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Citation Classics

Mitchell P. Chemiosmotic coupling in oxidative and photosynthetic phosphorylation. *Biol. Rev. Cambridge Phil Soc.* **41**:445-502, 1966.

This paper reviews and discusses the chemiosmotic hypothesis of coupling between oxidoreduction and phosphorylation in oxidative and photosynthetic phosphorylation systems. [The *SCI*® indicates that this paper was cited 605 times in the period 1966-1976.]

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"The basic concept discussed in this paper was that coupling in oxidative and photosynthetic phosphorylation systems could be achieved by the circulation of protons or their equivalent through the proton-conducting aqueous media on either side of a topologically-closed insulating membrane of low proton conductance. The respiratory chain or photoredox chain was conceived as being a generator of proticity plugged through the membrane, while the ATP synthase was conceived as being a biochemically separate reversible protonmotive ATPase, also plugged through the membrane, that would phosphorylate ADP when reversed by the flow of proticity from the respiratory or photoredox chain. Proticity is the protonic analogue of electricity.

"To facilitate testing, the chemiosmotic hypothesis was based on four main postulates: (1) The ATP synthase is a reversible protonmotive ATPase of characteristic $\rightarrow H^+/P$ stoichiometry; (2) Respiratory and photoredox chains are protonmotive systems of characteristic $\rightarrow H^+/2e^-$ stoichiometry, and appropriate polarity; (3) There are proton-linked solute porter systems for osmotic stabilisation and metabolite transport; (4) Systems 1 to 3 are plugged through a topologically-closed membrane of low permeability to solutes in general and to H^+ and OH^- ions in particular. These fundamental postulates were conceived as the basis of a network of functional interrelationships, constituting the rationale of chemiosmotic coupling.

"I suppose that my 1966 review has been frequently cited because it was the first paper in which the chemiosmotic rationale was discussed in depth, and examined stoichiometrically, thermodynamically, kinetically, and mechanistically in the light of available experimental data on the systems described by the four postulates.

"In 1961, the four postulates were almost entirely hypothetical. After sixteen years of experimental scrutiny, they are now generally accepted as experimentally tested facts. This procedure, from detailed conjecture, through rigorous experimental testing, to acceptable rationale or theory, is more characteristic of physics than of biochemistry. That may partly explain the frequency of citation of my 1966 revjew, which has acted as a source of the chemiosmotic conjecture that numerous experimentalists rightly sought to test to destruction. The survival of this conjecture has led to the general acceptance of the chemiosmotic principles in membrane bioenergetics. My 1966 review has therefore been cited by those who have sought to rationalise and explain their experimental observations in terms of the chemiosmotic theory, and also by those (including me) who have sought to develop the theory further. Proticity is now recognised as a major means of power distribution in biology.

"The fate of the chemiosmotic hypothesis was, and still is, in the lap of the gods of natural phenomena. It is they, not I, who have begun to make such a success of it!"