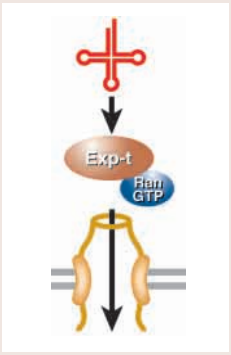
In this issue

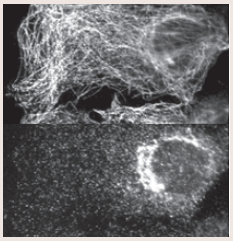
Adult stem cell plasticity – fact or fiction?

Given the obvious therapeutic potential of stem cells, great excitement greeted the claims that adult stem cells from bone marrow and the CNS can jump lineage. Subsequent work has suggested that the apparent transdifferentiation was due to contamination of the donor cells or their fusion with recipient cells, leading some investigators to dismiss adult stem cell plasticity as a fiction. Is it? In a Commentary on p. 599, Malcolm Alison and co-workers examine the evidence. Findings such as the observation that XY (rather than XXXY) mucosal cells appear in women who have received peripheral blood stem cells or bone marrow from male donors suggest that cell fusion cannot account for all transdifferentiation. Moreover, transdifferentiation of bone-marrow-derived stem cells has been observed in co-cultures separated by a semipermeable membrane so that fusion cannot occur. Alison and co-workers also discuss the problem of reproducibility, pointing out that, in cases where transdifferentiation could not be reproduced, conditions were not identical to those in the original experiments. The authors conclude that transdifferentiation probably does occur – but rarely – and that establishing whether transdifferentiated cells can undergo clonal expansion should be the next step.



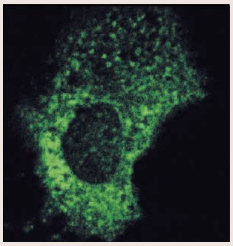
Exporting RNA

Nuclear export – and import – of proteins generally involves the karyopherin family of transport receptors and depends on the gradient of GTP-bound Ran set up across the nuclear envelope. But RNAs that function in the cytoplasm must also be exported. Do they use the same machinery? In a Commentary on p. 587, Bryan Cullen reviews work that has shown that in fact a variety of RNA export mechanisms exist – some karyopherin based, some not. Early analyses of retroviral RNA export indicated that these RNAs bind to adaptor proteins (e.g. HIV-1 Rev) that interact with the karyopherin Crm1, and subsequent work has revealed that Crm1 mediates Ran-dependent export of adaptor-bound snRNAs, rRNAs and certain mRNAs. tRNA export also seems to be Ran dependent, relying on the karyopherin Exp-t, which binds directly to tRNAs. Export of most mRNAs, by contrast, does not involve karyopherins or Ran. Instead these RNAs bind to a protein termed Tap (Mex67p in yeast), which, together with Nxt (Mtr2p), binds directly to nuclear pore components. A common feature of all these mechanisms, however, is the assembly of RNA into RNP complexes, which probably acts as an important proofreading mechanism.



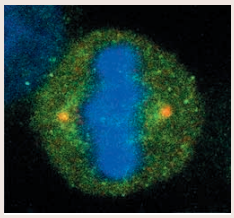
Uncoupling polarization and migration

Cytoskeletal reorganization is essential for polarization and migration of many cells. Both microtubules and actin filaments are implicated in control of polarity, and the formin-family proteins that coordinate them appear to play an important part. But what exactly are the roles of the two filament networks in polarization, and to what extent are they interdependent? Laura Machesky and co-workers have addressed these questions by analysing repositioning of the Golgi and microtubule-organizing centre (MTOC) in NIH3T3 cells polarizing and migrating in response to scratch wounds (see p. 743). By introducing mutant versions of cytoskeletal regulators (e.g. N-WASP and mDia-1) and drugs that selectively interfere with actin/tubulin dynamics, they show that MTOC positioning depends on microtubules, whereas Golgi positioning is controlled by actin. Migration, by contrast, appears to require both types of filament. Interestingly, the authors are able to uncouple it from MTOC/Golgi repositioning by introducing an inhibitor of ROCK (a Rho effector that functions in actin reorganization). Their findings thus not only indicate that actin and microtubules play distinct roles in establishment of polarity but also challenge the view that Golgi/MTOC polarization and cell migration are necessarily linked.



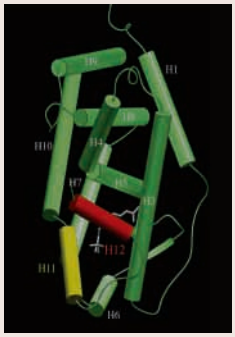
An RNA-binding ubiquitin ligase

RNA-binding proteins play critical roles in various aspects of cell function, such as splicing, transcription termination and mRNA storage. They are similarly essential for viruses whose replication strategies involve RNA intermediates. In a search for proteins that bind to hepatitis B virus (HBV) RNAs, Stefan Kreft and Michael Nassal have identified a human RNA-binding protein, hRUL138, that looks like nothing yet seen (see p. 605). hRUL138 is a 138 kDa cytoplasmic protein that is expressed in most tissues and could be associated with the ER. It contains a novel RNA-binding domain in which the only recognizable motif is a coiled-coil region. Remarkably, hRUL138 also contains the RING-H2 signature characteristic of certain ubiquitin ligases (E3 enzymes). Indeed, Kreft and Nassal show that this has self- and trans-ubiquitin-ligase activity in vitro and can drive proteasome-mediated degradation of hRUL138 in vivo. The cellular target RNA for hRUL138 is not yet clear; however, the unusual combination of RNA-binding and ubiquitin ligase activities in one protein raises some interesting possibilities. Other RNA-binding proteins or RNPs, for example, could be targets of the hRUL138 ubiquitin ligase, and it might use RNAs to increase target specificity.



GSK-3 and spindle dynamics

Glycogen synthase kinase 3 (GSK-3) is a ubiquitously expressed enzyme that is constitutively active in resting cells and phosphorylates a wide variety of proteins – from glycogen synthase to microtubule-associated proteins. During insulin signalling, the kinase PDK1 phosphorylates and activates protein kinase B (PKB), which in turn phosphorylates and *in*activates GSK-3. James Wakefield and co-workers now show that a similar pathway controls spindle dynamics at mitosis (see p. 637). They find that GSK-3 is present along spindle microtubules. In addition, they demonstrate that the phosphorylated form is concentrated at spindle poles and centrosomes, where phosphorylated, active PKB is also present. Using two distinct GSK-3 inhibitors, the authors show that inhibition of GSK-3 leads to an increase in the length of spindle microtubules and defective chromosome alignment at prometaphase. Furthermore, live microscopy reveals that this reduces chromosome movement and produces a prometaphase arrest. Wakefield and co-workers conclude that spatiotemporal control of GSK-3 activity is important for control of microtubule dynamics at mitosis. It could ensure stabilization of microtubules at centrosomes but allow them to remain dynamic elsewhere and thus scour the cytoplasm for chromosomes.



A guide to nuclear receptors

Nuclear receptors are ligand-activated transcription factors that bind to hormones such as oestrogen and progesterone, as well as a variety of other ligands, including vitamin D3 and prostaglandin J2. They form a large gene family – *C. elegans* alone has >270 members – and many have no known ligand. In Cell Science at a Glance, Marc Robinson-Rechavi and co-workers provide a brief introduction to these receptors, including a phylogenetic analysis of the known family members and a summary of their mode of action (see p. 585 + poster).