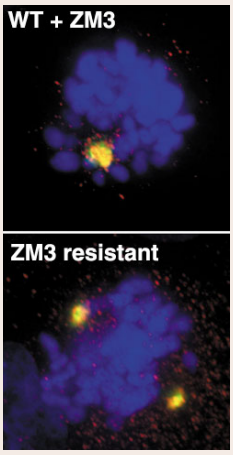
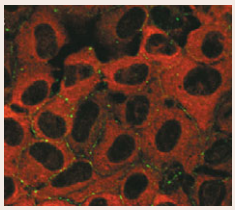
In this issue



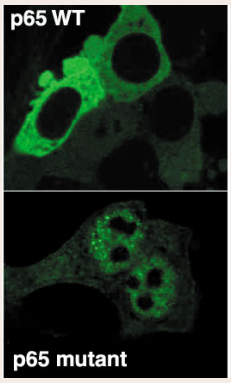
Cancer targets – Aurora B or alias

Aurora kinases regulate various aspects of mitosis and are therefore targets for potential new anti-cancer drugs. The Aurora A/B inhibitor ZM447439, for example, interferes with chromosome alignment, the spindle checkpoint and cytokinesis, making cells exit mitosis without dividing and die. Stephen Taylor and co-workers have combined chemical genetics and molecular genetics to establish whether this is due to inhibition of Aurora A or Aurora B – and thus gain further insights into the functions of these two kinases (see p. 3664). Closely analysing cell lines that stably express dominant negative forms of different Aurora kinases, they find that inhibition of Aurora B most closely mimics treatment of cells with ZM447439. Furthermore they find that a related compound, ZM2, that is much more specific for Aurora B has almost identical effects. By contrast, ZM3, which more potently inhibits Aurora A, produces a rather different phenotype – formation of monopolar spindles. The new work thus not only reveals that Aurora B is the critical target of ZM447439 but also establishes a role for Aurora A in generation of bipolar mitotic spindles.



Nedd4 plugs the gap

The gap junctions that connect neighbouring cells continually turn over, allowing tight regulation of intercellular communication. Proteasomes and/or lysosomes are thought to degrade the connexin proteins that make up these junctions, but how this is regulated has been unclear. Angel Alonso and co-workers now reveal that a ubiquitin ligase, Nedd4, is the key (see p. 3634). Like other ubiquitin ligases, Nedd4 promotes attachment of ubiquitin to its substrates, which marks them for degradation by the proteasome. Alonso and co-workers show that the most common connexin, Cx43, interacts with Nedd4 in vitro and define the regions of the proteins responsible – the interaction involves the C-terminus of Cx43 and all three WW domains of Nedd4. The authors then use coimmunoprecipitation and immunofluorescence analyses to demonstrate that Nedd4 and Cx43 interact in vivo. Critically, they also show that knocking down Nedd4 expression by RNAi leads to accumulation of excessive numbers of Cx43-containing gap junctions at the plasma membrane. Nedd4 therefore appears to play a pivotal role controlling the abundance of gap junctions in cells.

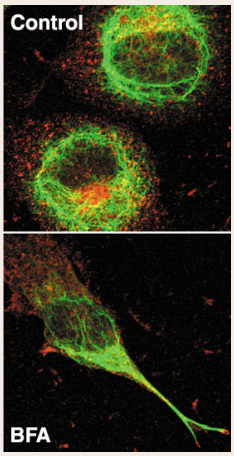


NF-κB – capped by 14-3-3

The transcription factor NF-κB has important roles in the immune response, cancer and inflammation. Its inhibitors, IκB proteins, generally anchor NF-κB in the cytoplasm until an activation signal from a ligand such as tumour necrosis factor α (TNFα) is received. IκBα, however, actively removes NF-κB from the nucleus in unstimulated cells or when signalling must be terminated. On p. 3695, Lluís Espinosa and co-workers implicate another important signalling mechanism – 14-3-3 proteins – in this process. 14-3-3 proteins control the activity, localization and stability of various signalling molecules. Espinosa and co-workers now demonstrate that 14-3-3 proteins interact with both p65 NF-κB and IκBα. They identify the binding sites involved and show that mutations in these cause p65 NF-κB and IκBα to remain in the nucleus. The authors go on to show that TNFα promotes recruitment of 14-3-3 proteins to NF-κB-dependent promoters and that dominant negative 14-3-3 constructs compromise the responses of these promoters to TNFα. 14-3-3 proteins thus appear to be critical for nuclear export of NF-κB, re-establishing the basal level conditions that allow it to be rapidly activated by stimuli such as TNFα.

UnTie'ing angiopoietins

Tie2 is a tyrosine kinase receptor on endothelial cells that regulates the formation and maintenance of new blood vessels. Its ligands are the angiopoietins Ang1 and Ang2. Ang1 stimulates Tie2. Ang2 is more controversial: sometimes it appears to activate the receptor; sometimes it inhibits it. On p. 3551, Daniel Dumont and co-workers reveal that this could be because of what happens after ligand binding. They find that both angiopoietins activate Tie2 but Ang2 is less effective, and only Ang1 induces internalization of the receptor by endothelial cells. Surprisingly, the authors observe that, after binding to Tie2, Ang1 and Ang2 are released back into the medium before the receptor is internalized (most tyrosine kinase receptors are instead internalized with their ligands). They also observe that Ang2 is released more quickly than Ang1. Since Ang1/Ang2 can re-bind to fresh cells once they have been released, the authors propose that they may be recycled and/or reused by endothelial cells. Given the different rates of Ang1 and Ang2 release, this could account for some of the differences in their effects.



Vimentin caught in membrane traffic jam

The cytoskeleton has important roles in membrane trafficking, providing tracks for vesicle transport and helping to maintain the integrity of various organelles. Intermediate filaments such as vimentin play their part and are required for vesicle transport and positioning of endosomes and lysosomes. On p. 3643, Victor Faundez and co-workers show that the reverse is also true: intermediate filament architecture depends on vesicle transport. They find that treatment of cells with brefeldin A (BFA), which blocks various steps in membrane trafficking, also disrupts the vimentin network. The authors demonstrate that the effect is not due to global changes in morphology or Golgi fragmentation induced by BFA. Moreover, they can mimic it by treating cells with mutant forms of ARF1, a small GTPase that regulates vesicle budding. Interestingly, the changes in vimentin architecture involve the reorganization of pre-existing filaments into bundles and are accompanied by relocation of ARF-1-regulated membrane adaptor complexes (AP1 and AP3) to the vimentin network. These findings thus reveal a reciprocal relationship between filament architecture and membrane trafficking and raise the possibility that adaptor proteins recruit factors that bundle intermediate filaments.

Development in press

TWEAKing mammary gland apoptosis

Unlike most organs, mammary glands undergo massive changes during adult life. Epithelial cells proliferate extensively during pregnancy to generate milk for the offspring. When lactation stops, these cells apoptose and the gland is remodelled to its resting state (involution). Baxter and co-workers have been investigating the regulation of involution and, in a paper published in *Development*, they report that this process can be halted by the conditional deletion of the gene encoding IKK2 (inhibitor of κB kinase). This is one of the kinases that regulate the NF-κB pathway, which controls many cellular responses, including apoptosis. The researchers report that the delayed mammary gland apoptosis and remodelling they see in the mutant is associated with decreased expression of the gene encoding the death receptor ligand TWEAK, whose promoter region contains binding sites for both NF-κB and forkhead transcription factors. These new insights into the control of apoptosis in the mammary gland may provide avenues for new therapeutic approaches for the treatment of breast cancer.

Baxter, F. O., Came, P. J., Abell, K., Kedjouar, B., Huth, M., Rajewsky, K., Pasparakis, M. and Watson, C. J. **(2006). IKK?/2 induces TWEAK and apoptosis in mammary epithelial cells.** ***Development*** 133**, 3485-3494.**