

Feature

Quick guide: ATP synthase

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Also known as... F_1F_0 ATP synthase, F_1F_0 ATPase, F-type ATPase. F_1 denotes the soluble catalytic headgroup where ATP synthesis and hydrolysis occur, and F_0 is the ion-translocating membrane domain (see Figure).

What is it? An enzyme that uses energy from the transmembrane proton electrochemical gradient, generated by oxidative metabolism or photosynthesis, to produce ATP from ADP and P_i . The enzyme can also act in reverse, hydrolysing ATP and pumping H^+ or Na^+ .

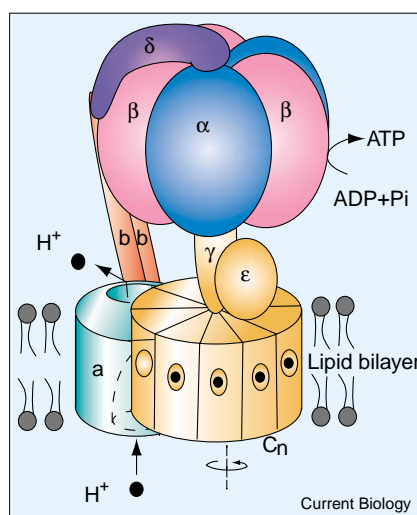
Where is it found? In energy-transducing membranes such as the plasma membrane of bacteria and blue-green algae, the inner membrane of mitochondria and the thylakoid membrane of chloroplasts. Hence, they play a fundamental role throughout nature producing the 'universal energy exchange currency' ATP.

It first came to prominence... in the early 1960s when lollipop-like structures were observed on mitochondrial membranes by electron microscopy. The large soluble domain, F_1 , can be detached and was shown to hydrolyse ATP. Later, ATP hydrolysis and synthesis were shown to be coupled to H^+ translocation through the complex, consistent with Peter Mitchell's chemiosmotic theory.

Its first heyday was... probably 1994 when the crystal structure of the F_1 headgroup was solved by John E. Walker and colleagues. The structure supported the 'binding change mechanism' proposed by Paul D.

Boyer — a sequential change in the binding affinities of the alternating catalytic sites in F_1 to promote tight substrate binding and product release during catalysis — and provided a structural basis for a rotary mechanism of catalysis. Walker and Boyer were awarded the Nobel Prize for Chemistry in 1997. Its second coming will be when the entire complex of F_0 is solved.

How does it work? As a molecular motor. There is good evidence that H^+ movement occurs at the interface between the fixed subunit a and the mobile subunit c oligomeric ring (see figure). The oligomeric c ring is attached to the central stalk and forms a spindle within the complex



An illustration of the *E. coli* F_1F_0 . F_1 is made up of five different subunits, with a stoichiometry $\alpha\beta\gamma\delta\epsilon$, and the composition of F_0 is abc_{10-12} . Strong evidence supports a mechanism whereby the central stalk of the soluble F_1 domain and the oligomeric ring of subunit c of the membrane sector rotate as one (shaded orange), coupling ion movement to ATP synthesis and hydrolysis.

that turns at several thousand revolutions per minute. The asymmetrical central stalk interacts with the subunits of the surrounding catalytic headgroup and couples events at the catalytic sites with H^+ movement.

Other speculated functions include... maintenance of an electrochemical gradient necessary for secondary transport and, in some bacteria, cytoplasmic pH, by working in reverse, hydrolysing ATP and pumping H^+ .

Does it have any relatives? Yes, the vacuolar ATPase (V_1V_0) and archaeal ATPase (A_1A_0). The V_1V_0 ATPase is a H^+ pump important for acidifying organelle interiors, and generating electrochemical gradients for secondary transport processes. F_1 is also related to DNA and RNA helicases.

Does it have commercial potential? It is implicated in many physiological roles and is likely to be a valuable target for therapeutic drugs. An inhibitor protein of human F_1F_0 , IF₁, may be useful for preventing tissue damage of the heart during ischemia by inhibiting ATP hydrolysis. V_1V_0 in *Plasmodium falciparum* appears to be a target of antimicrobial agents which interact at the ion-binding site.

Where can I find out more?

Boyer PD: The ATP Synthase — a splendid molecular machine. *Annu Rev Biochem* 1997, 66:717-749.

Walker JE: ATP synthesis by rotary catalysis (Nobel Lecture). *Angew Chem Int Ed Engl* 1998, 37:2309-2319.

Proton motive ATPases. *J Exp Biol* 2000, 203:1-170.

The Mechanism of F_1F_0 -ATPase. *Biochim Biophys Acta* 2000, 1458:221-510.

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