Joining ER to mitochondria

Mitochondria are often found near the endoplasmic reticulum (ER) but how these organelles are juxtaposed has been unclear. The mitochondrial GTPase Mfn2 has now been shown to control ER–mitochondrial tethering (*Nature* **456,** 605–610; 2008). Scorrano and colleagues found that Mfn2 localizes to ER–mitochondrial junctions and that *Mfn2*-null cells show reduced ER–mitochondrial tethering. This tethering requires GTPase activity of Mfn2 and a Ras-binding domain. Using Mfn2 mutants that were expressed either on mitochondria or on the ER, the authors showed that Mfn2 has to be present on the ER surface to restore tethering. The tethering role of Mfn2 could be recapitulated with isolated organelles *in vitro*. Mfn2 present on the ER can form homotypic or heterotypic interactions with either mitochondrial Mfn2 or Mfn1 to tether the two compartments.

Proximity of the ER to mitochondria has been suggested to facilitate mitochondrial uptake of Ca^{2+} released from the ER. Indeed, uptake of Ca^{2+} by mitochondria was reduced in *Mfn2*-null cells during IP3-mediated release, consistent with a crucial role for tethering in enabling mitochondrial Ca^{2+} uptake. Mutations in Mfn2 are associated with the neuropathy Charcot-Marie Tooth IIa. The role of Mfn2 in ER–mitochondrial tethering may cast light on the mechanisms underlying the disease. SS

pVHL secures glucose homeostasis

When challenged by increased metabolic loads, precipitated, for example, by pregnancy or obesity, insulin-producing pancreatic β cells increase their mass to maintain systemic euglycemia. This expansion induces hypoxia and hypoxia-inducible transcription factors (HIFs) that trigger neo-angiogenic programs to improve oxygen delivery. Hypoxia also shifts glucose metabolism from mitochondrial respiration to glycolysis, but whether this metabolic change affects insulin secretion remains unclear. Krek and colleagues (*Genes Dev.* **22**, 3135–3146; 2008) now demonstrate a key role of the pVHL–HIF1α pathway in the control of β cell metabolism, insulin secretion and whole-body glucose homeostasis.

β-cell-specific deletion of *Vhlh*, which encodes the ubiquitin ligase that targets HIF for degradation in normoxic cells, led to accumulation of HIF1α, expression of genes involved in glucose uptake and glycolysis, and increased levels of glycolytically derived ATP. Insulin secretion by β cells depends on glucose-stimulated ATP levels. Interestingly, $Vhlh^{-/-}$ mice become hypoglycaemic because of increased basal insulin secretion, whereas glucose-stimulated changes in cytosolic Ca^{2+} concentration, firing of action potentials and insulin secretion were impaired, eventually leading to systemic glucose intolerance. Concomitant β-cell-specific deletion of the *Hif1α* gene rescued these effects, proving that the pVHL–HIF1α axis is crucial in controlling glucose metabolism, with profound effects on whole-organism glucose homeostasis. SG

Par controls E-cadherin uptake

Adjacent epithelial cells are connected by adherens junctions, which are multiprotein complexes containing E-cadherin. Both maintenance and remodelling of adherens junctions require E-cadherin dynamics but how this process is regulated has been unclear. Cdc42, a Rho GTPase that regulates actin dynamics, and other members of the apical Par polarity complex were recently shown to function in vesicle trafficking. Studies by Baum and colleagues and Bellaiche and colleagues (*Curr. Biol.* **18,** 1631–1638 and 1639–1648, respectively; 2008) now show that the Par complex components Cdc42, aPKC and Par6 control E-cadherin endocytosis at epithelial adherens junctions in the developing *Drosophila melanogaster* notum.

Both groups report that loss of Cdc42 leads to mislocalization of apical polarity markers, including E-cadherin, abnormal adherens junction structures and basal cell de-lamination. An identical phenotype is seen in aPKC and Par6 mutant flies but, interestingly, not in mutants of the known Cdc42-aPKC-Par6 targets Baz (Par3) or Lgl. Live-cell imaging of GFP-tagged E-cadherin shows accumulation of apical puncta, which both groups attribute to failed apical E-cadherin endocytosis. Both groups demonstrate the involvement of the Cdc42 effector WASP and the Arp2/3 complex, as mutants of these actin regulators also show disrupted adherens junction organization and E-cadherin endocytosis defects.

Bellaiche's group also found that Cdc42-interacting protein 4 (Cip4) interacts with both WASP and the endocytosis-regulator Dynamin and that its depletion leads to failed E-cadherin endocytosis. Thus Cip4 provides a link between the Par complex and the endocytic machinery to regulate E-cadherin dynamics and adherens junction formation. CKR

Parkin' away damaged mitochondria

Mutations in the E3 ubiquitin ligase Parkin are associated with the early onset of Parkinson's disease. How Parkin influences neuronal survival is unclear but its function has been linked to mitochondrial integrity. Mitochondria rely on a high membrane potential for respiration. Youle and colleagues (*J. Cell Biol.* doi:10-183/jcb.200809125; 2008) show that Parkin is recruited specifically to mitochondria with low membrane potential and suggest that it mediates their elimination through autophagy, a process that targets organelles to the lysosomes. The authors observed that Parkin localized to a subset of mitochondria in the cell and that treatment with a drug that induces depolarization increases the number of mitochondria labelled with Parkin. Genetic studies have previously linked Parkin to the mitochondrial fission and fusion machinery and low membrane potential causes mitochondrial fragmentation. Cells expressing a mutant of the fission regulator dynamin-related protein 1 are resistant to mitochondrial fragmentation but their depolarization still occurs and is followed by Parkin recruitment. Conversely, a drug that induces fragmentation without affecting membrane potential did not increase Parkin recruitment. Parkin-labelled mitochondria mobilize the autophagy machinery through an unknown mechanism, leading to inclusion of Parkin-labelled mitochondria in autophagosomes and thus lysosomal degradation. Cells lacking the autophagy component ATG5, or cells treated with autophagy or lysosome inhibitors, did not degrade Parkin-labelled mitochondria. The next step is to test whether Parkin affects neuronal survival by mediating the degradation of non-functional mitochondria. NLB

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