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This Week's Citation Classic

Margoliash E & Schejter A. Cytochrome *c*. *Advan. Prot. Chem.* **21**:113-286, 1966. [Biochemical Res. Dept., Abbott Labs., North Chicago, IL and Dept. Chemistry, Univ. Pennsylvania, Philadelphia, PA]

This article is a review, as complete and thorough as we could make it, of all the information concerning cytochrome c that had been gathered from the time of its rediscovery in 1924 and preparation in 1930 by David Keilin,[1] until the early months of 1966. [The *SCI*® indicates that this paper has been cited over 270 times since 1966.]

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"Cytochrome c functions in the mitochondrial respiratory chain to transfer electrons between the reductase segment and cytochrome c oxidase. As it occurs in all eukaryotes, is small, and is the only respiratory chain heme protein that can readily be purified in water-soluble form, it has been studied extensively. An impressively large amount of work has been done on its structure, function, evolution and on the myriad other aspects of its biochemistry and molecular biology. As more information accumulates–for example, we now know the amino acid sequences of close to 100 eukaryotic cytochromes c –the protein presents an ever more attractive model for experimental approaches that are far more difficult in less well documented cases. This may be why this review has been cited so often. Even though apparently exhaustive, with 174 pages and 674 references, the flow of science since 1966 has left it far behind. Clearly, the review needs to be rewritten, even though as thorough an article is now likely to be several times longer.

"For such an enterprise to be really successful, it is best for the author to have spent much of his research life working on the subject, to have treated its delicate and uncertain growth with tender loving care and, if possible, to have been an actor or a spectator at the crucial turning points in its development. In this regard I have been very fortunate. I shall never forget how on arriving on September 10, 1951 for a sabbatical leave at the Molteno Institute, University of Cambridge, intending to study a complex phenomenon involving liver catalase in rats, Keilin gently dissuaded me from that unrewarding enterprise saying: 'Why don't you start by doing something simpler? Why don't you make some cytochrome c? It is such a pleasant preparation.' This conversation, *inter alia*, decided the course of my scientific life. It soon led to a simple preparation of pure and fully active cytochrome *c* and, after agonizingly slow progress, to the complete amino acid sequence of horse cytochrome *c* in the laboratory of Emil Smith in Salt Lake City in 1958-1960. Shortly thereafter (1962-1963) followed the realization that there was an obvious correlation between the primary structures of the cytochromes *c* of various species and their phylogenetic relationships. This last started a train of work that is still continuing.

"My coauthor, Abel Schejter, came in contact with cytochrome *c* while working with me on his PhD thesis in the mid-1950s at the Hebrew University in Jerusalem. The taste for it he acquired then has not left him, as he has continued to contribute, most effectively, to our knowledge of the protein.

"Following involvement in early work on the genetics, immunology, and X-ray crystallography of cytochrome *c*, the emphasis in more recent years has been on structure-function relations, physiological mechanisms of action, and the molecular biology of the protein. This last may soon provide cytochromes *c* of any desired amino acid sequence, and thus present a really practical approach to both structure-function and protein evolution problems.

"As the reader will notice, with some determination it is not too difficult to make a lifelong living out of a single protein, if one applies some imagination to the problem."

1. **Keilin D.** *The history of cell respiration and cytochrome.* Cambridge: Cambridge University Press, 1966. 416 p.