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The Unusual Enzymology of ATP Synthase

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From known metabolic pathways and the extent of the world's biomass, I estimate that ATP and the ADP and P_i from which it is formed participate in more chemical reactions than any other compounds on the earth's surface except water. A multisubunit enzyme complex, the remarkable ATP synthase, is responsible for most of the ATP synthesis. This ubiquitous enzyme consists of a transmembrane portion, called F_0, and an attached portion, called F_1. The F_1 portion when detached from the membrane acts as an ATPase. The enzyme in membranes of chloroplasts, mitochondria, and aerobic microorganisms forms ATP in photophosphorylation or oxidative phosphorylation; in anaerobes the enzyme uses ATP to create a membrane potential or pH gradient.

The combined efforts of many investigators, using chemical, physical, and genetic probes, have given considerable insight into the subunit composition, tertiary and quaternary structure, catalytic mechanism, and regulation of the synthase. Its structural and mechanistic characteristics are quite unusual and are thus of interest to those wanting a wider perspective of enzyme structure–function relationships as well as to the dedicated bioenergeticist. This short review gives a perspective of the structure and mechanism, of the unusual features, and of problems not yet resolved.

A general background and review of the mitochondrial ATP synthase is provided by Tyler (1984). Valuable reviews of the mitochondrial enzyme are provided by Hatefi (1985) and Vignais and Lunardi (1985); of the *Escherichia coli* enzyme by Fillingame (1981) and Senior (1985); of the chloroplast enzyme by Nelson (1981), Strotmann and Bickel-Sandkotter (1984), Merchant and Selman (1985), and Galmiche et al. (1985); of the enzyme from different sources by Cross (1981), Amzel and Pedersen (1983), Senior and Wise (1983), and Futai and Kanazawa (1983); and of the F_0 portion by Hoppe and Sebald (1984).[1]

Structure

Enzyme Composition. Concurrence has been reached that the soluble F_1 portion of the ATP synthases from most sources has three copies each of two subunits with masses of about 55 and 50 kilodaltons (kDa), designated α and β, and single copies of smaller subunits, designated γ, δ, and ϵ, with masses of roughly 30, 20, and 15 kDa. Although three subunit enzymes are well recognized in enzymology, the presence of subunits in a 3:1 ratio is strikingly unusual.

The subunit compositions of the F_0 portions are somewhat less well known. That from the *E. coli* is the simplest of any well-studied F_0 and consists of three subunits, commonly designated a, b, and c, with masses of about 30, 17, and 8 kDa, respectively, present in a stoichiometry of $a_1b_2c_{9-12}$. Additional subunits are associated with the F_0 component from eukaryotic sources (Fearnley & Walker, 1986). These may participate in the more sophisticated control requirements of the higher organisms.

The first complete amino acid sequence for an ATP synthase was obtained in the laboratories of Walker and of Futai by sequencing of DNA from the *unc* operon of *E. coli*. As summarized by Walker et al. (1985), complete sequences are also available for the synthase from bovine heart (by direct protein sequencing) and from *Rhodospirillum rubrum* and *Rhodopseudomonas blastica*, as well as sequences for some subunits from other sources including chloroplast α, β, and ϵ subunits. The larger subunits have strong sequence conservation. In sequences obtained from several widely divergent species, 48% of the β-subunit residues and 35% and of the α-subunit residues are identical, and many more conservatively replaced. The α and β subunits are moderately related; some 37% of the residues are identical or are conservatively substituted. The minor F_1 subunits and the F_0 subunits from various sources show much less conservation and homology, and some peptides showing homology are associated with either F_1 or F_0 portions or with subunits of different size. For example, the δ subunit of mitochondrial F_1 is homologous to the ϵ subunit from *E. coli*.

[1] References for many statements in this paper will be found in these reviews or furnished by the author on request. Some more recent references are given that will also serve as a guide to the literature.

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Tertiary and Quaternary Structure. Modest progress has been reported toward obtaining X-ray structural data (Pedersen & Amzel, 1985), and an armamentarium of other structural probes has been applied. These include electron microscopy, crosslinking, chemical labeling, proton exchange, structural prediction from primary sequence, energy transfer from specific labels, and genetic mutational approaches. What has emerged is an intriguing but still murky outline of a splendid molecular machine. Electron microscopy of mitochondria shows prominent 90-Å knobs of F_1 projecting from the inner membrane toward the matrix and similar structures on other coupling membranes. The γ subunit and other minor subunits are regarded as largely in a center core, surrounded by a ring of six masses of alternating α and β subunits, somewhat staggered into two layers (Tiedge et al., 1985). An important asymmetry is that the surrounded mass is not centrally located but displaced toward one side (Amzel & Pedersen, 1983).

The arrangement of subunits in F_0 is also quite uncertain. Primary sequence and other data suggest that the small subunit c of *E. coli* and the analogous subunit from other sources have two membrane-immersed helices with a hydrophilic connecting loop. Subunit b of *E. coli* is likely anchored by a hydrophobic helix of the amino terminus, with two helices forming a loop that projects above the membrane into the F_1. Subunit a is mostly membrane-localized by several hydrophobic helices. An interesting possibility currently being discussed in my laboratory is that nine copies of the small c subunit in groups of three could surround the membrane-imbedded helices of the a and b subunits. Such a structure could participate in a "rotational catalysis" discussed later. The reaction of the b subunits with membrane-localized hydrophobic photoactivatable probes (Hoppe & Sebald, 1985) may not mean that the c subunits are not on the outside of the F_0 but that the reagent can penetrate into the hydrophobic regions of F_0.

Distances between nucleotide binding sites and other derivatized locations on the chloroplast enzyme have been mapped by fluorescence energy transfer (McCarty & Hammes, 1987). The nucleotide binding sites are 36–45 Å apart and about 90–100 Å from the bilayer surface. This places catalytic sites far from the point of entry of translocated protons.

In electron micrographs, the bulk of the F_1 appears to be attached to the membrane by a narrower stalk. Such results and other data lead to structural sketches showing six alternate balls of the larger α and β subunits with minor and F_0 subunits predominating in the stalk. The major masses detected in electron microscopy could be derived from portions or domains of different subunits. Cross-linking studies have given some information about probable subunit associations, but it needs emphasis that present structural information gives little indication about how much intertwining of subunit portions may occur.

Assembly and Reconstitution. All of the *E. coli* synthase subunits are required for in vivo assembly, and many mutations in the *unc* operon impair assembly. Studies in Gibson's laboratory gave evidence that the assembly is an ordered process with addition of the F_1 β subunit to F_0 subunits a and c in the membrane as an initial step. This may be the preferred pathway, but subsequent assessments of in vivo assembly show that it is possible for the F_0 and F_1 to assemble independently and then combine to give an active complex (Aris et al., 1985; Fillingame et al., 1986). Continued analysis of mutational affects on assembly is giving a wealth of information to be correlated with folding and subunit interaction.

The complete separation of F_1 into its subunits and their reassembly into an active complex, as accomplished for *E. coli* by Dunn and Heppel and for a thermophilic bacterium by Kagawa, have provided an important means for study of the properties of isolated subunits. With the membrane-bound *R. rubrum* enzyme, Gromet-Elhanan found that exposure to LiCl leads to reversible dissociation of β subunits. Such separations have shown interesting features such as a very tight ATP binding site on the isolated α subunit of *E. coli* F_1 and two binding sites on the β subunit of the *R. rubrum* F_1.

Bound Nucleotides. Preparations of F_1 ATPase, as isolated from various sources, usually contain 1–4 tightly bound nucleotides per enzyme molecule. Although the chloroplast enzyme has been regarded by some as having only three nucleotide binding sites, recent findings (Xue et al., 1987) suggest that it, like the *E. coli* and heart mitochondrial enzymes, can bind up to six nucleotides per mole with apparent negative cooperativity of binding. With these enzymes, after exposure to MgATP and separation from medium nucleotides by a Sephadex centrifuge column, three nucleotides per enzyme remain bound at noncatalytic sites and one or more at catalytic sites depending upon exposure conditions. Those at noncatalytic sites are not replaced during catalytic turnover, although their very slow exchange is promoted by catalysis. The photolysis of 2-azidoadenine nucleotides tightly bound at noncatalytic or catalytic sites labels tyrosine residues on adjacent tryptic peptides of the β subunit. The same homologous peptides are labeled with the *E. coli*, heart mitochondrial, and spinach chloroplast enzymes (Wise et al., 1987).

Structural Asymmetry. The subunit stoichiometry $\alpha_3\beta_3\gamma\delta\epsilon$ and structural predictions from primary sequences of single copy subunits impose nonidentical interactions between the α and β subunits and the other single copy subunits. Thus, even in the absence of bound ligands, some heterogeneity of properties might be expected. Prominent asymmetry is likely imposed by nucleotide binding. The unusual asymmetry is strikingly evident in the chemical and catalytic properties of the enzyme. It is reflected in the prominent one-third sites reactivity of the β subunit with various reagents and in the specific interaction of the α subunit with lucifer yellow (Nalin et al., 1985), as well as in the negative cooperativity of nucleotide binding. The subunit stoichiometry for the *E. coli* F_0 points to similar asymmetrical interactions between subunits of F_0 and between F_0 and F_1 subunits. The relationship of these prominent asymmetries to the catalytic mechanism poses a major unsolved problem for the synthase and an unprecedented challenge for the field of enzymology.

Catalytic Mechanism

Coupling to Proton Translocation. There is increasing evidence that energy from oxidations can be transmitted by some means not involving the bulk electrochemical proton gradient (the protonmotive force) but there is abundant agreement that the formation of an ATP molecule can be coupled to the translocation of three H^+ across the membrane in which the synthase is imbedded. Any mechanism must account for this "chemiosmotic" coupling.

Two broad possibilities are readily evident. One is an indirect coupling mechanism in which the conformational changes accompanying H^+ movement through F_0 are transmitted through subunits and their interactions to catalytic sites. The other is a direct coupling in which the translocated H^+ are channeled through F_0 and F_1 to the catalytic site where they drive catalysis. From both structural and experimental considerations, an indirect conformational coupling mechanism is now supported by most workers in the field. Such con-

formational coupling is analogous to that being developed for other ion transport systems [see Brandl et al. (1986)] and has long been regarded by this reviewer as a fundamental characteristic of biological energy transducing systems.

The protein groups that contact or bind the translocated H^+ are not known for the synthase or for any protein(s) coupling H^+ translocation to active transport of solutes across membranes or to flagella rotation. Likely there is a similar underlying chemistry of the H^+ translocation in the ATP synthase, bacterial rhodopsin, lactose permease, flagellar rotors, and related systems. Mutational probes with the lactose permease (Kaback, 1987) have led to a suggestion of proton transfer involving three specific groups. A more general suggestion for the synthase has been the participation of "proton wires" in which a hydrogen-bonded chain of protonatable groups adds a H^+ on one side of the membrane and delivers a H^+ on the other. The recognition of a "Na^+ bioenergetics" (Skulachev, 1985), in which similar processes are coupled to Na^+ translocation, argues against proton wires and suggests that more than one group or atom may interact with the transported cations. We should probably be considering hydronium ion, H_3O^+, translocation, with requirements for binding akin to the multiple interactions for recognition of Na^+. Conformational changes accompanying the translocation would expose the binding region to solute on opposite sides of the membrane.

Subunit Function. The F_0 portion has a primary role in proton translocation across the membrane. A striking property, first shown with the mitochondrial enzyme by Beechey, is the facile reaction of dicyclohexylcarbodiimide (DCCD) with a membrane-imbedded carboxyl side chain of a small F_0 subunit analogous to the c subunit of *E. coli*. The DCCD derivatization occurs with a conserved glutamyl or aspartyl residue that is preceded and followed in the sequence by several hydrophobic residues. Reaction with only one of the multiple copies of the subunit blocks proton translocation and inhibits ATPase activity of the associated F_1. Extensive mutational probes have been reported from the laboratories of Altendorf, Cox, Fillingame, Hoppe, Sebald, and Simoni. They demonstrate that all three F_0 subunits of the *E. coli* enzyme are required for adequate proton translocation. Other interesting findings include evidence for a prominent participation of conserved residues of a membrane loop of the large subunit a in cooperation with c subunits for the coupled proton translocation (Cox et al., 1986) and interactions of second site revertants in subunit c suppressing the effect of a mutation in subunit b on H^+ translocation (Kumamoto & Simoni, 1987).

The nucleotide binding sites of the F_1 are on the α or β subunits or at interfaces of these subunits. The catalytic site appears to be predominately on the β subunit based on blocking of catalysis by derivatization or specific mutation of this subunit, the prominent sequence conservation, the presence of nucleotide binding sites on isolated β subunits, and the derviatization of specific sites on the β subunit by substrate analogues bound to the catalytic site.

Studies, particularly in McCarty's laboratory, show that the γ subunit of chloroplasts has a prominent role in interactions between the F_0 and F_1 catalytic sites. The α and β subunits alone or in combination have little or no ATPase activity, but experiments with the subunits from a thermophilic bacterium show that activity is conferred by association with either a γ or δ subunit (Yoshida, 1984). In F_1 from various sources the large α subunit appears to contribute to nucleotide binding. For example, mutations in the α subunit from *E. coli* block catalytic activity. Some of these mutant enzymes retain a capacity for slow catalysis by one catalytic subunit on the enzyme but have lost the site–site cooperativity necessary for rapid catalysis (Wise et al., 1984; Wood et al., 1987).

Predictions from the primary structure and other data suggest that the b subunit of F_0 projects above the membrane into the F_1 portion of the synthase. Thus, subunit b may have a prominent role in transmitting conformational changes to catalytic sites. But this is speculative, and the roles of b and the other subunits remain unsettled. Their importance is stressed, however, by the observation that mutations resulting in amino acid substitutions in all of the F_0 and most of the F_1 subunits of the *E. coli* synthase adversely affect catalysis in the assembled enzymes.

Formation of ATP. ATP is formed at a catalytic site by displacement of an OH group from P_i by ADP. Reversal of this reaction incorporates water oxygens into bound P_i. Reversal of ATP formation at the catalytic site accounts for the appearance of water oxygens in ATP made by photophosphorylation or oxidative phosphorylation. The continued reversal of ATP formation in the absence of a protonmotive force provided the basis for my initial suggestion of the binding change mechanism in which a principal role of energy input is to cause the release of ATP from the catalytic site. Reversal of bound-ATP formation continues on the isolated F_1 and when only one site is occupied, with an apparent equilibrium ratio of ADP/ATP near unity. ADP and P_i can be induced to add to F_1 and form tightly bound ATP. Chemical modifications or oligomycin binding in F_0 changes the properties of nucleotide binding in attached F_1 in the absence of a protonmotive force (Penefsky, 1985; Matsuno-Yagi et al., 1985), and binding of trinitrophenyl ATP opens the pathway for H^+ translocation (Wagner et al., 1986). These and other observations have led to increasing acceptance of the concept that conformationally driven binding changes originating in F_0 are transmitted to the distal catalytic sites to enable binding changes.

Bound Nucleotide Relationships. Extensive studies of the binding of nucleotides and of analogues giving covalent derivatization have documented apparent negative cooperativity of binding, the location of amino acid residues at or near binding sites, and the cooperativity between catalytic sites. Nucleotides bound to noncatalytic sites do not exchange with medium nucleotides during catalysis, and although a regulatory function has been postulated or assumed by many investigators, none has been convincingly demonstrated. For example, F_1 from *E. coli* depleted of bound nucleotides can be recombined with F_0 and do coupled phosphorylation of GDP while the noncatalytic sites remain empty (Wise & Senior, 1985).

Conformational Relationships. Early studies in Jagendorf's laboratory on exchanges of peptide protons showed that light induces large conformational changes in the F_1 portion of the ATP synthase of chloroplasts. A myriad of other studies have shown conformational changes related to nucleotide binding or catalysis. However, even large conformational changes may accompany various mechanisms, and the occurrence of conformational changes has not yet helped elucidate how catalysis is accomplished.

Catalytic Site Cooperativity. Evidence for some type of cooperativity between nucleotide binding sites came first from initial velocity studies with the isolated F_1 from liver and heart mitochondria. The suggestion of strong cooperativity between catalytic sites came from the effects on oxygen exchanges by heart submitochondrial particles of removal of medium P_i (during ATP hydrolysis) or medium ATP (during ATP syn-

thesis). Subsequent studies have given considerable support to the view developed in my laboratory that all three sites participate in sequential cooperativity, although some investigators prefer models in which catalysis occurs with only one regulated site or two alternating sites (Wang, 1985; Pedersen & Amzel, 1985; Bullough & Allison, 1986). There is persuasive evidence that products are not released from one catalytic site until substrates add at an alternate site. During synthesis or hydrolysis of ATP, the reversible cleavage of bound ATP, giving rise to oxygen exchanges, increases dramatically as substrate concentration is lowered. Bound reactants remain at a catalytic site when substrate concentration is far below that required for half-maximum velocity, an unusual property not shown by independent sites. The release of such bound reactants can occur in a kinetically competent manner (Cross et al., 1982; Leckband & Hammes, 1987).

Substrate binding or catalytic capacity might be retained under some conditions where cooperativity is diminished or lost. This is suggested by unpublished results from my laboratory for the remaining catalytic sites after covalent modifications of one catalytic and one noncatalytic site per enzyme by 2-azido nucleotides. Similarly, continuation of the extensive studies of nucleotide analogues in Schafer's laboratory (Weber et al., 1987) suggests that the binding of α-naphthoyl analogues is accompanied by distortion that eliminates cooperativity.

Catalytic Site Homogeneity. From the measurement of the distribution of ^{18}O in ATP formed from highly ^{18}O-labeled P_i, two important characteristics of the catalysis can be deduced. One is the extent of the reversal of bound ATP formation before ATP release. The other is whether the product arose by a single catalytic pathway [see review by Mitchell (1984)]. The ^{18}O species that are produced when the extent of oxygen exchange is modulated during net ATP synthesis by varying ADP or P_i concentrations, or by varying ATP concentrations during net ATP hydrolysis, correspond closely to those expected if each participating site is performing catalysis identically. In other words, a single reaction pathway for all product formation is indicated.

A Rotational Catalysis? The unusual structure of the synthase and the evidence that three catalytic sites participate in an identical sequential manner raise challenging questions about the mechanism. In order for synthase subunits of identical amino acid sequence to have identical function, I suggested a rotational catalysis such that conformational changes accompanying proton translocation drive a rotational motion of a core of noncatalytic subunits relative to the catalytic β subunits (Boyer & Kohlbrenner, 1981; Gresser et al., 1982). Subsequently, Cox et al. (1984) developed a more detailed model based on structural considerations and genetic analyses. It is very difficult to envisage how three catalytic subunits can have identical interactions with single copy subunits without such rotational movement. Analogy to aspects of the rotation of flagella, known to be coupled to proton translocation, is supportive.

A requirement of such a rotational model is that β subunits change their asymmetric positions as catalysis proceeds. When one β subunit of the mitochondrial enzyme is reacted with 2-azido-ATP, exposure to DCCD results in derivatization of a differnt β subunit. This demonstrates well the subunit asymmetry in reaction properties. The enzyme reacted with DCCD retains weak catalytic capacity. After catalytic turnover, 2-azido-ATP reacts with DCCD-labeled and unlabeled β subunits randomly, giving evidence for subunit positional interchange (Melese & Boyer, 1985), but more assessment with fully active enzyme is needed.

Kironde and Cross (1987) obtained evidence that the α subunits retain their asymmetry in isolated F_1 as catalysis proceeds. If rotational catalysis occurs, the α subunits might remain with the asymmetric core, or subunit positional interchange might require the interactions between F_1 and F_0 as in intact synthase structure. Known properties of multisubunit enzymes suggest that the striking asymmetry of the α and β subunits reflects the inherent properties of a trimer of α-β pairs and the conformational changes induced by nucleotide binding. Thus, catalytic cooperativity may not be dependent upon interactions with minor subunits. Support for this comes from observations from reconstitution studies showing that good catalytic capacity is obtained with either $\alpha_3\beta_3\gamma$ or with $\alpha_3\beta_3\delta$ forms (Yoshida, 1984). Association of the γ or δ subunits with the α or β subunits may promote stabilization of an active trimeric structure and not modify properties of the catalytic sites. In the intact synthase complex, minor subunits may be more restricted in their conformational changes, and the changes in both the F_1 and F_0 subunits essential for proton translocation would require the events of rotational catalysis. But such an unusual catalytic mechanism by this unusual enzyme obviously needs better experimental evaluation than is presently available.

The Next Decade. Continued application of structural, catalytic, and mutational probes will provide a wealth of useful data whose interpretation will be enhanced when, and if, suitable three-dimensional structural data from X-ray analysis become available. The path of proton translocation will be clarified. The proposed binding change mechanism with equivalence of all three catalytic sites will be assessed and hopefully some concurrence reached about this mechanism or others. Either a rotational catalysis or some unexpected features will emerge to account for the striking asymmetry of the synthase composition and subunit properties.

Registry No. ATP synthase, 37205-63-3.

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