Review–Hypothesis

Molecular mechanics of protonmotive F_0F_1 ATPases

Rolling well and turnstile hypothesis

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The reversible protonmotive F_0F_1 ATPases perform the uniquely important function of balancing the forces, and interconverting the potential energies, of phosphoryl transfer and proton translocation. The molecular mechanics of the processes of ligand conduction catalysed by the F_0F_1 ATPases is therefore especially interesting. This paper summarises the main structural and functional knowledge of the F_0F_1 ATPases in the light of current mechanistic hypotheses, and suggests a new type of rotating subunit hypothesis, which is related to that recently developed for bacterial flagellar motors.

Bioenergetics *F_0F_1 ATPase* *Biomechanics* *Rolling subunit hypothesis* *Chemiosmostic mechanism*

1. INTRODUCTION

The reversible protonmotive F_0F_1 ATPases constitute one of the most bioenergetically important, widely distributed and structurally conservative of all osmoenzyme families [1–15]. In *Escherichia coli*, the subunit compositions of F_0 and F_1 are $a_1b_2c_{10}$, and $\alpha_3\beta_3\gamma\delta\epsilon$, respectively; and the subunits have been completely sequenced [8–12]. The F_0 complex is a largely hydrophobic protein (M_r about 150000) that is integral with the lipid bilayer, and functions as a proton conductor when F_1 is absent. The F_1 complex is a hydrophilic protein (M_r about 380000) that is normally attached to the low protonic potential side (*N* side) of F_0, and contains the hydrolytic system. The normal functional activity of F_1 requires the complete complex, there are nucleotide-binding sites in both α and β subunits, complexes of α and β with γ or δ exhibit ATPase activity, and there are three hydrolytic centres, located in the β subunits or at the interfaces between the α and β subunits, which are arranged alternately in a hexagonal pattern [7–10,12–14,16–21], some asymmetry being associated with γ and ϵ, which may function as a rotating proton gate [1–10,12–14,22–25].

Prompted by the rapidly increasing structural and functional knowledge of the F_0F_1 ATPases, and by the development of a possibly relevant 'well and turnstile' concept of proton-driven molecular rotation [26], my aim in this paper is to outline the main chemical and osmotic actions catalysed by the F_0F_1 ATPases in the light of current mechanistic hypotheses, and to suggest how proton-driven rotation of the larger subunits of F_1 might help to explain the ATP/(P_i + ADP) antiport action, and other aspects of catalytic cooperativity that appear to be characteristic of these remarkable osmoenzymes.

2. CHEMIOSMOTIC MOLECULAR MECHANISMS

2.1. *Directly coupled chemiosmotic mechanism*

In 1974, a directly coupled chemiosmotic molecular mechanism of the protonmotive F_0F_1 ATPases was proposed [27,28], in which it was suggested that F_1 catalyses an in-line nucleophilic

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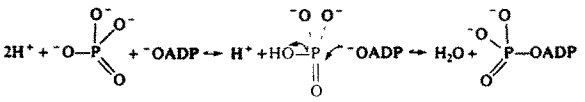
displacement on phosphorus that proceeds by way of a pentavalent transitional intermediate having trigonal bipyramidal geometry, and that the local process of phosphorylation of ADP, bound with inorganic phosphate in the hydrolytic domain, depends on the protonation of the phosphorus- and/or-enzyme-bound oxide ion that leaves the phosphorus centre at the high protonic potential side (*P* or left side) of the hydrolytic domain, as represented by eq.1:



(1)

It was further suggested (fig.1A) that components of F_1 catalyse the conduction of ATP from the hydrolytic domain to the aqueous *N* domain, and of P_i + ADP from the aqueous *N* domain to the hydrolytic domain, by a co-operative antiport process in which the total osmotic work available for ongoing ADP phosphorylation would depend on the difference (*n*) between the effective protonation states in which the ATP^{4-} and PO_4^{3-} + ADP^{3-} were conducted; and the apportionment of this work between the pushing in of PO_4^{3-} + ADP^{3-} and the pulling out of ATP^{4-} would depend on the set of ligands, including protons, with which both the input and output substrates were associated in the antiport conduction pathways connecting the hydrolytic domain with the aqueous *N* domain (see [28] pp.100–101).

These proposals were sharply criticised for what were considered to be chemical and energetic weaknesses [29–33]. In particular, Boyer [29] argued that phosphate ester monoanion hydrolysis, including that of ATP and ADP, very likely proceeds by a metaphosphate mechanism not involving pentacovalency; and that the observed poising of the ATP/(P_i + ADP) couple towards ADP phosphorylation in a catalytic site of F_1 was incompatible with what was described as "the primary use of energy for making a covalent bond between ADP and P_i, as in (the) chemiosmotic mode of ATP formation" [31]. However, the directly coupled type of chemiosmotic mechanism [27,28] explicitly included the ATP/(P_i + ADP) antiport mechanism for co-operatively pushing ADP + P_i into, and pulling ATP out of,

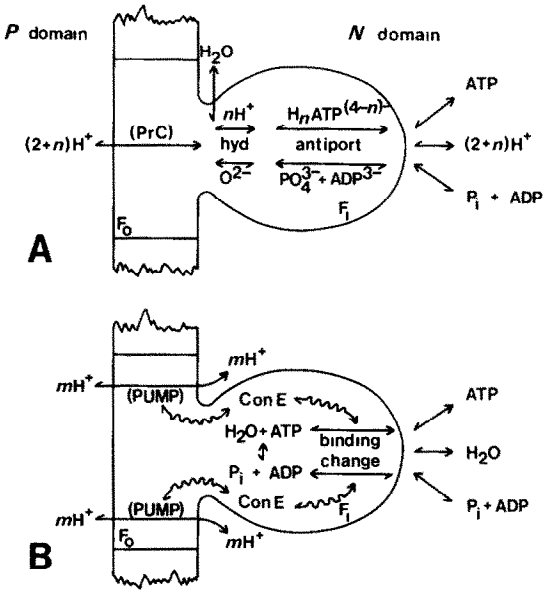


Fig.1. Ligand-conduction diagrams of possible (A) directly coupled and (B) conformationally coupled F_0F_1 ATP synthase mechanisms. *P* and *N* represent normally protonically positive and negative aqueous domains, respectively. In the directly coupled mechanism (A), the reversible hydrolytic site (hyd), catalysing O^{2-} protonation and abstraction, is shown towards the *P* pole of F_1, and the ATP/(P_i + ADP) antiport function (antiport) is shown towards the *N* pole. The extension of the antiport system to the *N* pole of F_1 is dictated by typography. The substrates may actually enter and leave at the sides of F_1. The protonmotive stoichiometry of $(2 + n)H^+$ per ADP phosphorylated is supposed to be determined by the ATP/(P_i + ADP) antiport function of F_1, as indicated in the text, and *n* cannot exceed 4. F_0 is supposed to function passively as a proton conductor (PrC). In the conformationally coupled mechanism (B), based on the description by Boyer [6], F_0 is supposed to function as a reversible proton pump (PUMP) system that is coupled by conformational energy transfer (Con E and wavy arrows) to the reversible hydrolytic sites in F_1 that go through cyclic changes of ATP and P_i + ADP binding (binding change). The protons are shown passing on either side of the *N* pole of F_1 to conform with Boyer's recent model in which reversible pumping is attributed to three regions of F_0, adjacent to the 3β subunits of F_1, distributed symmetrically around a central axis through F_0, normal to the membrane surface. The diagram thus shows only 2 of the 3 proton-pumping systems, each of which is supposed to translocate one proton per ADP phosphorylated in Boyer's model [6]. To get the stoichiometry right while showing only 2 proton pumps, $m = 3/2$.

the catalytic domain of F_1, as described above. Thus, this objection by Boyer [31] to the direct type of chemiosmotic mechanism was evidently based on a misunderstanding; and it appears that, with notable exceptions [3,5,7], this misunderstanding has been widely adopted [2,6,9,10,13, 34,37].

2.2. *Conformationally coupled chemiosmotic mechanism*

In the conformationally coupled binding-change mechanism (fig.1B) a conformationally mobile polypeptide system has been postulated as an essential energy-transmitting device, interposed between supposedly separate proton-pumping and hydrolytic domains in F_0F_1 ATPases; and the proton-pumping and hydrolytic functions have generally been attributed to the F_0 and F_1 components of the ATPase, respectively (see [6]). Thus, in what is described as the binding-change mechanism, Boyer [38,39] has specifically excluded the participation of protons, or their hydroxide or oxide ion equivalents, as shared intermediaries between the chemical and osmotic actions of the F_0F_1 ATPases. But, as previously pointed out [40], this exclusive aspect of Boyer's conformational coupling hypothesis should not be taken to imply that the directly coupled type of mechanism must conversely exclude the conformational interactions and mobilities that are characteristic of enzyme-catalysed processes. Indeed, it has been explicitly argued that the transfer of force and energy by conformational interaction would be no less functionally important in the directly coupled type of mechanism, involving overlapping and closely interrelated chemical and osmotic ligand-conducting domains [40–43], than in the essentially duplex conformationally coupled type of system, in which the hydrolytic and proton-pumping domains are supposed to be separate [6,38,39].

2.3. *Ligand binding and ligand conduction in the directly coupled chemiosmotic mechanism*

According to well-established principles of reversible enzymic catalysis (see [41], p.457, and [42], pp.20–21), one would expect intermediary couples, such as the ATP/(P_i + ADP) couple in the catalytic domain of F_1, to be poised near their midpoints in the special environments of the catalytic domains, just as the redox couples are poised in respiratory chain systems [43].

The phosphorylation of ADP involves the separation of P_i + ADP into H_2O and ATP. The total work of separation (fig.1A), is the sum of the work done in protonating the O^{2-} ion across the effective protonic potential difference on the *P* side of the hydrolytic domain, and the work done by the 2 + *n* protons driving the ATP/(P_i + ADP) antiport across the effective protonic potential difference on the *N* side of the hydrolytic domain. With the system operating reversibly, the sum of the two driving protonic potential differences, on either side of the hydrolytic domain, would be equal to the total protonic potential difference $\Delta\bar{\mu}H^+$ across the F_0F_1 molecule. Obviously, if the ATP/(P_i + ADP) couple were poised by solvation substitution and other environmental factors in the hydrolytic domain, so that little work would be done in the local abstraction and protonation of the phosphorus-and/or-enzyme-bound O^{2-} ion, most of the driving protonic potential difference would occur on the *N* side of the hydrolytic domain, and the ongoing process of ADP phosphorylation would be driven mainly by ATP/(P_i + ADP) antiport. These circumstances, together with the fact that it has recently been shown that the stereochemical configuration on the phosphorus centre of ATP is inverted during hydrolysis by a mitochondrial [44] and by a bacterial [45] F_0F_1 ATPase – thus favouring an in-line nucleophilic displacement mechanism involving a pentavalent intermediate (or an equivalent immobilised metaphosphate intermediate [1]) – suggest that the directly coupled type of chemiosmotic mechanism deserves more serious consideration.

The reader will appreciate that, as pointed out in recent reviews [3,5,7], the observed changes of binding of ATP, P_i and ADP [2,7,9,10,13,14, 34–39] may reasonably be regarded as a necessary requirement for the output of ATP and input of P_i + ADP, described as ATP/(P_i + ADP) antiport, during ADP phosphorylation by the F_0F_1 ATPases. In other words, as illustrated by fig.1, what I call directly-coupled ATP/(P_i + ADP) antiport, and what Boyer calls conformationally coupled binding change, account in different ways for the same substrate push-pull action, driving the counter-transfer of ATP and P_i + ADP between

the aqueous N domain and the reversible hydrolytic sites in F_1 during ongoing ADP phosphorylation. Therefore, the important question is not whether the counter-transfer of ATP and P_i + ADP occurs between the hydrolytic domain in F_1 and the aqueous N domain, or whether this is associated with the necessary changes of substrate binding. What we really want to know is how these push-pull processes occur, and how directly they may be driven by the current of protons flowing through the F_0F_1 ATPases.

2.4. *Possible rolling well and turnstile mechanisms*

The rolling well and turnstile type of mechanism, illustrated by a version outlined in fig.2, was produced by combining the general principles of the ternary state mechanism of the F_0F_1 ATPases [1] with those of the well and turnstile mechanism for torque development in flagellar motors [26], bearing in mind the analogy between F_0F_1 ATPases and actomyosin ATPases [46]. For ADP phosphorylation, this general type of mechanism depends on the following fundamental postulates, analogous postulates being applicable to protonmotive ATP hydrolysis.

(1) The negatively charged β subunits are in rolling contact with the positively charged γ subunit, and the surfaces of the β and γ subunits are uniquely matched and of equal effective circumference, so that the rotational orientations of the three β subunits differ by 120°.

(2) The hydrolytic site is formed by the juxtaposition of specific domains in the surfaces of the members of three α-β subunit pairs.

(3) The co-operative counter-transfer or antiport of ATP and P_i + ADP is catalysed between the hydrolytic site and the aqueous N domain through sites between α and β subunits; and the co-operative push-pull action is attributed to forces transferred by means of the rolling action of the subunits.

(4) The ligand-binding and ligand-conducting properties of the hydrolytic and substrate-translocating sites in the α and β subunits depend on the relative proximities and angular orientations of the surfaces of the subunits.

(5) The γ subunit (or γ-ϵ subunit complex) acts as a rotating proton gate, cyclically connecting the hydrolytic site formed in each α-β subunit pair to the proton well in F_0 through a proton-conducting domain.

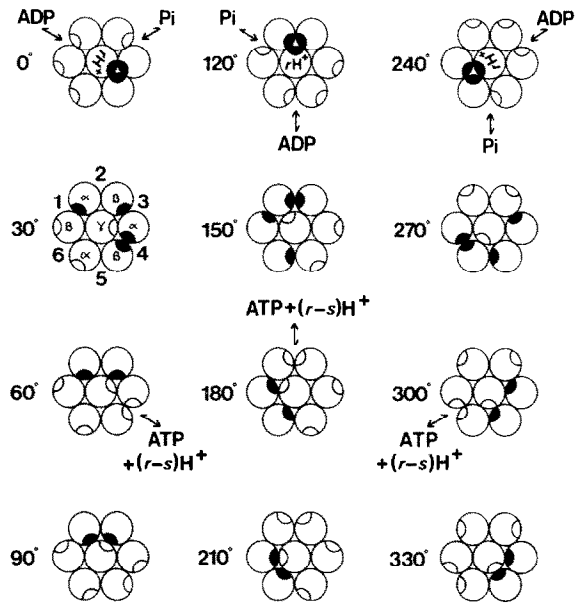


Fig.2. Illustration of a version of the rolling well and turnstile mechanism. The diagrams show the successive rotational positions of the α, β and γ (or $\gamma + \epsilon$) subunits of F_1 at 30° intervals, in a plane at right angles to the F_0-F_1 axis, in the course of a complete catalytic configuration cycle in which 3 ADP molecules are phosphorylated by the passage of $3r$ protons through F_0F_1. Pairs of α-β subunits with different surface-to-surface relationships are marked 1, 3, 5 and 2, 4, 6, respectively. In these diagrams the α and γ subunits rotate counter clockwise, and the β subunits rotate clockwise, all at the same angular velocity. The open and solid shapes represent the domains in α and β that form the hydrolytic site when juxtaposed. They are shown solid when a substrate molecule is enclosed. The open or solid shape in the central γ subunit (or γ-ϵ complex) represents the gate that transfers protons between the proton-conducting well in F_0 and the hydrolytic site. It is shown solid when r protons are transferred from it to the hydrolytic site. The net number of protons appearing in the aqueous N domain per ATP produced is s less than the r protons translocated, because s scalar protons are taken up per ADP phosphorylated at the pH of the N domain. Further explanations are in the text.

(6) The injection of r protons (equivalent to the $n + 2$ protons in fig.1) into the hydrolytic site by the protonmotive force, acting through the proton

gate in γ (or in the γ-ϵ complex), causes the development of torque by mutual net repulsion (see [26]) between the α, β, and γ subunits, which is intimately associated with the co-operative ATP/(P_i + ADP) counter-transfer or antiport process, and with the ongoing protonation and abstraction of O^{2-} from P_i + ADP to give ATP + H_2O + $(r - s)H^+$ (where r and s are the proton-motive stoichiometry and net scalar acid equivalents produced by ATP hydrolysis, respectively).

(7) Input of P_i, input of ADP, output of ATP, and phosphorylation of ADP, are catalysed between different α and β subunits at each of three stages, separated by 120°, in the complete 360° catalytic configurational cycle.

In the version of the rolling well and turnstile mechanism illustrated by fig.2, the diagrams show the successive rotational positions of the α, β and γ (or γ + ϵ) subunits of F_1 at 30° intervals, in a plane at right angles to the F_0-F_1 axis. The open and solid shapes represent the domains in α and β that form the hydrolytic site when juxtaposed. They are conveniently described as hsf (hydrolytic site forming) domains. These hsf domains are shown solid when a substrate molecule is enclosed. They are assumed to participate in substrate binding and translocation as well as in reversible ATP hydrolysis. The open or solid shape in the γ subunit (or γ-ϵ complex) represents the proton-conducting gate that transfers protons between the proton-conducting well in F_0 and the hydrolytic site. It is shown solid when r protons are transferred from it to the hydrolytic site. In this version of the mechanism, the α subunits are assumed to be in rolling contact with the β subunits, and the surfaces of the even α-β subunit pairs (2, 4 and 6 in fig.2) are assumed to be uniquely matched and of equal effective circumference, so that the members of each even α-β subunit pair go through the same sequence of surface-to-surface and angular relationships. It follows that the members of each odd α-β subunit pair (1, 3 and 5 in fig.2) are in rolling contact, but their angular relationships are shifted by 120° compared with the even α-β subunit pairs, and their surface-to-surface relationships are correspondingly shifted by 1/3 subunit circumference. The reader may best appreciate what is going on in the model outlined in fig.2 by running the eye down the columns.

3. EXPERIMENTAL IMPLICATIONS

3.1. *Experimental exploration of rolling well and turnstile models*

The postulates given in the previous section permit the construction of several fundamentally similar F_0F_1 ATPase models, which are sufficiently specific to be closely examined for compatibility with existing knowledge, and have sufficiently precise predictive capabilities to suggest new experiments that may help to elucidate the molecular mechanics of the F_0F_1 ATPases. The main aim of this short paper is to enable students of this rapidly evolving field of knowledge to explore the weaknesses and strengths of these rotatory ATPase models. However, it may be appropriate to comment briefly here on some interesting attributes, which may be indicative of the potentialities of this new type of model.

In the type of model defined by the above seven postulates, the F_1 molecule would undergo large-scale configurational changes associated with large functionally important changes of the local environment of the catalytic domains, without major changes of folding of the polypeptide chains within the individual subunits. This behaviour is consistent with observations on the relatively constant α-helix and β-sheet content of F_1 [4], and with observations indicating that the configurational changes in F_1 involve little internal frictional resistance, but depend on the viscosity of the external aqueous medium [47]. The fact that the phosphorylation of ADP requires relatively complete assemblies of functional α and β subunits with the γ subunit (7–10,13,14,17,20,21] is consistent with the notion (illustrated in fig.2) that each α and each β subunit is involved by its rolling action in co-operative activity with the β subunits and α subunits, respectively, on either side of it. It is a noteworthy feature of the version of this mechanism shown in fig.2 that, owing to the similar rolling relationships of the β subunits on the γ subunit and on the α subunits, the diametrically asymmetric features of all three α subunits would be aligned parallel throughout the catalytic configurational cycle. This feature is consistent with the observed asymmetry of the complete F_1 protein [7], and it could

be investigated more specifically as a means of testing the model described by fig.2. The initial proposition that the surfaces of the γ and β subunits are uniquely matched and of equal effective circumference is an important general requirement of the rolling well and turnstile type of mechanism that may be relatively easy to test.

Models of the F_0F_1 ATPases, such as that illustrated by fig.2, might be expected to explain the thioredoxin-modulated activation of the chloroplast F_0F_1 ATPase (and the simultaneous ejection of a tightly bound ADP molecule without phosphorylation) by the application of $\Delta\bar{\mu}H^+$ [48,49]. It is tempting to suggest that the ATPase is inactivated by the immobilising effect of tightly-bound ADP in the catalytic site (0, 120 or 240° in fig.2), and that expulsion of the ADP, and activation of the ATPase, is a proton-driven process that requires the irreversible expenditure of protonic energy above a protonmotive force threshold [48] that is modulated by the state of thioredoxin-reactive thiol groups in the γ subunit [25,49].

Amongst the possible variants of the model shown in fig.2, a version in which both P_i and ADP would enter by one of the separate pathways shown for P_i and ADP (at 0, 120 and 240° in fig.2) may be particularly worth considering. Scope is not available in this paper to outline models somewhat different from that of fig.2, which are consistent with the seven postulates defining the protonically driven rolling well and turnstile type of mechanism. But it may be appropriate to mention that, by analogy with bacterial flagellar motors [26], the ATP/(P_i + ADP) antiport function of the rolling well and turnstile type of mechanism could, in principle, be driven by Na^+, or by any other ion species, for which the system had the appropriate specificities corresponding to those of the normal system for protons. Such alternative ion species could not, of course, substitute for protons in the reversible protonation of O^{2-} to give H_2O in the hydrolytic process. The alternative ions that could, in principle, drive ADP phosphorylation would therefore correspond to the *n* extra protons shown in fig.1A.

4. CONCLUSION AND PROSPECT

As indicated in this paper, it is generally agreed that proton-driven ADP phosphorylation in F_0F_1 ATPases depends on the proton-coupled counter-transfer or antiport of P_i + ADP into, and ATP out of, hydrolytic sites in F_1. The main questions at issue are how the proton current that flows through F_0 drives this substrate antiport in F_1, and whether the proton current is incidentally associated with the protonation and withdrawal of O^{2-} from P_i + ADP to give ATP + H_2O, during ongoing ADP phosphorylation. The mechanical concept of the rolling well and turnstile has been introduced with the main object of stimulating new research initiatives that may help to settle these important questions, and bring us nearer to understanding how the F_0F_1 ATPases actually work.

With respect to the possible survival, and more quantitative development, of models based on the rolling well and turnstile concept, only time and diligent experimental scrutiny can tell.

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