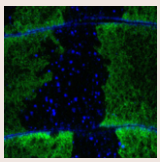
In this issue

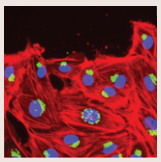


Characterising the role of Dmon1 in endosomal trafficking

Endosomal trafficking regulates the cellular transport of extracellular cargo from the plasma membrane to the lysosome through endocytic vesicles that mature along the way. Rab conversion, the replacement of the small GTPase Rab5 on endosomes with Rab7, is an important step in their maturation. Previous studies in other systems have shown that members of the Mon1 protein family are important for Rab7 recruitment, although the underlying mechanisms remain unclear. On page 1583, Thomas Klein and co-workers now characterise the *Drosophila* Mon1 homologue Dmon1 (encoded by CG11926). They find that loss of Dmon1 results in enlarged maturing endosomes that lack Rab7 and contain Notch and other transmembrane proteins as their cargo. The authors then investigate the *Drosophila* homologue of Ccz1p (which they refer to as Dccz1, encoded by CG14980), which in yeast has been found in a complex with Mon1, but whose functions in endosomal trafficking in metazoans are unknown. When they knock down *Dccz1* by using RNA interference, they observe a similar phenotype to loss of *Dmon1*, suggesting they act in concert. Moreover, depletion of *Rab7* also mimics the loss of *Dmon1* and *Dcc1*, further indicating that the loss of Rab7 at late endosomes is responsible for the observed effects. Surprisingly, *Dmon1* mutant cells do not have overactive receptor signalling, as would be expected because of the accumulation of receptors, such as Notch, in the maturing endosomes of these cells. This is the case even when receptor uptake into intraluminal vesicles is prevented. This suggests that other mechanisms exist for receptor inactivation.

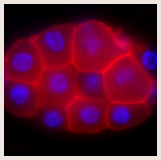
Probing the redox state of the ER

Protein homeostasis in the ER is strongly linked to the formation of native disulfide bonds during protein folding, which also requires thiol-disulfide exchange reactions that are catalyzed by members of the protein disulfide isomerase (PDI) family. Glutathione (GSH) maintains a fraction of PDIs in the reduced for, and GSH-mediated reduction results in the formation of its dimeric oxidised form glutathione disulfide (GSSG). The GSH:GSSG ratio is an established indicator of intracellular redox conditions and is considerably lower in the ER than in the cytosol. On the basis of this, possible oxidising functions of GSSG in the ER have been suggested. However, the actual oxidative capacity of the glutathione redox buffer – the electrochemical reduction potential of GSH–GSSG (E_{GSH}) – in the ER is not known. On page 1604, Christian Appenzeller-Herzog and colleagues report the development of a GSH-specific ER-targeted redox sensor that allows them to quantify the redox potential of GSH. They determine E_{GSH} in the ER of HeLa cells as -208 ± 4 mV, which is not sufficiently oxidising to maintain the known redox state of PDIs, suggesting that GSSG does not actively facilitate oxidative protein folding in the ER. Taken together, their data demonstrate that this sensor is an important tool to determine the reduction potential of GSH *in vivo* and could also be useful for investigating the ER redox state under pathological conditions involving ER stress.



Nck at the centre of endothelial cell migration

Reorganisation of the cytoskeletal architecture underlies the morphological and functional changes that are involved in directional cell migration. Extracellular signals that alter tyrosine phosphorylation, e.g. the activation of receptor tyrosine kinases (RTKs), are recognised by proteins that contain a Src homology (SH) 2 domain, such as the Nck family of adaptors, which then promote remodelling of the actin cytoskeleton. Although it is well established that Nck is involved in cell motility and adhesion, its exact roles during directional cell migration and the underlying mechanisms are unresolved. Here, Gonzalo Rivera and co-workers (p. 1637) use a combination of genetics and quantitative live-cell imaging to elucidate the role of Nck in endothelial cell migration. Upon functional abrogation of Nck they observe that cell migration is deficient and its directionality is impaired, mainly owing to the loss of front-to-rear polarity. Furthermore, they find that, when compared with wild-type cells, loss of Nck results in a reduced force from fibronectin-mediated cell–matrix adhesions, as well as reduced levels of myosin phosphorylation and Rho activity, but increased activities of Rac1 and Cdc42. On the basis of these data, the authors conclude that Nck promotes the directional migration of endothelial cells by coordinating the stimulation of protrusions at the cell front, as well as by stabilising the cell front through promoting the maturation of cell–matrix adhesions.



CDC-42 in polarisation: to be or not to be active

The polarisation of embryonic cells is essential for the execution of developmental programmes, and in many organisms is triggered by polarisation cues that result in an asymmetric localisation of PAR proteins. The activity and localisation of these proteins are controlled by small GTPases of the Rho family. In *Caenorhabditis elegans*, the establishment of radial polarity requires the Rho GTPase CDC-42 to exclude PAR-6 from sites of cell contact and therefore restrict it to contact-free cell surfaces, but it is not understood how CDC-42 is activated selectively at cell-free surfaces. Emily Chan and Jeremy Nance (p. 1692) aim to answer this question by analysing the functions of the 20 putative *C. elegans* Rho guanine exchange factors (GEFs) to identify those that activate CDC-42 during radial polarisation. They find that overexpressing either ECT-2 or CGEF-1 is sufficient to activate CDC-42 and to ectopically recruit PAR-6 to sites of cell contacts. However, both of these Rho GEFs localise to contact and contact-free sites at the cell cortex, so how can CDC-42 be activated at contact-free sites only? The authors had previously found that the Rho GTPase-activating protein (GAP) PAC-1 inhibits CDC-42 at cell contacts, and, taken together with the data presented here, this suggests that radial polarisation results from a competition between RhoGEFs, which activate CDC-42 throughout the cortex, and PAC-1, which inactivates it only at cell contact sites.

From *Development*

Adipocytes and wound healing

Acute wound healing, which restores the essential barrier function of the skin, requires the coordination of the proliferation and migration of both keratinocytes and fibroblasts for epidermal and dermal repair, respectively. Skin healing is known to involve communication between haematopoietic cells, keratinocytes and fibroblasts, but could it involve other intradermal cell types? In *Development*, Barbara Schmidt and Valerie Horsley have been investigating the involvement of intradermal adipocytes in skin wound healing in mice. They report that immature adipocytes are activated during the proliferative phase of acute skin wound healing and that mature adipocytes appear in healing wounds concurrently with fibroblasts. Moreover, by studying wound healing in mice with genetic defects in adipogenesis and in mice treated with pharmacological inhibitors of adipogenesis, they provide evidence that suggests that adipocytes are necessary for fibroblast recruitment and for dermal reconstruction. Further experiments are now needed to elucidate how adipocytes mediate fibroblast function during the healing of acute skin wounds and to determine whether they also aid the healing of chronic wounds.

Schmidt, B. A. and Horsley, A. (2013). Intradermal adipocytes mediate fibroblast recruitment during skin wound healing. *Development* **140**, 1517-1527.

From *Development*

Timely BMP patterns neural tube

In many embryonic tissues, graded signals (morphogens) provide the positional information that governs the pattern of cellular differentiation. It is widely thought that cells interpret morphogen gradients by producing corresponding levels of intracellular signalling activity, which regulate differential gene expression. But other, distinct mechanisms could also be used to interpret some morphogens. James Briscoe and co-workers investigate in *Development* the morphogen activity of bone morphogenetic protein (BMP) signalling in the chick dorsal neural tube. BMPs are thought to provide the positional information that specifies the spatial pattern of the dorsal interneurons. They report that in neural tube explants the duration of exposure to Bmp4 generates distinct levels of intracellular signalling and induces specific dorsal identities. Moreover, they find that a dynamic gradient of BMP activity progressively specifies more dorsal identities in the neural tube *in vivo*. Based on these results, the researchers propose a model for morphogen interpretation in which the temporally dynamic control of signalling is required to specify the spatial pattern of cellular differentiation.

Tozer, S., Le Dréau, G., Marti, E. and Briscoe, J. (2013). Temporal control of BMP signalling determines neuronal subtype identity in the dorsal neural tube. *Development* **140**, 1467-1474.