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Preface

Respiratory complex II: Role in cellular physiology and disease

The family of respiratory proteins termed complex II is evolutionarily conserved throughout both prokaryotes and eukaryotes. The members of the family include the membrane bound protein complexes succinate dehydrogenase (succinate-quinone reductase) and fumarate reductase (quinol-fumarate reductase). In mitochondria and many bacteria, complex II is an essential part of two metabolic pathways, i.e., the citric acid cycle and the electron transport chain involved in oxidative phosphorylation. The enzyme contains a number of redox active centers including a covalently bound flavin cofactor, three distinct iron–sulfur clusters, a heme b, and a quinone-binding site. Chemically, the oxidation of succinate at one of the two active sites of the enzyme results in reduction of the covalently bound FAD cofactor, the $FADH_2$ generated is then reoxidized by coenzyme Q_{10} (ubiquinone) at the second active site in the membrane domain of complex II. Thus, these reactions couple the citric acid cycle with quinone reduction to provide reducing equivalents to the respiratory chain as part of the overall energy generating system of the cell. Fumarate reductase is part of the anaerobic metabolism in many anaerobic and facultative bacteria and lower eukaryotes where it catalyzes the reverse reaction, i.e., quinol oxidation coupled with fumarate reduction. Both enzymes, however, can catalyze both succinate oxidation and fumarate reduction although they are poised to be more efficient in their preferred catalytic direction. These properties of the enzyme make complex II an excellent model system for the study of a number of different electron transfer reactions. The reversibility of the enzymes may also contribute to the association of complex II with a number of metabolic diseases which have become an area of intense investigation following the advances of human genomic analysis in the 21st century.

In this Special Issue of BBA Bioenergetics, a variety of timely topics related to complex II are reviewed. A particular focus is the relation of complex II to mitochondria-associated diseases in humans. These articles describe the diversity of human diseases affected by the malfunction or assembly of complex II and also discuss a variety of mechanisms by which dysfunction of the complex manifests itself in human disease. Although mitochondria-associated diseases have proven difficult to treat, new anti-cancer drugs that target complex II and are showing promise in treating specific types of tumors in animal and cellular models are described in these articles. Many of these advances in understanding the physiological consequences of mutations in complex II have been aided by analysis of X-ray crystal structures. The wealth of information provided by the analysis of the architecture of complex II is reviewed in this Special Issue providing insight into how mutations of the enzyme complex contribute to alterations in catalytic activity and reactive oxygen species formation. Structures are now available from bacterial succinate dehydrogenase and fumarate reductase to the succinate dehydrogenase from lower eukaryotes, as well as avian and mammalian sources. These articles show that the high degree of conservation of the overall structure of complex II should allow a number of useful models of complex II to be developed. As described in this issue such models are needed to fully understand the effects of mutations of nuclear encoded complex II subunits on mitochondrial physiology. In addition, the structures aid in defining discrete electron transfer pathways in the enzyme which when altered by mutation may contribute to the dysfunction of complex II associated with mitochondrial disease.

Although complex II is the smallest mitochondrial respiratory complex in terms of number of subunits, it nevertheless utilizes a variety of redox cofactors and therefore would seem to require additional factors to aid in its proper assembly. A previous Special Issue of BBA Bioenergetics (1817, 2012) had discussed the biogenesis/assembly of respiratory enzyme complexes describing the multiple components needed for proper assembly of these molecular machines. As discussed in this Special Issue, complex II now joins the other respiratory complexes where the need is shown for additional protein factors required for proper assembly of the complex. Two articles in the Special Issue describe how prokaryotes and eukaryotes utilize additional small proteins for assembly of the redox centers of complex II. These articles describe assembly factors which assist in the attachment of the covalently bound flavin and additional assembly factors apparently needed for assembly of the iron–sulfur clusters of the enzyme. There are also articles which focus on individual complex II subunits, describing the unique roles such proteins may play in aspects of mitochondrial physiology other than their structural/catalytic roles as part of the intact complex II. For example, one of the membrane anchor subunits of complex II may play a part in the mitochondrial protein import machinery and also there is a discussion of the potential role for the membrane domain of complex II in the putative mitochondrial K_{ATP} channel.

Although the articles in this Special Issue do not cover all aspects of complex II currently under active investigation, they do provide a thorough overview of the central relationship complex II has to cellular physiology. They also show the usefulness of complex II as a tractable experimental model for study of electron transfer mechanisms. Complex II remains a fascinating enzyme even after six decades of intense biochemical and biophysical investigations. There is still much to be learned about its assembly, catalytic mechanism, and its contribution to mitochondria-associated disease.

It has been my pleasure to act as a guest editor for this Special Issue on complex II. The enzyme has provided me with many exciting insights into the molecular function of respiratory proteins, as well as numerous puzzles which we are yet to understand. I expect that with the modern advances in biophysical and “omic” sciences, we may

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well address these puzzles over the next decade. I certainly appreciate the effort all of the contributing authors went to in preparing their articles. I also want to thank the editorial staff of BBA Bioenergetics, and in particular Sandra Tokashiki, whose help greatly eased the preparation of this issue.

Gary Cecchini is Senior Research Career Scientist of the Department of Veterans Affairs and Chief of Molecular Biology at the San Francisco VA Medical Center. He is also associated with the Department of Biochemistry & Biophysics of the University of California, San Francisco. He received his Ph.D. in Microbiology from the University of Illinois, Urbana-Champaign followed by a post-doctoral stint studying membrane transporters with Dale Oxender at the University of Michigan, Ann Arbor. There he became interested in flavoproteins by following the studies of Vince Massey and co-workers. Since joining UCSF and the SFVAMC, he has been studying complex membrane-bound flavoproteins that interact with quinones with an emphasis on complex II and complex I of the respiratory chain. His current research interests focus on the assembly and function of the redox centers of proteins and the mechanisms of control of electron transfer through respiratory chains including how alteration of ideal pathways contributes to disease.

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