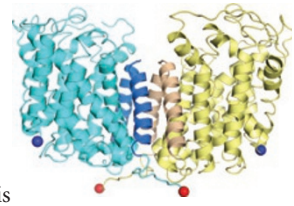
'Virtual' proton pumps



To survive the harsh acidic environment of the stomach, bacteria import certain amino acids into the cell, to be decarboxylated in a reaction that consumes acid and whose product is transported out of the cell. This cycle acts as a 'virtual' proton pump that keeps the cytoplasm above pH 5. A well-studied example is the arginine-dependent system of *Escherichia coli*, whose key component is AdiC, a member of the amino acid/polyamine/organocation (APC) transporter superfamily. AdiC imports arginine from the gastric juice and exports its decarboxylated product, agmatine. Now, two groups have solved crystal structures of *E. coli* (3.6-Å resolution) and *Salmonella* (3.2-Å resolution) AdiC in an outward-open, apo form. AdiC is a roughly barrel-shaped homodimer, each subunit consisting of 12 transmembrane helices arranged in two layers around a central cavity. The cavity's floor is formed by a pair of conserved aromatic residues, where mutations inhibit substrate binding and transport activity in AdiC and its orthologs, making it the likely substrate-binding site. AdiC is structurally similar to several Na^+-coupled symporters in distinct membrane protein families that are unrelated at the sequence level. A third structure of a distant AdiC ortholog, the proton-coupled wide-spectrum amino acid transporter ApcT, was solved at 2.35-Å resolution in an inward-facing apo state. Although the ApcT and *Salmonella* AdiC structures superimpose well, the authors of these papers point out that there is a significant discrepancy, a shift in register of 3-4 amino acids in transmembrane helices 6, 7 and 8, between these structures and that of the *E. coli* AdiC, which affects the putative substrate-binding site. Further biochemical, physiological and structural studies of APC transporters in different apo and bound forms will be required to advance our understanding of the similarities and differences between proton-coupled, sodium-coupled and ion-independent transporters and the details of the exchange cycle. (Gao *et al.*, *Science* **324**, 1565, 2009; Fang *et al.*, *Nature* advance online publication, doi:10.1038/nature08201, 5 July 2009; Shaffer *et al. Science* published online, doi:10.1126/science.1176088, 16 July 2009) *BK*

Switching pins

Protein modification by ubiquitin is a common way to control protein function and turnover. The number of ubiquitins added is important, with monoubiquitination eliciting a different function—for example, with p53 it signals nuclear export—than polyubiquitination, which in some cases marks a protein for degradation. E4 enzymes can determine the degree of ubiquitination, and now Siepe and Jentsch show that Pin1, a peptidyl prolyl *cis/trans* isomerase, is also involved. They began by showing that yeast Pin1 (also known as Ess1) is essential and controls the levels of the NF-κB–related Spt23 transcription factor. High levels of Pin1 result in low ubiquitination levels of Spt23, which in turn triggers Spt23 precursor processing and transcription activation, whereas low Pin1 levels lead to robust polyubiquitination of Spt23 and 26S-dependent degradation. This prompted the authors to investigate whether this mechanism is used elsewhere, and they examined the well-characterized p53 pathway in mammalian cells. In the presence of Pin1, p53 is mainly unmodified, but when the Pin1 inhibitor juglone is added, higher-molecular-mass forms of p53 are observed together with a decrease in cellular p53 levels, indicating that Pin1 regulates p53 levels through inhibition of p53 degradation via the ubiquitin-proteasome pathway. The ubiquitin ligase Mdm2 controls p53 stability, and Mdm2 and Pin1 seem to exert opposing effects and perhaps antagonize each other's function. The exact mechanism of Pin1's activity on p53 remains unclear, but for now the authors propose that Pin1-induced *cis/trans* isomerization controls ubiquitination status, effectively acting as a binary switch on polypeptide chains. (*Nat. Cell Biol.*, advance online publication, doi:10.1038/ncb1908, 13 July 2009) *MH*

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Acquiring acetyllysine

Acetylation of the ε-amino group of specific lysine residues in histone tails is a post-translational modification that has an important role in eukaryote gene expression. Two classes of enzymes are involved in this process: histone acetyltransferases catalyze the acetylation of lysine side chains, whereas histone deacetylases remove this modification. Although lysine side chains in other proteins—for example, p53—are known to be reversibly acetylated, it was not clear how frequently this modification occurs in eukaryotic cells. Choudhary *et al.* recently used high-resolution MS to show that approximately 1,750 proteins—at 3,600 total sites—are acetylated in human cell lines. Surprisingly, the identified proteins are involved in a broad range of cellular processes, including splicing, DNA replication and nuclear transport. The role of some of the newly identified acetylation sites was assessed further. One example is a lysine residue in the kinase domain of cyclin-dependent kinase CDC2. The acetylated status of the equivalent residue in the yeast ortholog Cdc28 was confirmed, and its mutation yielded variants that were unable to rescue a *cdc28*Δ yeast strain. An intriguing finding is that many of the identified proteins in the 'acetylome' are components of large macromolecular complexes, suggesting that this post-translational modification might be involved in regulating the assembly or disassembly of such complexes. (*Science* published online, doi:10.1126/science.1175371, 16 July 2009) *JMF*

Retroviruses *in utero*

During the long gestation of eutherian mammals, fetal growth is supported by the placenta, an organ of embryonic origin that connects the umbilical cord to the uterus wall, allowing the exchange of O_2 and CO_2 as well as nutrients and waste products with the mother's bloodstream. The placenta contains different layers, the most external being the syncytiotrophoblast, which is formed by trophoblast cells fused into a multinucleated layer. An unlikely protein has been proposed to have a role in this process: the retroviral envelope protein (Env). Initially identified in the human genome, *syncytin-1* and *syncytin-2* are *env* genes from endogenous retroviruses that are present exclusively in primates and expressed specifically in the placenta. These genes could promote cell-cell fusion *in vitro* via a mechanism akin to Env-mediated viral entry. Two mouse endogenous retroviral *env* genes, *syncytin-A* and *syncytin-B*, were shown to have similar properties in cell cultures. Although the data at hand supported a role for syncytins in placental formation, their physiological function remained to be established directly. Now Heidmann and colleagues provide conclusive evidence for such role, by knocking-out syncytin-A in mice. The heterozygous animals were normal and fertile, but when they were intercrossed, no homozygous null animals were born. This embryonic lethality could be accounted for by an abnormal syncytiotrophoblast layer in the placenta, with trophoblast cells failing to fuse in the absence of syncytin-A, resulting in impaired placental transport. This is a fascinating example of the impact of endogenous retroviruses on the evolution of their hosts. (*Proc. Natl. Acad. Sci. USA* **106**, 12127–12132) *IC*