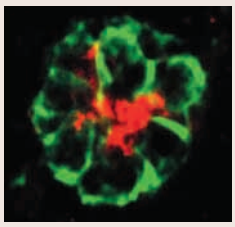
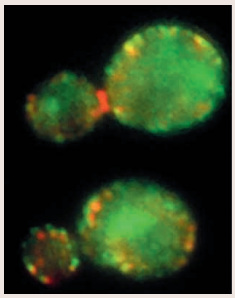
In this issue



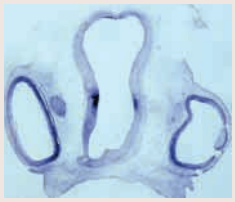
Signalling in 3D

'Physiological relevance' is essential in research into intracellular signalling. Nevertheless, much of our understanding of signalling has been gleaned from studies in 2D cell cultures or in vitro rather than in 3D contexts that mimic the situation in vivo. In a Commentary on p. 2377, Karen Schmeichel and Mina Bissell discuss the range of 3D model systems that now allow examination of how the 3D environment affects how cells perceive and interpret extracellular signals. These range from monotypic 3D cultures in which cells are embedded in laminin-rich reconstituted basement membrane, which have underscored the importance of the extracellular matrix in control of differentiation, to xenograft in vivo models. The latter are highlighting the importance of the stroma in control of organ function, showing, for example, that it is necessary for elaboration of mammary structure and plays an important role in promoting tumour development. Schmeichel and Bissell suggest that these models have immense potential for assessment of potential therapeutic agents but conclude that ultimate physiological relevance will be achieved only once we can model not just tissues but entire organs in vivo.



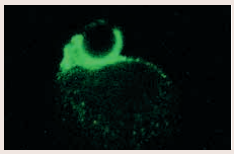
Actin' roles in endocytosis

Reorganization of the actin cytoskeleton is thought to play an important role in endocytosis, but the precise role of actin rearrangements and the specific actin-associated proteins involved have remained obscure. Kathryn Ayscough and co-workers now implicate two budding yeast proteins in the process: Sla1p, an adaptor that binds to the yeast homologue of the actin regulator Wiskott-Aldrich syndrome protein (WASP); and Sla2p, a yeast homologue of huntingtin-interacting protein (HIP1) that localizes to clathrin-coated pits (see p. 2551). The authors show that Sla1p and Sla2p interact in vitro, map the regions of the proteins responsible and demonstrate that the two proteins exist as a complex in vivo. They also show that *sla1* and *sla2* mutations impair endocytosis and that a truncated Slap1p construct containing the Slap2-interacting region inhibits both endocytosis and subsequent vesicle trafficking. Interestingly, Ayscough and co-workers find that the proteins have opposing effects on actin dynamics, using the actin-disrupting drug latrunculin A to show that Sla1p destabilizes F-actin whereas Sla2p stabilizes it. They therefore propose that Sla1p and Sla2p facilitate cycles of actin assembly and disassembly required for reorganization of the cytoskeleton during endocytosis.



Rethinking Wnt antagonists?

Wnt family members, such as Wingless, regulate cell fate and cell behaviour by binding to G-protein-coupled Frizzled (Fz) receptors, activating a canonical signalling pathway that stabilizes the transcription factor β-catenin and non-canonical mechanisms such as the planar cell polarity pathway. Secreted Fz-related proteins (SFRPs) antagonize Wnt signalling and are thought to function as competitive inhibitors that prevent Wnt molecules from interacting with Fz receptors. Work by Paola Bovolenta and co-workers, however, indicates that their mode of action might actually be more complex (see p. 2471). Using in vitro and in vivo approaches, they demonstrate that, during chick retinal development, SFRP1 promotes retinal ganglion and cone photoreceptor cell generation while inhibiting generation of amacrine cells. Interestingly, SFRP1 appears to promote retinal cell differentiation without affecting β-catenin-dependent transcription; in fact, the authors find that canonical Wnt signalling does not seem to operate in these cells under normal conditions. They implicate inhibition of glycogen synthase kinase 3β (usually a consequence of Wnt action rather than Wnt antagonism) in the SFRP1 effect. The authors therefore suggest that Wnt-independent mechanisms of SRFP1 action exist, perhaps involving direct binding of SFRP1 to Fz receptors.



MHC-II molecules and lipid rafts

MHC class II (MHC-II) molecules are best known for their function in antigen presentation – they promote T cell activation by displaying processed antigenic peptides on the surface of monocytes and other antigen-presenting cells. These cell surface molecules also have a lesser known signalling function, however, transmitting signals to tyrosine kinases and protein kinase C (PKC) that stimulate cell proliferation, cytokine release and apoptosis. Nuala Mooney and co-workers now delve further into MHC-II signalling (see p. 2565). They demonstrate that, in solid tumors expressing the MHC-II molecule I-A^k, engagement of I-A^k induces its recruitment to the detergent-insoluble glycolipid (DIG) fraction of the membrane – i.e. lipid rafts. The authors go on to show that PKCα is recruited to these rafts, and activated, when I-A^k is engaged. Furthermore, they show the disruption of the rafts by depletion of cholesterol blocks recruitment and activation of PKCα, as well as the actin rearrangements that occur during MHC-II signalling. These experiments thus reveal a critical role for lipid rafts in signalling by MHC-II molecules, placing recruitment of these molecules upstream of early signalling events such as PKC activation.

Sticky Wicket – a question of belief

The contributors to the Sticky Wicket column have expressed their opinions of scientific meetings on numerous occasions – Caveman has queried the motivation of 'skistoners', for example, and The Wicked Witch has damned the superstars who never stay around long enough to hear anyone else speak. Well now it's Mole's turn (see p. 2373). He ponders why we attend meetings in the first place. Is it to learn what's new – or is it to find out who to believe?

Development in press

Clonal expansion in stem cell niches

Stem-cell-associated stromal cells create a signalling microenvironment – a niche – that sustains the self-renewing and asymmetric properties of stem cell divisions. The *Drosophila* ovary is an ideal system for investigating how these niches form and recruit stem cells. In a study appearing in *Development*, Zhu and Xie have analysed the occupation of the ovarian niche by primordial germ cells (PGCs). They report that, as niche formation begins, one population of PGCs directly differentiates, while an anterior population, which lies adjacent to the cells that create the niche, develops into germline stem cells. These anterior PGCs exhibit distinctive division patterns and require *dpp* signalling to maintain normal proliferation. Importantly, lineage-tracing analyses revealed that a single PGC can occupy a whole niche through clonal expansion. These findings offer valuable insights into how other niches might form.

Zhu, C.-H. and Xie, T. Clonal expansion of ovarian germline stem cells during niche formation in *Drosophila*. *Development* **130**, 2579-2588.