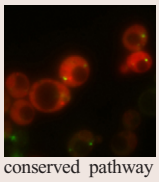
In this issue

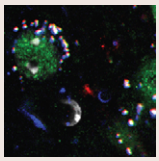
MINIFOCUS: Adhesion

In this issue, we present a collection of four articles discussing different aspects of cellular adhesion. Cell–cell and cell–matrix adhesions are crucial for the accurate maintenance of tissues, and perturbations in cell adhesion can have detrimental effects. First, the Cell Science at a Glance by Ronen Zaidel-Bar (p. 373) presents the Cadherin adhesome, or 'Cadhesome', which comprises over 170 proteins that have been shown to date to interact with cadherin, the main factor mediating cell–cell adhesions. On the basis of this extensive network, the author suggests that the cellular role of cadherin is far more complex than that depicted in textbook models. In the first of three Commentaries, Vania Braga and colleagues (p. 379) discuss the small GTPases that control the levels of active Rho, a well known regulator of cell–cell junctions, and propose that this control is reciprocal: junctions can also modulate the activity of small GTPases to drive contact-dependent cellular events. The second Commentary by Valerie Brunton and colleagues (p. 393) explores the role of E-cadherin in tumour cell invasion and metastasis. They emphasize the importance of the interplay between E-cadherin and cell–ECM interactions mediated by integrin matrix receptors. In our final Minifocus article, Stephan Huveneers and Johan de Rooij (p. 403) have a close look at the mechanotransduction at cell–cell junctions, which they suggest emerges as an important signalling mechanism with relevance for tissue development and disease.



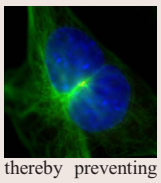
Get(3)-ting tail anchored proteins sorted

Tail-anchored membrane proteins exhibit strongly hydrophobic segments embedded in the membrane, and to avoid the aggregation of these segments before membrane insertion, they are targeted to membranes post-translationally. Their secretion involves a cascade of proteins, which cooperates in a conserved pathway to accept the newly synthesised tail-anchored proteins from ribosomes, guiding them to a receptor at the endoplasmic reticulum (ER) where membrane integration takes place. An important component of the GET-pathway is the ATPase Get3, which shuttles the target protein through the cytosol. The conformation of Get3, and thus its ability to interact with tail-anchored proteins, is controlled by its nucleotide state. However, it is not known how the GET pathway reacts to energy depletion, which might prevent membrane insertion and result in the accumulation of hydrophobic proteins in the cytosol. Now, Blanche Schwappach and colleagues (p. 473) analyzed the localisation of Get3–GFP foci under different conditions of cellular stresses that perturb membrane insertion. They find that under conditions of energy depletion, such as glucose starvation, Get3 has a second function as an ATP-independent holdase that makes use of its chaperone activity to bind hydrophobic protein segments. Moreover, they show that Get3 moves to deposition sites for protein aggregates, and thereby supports the sequestration of tail-anchored proteins when membrane insertion is inhibited, suggesting that the GET pathway acts as a quality control platform in cellular proteostasis.



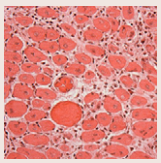
Optineurin – lending a helping hand to clear protein aggregates

The accumulation of misfolded proteins is a hallmark of many neurodegenerative diseases including Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS). Misfolded proteins are usually degraded by the ubiquitin–proteasome system, but they can also activate autophagy. Optineurin is present in protein inclusions in various neurodegenerative diseases and has recently been shown to be an autophagy adaptor, but its role in the aggregation process is unclear. On page 580, Ivan Dikic and colleagues used two aggregation-prone protein models to investigate the role of optineurin; a short fragment of the protein huntingtin (htt) with an extended polyglutamine (polyQ) mutation and mutations of superoxide dismutase1 (SOD1), which are used as models of HD and ALS, respectively. They show that optineurin recognizes htt and SOD1 aggregates though its C-terminal domain in a manner that is independent of ubiquitin and participates in their degradation. Mechanistically, the authors demonstrate that optineurin-mediated degradation is regulated by its phosphorylation by TANK1 binding kinase 1, which results in recruitment of the autophagy machinery. They also find that depletion of optineurin in HeLa cells leads to a substantial increase in protein aggregation, and silencing of the zebrafish orthologue results in fish with a motor axonopathy phenotype similar to that of ALS. These results support a protective role of optineurin in neurodegenerative disorders associated with intracellular protein aggregation.



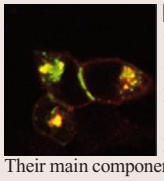
Role of Lats1 in tumorigenesis

The Hippo pathway is a conserved pathway that regulates cell growth, organ size and stem cell self-renewal. In mammals it consists of a number of kinases, including Lats1 and Lats2, and the transcriptional coactivators Yap and Taz. Upon activation of the pathway, Lats1 and Lats2 phosphorylate Yap and Taz, thereby preventing their nuclear translocation and inhibitory effects on the transcription of cell-proliferative and anti-apoptotic genes. Downregulation of Lats1 and Lats2, or overexpression of Yap and Taz is frequently observed in human cancers, but the underlying mechanisms are not well understood. On page 508, Hiroshi Nojima and colleagues aim to shed light on the tumour suppressor role of the Hippo pathway by generating knockout mice and cell lines that lack the N-terminal LCD1 region of Lats1 ($Lats1^{\Delta N/\Delta N}$). At their N-termini, Lats1 and Lats 2 have two conversed regions (Lats conserved domains 1 and 2; LCD1 and LCD2), which have been suggested to have a role in tumour suppression. Some $Lats1^{\Delta N/\Delta N}$ mice were born, albeit with a very low birth rate, and grow normally. By contrast, $Lats1^{\Delta N/\Delta N}$ mouse embryonic fibroblasts displayed dramatic mitotic defects and showed abnormal cell growth, similar to that observed in tumour cells. Importantly, expression of Lats2 was downregulated in these cells, whereas YAP was overexpressed; this results in the stabilisation of YAP, because its phosphorylation by both kinases is required for its inactivation, and, eventually, abnormal growth and tumorigenesis.



The timing of Ezh2 action in stem cell differentiation

The maintenance of a correct differentiation program is essential for tissue homeostasis and repair. Polycomb group (PcG) proteins mediate the epigenetic silencing of genes and have been implicated in regulating the fate of adult stem cells and their differentiation state. Polycomb repressive complex 2 (PRC2) consists of the four subunits Ezh2, Suz12, EED and RbAp48; Ezh2 is responsible for the trimethylation of lysine 27 of histone H3 (H3K27me3), which transcriptionally represses key factors involved in lineage specification. Studying the role of PRC2 in adult stem cells has been hampered owing to the prenatal lethality of PRC2-subunit knockouts, but satellite cells (the primary muscle stem cells) provide a suitable system to investigate the function of PRC2. Here (p. 565), Jennifer Pell and colleagues use genome-wide histone methylation maps of satellite cells together with two conditional Ezh2-null mouse strains to elucidate the role of Ezh2 in muscle differentiation *in vivo*. They find that mice lacking Ezh2 in satellite cells show decreased muscle growth and a reduced number of stem cells, whereas, surprisingly, depletion of Ezh2 after the onset of terminal differentiation did not impede muscle repair. Genome-wide H3K27me3 mapping in isolated primary satellite cells confirmed that Ezh2 mediates the silencing of factors associated with lineage specification within a proliferative progenitor population, but not that of genes involved in terminal differentiation.



How claudins keep junctions tight

Tight junctions (TJs) separate the internal space of multicellular organs and organisms from external compartments and form a paracellular diffusion barrier. TJs consist of a set of branched intramembranous strands of protein particles that bring the plasma membranes of opposing cells into molecular contact. Their main components are the different claudins, as well as occludin, marvelD3 and tricellulin; the latter three constitute the TJ-associated marvel protein (TAMP) family. However, not much is known with regard to the functions of the different TAMPs, or their interactions with claudins. In this study (p. 554), Ingolf Ernst Blasig and colleagues present a systematic analysis of the homophilic and heterophilic interactions formed by claudins and TAMPs using co-expression experiments in TJ-free HEK-293 cells. Fluorescence resonance energy transfer measurements show that all TAMPs can form homophilic cis-interactions at the plasma membrane, but these are weaker than the homophilic and heterophilic interactions of claudins. Furthermore, the authors find that heterophilic interactions occur between classic claudins and TAMPs that change TJ strand formation, as determined by freeze facture electron microscopy and mobility analysis. Taken together, these data suggest that claudins form the backbone of the TJ strands. The interactions of the claudins with TAMPs determine the behaviour of TAMPs, such as binding properties and localisation. By contrast, TAMPs improve the TJ strand network to obtain the typical physiological morphology of claudin TJ strands.