

Opo opposes Numb in the eye

Tissue morphogenesis requires the polarized trafficking of adhesion receptors. Martínez-Morales and colleagues refine the role for the transmembrane protein Opo in this context, and find that it opposes Numb-mediated endocytosis of integrin β_1 (*Dev. Cell* <http://doi.org/jhp>; 2012).

The authors previously found that Opo is essential for folding of the optic cup in medaka fish by regulating the polarization of focal adhesion components. To better understand the function of Opo, they performed a yeast two-hybrid screen that identified the encocytic adaptors Numb-like (Numbl) and Dab2 as Opo interacting proteins. Interactions with Numb, Numbl and Dab2 were confirmed *in vitro* and in mammalian cells, and required an NPXY sequence in Opo also present in integrin β_1 . Opo colocalized with clathrin-coated endocytic vesicles and inhibited Numb-mediated endocytosis of integrin β_1 in HeLa cells. Fluorescence recovery after photobleaching (FRAP) analysis demonstrated that basal, but not apical, transport of integrins was affected in medaka *opo* mutants. Electron microscopy confirmed the basal accumulation of vesicles in *opo* mutant neuroblasts, and integrin uptake was enhanced in retinae of *opo* mutants *in vivo*. Injection of Numb or Numbl RNA into medaka or zebrafish embryos caused morphogenesis defects similarly to those seen in *opo* mutants,

agreeing with Numb and Opo functioning in an antagonistic manner. Genetic interactions were also observed between Numb proteins and Opo in medaka embryos. The precise molecular function of Opo requires further investigation but could involve inhibiting integrin binding to the Numb adaptors. CKR

miR-211 negotiates life and death decisions

Endoplasmic reticulum (ER) stress promotes the unfolded protein response (UPR), which is characterized by induction of the IRE1, PERK and ATF6 effector proteins. PERK promotes both survival and apoptosis, but it remains unclear how these activities are balanced. Diehl and colleagues now report that a PERK-induced microRNA has a key role in this process (*Mol. Cell* <http://doi.org/jhq>; 2012).

The authors found that ER stress upregulated miR-211 expression in a PERK- and ATF4-dependent manner. PERK and ATF4 are also known to induce expression of the pro-apoptotic protein CHOP. Intriguingly, miR-211 decreased CHOP expression in response to ER stress, but not by targeting *CHOP* mRNA. Instead, miR-211 bound *CHOP* promoter regions and elicited H3K27me3 methylation marks and Ago1 accumulation to silence *CHOP* expression.

Inhibition of miR-211 increased ER-stress-induced apoptosis in wild-type, but not in

CHOP-null, cells. This relationship might also be relevant in cancer, as miR-211 expression was elevated in mouse mammary tumours and correlated inversely with CHOP expression. Higher miR-211 expression was also observed in primary human lymphomas compared to normal B lymphocytes. The authors conclude that PERK-ATF4 signalling promotes accumulation of CHOP but also miR-211, which in turn limits CHOP expression and increases survival. EJC

Aged muscle drives stem cell demise

Quiescent satellite cells lie beneath muscles, and their self-renewal and differentiation abilities (once they have been activated) ensure muscle repair. These properties, as well as the number of satellite cells, decline with age. Brack and colleagues now show that the muscle fibres that constitute the satellite-cell niche provide signals that induce satellite cells to exit quiescence and lose self-renewal capacity (*Nature* <http://doi.org/jhr>; 2012).

Using a pulse-chase of histone-2B-GFP to monitor proliferation of satellite cells in mice, they observe that a subset of aged satellite cells cycle more frequently at homeostatic conditions and express fewer quiescence-associated markers, as well as more differentiation- and apoptosis-associated markers, than surrounding satellite cells. Aged cycling satellite cells injected into muscle were shown to contribute less to myofibres. Interestingly, the authors found that fibroblast growth factor 2 (FGF2) is expressed at higher levels in aged muscle fibres than in younger fibres. Incubation of cultured quiescent adult satellite cells with aged muscle fibre extracts or with FGF2 induced their proliferation; treatment of aged satellite cells with inhibitors of FGF receptors had the converse effect. The authors found that aged satellite cells express an inhibitor of FGF signalling, Sprouty, but its inhibitory effect can be overcome by the high levels of FGF2 produced by the muscle fibres. Finally, using a combination of pharmacological and genetics approaches, they showed that FGF modulation *in vivo* can indeed influence the regenerative capacity of satellite cells. NLB

Chaperoning tumour bioenergetics

Cancer cell growth and maintenance requires the ability to adapt and respond to multiple different environmental cues and stresses. Altieri and colleagues now report that heat shock protein 90 (HSP90), which regulates protein-folding quality control, also controls energy production and stress responses to promote tumour cell survival and growth (*Cancer Cell* **22**, 331-344; 2012).

Using small-molecule inhibitors, the authors showed that the mitochondrial, but not the cytosolic, HSP90 pool regulates tumour cell bioenergetics by controlling the mitochondrial recruitment of hexokinase-II, a key glycolysis enzyme that also couples glucose metabolism to oxidative phosphorylation. They further demonstrated that HSP90 inhibition and impaired hexokinase-II activity deregulate key bioenergetic pathways by activating AMP-activated kinase (AMPK) and inhibiting mammalian target of rapamycin complex-1 (mTORC1). These signalling events were shown to promote tumour cell survival by inducing autophagy. HSP90 inhibition and the resulting mitochondrial proteotoxic stress and impaired bioenergetic responses also activated the unfolded protein response stress pathways in the endoplasmic reticulum, leading to tumour cell viability and proliferation. HSP90-controlled tumour bioenergetics promoted melanoma cell growth *in vitro* and prostate tumour growth in a genetic mouse model, and also correlated with negative outcome in lung cancer patients. These findings demonstrate that HSP90 integrates multiple pathways underlying energy production, survival and stress responses to provide a cytoprotective and proliferative advantage to tumour cells. AIZ

By Emily J. Chenette, Nathalie Le Bot, Christina Karlsson Rosenthal and Alexia-Ileana Zarmytidou