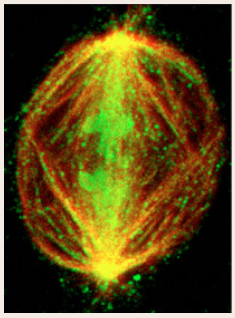
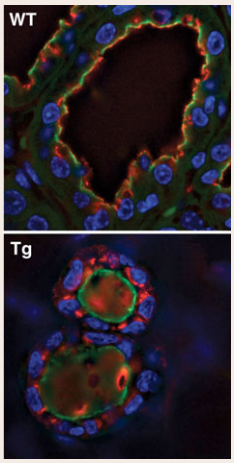
In this issue

by Jane Bradbury



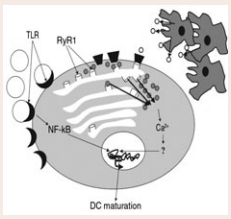
Spindles stretch titin-ically

The giant protein titin provides the elastic force that returns stretched muscle to its resting length. But its elastic properties may not be restricted to muscles, suggest Arthur Forer and co-authors on p. 2190. Titin, they report, might also provide elasticity to the spindle and spindle matrix when insect spermatocytes divide. The authors have raised antibodies against three different fragments of titin and used them to determine the localisation of titin in dividing crane fly and locust spermatocytes. In both species, the antibodies stain the spermatocyte spindle (at all stages of division), the spindle fibres, and the structures that extend between partner chromosomes during anaphase. The spindle matrix proteins skeletor, megator and chromator, the authors report, as well as actin and myosin, are present in many of the same structures and colocalize with titin. They therefore propose that interactions between titin and these proteins might give the spindle and its matrix elastic properties.



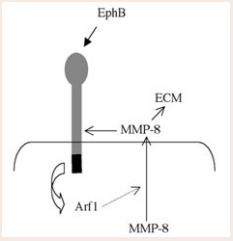
Rho signalling delivers the milk

Milk secretion by mammary glands is established at birth by a complex set of coordinated switches, one of which involves the sealing of tight junctions between secretory epithelial cells. Now Andreas Fisher and co-workers report that the Rho effector protein PKN1 (protein kinase N1) is an important player in the process (see p. 2272). By making transgenic mice that express constitutively active PKN1 in the mammary epithelium, the authors show that, although the mammary glands of these mice develop normally during pregnancy, the mice lactate poorly and their glands involute soon after parturition. By injecting radioactive sucrose intraductally, the authors demonstrate that the epithelial tight junctions in the lactating transgenic glands are poorly sealed. Also, by analysing mammary epithelial cell cultures, they reveal that PKN1 expression interferes with tight junction sealing whereas dominant-negative PKN enhances the process. Together, these observations implicate PKN1 and Rho signalling in the pathway that keeps tight junctions open during pregnancy. The authors suggest that the downregulation of Rho signalling at birth leads to tight junction sealing.



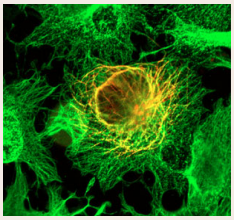
Coffee break for dendritic cell Ca^{2+}

The first step in an adaptive immune response (one tailored to individual pathogens) is maturation of dendritic cells (DCs). These cells live in peripheral tissues and, when microbial products bind to their Toll-like receptors (TLRs), they mature into antigen-presenting cells. These then migrate to lymph nodes, where they stimulate naive T cells. An increase in intracellular Ca^{2+} is also involved in DC maturation, but what drives Ca^{2+} release? On p. 2232, Susan Treves and co-authors provide the first evidence that the type 1 ryanodine receptor (RyR1), an intracellular Ca^{2+} channel found mainly in skeletal muscle, is involved in DC maturation. They show that treatment of immature DCs with the RyR1 agonist caffeine increases intracellular Ca^{2+} levels and that concomitant treatment of these cells with caffeine and suboptimal amounts of TLR ligands leads to DC maturation and stimulation of T-cell functions. The authors propose, therefore, that DC maturation involves cooperation between RyR1-mediated and TLR-mediated signalling, particularly when the levels of TLR ligands are suboptimal.



Ephrin-B1 signal for invasion

Ephrins function as ligands for Eph receptors in many physiological processes, including development of the nervous system. But they also have receptor-like activity themselves. On p. 2179, Ryuichi Sakai and colleagues reveal that this type of 'reverse signalling' by ephrin-B1 promotes the invasive properties of cancer cells by regulating the secretion of matrix metalloproteinase 8 (MMP-8). Ephrin-B1, a transmembrane protein, is often overexpressed in highly invasive tumours. The authors show that binding of the Eph receptor B2 (EphB2) to ephrin-B1 expressed by pancreatic cancer cells promotes their secretion of MMP-8. This reverse signalling activity requires the intracellular C-terminus of ephrin-B1 and involves the activation of Arf1 GTPase, a regulator of membrane trafficking. Furthermore, report the authors, the promotion of pancreatic tumour cell invasion in vivo by ephrin-B1 also requires an intact C-terminus. Thus, they propose, the C-terminus of ephrin-B1 regulates the invasive potential of cancer cells by stimulating the secretion of MMP-8, which promotes extracellular matrix degradation and, consequently, invasion.



CLIMPing down on the translocon

Transmembrane and secretory proteins are made on polysomes attached to the membranes of the ER. Individual ribosomes within the polysomes are attached to the ER by translocon complexes (TCs), which contain numerous transmembrane proteins. The lateral movement of TCs within ER membranes is severely restricted. How is this achieved? The answer, suggest Gert Kreibich and colleagues, is CLIMP-63-mediated binding of microtubules to the ER (see p. 2248). Microtubules are often seen near the ER, and CLIMP-63 is one of the proteins thought to mediate the interaction between these two structures. The authors use fluorescence recovery after photobleaching (FRAP) to show that breakdown of microtubules induced by drugs or overexpression of the microtubule-severing protein spastin increases the lateral mobility of TCs. Knocking down CLIMP-63 by RNAi also greatly increases TC lateral mobility. Thus, propose the authors, the CLIMP-63-mediated interaction between microtubules and the ER might immobilise TCs within membrane-bound polysomes and could help to segregate the rough and smooth ER.

Development in press

Transitin' with Numb

Neurons and glia are generated in the developing CNS by asymmetric division of stem cells in the neuroepithelium. Orientation of the cleavage plane is reported to be important for the localisation of cell-fate determinants, which determine the destiny of the two progeny. In a paper appearing in *Development*, Wakamatsu et al. report that the cytoskeletal component transitin (an intermediate filament protein) also plays a critical role, physically interacting with the cell-fate determinant Numb and anchoring it to the cortex of mitotic neuroepithelial cells. Cell-tracing experiments reveal that movement of this basally located transitin-Numb complex asymmetrically localises Numb to one daughter cell, even when the cleavage plane is perpendicular to the ventricular surface. Interestingly, knocking down transitin by RNAi both reduces the levels of basally located Numb and also promotes differentiation. The goal now is to establish the mechanisms by which transitin can drive cell differentiation as well as the lateral movement of Numb.

Wakamatsu, Y., Nakamura, N., Lee, J.-A., Cole, G. J. and Osumi, N. (2007). Transitin, a nestin-like intermediate filament protein, mediates cortical localization and the lateral transport of Numb in mitotic avian neuroepithelial cells. *Development* **134**, 2425-2433.