, knockdown of optineurin or TBC1D17 enhances recruitment of Rab8 to the tubules. Thus, the authors suggest, optineurin negatively regulates Rab8 function by bringing together Rab8 and its GAP TBC1D17.



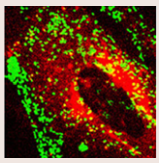
PLK1 gets desynapsis going

During meiosis, completion of homologous recombination and disassembly of the synaptonemal complex (SC), which facilitates chromosome synapsis, must be coordinated during the prophase to metaphase I (G2/MI) transition to avoid the formation of aneuploid gametes. Kinase activity promotes exit from meiotic prophase, but exactly which kinase triggers SC disassembly, the first step in the G2/MI transition? On page 5061, Mary Ann Handel and co-workers implicate polo-like kinases (PLKs) in this process in mouse spermatocytes *in vivo* and during exit from prophase, which has been induced *ex vivo* by the phosphatase inhibitor okadaic acid (OA). The authors report that all four kinase-proficient mouse PLKs are expressed during the first wave of spermatogenesis, but that only PLK1 localises to the SC during the G2/MI transition. They show that several SC central element proteins, including synaptonemal complex protein 1 (SYCP1) and testis expressed protein 12 (TEX12), are phosphorylated during the G2/MI transition, and that PLK1 phosphorylates SYCP1 and TEX12 *in vitro*. Moreover, the PLK1 inhibitor BI 2536 impairs the phosphorylation and removal of central element proteins from the SC and inhibits OA-induced exit from meiotic prophase. Thus, the authors suggest, PLK1-mediated phosphorylation is required for the first stage of SC disassembly in mammalian spermatocytes.



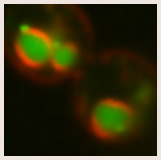
ECM area threshold for focal adhesion assembly

Integrin-based focal adhesion (FA) complexes – which also contain actins, cytoskeletal elements, such as talin and vinculin, and signalling molecules – form following integrin activation and ligand binding, and transmit anchorage and traction forces between the cell and the extracellular matrix (ECM). To investigate the physical parameters of the ECM that control assembly of FAs and force transduction in non-migrating cells, Andrés García and colleagues (p. 5110) have been examining stable FA assembly and force transduction in mouse fibroblasts exposed to artificially engineered ‘nanoislands’ of the integrin ligand fibronectin (FN). The authors report that the size of the individual nanoisland, and not the number of islands or total adhesive area, controls integrin–FN clustering and adhesion strength. They identify a threshold for the ECM area below which few integrin–FN clusters form, and show that this adhesive area threshold is not constant but is regulated by the recruitment of talin and vinculin to the FA complex, and by the cytoskeletal tension applied to these adhesive clusters. On the basis of their results, the authors propose a force equilibrium model for ECM area-controlled assembly of integrin–FN clusters, which provides a simple, local regulatory mechanism for the assembly and disassembly of adhesive structures and the transmission of adhesive forces.



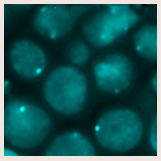
Rab1A brings a touch of colour

Mammalian skin pigmentation is determined by melanocytes, a type of skin cell that synthesises melanin pigments and stores them in melanosomes. These specialized organelles are formed and mature around the nucleus of the melanocyte, and are then transported to the cell periphery by coordinated bidirectional microtubule-dependent and unidirectional actin-dependent movements. The mechanisms of retrograde microtubule-dependent and actin-dependent melanosome transport have been determined, but very little is known about anterograde melanosome transport. Here (p. 5177), by performing a genome-wide screen of members of the mouse Rab family, Mitsunori Fukuda and colleagues identify the small GTPase Rab1A as a potential component of the anterograde microtubule-dependent melanosome transport machinery in mouse melanocytes. The authors report that Rab1A, which was originally described as a Golgi-resident Rab, localizes to mature melanosomes in cultured melanocytes, and show that functional ablation of Rab1A induces perinuclear melanosome aggregation. In addition, they use time-lapse microscopy to show that anterograde, but not retrograde, melanosome transport is suppressed in Rab1A-deficient melanocytes. Together, these results provide the first clues to the machinery involved in anterograde melanosome transport.



Hyperactive Vps21 drives class E compartments

During endosomal maturation, transmembrane proteins targeted for lysosomal degradation are sorted into intralumenal vesicles (ILVs) by endosomal sorting complexes required for transport (ESCRTs). ESCRT dysfunction blocks ILV budding and induces the formation of aberrant stacks of flattened endosomal cisternae called class E compartments. The origin of these compartments is a long-standing mystery, but now Greg Odorizzi and co-workers (p. 5208) suggest that they form in the yeast *Saccharomyces cerevisiae* because of hyperactivity of Vps21, the yeast orthologue of the Rab5A GTPase that promotes early endosomal fusion activity in metazoans. The authors show that the formation of class E compartments requires Vps21, and that the compartments accumulate GTP-bound Vps21 and its effector CORVET (an endosomal tethering complex). E compartments also accumulate Ypt7, the yeast orthologue of Rab7 (which promotes the fusion of late endosomes with lysosomes in metazoans), but do not accumulate the Ypt7 effector HOPS (a tethering complex that is homologous to CORVET). Given these results, the authors suggest that ESCRT dysfunction causes the failure of the Rab5–Rab7 conversion that is thought to guide endosomal maturation, which results in Vps21 hyperactivity that drives the class E compartment morphology.



PKA seals mRNA fate when times are hard

Yeast cells contain two types of RNA nucleoprotein granules – processing bodies (PBs) and stress granules (SGs) – which form in response to stress and in stationary cells, but what are the signalling pathways that induce the formation of these partly overlapping granules? On page 5221, Paula Portela and colleagues investigate the function of the protein kinase A (PKA) signalling pathway in PB and SG formation, and in translational regulation in the yeast *Saccharomyces cerevisiae* during glucose starvation and in stationary phase cells. Previously, the authors showed that the PKA catalytic isoforms Tpk2 and Tpk3 localise to PBs and SGs in yeast. Here, they report that Tpk2 and Tpk3 are associated with the translation initiation factors Pab1 and Rps3 in exponentially growing cells, but that glucose starvation promotes the loss of these interactions followed by the accumulation of Tpk2 and Tpk3 in PBs. Deletion of *TPK2* or *TPK3* affects the capacity of yeast cells to form granules and arrest translation properly in response to glucose starvation or stationary phase, and increases the abundance of the translation initiation factors eIF4G$_1$ and Rpg1. Together, these data reveal several ways in which the PKA pathway coordinates the fate of mRNAs with the nutritional environment and growth status of yeast cells.