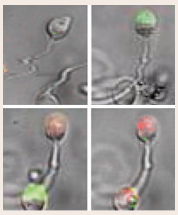
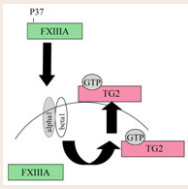
In this issue



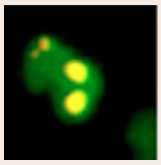
The acrosome reaction in real time

The sperm acrosome reaction (AR), which is an essential step in mammalian fertilisation, involves the calcium-dependent exocytosis of the acrosome (a single large vesicle in the apical sperm head). During the AR, acrosomal proteolytic enzymes are released and the inner acrosomal membrane (IAM) is exposed, but little is known about the temporal relationship between these two events. Now, Claire Harper and colleagues (p. 2130) address this issue by visualising AR progression in real time in living human sperm. Using two probes to detect the exposure of acrosomal content and of the IAM simultaneously, the authors show that the AR is a two-phase process – membrane fusion between the acrosome and the plasma membrane (which exposes acrosomal content) occurs rapidly, whereas the dispersal of acrosomal content (to reveal the IAM) is a very slow process that takes up to 12 minutes. The authors go on to show that sperm cells in which the AR is induced by the calcium ionophore A23187 survive for approximately 30 minutes. By contrast, most sperm cells that undergo spontaneous AR are those that are already non-motile or non-viable, which suggests a mechanism by which poor-quality sperm might be eliminated in vivo. These data provide the first insights into the dynamics of the AR.



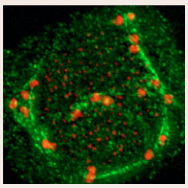
Boning up on transglutaminases

The calcification of the extracellular matrix (ECM) is crucial for bone formation, and inappropriate calcification is a hallmark of osteoarthritis. Mature chondrocytes (which have undergone hypertrophic differentiation) stimulate calcification and ECM remodelling, but the factors that drive chondrocyte maturation remain poorly understood. Chondrocyte transglutaminase (TG) enzymes, particularly TG2, are known to have an important role in hypertrophic differentiation, and Kristen Johnson and colleagues (p. 2256) now show that TG2 acts in concert with another chondrocyte TG, Factor XIIIA (FXIIIA). The authors show that exogenous FXIIIA induces hypertrophic differentiation in chondrocytes, even when its TG catalytic activity is abolished by site-directed mutagenesis. FXIIIA stimulates the rapid relocation of TG2 to the cell surface (a process that is known to be necessary for TG2-dependent differentiation), as well as the phosphorylation of p38 MAP kinase. Moreover, exogenous FXIIIA engages the α1-integrin subunit, and crosslinking between α1- and β1-integrin stimulates TG2 relocation even when FXIIIA is absent, which indicates that FXIIIA acts via an α1β1-integrin-dependent pathway. Thus, TG2 and FXIIIA comprise a functional network that accelerates chondrocyte maturation.



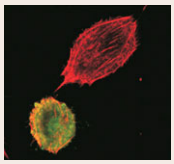
The unsolved case of nucleolar TERT

The ribonucleoprotein telomerase extends the replicative lifespan of cells by inhibiting telomere shortening, but little is known about the site of its biogenesis. The two essential components of telomerase both associate with nucleoli in human cells – the RNA moiety (TERC) is processed and matured there, and the protein catalytic subunit (TERT) shuttles between nucleoli and the nucleoplasm. Are nucleoli, therefore, the sites of telomerase biogenesis? On page 2169, Jun Jian Huang and colleagues show that this is unlikely to be so. By analysing a series of TERT-GFP constructs, the authors show that a short, positively charged peptide sequence within the C-terminus of TERT acts as a nucleolar-targeting sequence (NTS). The authors replace three of the positively charged amino acids within the NTS with alanine residues, and show that the mutant protein does not localise to the nucleolus, even in response to DNA damage (which promotes the nucleolar accumulation of TERT in cancer cells). Surprisingly, however, mutant TERT counteracts telomere shortening in both fibroblasts and cancer cells; moreover, the mutant protein extends the replicative lifespan of fibroblasts, as wild-type TERT does. The authors conclude that the nucleolar localisation of TERT is not required for telomerase activity or biogenesis.



A meiotic mission for SMG7

Proteins that contain ever shorter telomere 1 (EST1) domains have evolutionarily conserved roles in nonsense-mediated mRNA decay (NMD) and telomere metabolism, but little has been known about how these proteins function in intact multicellular organisms. Now, however, Karel Riha and colleagues (p. 2208) identify SMG7, an essential EST1-domain-containing protein in *Arabidopsis*, and characterise its role in whole plants. As well as showing that NMD is impaired in plants that carry a hypomorphic *smg7* mutation, the researchers uncover a novel role for SMG7 – they show that the mutant plants are sterile, and that this results from a defect in meiosis. Pollen mother cells within the floral buds of the mutant plants arrest at the anaphase-telophase transition in meiosis II, and exhibit delayed chromosome decondensation and aberrant rearrangement of the mitotic spindle. Notably, treating wild-type *Arabidopsis* with a proteasomal inhibitor leads to a similar phenotype; the authors hypothesise, therefore, that SMG7 is required for the downregulation of cyclin-dependent kinases (a key requirement for exit from anaphase II). These results expand the functional repertoire of EST1-domain-containing proteins.



Actin makes a move with annexin A2

The dynamic remodelling of the actin cytoskeleton is crucial for cell adhesion and motility, and can be triggered by stimuli that activate the insulin receptor (IR) and other receptor tyrosine kinases. IR activation promotes cell motility by disrupting cell-substrate contacts, but many of the steps in this signalling cascade are unknown. On page 2177, Volker Gerke and colleagues now identify a key stage in the pathway – the tyrosine phosphorylation of the phospholipid- and actin-binding protein annexin A2. The authors use baby hamster kidney cells that overexpress the human insulin receptor to show that annexin A2 is tyrosine phosphorylated in response to insulin; in addition, annexin A2 and the IR co-immunoprecipitate, which suggests that the IR phosphorylates annexin A2 directly. Rho/ROCK signalling, the authors show, mediates insulin-induced morphological changes, and knocking down annexin A2 inhibits insulin-triggered Rho activation and actin rearrangements. Importantly, a phosphotyrosine-mimicking annexin A2 mutant induces actin rearrangements in the absence of insulin. The authors propose, therefore, that the tyrosine phosphorylation of annexin A2 links IR activation to Rho/ROCK-mediated actin rearrangement and cell adhesion.

Development in press

Developing the CNS with Src kinases

During nervous-system development, axons are guided by many attractive and repulsive cues. For example, members of the RYK/Derailed family of inactive receptor tyrosine kinases guide axons in the *Drosophila* ventral nerve cord and in the mammalian brain by acting as Wnt receptors. In a paper published in *Development*, Lee Fradkin and colleagues reveal how these kinase-inactive RYKs might transduce Wnt signals. The authors report that WNT5-mediated signalling through Derailed in the *Drosophila* embryonic CNS involves the non-receptor Src family tyrosine kinases SRC64B and SRC42A. *Src64B/Src42A* double mutants, they show, have defects in the formation of the nerve-fibre tracts that connect the two sides of the brain (commissures); these are similar to the defects that are seen in *Wnt5* and *derailed* mutants. Derailed and SRC64B, they report, form a complex, the formation and/or stability of which requires SRC64B activity. Furthermore, the mammalian orthologues of these proteins also form complexes together. Thus, Src family kinases might play novel roles in Wnt5/Derailed signalling during CNS development in flies and in mammals.

Wouda, R. R., Bansraj, M. R. K. S., de Jong, A. W. M., Noordermeer, J. N. and Fradkin, L. G. (2008). Src family kinases are required for WNT5 signaling through the Derailed/RYK receptor in the *Drosophila* embryonic central nervous system. *Development* **135**, 2277-2287.