CHANNELS

Under pressure

Nature **483**, 176–181 (2012)
Nature **483**, 209–212 (2012)

Mechanical stimuli generate cationic currents across cell membranes, suggesting that ion channels are involved in this process. Previous work showed that the conserved transmembrane Piezo proteins are necessary and sufficient for mechanotransduction. Now, Coste *et al.* establish the Piezo proteins as the first cation channels that respond to mechanical stimuli. Overexpression of mammalian and *Drosophila* Piezo proteins in HEK293 cells produced pressure-activated cationic currents. The authors observed that Piezo proteins, similarly to known ion channels, were assembled into oligomers to form the ion channel pore. Photobleaching experiments in cells expressing GFP–tagged Piezo, protein electrophoresis under native conditions and *in vitro* and *in vivo* crosslinking experiments showed that Piezo proteins form homotetrameric complexes of ~1,200 kDa. The authors did not detect any other proteins tightly associated with Piezo proteins. In contrast, they observed that recombinant Piezo, after reconstitution in lipid bilayers, is all that is required to conduct both sodium and potassium, functioning as a nonselective cationic channel. In an accompanying paper, Kim *et al.* report the physiological role of the *Drosophila* homologue DmPiezo. They show that DmPiezo is expressed in sensory neurons and, along with the Pickpocket ion channel, is required for the larval response to mechanical stimulation. Together, these papers establish Piezo as the first class of cation channel that mediates mechanotransduction *in vivo*. *AC*

SYSTEMS BIOLOGY

Cross-talking PTMs

Mol. Syst. Biol. **8**, 571 (2012)

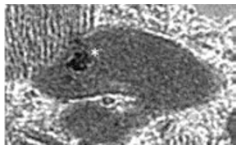
Large-scale studies investigating the relationship between one post-translational modification (PTM) and another in prokaryotes have been lacking. van Noort *et al.* evaluated cross-talk between phosphorylation and acetylation in *Mycoplasma pneumoniae*, a pathogen with a simple genome encoding only one protein phosphatase, two serine/threonine kinases and two lysine acetyltransferases (KATs). Using quantitative proteomics, the authors profiled phosphorylation and acetylation sites in wild-type bacteria and compared them to those found in bacteria deficient for the phosphatase, a kinase or a KAT. They reported that some of the phosphorylation sites showed inverted responses to deletion of a kinase compared to deletion of the phosphatase, whereas other sites were affected by deletion of both kinases, indicative of a dynamic regulatory network. Most of the modified proteins had multiple modifications, and over one-third of these showed coupling between phosphorylation and acetylation. Overall acetylation was detected as frequently as phosphorylation; knockout of one of the kinases or the phosphatase affected 81 acetylation sites, with the kinase mutations having opposing effects on levels of acetylation. Knockout of either KAT affected ~20% of the phosphorylation sites. The authors also integrated data on protein-protein interactions, finding that modified sites are frequently located at interaction interfaces and raising the possibility that PTMs regulate oligomeric protein assemblies. Taken together, these data provide evidence for combinatorial activity of PTMs in protein interaction networks. *AD*

METALS

Iron from the heart

Proc. Natl. Acad. Sci. USA **109**, 4152–4157 (2012)

HOSSEIN ARDEHALI



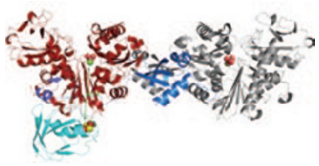
ATP-binding cassette (ABC) proteins transport various substrates across cell membranes, but the physiological importance of mitochondrial ABC proteins is only beginning to emerge. For example, ABCB8 localizes to the inner mitochondrial membrane and is known to have protective effects against oxidant-induced cell death, but its function is not known. Ichikawa *et al.* use a tamoxifen-dependent Cre recombinase to conditionally delete the gene encoding ABCB8 from cardiac tissue in mice, resulting in a progressive decrease in cardiac function consistent with cardiomyopathy. Mitochondrial architecture in cardiac tissue was damaged in knockout mice, and the organelles accumulated electron-dense material reminiscent of iron overload. In cultured cells, siRNA–mediated knockdown of ABCB8 resulted in mitochondrial iron accumulation, and overexpression of ABCB8 decreased mitochondrial iron content. The authors developed an assay to assess export of radiolabeled metals from mitochondria of HEK293 cells, confirming ABCB8-dependent iron but not phosphorus export. The authors also found that the activity of cytosolic but not mitochondrial Fe-S cluster–containing enzymes was compromised in cardiac tissue of ABCB8 knockout mice. These data indicate that ABCB8 is important for normal cardiac function and iron homeostasis. *AD*

METALLOENZYMES

One-way e^- traffic

Proc. Natl. Acad. Sci. USA, published online 19 March 2012, doi:10.1073/pnas.1117126109

JAE-HUN JEOUNG AND SANDRA HENNIG



The corrinoid/iron-sulfur protein (CoFeSP) participates in the reductive acetyl-CoA pathway, transferring a methyl group from a methyltransferase to acetyl-CoA synthase. CoFeSP, composed of two subunits, is active in the Co(I) state but can be oxidized to an inactive Co(II) state. Whereas other metalloenzymes rely on a dedicated reductive metallo-ATPase to provide them with an electron, extrapolation from other cell processes had suggested that CoFeSP could function independently of an activating partner. Hennig *et al.* now demonstrate that CoFeSP from *Carboxydothermus hydrogenformans* does pair with an ATPase in their examination of an open reading frame situated between the genes encoding the two CoFeSP subunits. The expressed protein, termed 'reductive activator of CoFeSP' (RACo), is a homodimer with a [2Fe-2S] cluster in each monomer. ATP hydrolysis by RACo reduced CoFeSP from the Co(II) to Co(I) state in stoichiometric fashion. SDS-PAGE and size-exclusion chromatography showed that RACo formed a complex with CoFeSP in the Co(II) state but not in the Co(I) state. RACo's structure includes an N-terminal ferridoxin-like domain containing the [2Fe-2S] cluster, a C-terminal ASKHA domain containing the nucleotide-binding site ~40Å from the metal cluster and a middle domain that mediates dimerization. Though specific mechanistic details await further study, this first demonstration of redox state–dependent assembly among ATP-dependent activators extends our understanding of biological electron transfer. *CG*

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