Japan Academy Prize to:

Masamitsu Futai
Dean and Professor, Faculty of Pharmaceutical Sciences and Department of Biochemistry, Iwate Medical University
Professor Emeritus, Osaka University

For “Studies on the Synthesis and Cellular Use of Biological Energy”

Outline of the Work:

Dr. Masamitsu Futai has been addressing the basic biological question, “How energy is generated and utilized in living organisms.” “Biological energy currency,” adenosine triphosphate (ATP), is synthesized in mitochondria, chloroplasts and bacterial membranes. Dr. Futai has shown the basic structure and mechanism of ATP synthase (F-ATPase) (also known as F,F; or coupling factor), which synthesizes ATP coupling with proton (H⁺) transport. He has also shown the mechanism and roles of H⁺ translocation into lumen of diverse endomembrane organelles and extracellular compartments.

1. ATP synthase (F-ATPase): Structure and mechanism

Dr. Futai started working on E. coli F-ATPase because he had recognized that the mechanism of biological energy transformation should be similar among organisms. He first isolated membrane vesicles, which could be used for studying energy generation. F-ATPase with eight subunits (α, β, γ, δ, ε, a, b, c) was purified from these vesicles. All subunits were identified genetically by complementation and biochemically by their isolations. He was able to isolate the entire genes encoding F-ATPase, and, thus, the primary structures of all the subunits became known. This progress provided key tools for studying enzyme mechanisms.

Focusing on sequence conservation, he found the β subunit Lys and Glu residues to be responsible for catalysis and the α subunit Arg to be required for cooperativity between three catalytic sites. These findings are consistent with the first X-ray structure of bovine α3β3γ complex reported by J. Walker in 1994. The transmembrane H⁺ pathway is formed from Arg and Asp residues of the a and c subunits, respectively. The presence of three β and ten c in the entire F-ATPase is consistent with P. Boyer’s binding change mechanism, which predicts subunit rotation during ATP synthesis or hydrolysis. To confirm the rotational catalysis, Dr. Futai immobilized a purified F-ATPase or that localized in an isolated membrane. Upon ATP addition, the probe attached to the γεc10 subunit complex rotated in an anti-clockwise direction. Single molecule studies indicated that the subunit complex rotates in a stochastic manner, and alternates between an active and inhibited state.

2. Proton transport coupled with ATP hydrolysis

Energy generated by ATP hydrolysis is coupled with metabolism, mechanical movement, ion transport, cellular trafficking, etc. Dr. Futai is interested in H⁺ transporting ATPases, which create acidic pH in lumen of organelles and extracellular compartments. He isolated the gene encoding for the α and β subunit of gastric proton pump (H⁺/K⁺ ATPase). It was similar to Na⁺/K⁺ ATPase in the transmembrane structure and catalytic mechanism leading to ion transport. However, H⁺/K⁺ ATPase is expressed only in the plasma membrane of gastric parietal cells. As predicted by the specific gene expression, he found a DNA binding protein required for H⁺/K⁺ ATPase gene expression.

The second H⁺ transporting ATPase given focus in his study is the mammalian V-ATPase (vacuolar ATPase), which
is found in endomembrane organelles including lysosomes, endosomes, and secretory granules. V-ATPase is similar to F-ATPase in subunit organization, higher-ordered structure, and rotation during catalysis, although it transports $H^+$ physiologically.

3. Physiological roles of proton transporting V-ATPase

Consistent with localization in various organelles, Dr. Futai found the 2 ~ 4 isoforms for V-ATPase subunits C, E, G, a, and d. The transmembrane subunit a has $a_\alpha$, $a_\alpha$, $a_\gamma$, and $a_\gamma$ isoforms: $a_\gamma$ is kidney specific, whereas the others are ubiquitous. Similarly, $d_1$ and $d_1$ isoforms are ubiquitous and kidney specific, respectively. The osteoclast V-ATPase with $d_2$ and $a_3$ transport $H^+$ through the plasma membrane to the bone resorption compartment. Thus, mutations in osteoclast V-ATPase cause osteopetrosis, so this enzyme will be a new pharmaceutical target for treating osteoporosis.

V-ATPase with $a_\gamma$ isoform acidifies lumens of secretory granules for accumulation of hormones or neurotransmitters. For insulin, $a_3$ isoform itself in the granule is necessary for secretion. V-ATPase is also required for endocytosis: During albumin endocytosis in kidney cells, subunits $a_2$ and c in the early endosome recruit factors to generate transport vesicles, which carry cargo molecules to lysosomes. Thus, defects of V-ATPase cause serious diseases. He has studied the roles of other isoforms applying a similar approach.

Dr. Futai’s publications are cited in numerous papers and well-known textbooks on cell biology and biochemistry. He has contributed to the international community including the International Union of Biochemistry and Molecular Biology as a Japanese delegate, the Federation of Asian and Oceanian Biochemists and Molecular Biologists as its President, and the American Society for Biochemistry and Molecular Biology as an Editorial Board Member.

Research Articles

of vacuolar-type H\(^+\)-ATPase, inhibits acidification and protein degradation in lysosomes of cultured cells. \textit{J. Biol. Chem.}, 266, 17707-17712.


