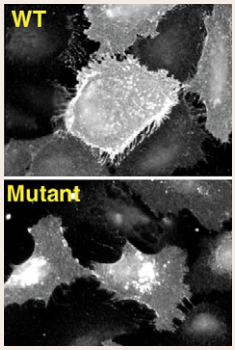
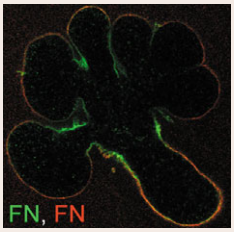
In this issue

by Jane Bradbury



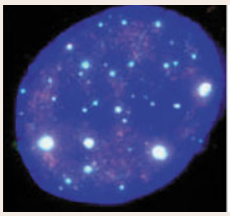
ADAMant about location

ADAM family proteins are membrane proteins that were first shown to function in sperm-egg fusion. Each contains a disintegrin domain and a metalloproteinase domain (though not all are catalytically active), and they are important regulators of cell adhesion and recognition – for example, in muscle and brain development. Ulrike Novak and colleagues have been studying how ADAM22, a catalytically inactive ADAM expressed in the brain, reaches the cell surface. On p. 3296, they report that the cytoplasmic domain of ADAM22 interacts with 14-3-3 proteins. These proteins regulate many important cellular processes – usually by binding to phosphorylated residues in their target. The authors show that brain-expressed 14-3-3 proteins interact preferentially with the phosphorylated precursor form of ADAM22, mainly through the first of two 14-3-3-binding sites in its cytoplasmic tail; ADAM22 mutants that lack these binding sites fail to accumulate normally at the cell surface unless an ER-retention motif is also deleted. Thus, 14-3-3 proteins might help to transport ADAM22 to the cell membrane by masking ER-retention signals – a novel role for this family.



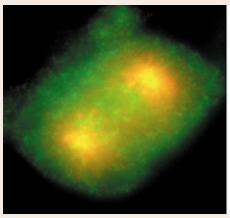
Fibronectin branches out

Branching morphogenesis occurs during the development of many vertebrate organs. In developing mouse salivary glands, for example, deep clefts that form on the surface of primary buds subdivide them into secondary buds, which then grow out. This process is thought to be driven by cell migration and is repeated multiple times to produce a multilobular, branched structure – the buds then develop into secretory units connected by hollow ducts. Melinda Larsen, Cindy Wei and Kenneth Yamada now reveal that branching morphogenesis involves both cell movement and directional assembly of the matrix protein fibronectin (see p. 3376). The authors report that during branching morphogenesis individual epithelial cells in the salivary gland bud move rapidly but randomly. These movements alone cannot explain the highly ordered process of branching morphogenesis. Instead, examination of fibronectin dynamics indicates that this matrix polymer, which is essential for branching morphogenesis, assembles a wedge at the base of developing clefts that moves into the gland. In this way, fibronectin promotes the separation of the actively jostling epithelial cells to facilitate cleft formation and branching morphogenesis.



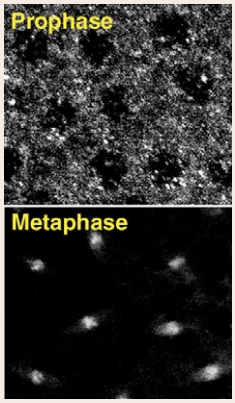
PML body shop for damaged DNA

Promyelocytic leukaemia nuclear bodies (PML-NBs) are one of numerous distinct subnuclear structures that are thought to compartmentalize the nucleus. They contain the PML protein and are associated with various nuclear functions, including transcriptional regulation, apoptosis and the maintenance of genome stability. Now, Stig Ove Bøe and co-authors report that PML-NBs are predetermined processing sites for damaged DNA (see p. 3284). The authors use time-lapse confocal imaging to show that foci of single-stranded DNA (ssDNA) colocalize with preformed PML-NBs within an hour of exposure of cells to UV irradiation. Furthermore, they report, RNAi-mediated depletion of PML (which causes PML-NBs to disappear) prevents formation of these foci after UV exposure. It also sensitizes the cells to UV-induced apoptosis and inhibits S-phase progression in the presence of DNA damage caused by etoposide. Because PML-NBs are present even in unperturbed cells and contain several DNA repair proteins, the authors conclude that they are processing sites for damaged DNA, whether this is produced during normal DNA replication or in response to stresses such as irradiation.



Cyclin' timer for sister separation

During mitosis, cohesin holds the replicated chromosomes together until, at anaphase, its proteolytic cleavage by separase ensures that cell division produces two identical daughter cells. Separase activity is controlled in higher eukaryotes by the inhibitor securin, but cyclin B1 also binds to phosphorylated separase. On p. 3325, Andrew Holland and Stephen Taylor provide new insights into the role of this interaction by reporting that cyclin-B1-mediated inhibition of excess separase is essential for timely chromosome disjunction. They show first that mitosis-specific phosphorylation of human separase on S1126 is required to initiate but not maintain cyclin B1 binding. Then they show that overexpression of a non-phosphorylatable form of separase (S1126A) induces premature loss of sister chromatid cohesion in human cells: securin-mediated inhibition of separase fails because of the overabundance of separase; cyclin-B1-mediated inhibition fails because separase phosphorylation is prevented. Surprisingly, however, chromatid cohesion in these cells is normal in early mitosis. Thus, suggest the authors, yet another inhibition mechanism must prevent cleavage of cohesin by separase during early mitosis.



A GRIPping tale of Golgi inheritance

How a new Golgi complex is produced when cells divide is an important problem in cell biology. Is a new one made from the ER or is the Golgi a unique organelle that duplicates through a template-based mechanism? And how general is the mechanism? On p. 3399, Robert Eisman, Thomas Kaufman and colleagues reveal that in *Drosophila* embryos a template-based mechanism is most likely and implicate the protein centrosomin's beautiful sister (Cbs) in the process. Peripheral membrane proteins called golgins, which often contain a conserved GRIP domain responsible for Golgi localization, have been implicated in Golgi inheritance in vertebrates. The authors report that Cbs also contains a GRIP domain and relocalizes from the cytoplasm to the chromosomes during late prometaphase in flies. This relocalization requires the Cbs GRIP domain and the ADP-ribosylation-factor-like GTPase Arl1. Moreover, it is essential for maintenance of the *trans*-Golgi complex during embryogenesis and centrosome maturation during mitosis. Thus, the embryonic *Drosophila* Golgi complex is more 'vertebrate-like' than previously recognized, making *Drosophila* a good organism for future studies of Golgi inheritance.

Development in press

Cyclin to the terminal

Several cyclins are responsible for regulating the cell cycle. Distinct roles of cyclins that act in the same phase of the cell cycle can be difficult to define, however. In a paper appearing in *Development*, Jacobs and colleagues examine the particularly puzzling case of cyclin A, which is essential for the viability of fly embryos but not needed for all types of mitosis. In the embryonic ectoderm, cyclin A is required only for the very last division before cells become post-mitotic. The researchers have found that this is because, during normal mitotic cycles, cyclin A and cyclin E function redundantly to prevent the premature activity of Fizzy-related/Cdh1 (Fzr), which targets the B-type cyclins and String/Cdc25 for degradation. By contrast, before terminal mitoses, cyclin E is inactivated early, leaving cyclin A to work alone – this means that in cyclin A mutants untimely Fzr activation prevents completion of the division programme. Cyclin A also appears to be crucial for terminal mitoses in neuroblast lineages.

Reber, A., Lehner, C. F. and Jacobs, H. W. (2006). Terminal mitoses require negative regulation of Fzr/Cdh1 by Cyclin A, preventing premature degradation of mitotic cyclins and String/Cdc25. *Development* **133**, 3201-3211.