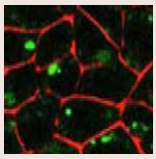
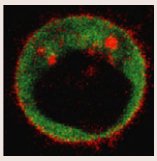
In this issue



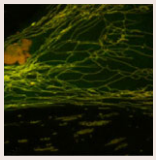
The latest word in cytokine crosstalk

Feedback inhibition of pro-inflammatory cytokine-mediated signalling is essential for preventing chronic inflammation. Crosstalk between cytokine signalling pathways occurs at multiple levels; for example, interleukin-1β (IL-1β) inhibits IL-6-mediated signalling by acting at IL-6 target gene promoters, by regulating expression of the IL-6 feedback inhibitor SOCS3 and by suppressing IL-6-induced activation of the transcriptional activator STAT3. On page 947, Fred Schaper, Heike Hermanns and colleagues shed light on the molecular details of this latter mechanism. They first show that inhibition of IL-6-mediated STAT3 activation by IL-1β requires activation of the p38 MAPK signalling pathway. Second, IL-1β triggers increased internalisation and degradation of the gp130 subunit of the IL-6 receptor (which also forms receptors for other IL-6-family cytokines). Third, IL-1β-induced gp130 internalisation requires phosphorylation of Ser782 in the cytoplasmic domain of gp130. Fourth, the authors identify MAPK-activated kinase 2 (MK2; a downstream target of p38) as the kinase that phosphorylates gp130 Ser782. Finally, the authors show that TNFα and cellular stress also induce this novel inhibitory pathway of cytokine crosstalk.



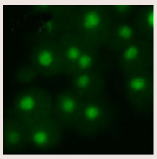
Twice as nice: TRPC3 in BCR signalling

Ca^{2+} signalling is crucial for B-cell activation. Although the roles played by store-operated Ca^{2+} entry (SOCE) channels in this process are well known, the physiological importance of diacylglycerol (DAG)-activated Ca^{2+} entry pathways have remained elusive. Now, on page 927, James Putney, Jr, Yasuo Mori and colleagues describe the crucial role of the transient receptor potential canonical 3 (TRPC3) channel in the context of B-cell receptor (BCR) signalling. Using avian DT40 B cells, the authors show that native TRPC3 forms DAG-activated Ca^{2+}-entry channels, but not SOCE channels. The influx of Ca^{2+} via TRPC3 following BCR activation amplifies the Ca^{2+} signal, as well as downstream activation of the transcription factor NFAT, by controlling translocation of phospholipase Cγ2 (PLCγ2) to the plasma membrane; it also sustains the translocation of protein kinase Cβ (PKCβ), leading to activation of extracellular signal-related kinase (ERK). Interestingly, the authors also show that direct association of TRPC3 and PKCβ maintains localisation of PKCβ at the plasma membrane, leading to sustained BCR-induced MAPK activation. Thus, TRPC3 sustains PKCβ and ERK activation in B cells by functioning as both a DAG-activated Ca^{2+}-entry channel and a scaffolding platform at the plasma membrane.



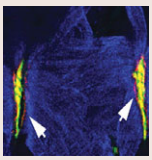
Aged cells: in the PINK1

Mitochondrial elongation is observed on entering senescence in many cell types – but the functional consequence of this change in mitochondrial dynamics has been unclear. Marina Jendrach and colleagues now report that mitochondrial elongation in senescent cells enables resistance to oxidative stress (p. 917): senescent cells are resistant to mitochondria-targeted photodamage, whereas young cells exhibit mitochondrial fragmentation and a loss of mitochondrial membrane potential upon the same treatment. Notably, mitochondrial elongation in senescent cells correlates with decreased expression of two mitochondrial fission factors, Drp1 and Fis1. Furthermore, compared with young cells, senescent cells express higher levels of a ubiquitous kinase known as PINK1; mutations in *PINK1* have been linked to neuropathology in Parkinson's disease (PD). PINK1 does not seem to be directly involved in mitochondrial fission or fusion events, but knockdown of its expression makes senescent cells prone to photodamage. Finally, the authors show that decreased expression of Drp1 and Fis1 is required for increased PINK1 expression in senescent cells. Therefore, alterations in mitochondrial dynamics via Drp1 and Fis1 trigger a PINK1-mediated protective mechanism in senescent cells that, when dysregulated, might contribute to the progression of age-related diseases, including PD.



Dual regulation of a *Dicty* STAT

The *Dictyostelium* STAT orthologue STATc is activated when cells are exposed to hyperosmotic stress, and Jeffrey Williams and colleagues (p. 837) present evidence for two complementary pathways for its activation: an orthodox STAT signalling pathway that activates the STATc tyrosine kinase and a parallel pathway that inhibits the STATc tyrosine phosphatase. PTP3, which de-phosphorylates STATc, is itself phosphorylated and is thereby inhibited by stress, leading to a net STATc activation. There are two stress-induced phosphorylation sites on PTP3: serine residues 448 and 747. Stress induces intracellular cGMP accumulation, and 8-bromo-cGMP, its membrane-permeable form, activates STATc. This response is abrogated in a null mutant for cGMP-binding protein C (GbpC), a founder member of the ROCO protein family. Surprisingly, phosphorylation at Ser448 and Ser747 is not induced by 8-bromo-cGMP, indicating a PTP3-independent activation pathway. The authors propose that cGMP functions as a positive STATc regulator by acting via GbpC on the STATc tyrosine kinase. So which second messenger directs phosphorylation of PTP3 and thereby induces STATc activation? By showing that agents that elevate intracellular Ca^{2+} levels are potent STATc activators that stimulate Ser448 and Ser747 phosphorylation, the authors prove that intracellular Ca^{2+} fits the bill nicely.



Analysing integrin turnover in vivo

Dynamic turnover of integrin adhesion complexes (IACs) is important for regulating the strength and duration of cell adhesions, which, in turn, influence processes such as cell migration and tissue morphogenesis. In vitro studies have helped to shed light on the mechanisms underlying IAC dynamics; now, Guy Tanentzapf and colleagues (p. 939) analyse this issue for the first time in a live animal by studying myotendinous junctions (MTJs) in *Drosophila* embryos and larvae. They find that stable, long-term IACs in MTJs are dynamic, and that IAC turnover requires clathrin-mediated endocytosis of integrins from the plasma membrane. In line with the known role of Rab GTPases in regulating integrin turnover in migrating cells, Rab5 is found to regulate IAC turnover and, consequently, the integrity of MTJs in vivo. Finally, the authors show that the increase in the size of MTJs that occurs as *Drosophila* larvae develop correlates with a decrease in the mobility of several IAC components. Therefore, they conclude, the turnover of stable, long-term IACs is regulated by coordinated recycling of IAC components by clathrin-mediated endocytosis, and this process is developmentally regulated to maintain tissue integrity during morphogenesis.

Development in press

Pigs cytolinks Notch to morphogenesis

Developmental cell shape changes are largely mediated by the cytoskeleton, but how do signalling pathways impinge on the cytoskeleton to direct morphogenesis? In a new study published in *Development*, Katja Röper and colleagues suggest that Pigs, a 'cytolinker' that contains an actin-binding and a microtubule-binding domain, enables Notch signalling to coordinate cytoskeletal changes in *Drosophila*. *pigs* (*pickled eggs*) was recently identified as a Notch target gene. To test whether Pigs links Notch-induced cell-fate decisions and morphogenesis, the researchers generated a null *pigs* mutant. Mutant flies are flightless because of flight-muscle degeneration, they report, and female mutants are sterile because of disrupted oogenesis and defective follicle-cell differentiation, similar to those defects caused by disrupted Notch/Delta signalling in these tissues. In addition, Notch signalling is increased in several tissues in the *pigs* mutants. Together, these results suggest that Pigs acts downstream of Notch as a morphogenetic read-out and as part of a negative loop that regulates Notch activation during morphogenesis in certain tissues.

Pines, M. K., Housden, B. E., Bernard, F., Bray, S. J. and Röper, K. (2010). The cytolinker Pigs is a direct target and a negative regulator of Notch signalling. *Development* **137**, 913-922.