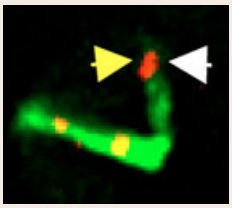
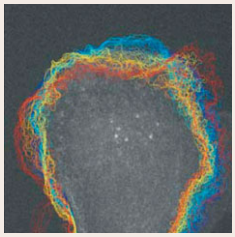
In this issue

by Jenny Bangham



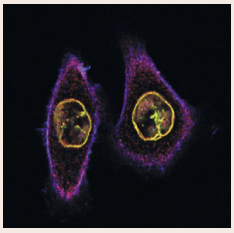
Controlling the Rabl

We know a lot about the mechanisms that control capture of chromosomes by spindle microtubules at mitosis in budding yeast. But how this occurs in fission yeast and what ensures sister chromatids attach to microtubules emanating from opposite poles ('bi-orientation)' are less clear. On p. 3345, Jonathan Millar and colleagues reveal the part the ten-component Dam1/DASH complex plays by examining its role in fission yeast that have a disrupted 'Rabl' configuration. During interphase, centromeres are clustered at the nuclear envelope in a region closest to the spindle pole body (this is the so-called Rabl configuration). In cells that lack the centrosomin-like protein Mto1, the Rabl configuration does not form correctly – one pair of sister chromatids becomes unclustered from the others. The researchers used 3D live-cell fluorescence microscopy to examine what happens to these as the cells enter mitosis. Analysing *Dam1* mutants, they find that the Dam1/DASH complex is needed for intranuclear spindle microtubules to retrieve unclustered kinetochores (the complexes that link sister chromatids to microtubules). When they watch this process in more detail, they see that (unlike in budding yeast) unclustered kinetochores are retrieved at the plus end of a depolymerising spindle microtubule. The authors suggest that the Dam1/DASH complex couples the movement of kinetochores to depolymerisation of spindle microtubules.



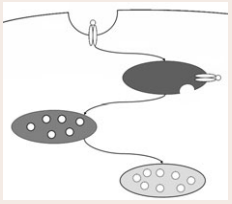
mDia2 – the lamella's formin'

Cell migration relies on the dynamics of two overlapping F-actin networks – one at the edge of the cell (the lamellipodium) and one a few micrometers below the surface (the lamella). Actin-associated proteins regulate both these networks. On p. 3475, Clare Waterman-Storer and colleagues show that one such protein, mammalian Diaphanous-related formin (mDia2), a key nucleator of actin filaments, is crucial for regulating several aspects of F-actin dynamics in the epithelial cell lamella. Studying live cells, they show that mDia2 associates with the actin network in the lamella – but not the lamellipodium. They have blocked mDia2-mediated actin polymerisation by using antibodies or dominant negative constructs and followed the dynamics of F-actin by quantitative fluorescent speckle microscopy (which tracks randomly incorporated fluorescently tagged actin within a polymer). They find that mDia2 affects the stability and organisation of the lamella and is needed to maintain a stable pool of polymerization-competent F-actin filaments at focal adhesions (the structures that link the actin network to the substrate). Interestingly, mDia2 affects the kinetics of F-actin in both the lamella and lamellipodium; mDia2 at focal adhesions might thus somehow regulate the differential polymerisation of these two networks.



Nesprin 3 pinned down

The Nesprins are the only protein family known to localise specifically to the outer membrane of the nuclear envelope. Nesprins 1 and 2 connect the outer and inner membranes through their interactions with Sun proteins and help to position the nucleus via links to actin filaments. Nesprin 3, which was discovered more recently by Arnoud Sonnenberg and colleagues, is less well characterised. On p. 3384, the researchers now describe the complex interactions that localise nesprin 3 to the outer nuclear membrane. They show that the last four residues in its C-terminal KASH domain interact with Sun proteins. They also show that nesprin 3 associates with the N-terminal actin-binding domain (ABD) of plectin – a member of the plakin family that regulates actin dynamics. They find that overexpression of plectin's ABD stabilises the actin cytoskeleton and that this, in turn, disrupts the binding of plectin dimers to nesprin 3 – this indicates that actin dynamics influence the plectin–nesprin-3 interaction. As well interacting with nesprin 3 at its N-terminus, plectin can also bind to intermediate filaments via its C-terminus. The authors therefore suggest that the nesprin-3–plectin interaction links the nucleus to the intermediate filament system.



Internal affairs – the STATs

JAK/STAT signalling couples various receptors to regulation of gene expression, controlling many aspects of the immune system and several developmental pathways. On p. 3457, Stéphane Noselli and colleagues investigate the role of receptor endocytosis in this pathway. Using *Drosophila melanogaster* follicle cells as a model, they focus on the interaction between the ligand Unpaired and its receptor Dome. Using endocytic markers, they identify Dome in early and late endosomes and show that it is mislocalised in cells that have a mutated clathrin heavy chain. The authors therefore suggest that clathrin-mediated internalization controls the amount of Dome available for ligand interactions. By monitoring the activity of STAT transcription factors, they also demonstrate that mutations in several components of the endocytic pathway block signalling. This shows that both internalization and trafficking are required for JAK/STAT signalling; however, the authors were surprised to find that mutations in Rab11 – a protein specifically required for recycling from endosomes – do not affect STAT activity. Consequently, they conclude that that ligand-bound Dome is targeted to the lysosome for both signalling and degradation, suggesting that endocytosis, but not recycling, regulates JAK-STAT signalling.

Chronic inflammation clarified

Chronic inflammation in tissues is characterised by the persistence of leukocytes, continual tissue damage and tissue repair. On p. 3372, Anna Huttenlocher and colleagues describe the first zebrafish model of chronic inflammation and use it to investigate the role of hepatocyte growth factor activator inhibitor 1 (HAI-1, a cell-surface-bound serine protease inhibitor) in the recruitment of neutrophils. The zebrafish has emerged as a useful model of human immunity – its transparency means that immune cells can be tracked easily. HAI-1 mutants – which the researchers identified during a large insertional mutagenesis screen – have a phenotype reminiscent of the human skin condition psoriasis: abnormal epithelial morphology, epidermal hyperproliferation, and inflammation in areas of hyperproliferation. The researchers show that neutrophils behave very differently in response to chronic inflammation than they do in response to wounding. They also show that the HAI-1-mutant phenotype can be rescued by knocking down the type II transmembrane serine protease matriptase, concluding that matriptase functions downstream of HAI-1 in regulation of epidermal proliferation and inflammation.

Development in press

BETs on for spermatogenesis

The conserved bromodomain motif binds to acetylated lysine residues in histones. Although some bromodomain proteins are implicated in chromatin remodelling, the in vivo roles of most are poorly understood. Now, in a paper appearing in *Development*, Shang and colleagues report that Brdt, a testis-specific member of the BET subfamily of double-bromodomain proteins, is essential for male germ cell differentiation. They report that mice possessing two copies of a mutant *Brdt* allele that produces a protein that lacks the first bromodomain ($Brdt^{\Delta BD1}$) are viable but that the males are infertile. The morphologically abnormal sperm that these animals make lack the heterochromatin foci at the perinuclear envelope seen in elongating wild-type spermatids. The researchers also find that there is increased expression of testis-specific histone H1t in $Brdt^{\Delta BD1/\Delta BD1}$ testes. Furthermore, they show that wild-type Brdt (but not $Brdt^{\Delta BD1}$) associates with the *H1t* promoter. Their results indicate that Brdt is involved in the chromatin condensation that occurs during the late stages of spermatogenesis – significantly, some infertile but otherwise healthy men have mutations in the human *BRDT* gene.

Shang, E., Nickerson, H. D., Wen, D., Wang, X. and Wolgemuth, D. J. (2007). The first bromodomain of Brdt, a testis-specific member of the BET sub-family of double-bromodomain-containing proteins, is essential for male germ cell differentiation. *Development* **134**, 3507-3515.