Say Yes to self-renewal

The combination of leukaemia inhibitory factor (LIF) and serum is sufficient to maintain embryonic stem cell (ESC) self-renewal. On page 1136, Cecilia Annerén and colleagues now provide further insight into the molecular mechanisms regulating this process. Previous studies have shown that LIF activates gp130; this signal transducer then activates – among others – Src family kinase (SFK) signalling pathways. Focusing on the SFK Yes, Annerén and coworkers identify a network of signalling events that ensure sustained ESC self-renewal in response to LIF. Direct interaction of the Yes SH2 domain with gp130 activates the kinase and recruits the Yes-associated protein YAP. This, in turn, results in the tyrosine phosphorylation of YAP and its translocation to the nucleus. There it acts as a transcriptional co-activator by binding to TEAD2, a member of the TEA domain protein family. Formation of the YAP–TEAD2 complex leads to increased transcription of Oct-3/4 and Nanog, thereby promoting ESC self-renewal. In addition, this system seems to be carefully balanced by an autoregulatory loop to ensure the proper maintenance of cell fate. The authors show that overexpression of Nanog substantially decreases TEAD2-dependent transcriptional activity through an as-yet-unknown mechanism.

Mitochondria: in the PINK1

The gene encoding the mitochondrial PTEN-induced putative kinase 1 (PINK1) is required to clear depolarized mitochondria from the cell by mitophagy (mitochondrial autophagy). Mutation of PINK1 causes mitochondrial dysfunction, which has recently been linked to the development of the neurodegenerative movement disorder Parkinson’s disease. However, the mechanistic role of PINK1 in mitochondrial and cellular function under physiological conditions is not yet understood. On page 1115, Veerle Baekelandt and colleagues now demonstrate that PINK1 is a key regulator of mitochondrial homeostasis and energy metabolism under physiological conditions. The authors show that depletion of PINK1 by RNAi triggers fragmentation of the mitochondrial network, mitochondrial membrane depolymerisation and increased production of reactive oxygen species, which is indicative of changes in mitochondrial physiology. Furthermore, depletion of PINK1 or targeted gene knockout of PINK1 in mouse brain impairs mitochondrial ATP synthesis, especially under conditions of increased energy demand, thereby indicating that PINK1 is crucial for cellular energy maintenance. The authors conclude that these findings demonstrate that PINK1 is key to the regulation of mitochondrial function, and also provide further insight into how the loss of PINK1 function might lead to neurodegeneration in Parkinson’s disease.

Hair cells feel the stress

When the hair cells in the inner ear die, the ability to hear is lost. Known triggers of deafness include old age, noise and ototoxins such as aminoglycoside antibiotics. On page 1145, Emily Towers and colleagues shed light onto the cellular mechanisms that link damage-inducing factors and hearing loss. It has been shown previously that mutations in the transcription factor Pou4f3 result in deafness; Towers and colleagues now show that Pou4f3 can alter the expression pattern of Caprin-1 by the repression of a promoter in the Caprin-1 5’ flanking sequence. When Caprin-1 repression is relieved, the enhanced Caprin-1 expression results in increased stress granule formation in an inner ear sensory epithelial cell line. To investigate how this process is related to deafness, the authors expose rat cochlear explants to the antibiotic neomycin. Following treatment, hair cells begin to die within 6 to 12 hours. At the same time, Pou4f3 transcript levels decrease, whereas – in line with the observations in vitro – the levels of Caprin-1 mRNA and the number of stress granules increase. Pou4f3 and Caprin-1, therefore, are not only components of the stress response activated following exposure to ototoxins, but might also have an important role in the mechanism underlying deafness.

Neutrophils eat in two ways

When it comes to destroying pathogens, neutrophils aren’t picky. Regardless of the type of pathogen, neutrophils recognise the target and migrate to the infection site to engulf it. On the basis of such a standard response, one might expect that all pathogen-recognition signals culminate in the same phagocytic response. On page 1106, Volkmar Heinrich and colleagues now show that this isn’t so. Using a dual-micropipette system, they discover that neutrophils elicit target-specific responses to distinct immune threats. Phagocytosis of a zymosan particle – an insoluble fraction from yeast cell walls that mimics fungal infection – begins with protrusion of a transient cellular pedestal that initially pushes the target away. During this phase, pseudopod growth occurs in a direction normal to that of the cell–target contact zone. Phagocytosis of antibody-coated beads similar in size to zymosan particles, however, is quite different: there is no ‘push-out’ phase and the process instead begins with the formation of pseudopodial lamellae that move tangentially to the bead surface. As a result, the beads are engulfed approximately 2.5 times faster. Actin is a key regulator of these differences, playing a dual role in mediating, on the one hand, protractive deformation following zymosan recognition and, on the other hand, inhibiting this deformation locally during antibody-mediated phagocytosis.

Visualising collective cell mobilisation

Wound healing is dependent on the collective mobilisation of cells surrounding a wound to the wound edge. Quantitatively assessing the behaviour of such a body of cells within an epithelial sheet has proved difficult, with many current methodologies being reliant on advanced computer technologies. Yutaka Matsubayashi, Paul Martin and co-workers reveal, on page 1017, a new and simple technique to visualise and quantitatively track the mobilisation of a large number of individual cells. The authors applied this technique to study cellular migration of cultured epithelial cells, following an artificial scratch wound, and visualised a ‘white wave’ of cells that moved back from the wound edge. The authors determined that only a finite number of cells are mobilised, thereby imposing a putative limit on the size of wound that can heal naturally. Indeed, the contractile force exerted on cells in intact epithelia by the motor protein non-muscle myosin II negatively regulates this collective mobilisation of epithelial cells, which could prevent excessive cellular migration to a wound site. Interestingly, however, inhibiting myosin II activity was found to accelerate the healing of large wounds over the long term, probably through enhanced cellular mobilisation. Thus, the authors propose that modulating this cellular mobilisation wave might be a future therapeutic target for improved wound healing.

Development in press

Keeping an Eya1 on lung cell polarity

To function correctly, the epithelial cells that line the tubes and air sacs of mammalian lungs need to be polarised. Little is known about the mechanisms that control cell polarity in the lung epithelium but, in Development, David Warburton and co-workers now implicate the protein phosphatase Eya1 in cell polarity control in the mouse distal embryonic lung epithelium, which represents the epithelial progenitor pool. The researchers show that distal embryonic lung epithelium is polarised with characteristic perpendicular cell divisions. They report that several spindle orientation regulatory proteins and the cell-fate determinant Numb are asymmetrically localised in distal embryonic lung epithelium. Furthermore, interfering with the function of these proteins in vitro randomises spindle orientation and alters cell fate. Importantly, the researchers show that interfering with Eya1 function in vivo or in vitro results in defective epithelial cell polarity and mitotic spindle orientation, disrupts Numb segregation and inactivates Notch signalling, thereby establishing Eya1 as a crucial regulator of the complex behaviour of distal embryonic lung epithelium.