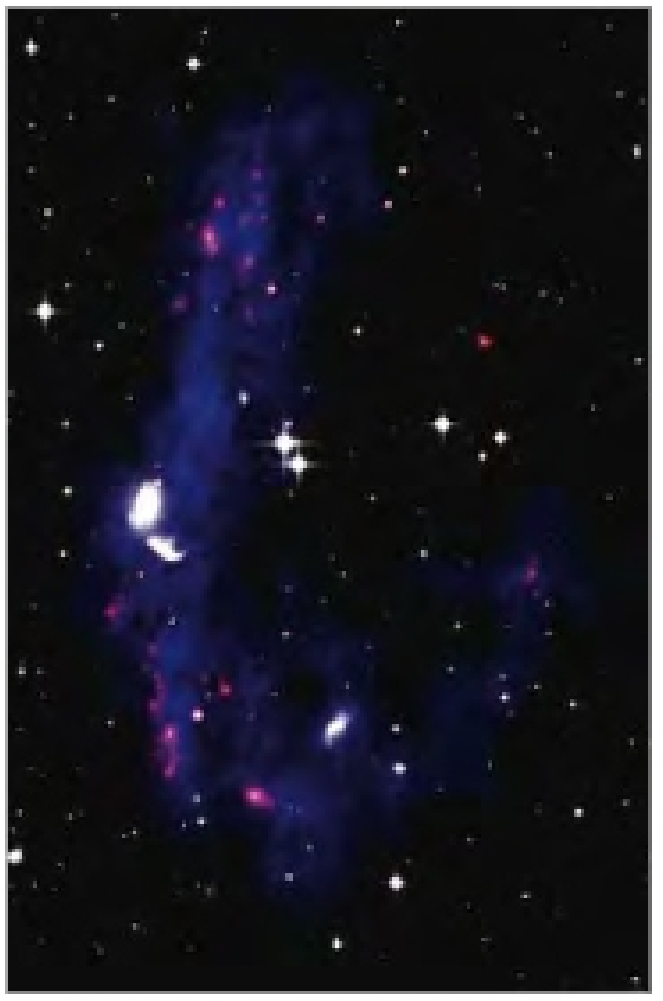
P.-A. DUC/CEA-CNRS/N. RAGAN, NJU/NSF/NASA

Figure 2 | Collision remnant. A multi-wavelength image of the hyper-extended ring galaxy NGC 5291.

observation[9], especially of systems where the companion is somewhat less massive than the primary disk, and is in or near a gravitationally bound orbit. Recent extensions have taken into account observations of several extreme processes, among them high-velocity collisions between galaxies that fall together from distant points, but that are both bound to a greater structure such as a galaxy group or cluster. The interacting system NGC 5291 (ref. 10) is a prominent example of the hyper-extended rings that can result (Fig. 2).

In large rings, the gas density is likely to be low, so the star formation rate will also be low. Mapelli and colleagues' central idea is that such a weak ring will generally be so dim as to be barely visible, and that the huge disk that it leaves behind it as it propagates outwards will look remarkably like a GLSB. Moreover, in the time (a billion years or so) that it takes the material to travel out to such large distances, the high-speed companion will in many cases have moved off the immediate scene. It is therefore hardly surprising if we see no obvious evidence of the past fracas.

The authors[4] use extensive data on four GLSBs to select, from a grid of computer simulations with a range of initial collision parameters, those models, and the times during their evolution, that are most like the observed systems. In all four cases, a model is found in which the surface-brightness profiles, optical colours, and the gas distributions and kinematics of the simulated galaxy all agree well with observations. In three out of four cases, possible companions are also in view.

The obvious consequence of the hypothesis is that GLSBs are disturbed bodies, and not the stable, quiescent galaxy disks that they had been assumed to be. This means that hierarchical galaxy-formation theory within a CDM model is not required to yield GLSBs as final products: the challenge they represent to the theory vanishes. In fact, the best-fit models of Mapelli *et al.* all include 'haloes' of CDM surrounding the colliding galaxies.

Sound as it might like a fractured fairy tale or a Wagner opera gone wrong, the evidence seems to suggest that cosmic gentle giants spring from bejewelled rings. But mysteries remain, such as how smaller, gas-rich low-surface-brightness galaxies form, and how they persist so quietly until they are lit up by a collision. With rapid advances in our understanding of galaxy formation, the prospects are bright for a speedy resolution. ■

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STRUCTURAL BIOLOGY

Ion pumps made crystal clear

David C. Gadsby

The function of every cell in our bodies depends on the work of proteins known as ion pumps. Several new crystal structures cast fresh light on how three different pumps deal with their distinct cargoes of ions.

Ion pumps toil tirelessly in cells throughout all kingdoms of life, transporting ions across membranes. To investigate the workings of these microscopic machines, X-ray crystal structures of a calcium ion pump known as SERCA have been determined[1–5]. But although those structures depict SERCA in several conformations, none of them caught the pump in the act of releasing its cargo of ions. Moreover, nagging questions remained about how much SERCA might differ from other, genetically related ion pumps — such as those that transport ions of different sizes and charges from calcium, or that require additional protein subunits. In this issue, three papers[6–8] from the same group go a long way towards addressing those concerns by describing the first atomic structures of a SERCA pump with its ion pathway open[6] and of two related proteins — a sodium–potassium pump[7] and a proton pump[8].

The three pumps described in these papers belong to a family known as phosphorylated-type (P-type) pumps, named after the phosphate group whose addition and removal controls their activity. P-type pumps inhabit all our cells and are essential for life. Without sodium–potassium pumps, many vital functions would fail. For example, there would be no electrical signals in our brains or hearts, or in any nerves or muscles; and without SERCA pumps, there would be no muscle contraction.

Not surprisingly, P-type pumps are hot targets for therapeutics — for example, digoxin (a treatment for heart problems) targets sodium–potassium pumps, and the latest antacids act on the proton–potassium pumps in our stomachs. So the stakes are high — determining the structure and mechanism of each P-type pump is crucial for further drug discovery.

P-type pumps reside either in the surface membranes of cells or in the membranes of intracellular organelles such as the endoplasmic or sarcoplasmic reticulum. In all cases, one end of the pump opens to the cytoplasm and the other end opens either to the outside of the cell or to the interior (lumen) of the organelle. The pumps adopt two main conformations[9], known as E1 and E2 (Fig. 1, overleaf). The ion-binding sites are found deep inside the region of the pump that crosses the membrane; in E1, these sites are accessible to ions in the cytoplasm. Ion binding promotes the phosphorylation of the pump, in which a phosphate group is added to a single amino-acid residue. The source of the phosphate is an ATP molecule; a side product (ADP) is formed that briefly remains associated with the pump. In the resulting E1P state, the bound ions are occluded — they are inaccessible from either side of the membrane. The pump then releases the ADP and relaxes to the E2P conformation, whereupon a pathway opens to the extra-cytoplasmic side, allowing the ions to escape.

Transport in the reverse direction begins when ions from the cell exterior or the sarcoplasmic reticulum bind to the exposed binding sites in the E2P state, triggering dephosphorylation of the pump. This yields another state with occluded ions, E2. The pump then relaxes back to the E1 state, reopening the ion pathway

to the cell interior and releasing the counter-transported ions to the cytoplasm.

The cycle is strictly controlled so that access to the ion-binding sites alternates between the two sides of the membrane[10], with the ions becoming temporarily occluded after each ion-binding event. Evolution has tailored this mechanism to transport ions against the prevailing ion gradient while avoiding ion leaks in the opposite direction. Because the occluded states are relatively stable, it is these conformations that predominate in the previously determined SERCA crystal structures[1–5].

The five structures presented in the current papers[6–8] constitute a landmark in the history of investigations into P-type pumps. Pedersen *et al.*[8] (page 1111) report the E1 conformation of the proton pump AHA2 from the *Arabidopsis thaliana* plant, in complex with an analogue of ATP (Fig. 1a; the ATP analogue is chemically more stable than ATP itself, and so remains intact during crystallization). The pump generates the proton gradients (and so the electrical potentials) across the cell membrane that act as an energy source for plant and yeast cells. It belongs to a subfamily of P-type pumps — known as subfamily III — whose members have a relatively small binding domain for ATP. SERCA belongs to subfamily II, and so has a larger ATP-binding domain. But, aside from this expected difference, it can now be seen that the two pumps share the same arrangement of transmembrane helices and the same relative positions of their three cytoplasmic domains (Fig. 1).

The second paper (Morth *et al.*[7], page 1043) reveals the E2 conformation of the sodium–potassium pump — a subfamily II protein — isolated from pig kidneys (Fig. 1b). The pump is in complex with an MgF_4^{2-} ion, which mimics a phosphate group, and occluded rubidium ions act as substitutes for the potassium ions that would be found *in vivo*. The sodium–potassium pump consists of three subunits, α, β and γ. The α-subunit is the largest, and is structurally similar to the entire SERCA protein. Morth and colleagues' structure[7] shows that, despite the presence of the β- and γ-subunits, the conformation of the α-subunit closely matches that of the analogous SERCA complex[4]. The two trapped rubidium ions are the first counter-transported ions large enough to be directly observed in the crystal structure of a P-type pump; they are in nearly the same positions as those thought to be adopted by the counter-transported H^+ ions in SERCA.

The structural differences between SERCA and the α-subunit of the sodium–potassium pump are remarkably small. They can be attributed to minor differences in the proteins' complement of amino acids, specific interactions of the α-subunit of the sodium–potassium pump with its other subunits, and the need for the sodium–potassium pump to coordinate two rubidium (or potassium) ions instead of two or three protons. Taken together with the previously obtained SERCA structures[1–5], the structure of AHA2 (ref. 8) and that of the sodium–potassium pump[7] show us that P-type pumps — or, at least, those in subfamilies II and III — share the same architecture regardless of the size, charge or number of ions that they transport, and that their differences are largely confined to the ion-binding pocket.

Olesen *et al.*[6] (page 1036) provide yet more bounty in the form of three new SERCA structures. The first of these shows SERCA in the E1P conformation, with two occluded calcium ions and an ADP-mimic bound to the protein. The phosphate group is firmly integrated into the pump protein, making this a true E1P state of SERCA. This is in contrast to previous structures[3,4] that were only 'E1P-like' because their phosphate mimics were more loosely attached.

Olesen and colleagues' other two structures[6] show E2 forms of SERCA. Previously obtained crystals of SERCA in the E2 state[2,4,5] required a pump inhibitor (such as thapsigargin) to be bound to the protein to stabilize the structure. But the new crystals[6] required no inhibitors, and so the structures are more likely to represent natural E2 conformations of SERCA. In fact, one of the new E2-SERCA structures (Fig. 1c) looks rather like an analogous E2-SERCA complex that was bound with thapsigargin[5]. It therefore seems that thapsigargin doesn't distort occluded E2-SERCA structures as had been feared.

But the crowning glory of this work[6] is a structure determined in the presence of a phosphate mimic (BeF_3^-), revealing a long-sought conformation of SERCA. Previously obtained biochemical data suggested that calcium ions bind weakly to SERCA pumps treated with BeF_3^-; such weak binding is consistent with the presence of an open ion pathway in the pumps[11]. This is finally confirmed by Olesen and colleagues' structure of the SERCA–BeF_3^- complex (Fig. 1d), in which the transmembrane helices are splayed apart, creating a funnel-shaped pathway. At its narrow end, this pathway leads to some of the ion-binding amino-acid

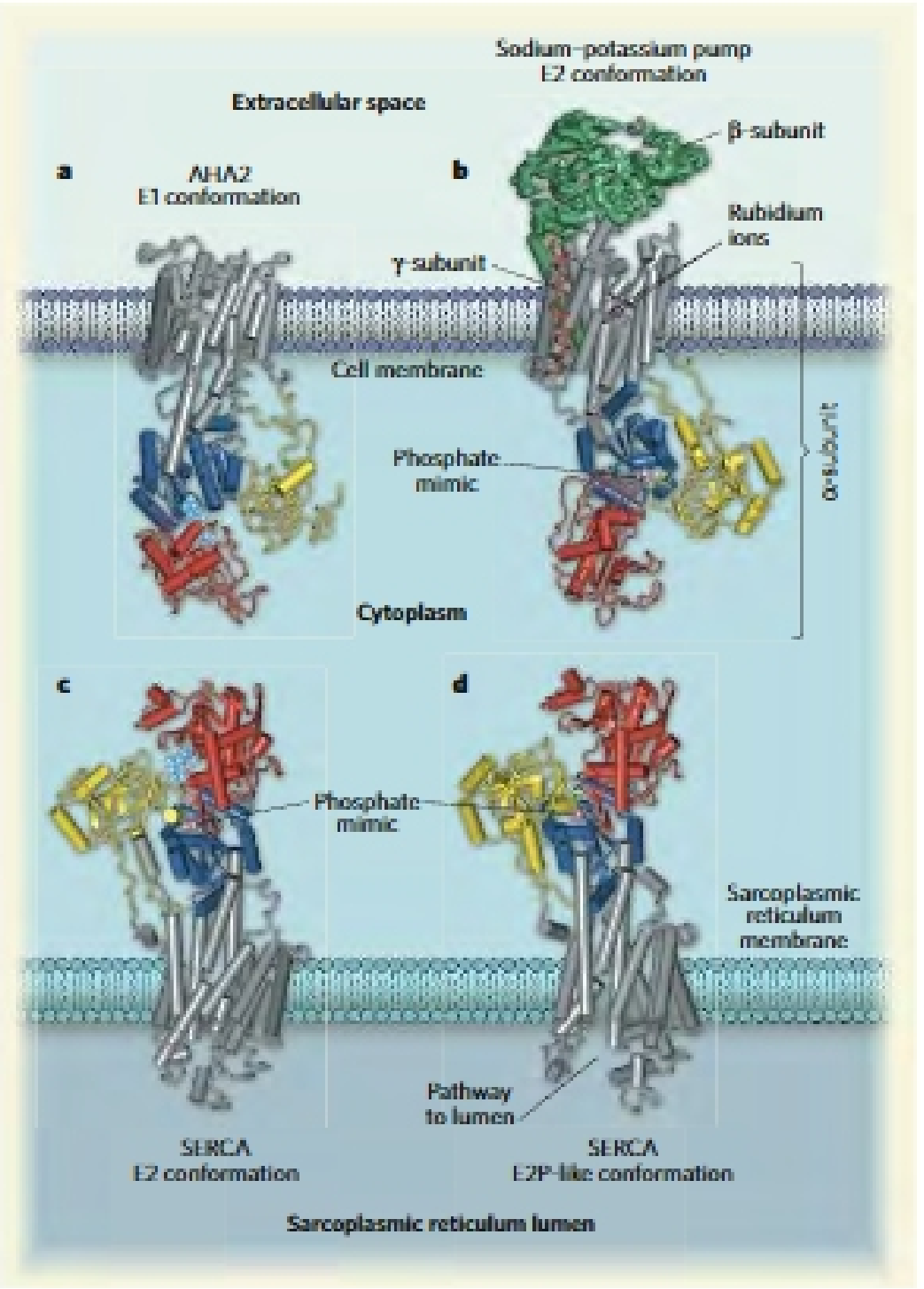

Figure 1 | Three P-type ion pumps have similar structures. P-type ion pumps transport ions across either cell membranes (**a**,**b**) or membranes of intracellular organelles such as the sarcoplasmic reticulum (**c**,**d**). **a**, Pedersen *et al.*[8] report the crystal structure of the AHA2 proton pump in the E1 conformation — ion-binding sites in the transmembrane region (grey rods) bind protons (positions not established) from the cytoplasm. **b**, Morth *et al.*[7] report the structure of the sodium–potassium pump in the E2 conformation. This comprises an α-subunit (which is structurally similar to the other pumps illustrated), a β-subunit (green) and a γ-subunit (single red helix). The pump is in complex with a phosphate mimic (MgF_4^{2-}), and two rubidium ions are trapped in the transmembrane region. **c**,**d**, Olesen *et al.*[6] report new structures of SERCA, a calcium ion pump. **c**, Here, SERCA is in the E2 conformation, in complex with AlF_4^- (another phosphate mimic). Two or three protons (positions not established) are trapped in the transmembrane region. **d**, This structure shows SERCA in complex with the BeF_3^- phosphate mimic. The conformation imitates the E2P state of the pump — a pathway is open to the lumen. In all cases the ATP-binding domains are red, phosphorylation domains are blue, key connecting regions to the transmembrane domain are yellow and ATP analogues (where bound) are pale blue. (Crystal structure images were prepared by A. Takeuchi.)

residues, which would thus be exposed to the lumen of the sarcoplasmic reticulum *in vivo*.

The five new structures[6–8] answer many long-standing questions about P-type ion pumps, but they also prompt further questions. The similarity between the analogous E2 forms of SERCA and of the α-subunit of the sodium–potassium pump suggests that SERCA structures will be useful models for other P-type pumps in subfamily II. But the overall similarity of the AHA2, SERCA and sodium–potassium-pump structures raises the question of how each protein selects only its preferred ions for transport. Higher-resolution structures of the pumps, in at least their two occluded conformations, are required to answer this question.

Issues specifically concerning the sodium–potassium pump also remain unresolved. In cells, this pump exports three sodium ions at a time from the cytoplasm, but then imports only two potassium ions, which are bound as seen in the new structure[7]. Other structures are sorely needed if we are to learn how the three sodium ions are handled. Furthermore, electrical signals generated by this pump during sodium-ion release suggest that the three sodium ions leave at different speeds, one after the other[12]. Does this mean that there is more than one escape route for these ions, implying that there might be more than one open-pathway conformation of the pump? SERCA also releases its two calcium ions sequentially[13], so might another open E2P conformation of this pump exist? Perhaps more fundamentally, the locations of the cytoplasmic ion pathways remain unidentified.

The remarkable structures reported today[6–8] will undoubtedly whet biologists' appetites. Would it seem greedy to ask for more ion-pump structures for Christmas? ■

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MOLECULAR BIOLOGY

Genome under surveillance

Karen M. Arndt

Decoding the information stored in DNA requires an intricate balance between processes that turn gene expression on or off. A protein that influences the packaging of DNA regulates this balance genome-wide.

Organisms store instructions for their own existence in DNA. Specific proteins access and read the DNA sequence either to replicate it or to mediate gene expression. But this DNA-reading process is impeded by chromatin — tight packages of DNA and histone proteins that are essential for nuclear compartmentalization of the genome. Strategies for opening chromatin are therefore crucial for basic molecular processes such as gene transcription; this is not to say that restricting access to the genome is less important. On page 1031 of this issue, Whitehouse *et al.*[1] describe an elegant chromatin-based mechanism by which yeast (*Saccharomyces cerevisiae*) cells prevent inappropriate transcription.

Once considered static, chromatin is now viewed as a dynamic structure that regulates almost all aspects of DNA metabolism and genome inheritance. On a local scale, the positioning of nucleosomes (fundamental units of chromatin, comprising octamers of histone proteins wrapped by the DNA double strand) profoundly affects DNA-binding proteins' access to their target sequences. On a global scale, nucleosome positioning is non-random. For example, promoter sequences, which control transcription, are typically nucleosome-deficient, whereas coding regions tend to be nucleosome-rich[2,3]. Several strategies probably determine such consistent nucleosomal patterns. These include nucleotide sequences[4,5] and structural features of DNA[3] that disfavour or favour nucleosome formation, and active mechanisms such as competition between transcription factors and histones for binding to DNA, and enzyme-mediated chromatin remodelling[6].

Despite having been discovered almost two decades ago, the global effects of chromatin-remodelling factors are not fully understood. Although several studies had measured the transcriptional impact of mutating a chromatin-remodelling factor[6], it remained unknown whether these transcriptional effects are direct or indirect, or whether they are associated with changes in chromatin structure.

One chromatin-remodelling factor is the yeast Isw2 protein, which is a member of an evolutionarily conserved group of enzymes that alter chromatin structure using ATP as a source of energy. Different chromatin-remodelling factors alter chromatin structure in different ways, including nucleosome sliding, nucleosome assembly and disassembly, and

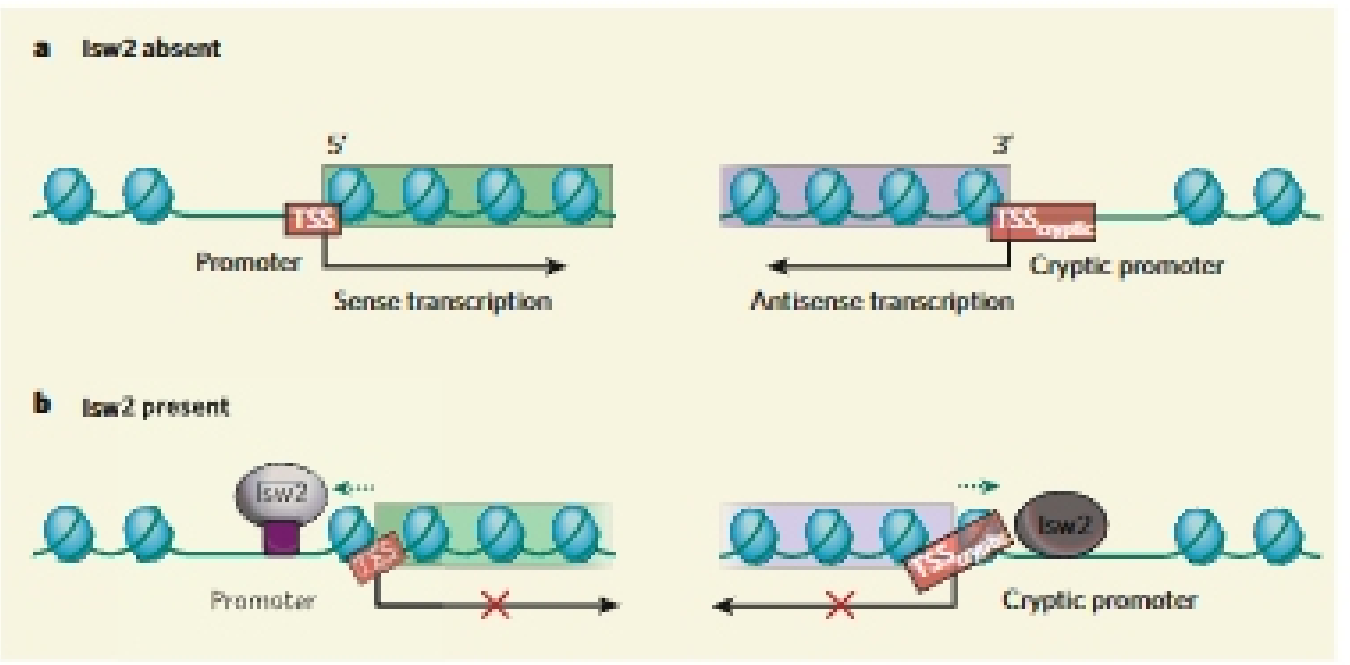

Figure 1 | The Isw2 protein represses transcription by altering nucleosome positions. a, Whitehouse *et al.*[1] show that, in yeast strains lacking Isw2 activity, nucleosomes are shifted towards coding regions at either the 5′ or 3′ ends of genes, and transcription is initiated either in the sense or antisense direction, respectively. TSS, transcription start site. b, Normally, specific DNA-binding proteins (magenta) recruit Isw2 to sequences within promoter regions, which are located within intergenic regions on the 5′ side of the coding regions. There, Isw2 slides nucleosomes towards intergenic regions, over sequences required for efficient initiation of transcription, such as the transcription start site. Isw2 is also recruited near the 3′ end of genes through an unknown mechanism. There, it also directs nucleosomes towards intergenic sequences, which may harbour cryptic signals for initiation of antisense transcription. So Isw2 functions as a transcriptional repressor.