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Molecular motors

What makes ATP synthase spin?

Paul D. Boyer

Many years ago, when enzymes were first recognized as being proteins, few people could have imagined the wondrous, precise and diverse structures that make possible their catalytic and other functions. The ATP synthase enzyme, for example, performs catalysis as a molecular machine with an unexpected internal rotary mechanism. On page 263 of this issue, Rastogi and Girvin[1] report the latest insights into this mechanism. Using sophisticated NMR and chemical probes, they have revealed structural changes in a critical subunit that could drive the rotation.

ATP synthase, also known as F_1F_0 ATPase, catalyses the formation of ATP (adenosine triphosphate) from ADP (adenosine diphosphate) and P_i (inorganic phosphate), in processes known as oxidative phosphorylation (driven by oxidations in animal cells and microorganisms) and photophosphorylation (driven by light in plant cells). Once formed, ATP is cleaved back to ADP and P_i, as it provides the energy to drive a myriad of metabolic processes including biosyntheses, muscle contraction, and nerve and brain function.

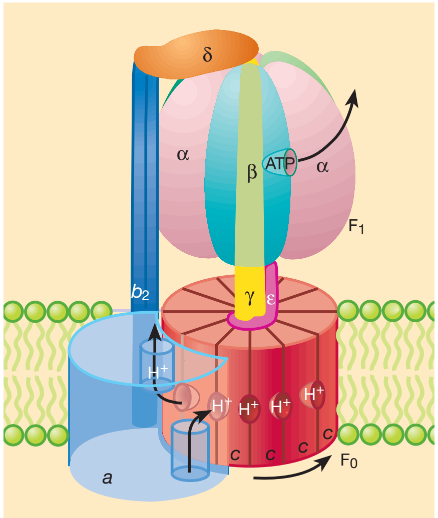

Figure 1 **Model of the *Escherichia coli* ATP synthase. The enzyme consists of two parts known as the F_1 and F_0 portions. The F_1 portion comprises three α subunits, three β subunits, an ϵ, δ and γ subunit. The F_0 portion contains one *a* subunit, one *b* subunit and 9–12 *c* subunits. (Courtesy of R. L. Cross, State Univ. New York, Syracuse.)**

A model of the enzyme (Fig. 1) shows a hydrophilic F_1 portion above the F_0 part, which is embedded in a phospholipid bilayer membrane. The F_1 portion from various sources is made up of three α subunits, three β subunits and one each of the γ, δ and ϵ subunits. The three catalytic sites are found mainly on the β subunits. In the F_0 portion from the bacterium *Escherichia coli*, there are one *a* subunit, two *b* subunits and 9–12 *c* subunits. The F_0 portion from various plants and animals is more complex, but it still contains the multiple copies of *c*-type subunits.

As demonstrated by Peter Mitchell[2], energy from oxidation–reduction reactions is captured by the formation of an electrochemical gradient of protons across the membrane. This advance — and the growing knowledge about proteins and the ATP synthase enzyme — provided the basis for a suggestion that I made a quarter of a century ago[3]. The idea was that the protonation and deprotonation of a carboxyl group in F_0, as protons cross the membrane, results in protein conformational changes coupled to the formation of ATP. Rastogi and Girvin[1] now clothe this concept with reality.

Since this proposal, much has been learned about the ATP synthase. The three catalytic sites are known to pass sequentially through three different conformations associated with substrate binding, formation of tightly bound ATP, and release of the ATP. These changes are thought to occur through a rotational catalysis in which, as indicated in Fig. 2 (overleaf), rotation of the γ subunit causes the requisite sequential changes in the β subunits[4].

The concept of a binding-change mechanism with rotational catalysis received strong support five years ago when John Walker's group reported[5] the X-ray structure of the major portion of F_1. This structure was consistent with the idea that three different conformations of the β subunits are interconverted by rotation of the γ subunit. Avail-

NATURE

100 YEARS AGO

The authors of this research on the vibrations of gun barrels were induced to make an experimental investigation of the behaviour of rifle barrels, in order to clear up certain difficulties connected with that which is known in ballistics as the *error of departure.* It had been noticed that in shooting with a rifle (whether loosely, or firmly fixed), that the initial tangent to the trajectory — “die Anfangstangente der Flugbahn” — does not coincide, as would be expected, with the axis of the bore of the barrel, when produced, but is more or less inclined to it at a small angle; this is called *the angle of error of departure* ... The collection of photo-chronographic records, twenty-eight in number, show the manner in which a rifle barrel vibrates when subjected to the concussion due to an explosive… The authors show that the experimental results agree well with figures calculated on the assumption that the rifle barrel is a cylindrical tube.

From *Nature* 16 November 1899.

50 YEARS AGO

‘Data’

***Nature* of September 3 contained a letter under this heading. In it Prof. A. V. Hill asks that the word be used in its original sense, that is, as the plural of datum, for which he gives the “Oxford English Dictionary” definition “A thing given or granted” and so on. He adds that there may sometimes be an excuse for regarding data as a collective singular in the same way as agenda…. In my view, the word ‘data’ has now come to be generally accepted as having a wider meaning than one based on its Latin derivation. It is used, still as the plural of datum, to indicate a collection of facts or, more often, figures, and these may, indeed, be regarded as ‘things given’ to the reader for the argument or discussion based on them. Changes in the meaning of a word are common in a language that is still alive and should, I suggest, be welcomed as a sign of life. On the other hand, not even Prof. Hill will convince me that one may deliberately change the grammar of a word. ‘Data’ was a plural noun; for literate English writers it still is, and I contend that it always should be.**

From *Nature* 19 November 1949.

Many more extracts like these can be found in *A Bedside Nature: Genius and Eccentricity in Science, 1869–1953*, a 266-page book edited by Walter Gratzer. Contact Lisa O’Rourke. e-mail: l.orourke@nature.com

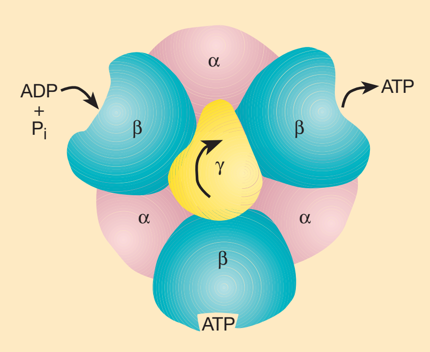

Figure 2 **How rotation of the γ subunit drives catalysis. During ATP synthesis, rotation of the γ subunit causes sequential changes in the β subunits. A rotation of 120° changes the β subunit that binds ADP and P_i to a form with tightly bound ATP. The subunit with tightly bound ATP then changes to a form that releases ATP, and the third subunit prepares to bind another ADP and P_i.**

ability of the X-ray structure also allowed clever disulphide cross-linking experiments to be designed, showing the positional interchange of the β subunits as catalysis proceeds[6,7]. Specialized fluorescence techniques provided strong evidence for the rotation[8]. Rotational catalysis finally became widely accepted in 1997 when Noji *et al.*[9] dramatically showed the rotation directly. They attached a fluorescently labelled actin filament to the γ subunit of the F_1 portion fixed on a slide, then watched the filament spin as the enzyme cleaved ATP.

Other studies have looked into the arrangement of the subunits (Fig. 1). The many copies of the *c* subunit in the F_0 portion are arranged in a ring, with a conserved carboxyl group near the middle of one of the two hydrophobic helices that cross the membrane. These two helices are connected by a polar loop with conserved residues. The *b* and δ subunits form a stator, which assures that rotational movement of the γ subunit drives conformational changes in the β subunits. The ε and γ subunits contact each other and the polar loop of subunit *c*. The *a* subunit contacts the ring of *c* subunits and provides groups that probably participate in proton transfer through the F_0 portion. Such proton transfer is thought to cause the ring of *c* subunits to move in a step-wise fashion relative to the *a* subunit. This results, in turn, in rotation of the ε and γ subunits.

But does proton translocation cause meaningful changes in the conformation of the *c* subunit — changes that might drive the rotation? This is the problem that has been elegantly addressed by Rastogi and Girvin[1]. To do this, they used two main methods. One was to measure the location and distance constraints provided by selected cysteine insertions that allowed disulphide-bond formation. The other was NMR, which gave structure and distance constraints from ^{13}C- and ^{15}N-resolved three-dimensional NOESY data.

Fillingame and colleagues[10] have used the NMR approach to provide a structure for the monomeric *c* subunit. Combining this with disulphide-crosslinking and other data, these authors developed a model for the structure of the *c*-subunit ring and its interactions with the *a* subunit. They found that the key residue, an aspartic acid at position 61 (Asp61), was lodged at the centre of four α-helices of a *c*–*c* dimer. They proposed that, as deprotonation and protonation occur when the ring of *c* subunits interacts with the *a* subunit, the critical carboxyl group might move towards the periphery of the ring by a swivelling of adjacent helices.

The oligomeric model developed by Rastogi and Girvin[1] provides insight into the catalytic mechanism. These authors deduced the conformations of the protonated and deprotonated forms of the *c* subunit. When Asp61 is deprotonated, there is a dramatic 140°-rotation of the carboxy-terminal helix with respect to the amino-terminal helix. The authors suggest two ways in which rotation of this helix might drive rotation of the γ subunit. In one, the *a* subunit moves with the carboxy-terminal helix of the *c* subunit, providing a 30° relative movement of the ring with respect to the *a* subunit. In an alternative, a negative charge, or 'proton hole', is envisaged. This traverses the ring until it encounters an ε subunit, which is then displaced to an adjacent *c* subunit, accomplishing a 30° rotation of the ε–γ stalk.

Although progress, including the work of Rastogi and Girvin, is commendable, questions and uncertainties remain. In unveiling the details of how nature accomplishes this remarkable catalysis, we will probably uncover yet more surprising features. ■

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erratum In the opening paragraph of the News and Views article "Carbon cycle: The blast in the past" (*Nature* **401,** 752–755; 1999) the figure 2,000–4,000 gigatonnes of carbon should have been rendered as 2–4 million million tonnes or 2–4 billion billion grams (not 2–4 billion billion tonnes).

Daedalus

Frankenstein lives!

The adult immune system attacks foreign proteins ferociously, even those of a life-giving transplant. Yet a fetus in the womb accepts foreign cells quite amicably. Even better, it thereafter regards them as part of itself. When adult, it will accept more transplants from the owner of the cells.

So Daedalus has a new strategy of organ transplantation. Take a cohort of expectant mothers, and extract some cells from each fetus by standard amniocentesis methods. Then inject each fetus with cells from all the others. They will grow up into a cohort of mutually immunocompatible adults, any of whom can give a transplant to any of the others, or receive one, with no rejection problems at all.

The organ-donor card of each member should specify his cohort; if he met a fatal accident, his organs could be given at once to any other members in need of them. Cohort members should be as closely related as possible, so that transplants between them would be physically as well as immunologically similar, and to give each member a sound genetic motive for providing another with a transplant. Mothers from one extended family, or from a fairly inbred village, are obvious cohort founders, but the bigger the cohorts the better. If (improbably) immunological tolerance is inherited, cohorts could be merged in successive generations until in time the whole of humanity shared the same immunological compatibility. But even a mass of small cohorts would revolutionize the transplant business. Rejection problems would cease, and recipients would no longer face a lifetime of drug-taking.

Transplant surgery would boom. Not only skin, hearts, livers and kidneys, but all parts of the body could be exchanged — even brains and pieces of brain. The successful introduction of fetal brain tissue into adult brains suggests that a composite brain might rewire itself into a functional unit quite well. Total death could thus be averted. From a dozen oldsters, all suffering from different infirmities and brain deficits, a surgeon could assemble a perfectly healthy composite individual. The composite would have memories and skills from each of its predecessors, who would all survive as subsidiary personalities in the new joint venture. **David Jones**

The Further Inventions of Daedalus (Oxford University Press), 148 past Daedalus columns expanded and illustrated, is now on sale. Special *Nature* offer: m.curtis@nature.com