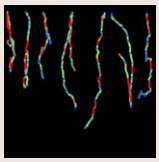
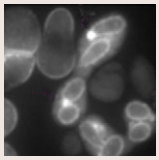
In This Issue



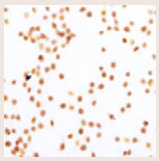
Tumour migration: ERK2 goes it alone

The two predominant isoforms of the extracellular signal regulated kinases are ERK1 and ERK2 (also known as MAPK3 and MAPK1, respectively). These are often considered to be functionally redundant and any differences between the signalling pathways mediated by each of the isoforms have been attributed to their different expression levels. On page 1465, Jim Norman and colleagues now challenge this view by dissecting a specific role for ERK2 in tumour cell migration. Knockdown of the gene encoding ERK2, but not ERK1, with isoform-specific siRNAs results in impaired invasion of breast cancer cells into Matrigel and reduces migration rates on a cell-derived matrix. This effect is rescued by the ectopic expression of ERK2 but not by an equivalent increase in ERK1 expression levels. In addition, the authors identify 27 genes whose expression is specifically controlled by the ERK2 isoform. Two of these genes encode liprin-β2 and the small GTPase Rab17, both of which are upregulated in the absence of ERK2 (but not ERK1). Furthermore, decreasing the expression levels of these proteins promotes invasion of three cancer cell lines into Matrigel, whereas overexpression of either protein impairs cell motility. The authors conclude that ERK2 – but not ERK1 – drives tumour cell motility and invasion by suppressing the gene expression of Rab17 and liprin-β2.



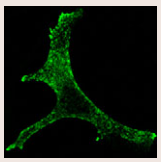
Actin runs rings around spores

In the fission yeast *S. pombe*, gametogenesis occurs through a process referred to as sporulation. In this process, each of the haploid nuclei that is generated during meiosis becomes encapsulated by the forespore membrane (FSM), which ultimately forms the plasma membrane of the newly formed gametes. A number of proteins are known to be crucial for FSM assembly and sporulation. These include actin and actin regulators, as well as components of the septation initiation network (SIN). Here, Hongyan Yan and Mohan Balasubramanian (p. 1429) investigate the roles of these proteins in the sporulation process and show that, during sporulation, F-actin assembles into four ring-like structures: the meiotic actin rings (MeiARs). Assembly, maintenance and constriction of MeiARs, as well as the correct spore formation, require Arp2/3 and the formin For3, known actin nucleators. In addition, actin polymerisation is necessary for the recruitment of these and other proteins to the leading edge – the ring-like structure that guides FSM assembly – and that loss of the actin ring leads to an excessive assembly of deformed FSMs. Furthermore, a fully functional SIN is required for the closure of MeiARs during sporulation. Together, these data highlight a crucial role for these actin rings in recruiting the protein complement that is required for sporulation, and in promoting FSM assembly and spore formation.



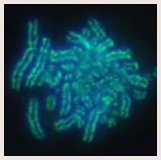
Pro-apoptotic miRNAs battle with BCL2

Apoptosis is essential for the removal of unwanted or damaged cells from an organism. A decrease in the susceptibility of cells to apoptosis can not only cause cancer, but can also result in resistance to anti-cancer drugs that act by inducing apoptosis. BCL2 is an anti-apoptotic protein that prevents disruption of the mitochondrial membrane potential and the release of cytochrome *c*. It is overexpressed in a variety of tumours, where it confers resistance to conventional chemotherapy. On page 1568, Richa Singh and Neeru Saini now describe the pro-apoptotic effects of three microRNAs (miRNAs) that downregulate *BCL2* expression. Using computational and experimental approaches, they show that miR-24, miR-195 and miR-365 negatively regulate BCL2 by binding to the 3′ UTR of the *BCL2* gene. Overexpression of each of the miRNAs reduces *BCL2* expression and BCL2 protein levels and, furthermore, leads to apoptosis through disruption of the mitochondrial membrane potential and the release of cytochrome *c*. Finally, the authors report that overexpression of these miRNAs in MCF7 breast cancer cells augments the apoptotic effect of the etoposide, by increasing the proportion of cells that undergoes apoptosis after exposure to the chemotherapeutic agent. They hope that this miRNA-mediated pro-apoptotic effect can be exploited to develop new therapeutic strategies.



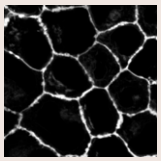
Melanoregulin finds its function

Melanosomes are large membranous organelles that synthesise and transport the pigment melanin. A complex comprising Rab27, melanophilin (MLPH) and myosin Va is involved in transporting melanosomes along actin filaments, and loss of this complex causes perinuclear clustering of these organelles. This can be reversed by mutations in the melanoregulin (*MREG*) gene, but the way in which MREG affects the movement of melanosomes has remained unclear. Mitsunori Fukuda and colleagues (p. 1508) now identify a function for MREG in microtubule-based melanosome transport. Reducing the expression MREG has no effect on melanosome trafficking. However, in melanocytes that lack functional Rab27A, shRNA-mediated knockdown of MREG results in redistribution of the organelles to the plasma membrane. A similar effect is observed when the function of the dynein–dynactin complex is impaired. This leads the authors to conclude that MREG is involved in retrograde melanosome transport along microtubules. Furthermore, they show that MREG mediates this function by associating with the Rab-interacting lysosomal protein (RILP), which binds to the dynactin subunit $p150^{Glued}$ and has a role in lysosomal trafficking. These findings suggest that a common mechanism involving RILP is involved in the regulation of lysosome and melanosome motility.



Condensin I and II unravelled

Condensins are large protein complexes whose name reflects their roles in establishing and maintaining chromosome condensation during cell cycle progression. Vertebrates contain two such complexes, condensin I and condensin II, both of which are essential for establishing mitotic chromosome architecture and for mediating chromosome segregation. Their individual cellular roles have, however, remained somewhat of a mystery. To elucidate these functions, Damien Hudson and co-workers (p. 1591) establish conditional knockouts of essential components of condensin I (CAP-H) and condensin II (CAP-D3) in chicken DT40 cells. Using this set-up, they show that both condensin complexes are essential for cell division and survival. During anaphase, cells that lack functional condensin II display a large number of anaphase bridges; cells without condensin I, however, form finer chromatin threads. In addition, the absence of condensin I results in shorter and wider chromosomes during metaphase, but loss of condensin II results in the formation of long, stretched chromosomes that are twisted and bent. On the basis of these observations, the authors propose that condensin II mediates long-range DNA interactions that provide axial rigidity, whereas condensin I uses this initial structure to wrap DNA into compact chromatin loops.



Ion pump moonlights in cell adhesion

The Na^+/K^+-ATPase is an ion pump that is important for epithelial cell function. It establishes and maintains the membrane potential of the basolateral membrane and mediates solute transport. Recent studies have uncovered another role for the Na^+/K^+-ATPase, by showing that it also acts as an adhesion molecule in the adherens junctions that connect neighbouring epithelial cells. This function requires the interaction of the extracellular domains of two β1 subunits of Na^+/K^+-ATPase on opposing cells. Here, Olga Vagin and colleagues (p. 1605) dissect this interaction and describe the specific amino acid region that is important for mediating Na^+/K^+-ATPase trans-dimerisation. To identify individual residues that mediate the homomeric interaction, they map the amino acid sequences of dog and rat Na^+/K^+-ATPase onto a high-resolution structure of the β1 subunit. In addition, they make use of the observation that species-specific amino acid regions are important for β1–β1 interactions: mutations in the dog β1 subunit that mirror the amino acid sequence of the β1 subunit of rat Na^+/K^+-ATPase reduce the ability of the mutant protein to interact with the endogenous dog Na^+/K^+-ATPase. Site-directed mutagenesis of these species-specific residues reveals that the amino acid region 198–207 in the β1 subunit is crucial for the homomeric interaction of Na^+/K^+-ATPases that supports epithelial cell–cell adhesion.