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Review

Recent advances in cytochrome bc_1: Inter monomer electronic communication?

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ABSTRACT

The ubihydroquinone: cytochrome *c* oxidoreductase, or cytochrome bc_1, is a central component of photosynthetic and respiratory energy transduction pathways in many organisms. It contributes to the generation of membrane potential and proton gradient used for cellular energy production (ATP). The three-dimensional structures of cytochrome bc_1 indicate that its two monomers are intertwined to form a symmetrical homodimer. This unusual architecture raises the issue of whether the monomers operate independently, or function cooperatively during the catalytic cycle of the enzyme. In this review, recent progresses achieved in our understanding of the mechanism of function of dimeric cytochrome bc_1 are presented. New genetic approaches producing heterodimeric enzymes, and emerging insights related to the inter monomer electron transfer between the heme *b* cofactors of cytochrome bc_1 are described.
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1. Introduction

The ubihydroquinone: cytochrome *c* oxidoreductase (cytochrome bc_1 or complex III) is a multi-subunit membrane bound enzyme central to photosynthetic and respiratory electron transport chains of many organisms, including bacteria, archaea, eukaryotic mitochondria and chloroplasts [1–3]. This enzyme catalyzes oxidation of hydroquinone (QH_2) to quinone (Q) and transfers the resulting electrons, usually via a *c*-type cytochrome, to the reaction centers in photosynthetic and cytochrome *c* oxidases in aerobic respiratory growth conditions. It couples the free energy released by these reactions to the translocation of electrons and protons across membrane to contribute to the formation of proton motive force used for ATP synthesis [4].

The static three dimensional (3D) structures of cytochrome bc_1 indicate that it is a symmetrical homodimer [5–9] with at least three catalytic subunits: the Rieske Fe/S protein with a high potential [2Fe2S] cluster, the cytochrome *b* with two *b*-type (one low potential (b_L) and one high potential (b_H)) hemes, and the cytochrome c_1 with a *c*-type heme [10] (Fig. 1). Additional subunits in variable numbers are also present in some species [6–8,11]. The Q-cycle model is generally used to describe the mechanism of function of cytochrome bc_1 [4,12,13]. Accordingly, two QH_2 molecules are oxidized at a QH_2 (Q_o) site on the positive side, and one Q molecule is reduced at a Q reduction (Q_i) site on the negative side, of the membrane. Each QH_2 oxidation is initiated by the oxidized Fe/S protein, which accepts one electron and transfers it to cytochrome c_1 via a large-scale movement of its cluster bearing extrinsic domain [14,15]. This electron is then transferred from cytochrome c_1 to other downstream electron carriers and terminal acceptors. The second electron from QH_2 oxidation is conveyed to the low potential hemes b_L and b_H, and then to a Q forming a stable semiquinone (SQ) at the (Q_i) site (Fig. 1). Following a second turnover of a Q_o site, the SQ at the Q_i site is converted to QH_2 and released from the enzyme, completing the catalytic cycle [12]. This model accounts well for the electron transfer pathways between the cofactors of a monomeric cytochrome bc_1. However, it does not describe whether the two consecutive QH_2 oxidations, which are required to complete a full catalytic cycle, take place at the Q_o site of a given monomer or at the two distinct Q_o sites of the dimeric enzyme. The 3D structures of cytochrome bc_1 revealed that its cofactors, except the mobile [2Fe2S] clusters, are distributed symmetrically within the dimeric enzyme. Moreover, the distances separating the hemes b_L–b_H in a given monomer, and the hemes b_L–b_L between the two monomers are quasi-identical (Fig. 1). These findings raised a number of intriguing questions (e.g., see [16,17]), including the independent or co-ordinated functions of cytochrome bc_1 monomers. The architecture of cytochrome bc_1 might play a functional role

Abbreviations: Q, quinone; SQ, semiquinone; QH_2, hydroquinone

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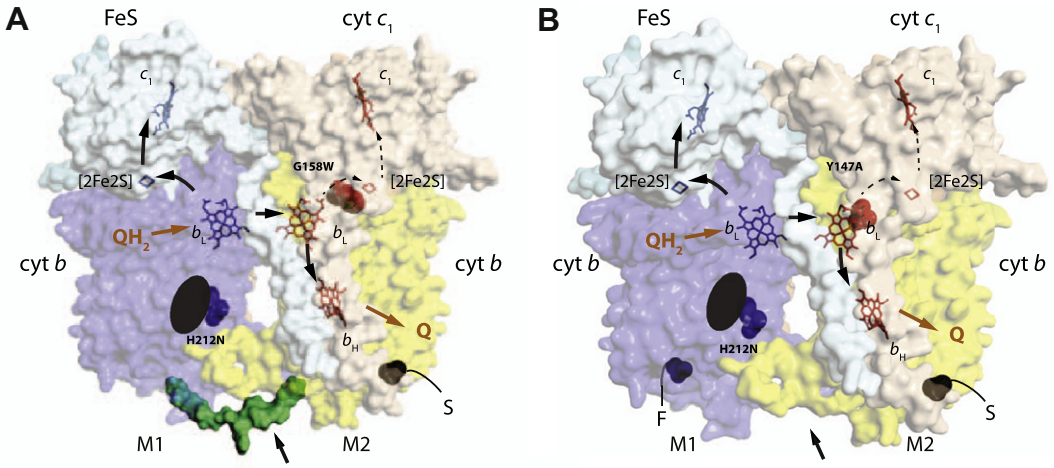

Fig. 1. Structure and function of heterodimeric cytochromes bc_1. (A) A hypothetical structural model for a non-native heterodimeric cytochrome b-bc_1. The 3D structure of cytochrome bc_1 (PDB entry 1ZRT) was modified to include the Q_i site H212N mutation (blue) on one monomer (M1) and the Q_o site G158W mutation (red) on the other (M2) to depict a heterodimeric enzyme produced by the one-plasmid system [29]. The carboxyl end of one cytochrome b (blue) is linked to the amino end of the other (yellow) with a peptide (green) indicated by an arrow to create cytochrome b-b that is not naturally present in cytochrome bc_1. S refers to the Strep–tag on the carboxyl terminal end of cytochrome b-b. The Fe/S and cytochrome c_1 subunits are shown in light blue and light brown, with the cofactors ([2Fe2S] and hemes b_H, b_L and c_1) in monomer M1 in blue and those in M2 in red. The black arrows indicate the electron transfer pathways across the monomers, Q and QH_2 correspond to quinone and hydroquinone, respectively. The black ellipsoid indicates the absence of heme b_H on monomer M1. (B) A hypothetical structural model for a native-like heterodimeric cytochrome bc_1. The 3D structure of cytochrome bc_1 (PDB entry 1ZRT) was modified to include the Q_i site H212N mutation (blue) on one monomer (M1) and the Q_o site Y147A mutation (red) on the other (M2) to depict a heterodimeric enzyme produced by the two-plasmids system [32]. The labels are as in A, and note the absence (indicated by an arrow) of the peptide linking together the cytochromes b, and the presence of Flag-(F) and Strep (S)-tags on the carboxyl terminals of two cytochrome b on monomers M1 and M2, respectively.

in addition to the structural stability of the enzyme if the two consecutive QH_2 oxidations alternate between the two Q_o sites of the dimeric enzyme, or if inter monomer electronic communication occurs between the heme cofactors. A number of hypothetical models, including "dimeric Q cycle" [18], "alternating Q cycle" [19] or "heterodimeric Q cycle" [20], invoking different structural and functional interactions between the Q_o and Q_i sites within one monomer, or between both monomers, of cytochrome bc_1 have been described. Initially, peculiar transient kinetics data were interpreted as indication of a dimeric Q cycle mechanism for QH_2 oxidation [18] despite other possible explanations. In recent years, more convincing experimental approaches [21–23] and theoretical calculations [24] were reported. In this review, we survey recent studies on inter monomer electronic communication within cytochrome bc_1. We describe the different genetic systems used to produce asymmetric cytochrome bc_1 heterodimers, and critically assess the outcomes of these efforts in understanding the mechanism of function of dimeric cytochrome bc_1.

2. Recent approaches to probe inter monomer electronic communication in cytochrome bc_1

2.1. Half of the sites reactivity

Early on, Trumpower and colleagues described that one molecule of stigmatellin (a Q_o site inhibitor) per dimer was sufficient to completely inhibit cytochrome bc_1 [25], and that when yeast cytochrome bc_1 is inhibited by antimycin A (a Q_i site inhibitor) the amount of cytochrome c_1 reduced corresponded to half of that present in cytochrome bc_1 [21]. These studies assumed that equilibrium between the two hemes b_H is attained via electron transfer between the hemes b_L to support the "half of the sites reactivity" model for yeast [26] and bacterial [27] cytochrome bc_1. More recently, a *Paracoccus denitrificans* strain that produces a quasi-wild type and a Q_o site defective mutant variants of cytochrome bc_1, tagged with His- and Strep-epitopes, respectively, (see below "two-plasmids system" for details) was described [28]. The quasi-wild type form of cytochrome bc_1 used in this study lacked the amino terminal acidic part of cytochrome c_1 and produced a dimeric enzyme, which otherwise forms a tetramer in its native state. From this strain, homodimeric (with two wild type Q_o, or two mutant Q_o sites) and heterodimeric (with a wild type Q_o site in one monomer, and a mutant Q_o site in the other monomer) cytochrome bc_1 were purified by affinity chromatography with appropriate epitope-tags. Purified homodimeric wild type and heterodimeric mutant cytochromes bc_1 exhibited comparable extents of cytochrome c_1 and cytochrome b_H reductions and enzyme activities, but antimycin-mediated stimulation was observed only with the homodimeric wild type enzyme. These findings suggested that only one of the two Q_o sites of the wild type homodimer, or the mutant heterodimer is active, and that inter monomer electron transfer occurs in cytochrome bc_1 [28]. These interesting data are consistent with the alternating Q cycle model [19], although they do not prove directly the occurrence of either an inactive Q_o site in wild type, or inter monomer electron transfer between the hemes b_L in the heterodimeric mutant cytochrome bc_1. In addition, this *P. denitrificans* mutant provides no information about the physiological ability of a heterodimeric cytochrome bc_1 to support cellular growth.

2.2. One-plasmid system

More recently, a different genetic system to probe inter monomer electron transfer in dimeric cytochrome bc_1 was reported by Osyczka and collaborators [29]. They adapted a previously described *Rhodobacter capsulatus* genetic system [30] to carry an ingenuously modified *petABC* (structural genes of cytochrome bc_1) operon. Two copies of *petB* (encoding cytochrome b) were connected to each other via a designed linker sequence to form a fused *petB-B* gene on a single plasmid, to produce a 'cytochrome b-b' subunit, which is tagged with Strep-epitope at its carboxyl end [29] (Fig. 2A). This "one-plasmid" system was considered to produce a non-native but fully active dimeric "cytochrome b-bc_1" in which

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