Journal of Bioenergetics and Biomembranes, Vol. 33, No. 3, 2001

Introduction: Complex I—An L-Shaped Black Box

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What is complex I? What does it do? How important is it? Why do you study it? What do you know about it? Obviously, we do not have complete answers to these questions, but we hope to provide the best answers in this minireview series. In the last decade, review articles published during this time attest to the significant advancement in complex I research (see Ohnishi, 1993; Brandt, 1998). It seems timely, therefore, to collect and compile our current knowledge on complex I to which investigators, both in the basic sciences and in the clinical field, have contributed.

Complex I is a canonical name for the mammalian NADH–ubiquinone oxidoreductase of the mitochondrial respiratory chain. It is more commonly used as a generic name for a family of NADH–quinone oxidoreductases, which include bacterial enzymes and Na^+-translocating enzymes found in certain organisms.

Incidentally, this is the 40th year since the respiratory enzyme complexes were first isolated from bovine heart mitochondria in 1961 (Hatefi *et al.*, 1961). During the past four decades, significant progress has been made in this field, and the amount of information available today about the structure and mechanisms of the complexes of the oxidative phosphorylation system is enormous. Our knowledge of the structure, among other things, has advanced considerably in the last few years after successful crystallization of most of the complexes.

Based on the current information of the structure of the individual enzyme complexes, Fig. 1 illustrates the mitochondrial oxidative phosphorylation system. One great omission here is obviously the structure of complex I. As of this writing, there is no structural information on complex I that is comparable to the crystallographic data available for other complexes. The only reports regarding the structure of complex I imply that complex I has an L-shaped structure consisting of a membrane domain and a peripheral arm extending to the cytosol (Hofhaus *et al.*, 1991; Guénebaut *et al.*, 1998; Grigorieff, 1998). Thus, at this moment, we must leave it as a "big L-shaped black box."

The progress of complex I research seems to be lagging, but this is certainly not due to the lack of interest by investigators. Its structural complexity may be the primary reason; the mammalian enzyme consists of at least 42 different subunits and even the bacterial counterparts, although somewhat smaller, are still bulky, lodging 13 to 14 subunits, which correspond to the larger subunits of the mammalian enzyme (Yagi, 1993).

Many researchers, even those outside the field of bioenergetics, have begun to realize the importance of complex I research. This is evident in the progressively growing number of publications relating to complex I, as depicted in Fig. 2. As you will notice, there was a fairly long, dormant period after a report on the isolation of complex I was published in 1961. The first major milestone in complex I research was a demonstration showing that complex I is a proton pump (Ragan and Racker, 1973). This prompted a number of investigators to explore the mechanisms of the so-called coupling site 1. In the mid-1980s, it was found that the seven unidentified genes in mtDNA are coding for complex I subunits (Chomyn *et al.*, 1985). Shortly after that, the first case of mitochondrial diseases caused by defects in genes encoding complex I subunits was reported (Wallace *et al.*, 1988). The lagging nature of complex I research finally ended and complex I suddenly became a popular subject in a broader range of fields. In fact, a large number of publications in the 1990s were concerned with mitochondrial diseases and, in the past few years, with apoptosis. As shown in the "growth curve," complex I research is still in the log phase and, in that sense, it remains young and developing despite its long history.

We are now at the beginning of a new millennium. We have very high hopes for resolving unsolved problems and

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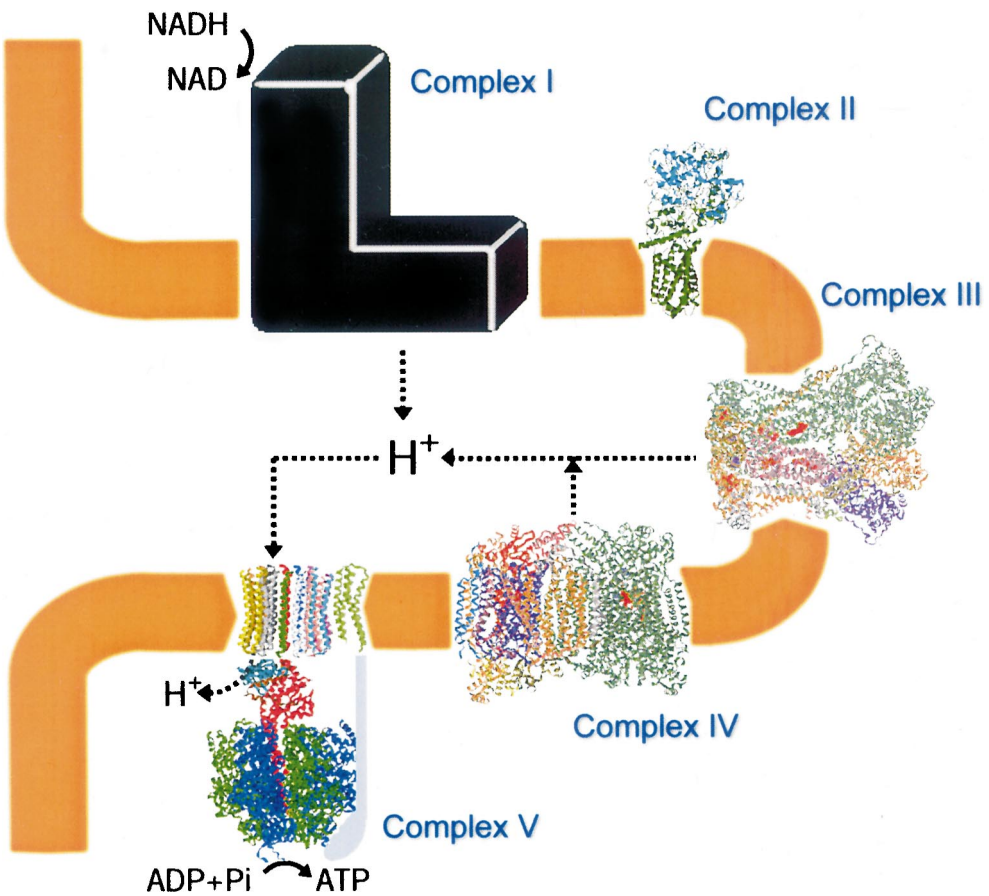

Fig. 1. A schematic representation of the oxidative phosphorylation system. The three-dimensional structures of the individual complexes were obtained from the PDB database. The coordinates used are as follows: complex II, 1FUM, as represented by fumarate reductase; complex III, 1BCC, 1BE3, and 1QCR; complex IV, 2OCC. Ribbon diagrams were generated using the VMD program (Humphrey *et al.*, 1996).

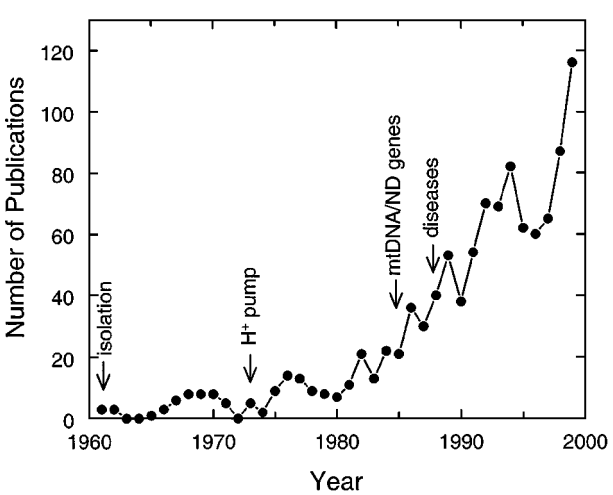

Fig. 2. The number of publications relating to complex I between the years 1961 and 1999. A few milestones of complex I research are marked.

untangling mysteries surrounding this enzyme complex. In this minireview series, we have assembled what we know today, although it is not meant to be completely comprehensive or definitive. There is no doubt that the contents of the "black box" will finally be revealed in the near future and we will be able to report a more accurate and concise description of complex I.

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