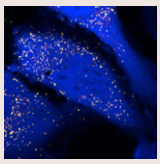
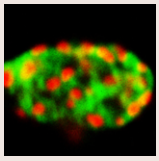
In this issue



NBR1 mediates pexophagy

Large cytoplasmic materials are selectively sequestered and degraded in lysosomes in a process called selective autophagy. Substrate selection is mediated by cargo receptors such as NBR1, p62, NDP52 and optineurin, although their precise roles are not well understood. On page 939, Peter Kim and colleagues test the hypothesis that autophagy receptors confer substrate selectivity in autophagy. Specifically, they examine the role of autophagy receptors NBR1 and p62 in the selective autophagy of peroxisomes (pexophagy) in mammalian cells. Overexpressing NBR1 induced peroxisome localisation to lysosomes, indicating that NBR1 can promote the activation of pexophagy. p62, however, is not required when NBR1 is in excess, but instead increases the efficiency of NBR1-driven pexophagy. Mutagenesis studies of NBR1 were then used to investigate the mechanism underlying NBR1-mediated pexophagy. The authors identify four domains that are necessary to mediate pexophagy: the amphipathic α-helical J domain, the ubiquitin-associated (UBA) domain, the LC3-interacting region and the coiled-coil domain. Interestingly, some of the substrate specificity was shown to come from NBR1 itself by coincident binding of the phospholipid-binding J and ubiquitin-binding UBA domains to peroxisomes. Taken together, these findings indicate that NBR1 is the specific autophagy receptor for pexophagy in mammalian cells.



Bulk endocytosis at the synapse: role of Dap160

The recycling of synaptic vesicles at the synaptic periactive zone (PAZ) is mainly achieved by clathrin-mediated endocytosis and bulk endocytosis. The endocytotic factors executing these events such as the GTPase dynamin are controlled by large scaffolding proteins that include dynamin-associated protein of 160 kDa (Dap160) in *Drosophila* (Intersectin in mammals). Dap160 has been suggested to coordinate dynamin's function at the PAZ through interactions that involve several of its SH3 domains, but the exact roles of these domains are not understood. Here (p. 1021), Oleg Shupliakov and colleagues use expression of Dap160 mutants lacking SH3 domains A and B (ΔAB) to investigate the molecular basis for the control of dynamin by Dap160. They find that under rest conditions, Dap160 and dynamin colocalize to the distal pool of synaptic vesicles and together relocate to the PAZ during synaptic activity. However, ΔAB mutants are unable to accumulate dynamin at the PAZ during stimulation and large bulk endocytic structures and vesicles accumulate in this synaptic region, but, interestingly, clathrin-mediated endocytosis is unaffected. Moreover, the authors show that the lack of SH3 domains does not affect the development of the neuromuscular junction, which indicates that the architectural role of Dap160 is separate, and mediated through other protein domains. Taken together, these data reveal new insights into the role of Dap160 in suppressing bulk endocytosis at the synapse.

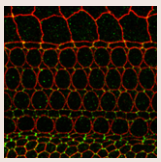
Upcoming Commentaries and Cell Science at a Glance posters

Cell Science at a Glance posters

- Virus entry at a glance *Ari Helenius*
- Regulation of mTORC1 and its impact on gene expression *David M. Sabatini*

Commentaries

- Controlling DNA replication origins in response to DNA damage *John F. X. Diffley*
- CORVET and HOPS tethering complexes *Christian Ungermann*



Angulins: a family is born

The intercellular space formed at tricellular contacts, where the corners of three epithelial cells meet, is sealed by specialised structures called tricellular tight junctions (tTJs). Tricellulin and lipolysis-stimulated lipoprotein receptor (LSR) are the known protein components of tTJs, with LSR recruiting tricellulin to the tTJs. Mikio Furuse and colleagues (p. 966) now examine the cellular functions of two LSR-related proteins, immunoglobulin-like domain-containing receptor 1 (ILDR1) and ILDR2. A bootstrap analysis of all three proteins showed that they are evolutionarily conserved among vertebrates. Next, the authors demonstrated that, similar to LSR, ILDR1 and ILDR2 localise to tricellular contacts in epithelial cells and recruit tricellulin; moreover, at least one of these three proteins is expressed in each of the epithelial tissues examined, and the expression of any one of them is sufficient to recruit tricellulin. ILDR1 and ILDR2, say the authors, therefore might be found at tTJs. LSR contributes to epithelial barrier function, and the authors show that, whereas ILDR1 is involved in such functioning, the requirement for ILDR2 is less. Further analysis of *ILDR1*, mutation of which underlies a familial deafness at the DFNB42 locus in humans, shows that most DFNB42-associated ILDR1 mutant proteins are defective in tricellulin recruitment. Considering these findings, the authors propose grouping LSR, ILDR1 and ILDR2 together to form the angulin protein family.

From *Development*

Lipid leads the way in wound healing

During epithelial wound healing, actin assembles at the leading edge of cells bordering the wound, forming dynamic protrusions and, in some cases, an actomyosin cable. Together, these actin-rich structures are essential for wound closure. The process of dorsal closure in *Drosophila melanogaster* shares many characteristics with wound healing and is a convenient system for cell biological analysis. In *Development*, building on earlier results showing that the apical polarity determinant Par3/Bazooka (Baz) is lost from the leading edge of cells during dorsal closure, Tom Millard and colleagues now uncover a molecular mechanism by which Baz localisation regulates actin dynamics. Baz is known to bind the lipid phosphatase Pten, and the authors find that loss of Baz from the leading edge causes Pten redistribution. This, in turn, leads to an accumulation of the lipid PIP3 at the leading edge, which promotes formation of actin protrusions required for closure. This pathway is conserved during both dorsal closure and wound healing, offering a mechanistic basis for actin assembly during epithelial closure.

Pickering, K., Alves-Silva, J., Goberdhan, D. and Millard, T. H. (2013). Mice deficient in H^+Par3/Bazooka and phosphoinositides regulate actin protrusion formation during *Drosophila* dorsal closure and wound healing. *Development* **140**, 800-809.

From *Disease Models & Mechanisms*

Multipurpose cell-based fascin bioassay

The actin-bundling protein fascin is involved in tumour invasion and metastasis, whereas fascin deficiency is implicated in some developmental brain disorders. Because this association with diverse clinical problems makes the fascin pathway a desirable drug target, in *Disease Models & Mechanisms* Linda Restifo and colleagues devised an assay for fascin function that is based on the characteristic 'filagree' phenotype of cultured fascin-deficient mutant *Drosophila melanogaster* neurons. When used to screen 1040 known compounds, the assay identified 34 fascin-pathway blockers (potential anti-metastasic agents) and 48 fascin-pathway enhancers (potential cognition-enhancing agents). The screen also revealed neurotoxic effects of other drugs. Notably, statins induced a unique morphological disruption of the cultured neurons. These results suggest that this cell-based fascin bioassay should be useful for drug discovery and also identifies primary cultures of *Drosophila* neurons as a promising neurotoxicity screening platform.

Kraft, R., Kahn, A., Medina-Franco, J. L., Orlowski, M. L., Baynes, C., López-Vallejo, F., Barnard, K., Maggiora, G. M. and Restifo, L. L. (2013). A cell-based fascin bioassay identifies compounds with potential anti-metastasis or cognition-enhancing functions. *Dis. Model. Mech.* **6**, 217-235.