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REVIEW

Generation of Membrane Potential by Cytochrome *bd*

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Abstract—An overview of current notions on the mechanism of generation of a transmembrane electric potential difference ($\Delta\psi$) during the catalytic cycle of a *bd*-type triheme terminal quinol oxidase is presented in this work. It is suggested that the main contribution to $\Delta\psi$ formation is made by the movement of H^+ across the membrane along the intra-protein hydrophilic proton-conducting pathway from the cytoplasm to the active site for oxygen reduction of this bacterial enzyme.

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Keywords: respiratory chain, terminal oxidase, cytochrome *bd*, heme, protonmotive force, membrane potential

INTRODUCTION

In 1974, L. A. Drachev and co-authors at the Belozersky Institute of Physico-Chemical Biology of Lomonosov Moscow State University developed an electrometric method for direct measurement of electrical activity of coupling membranes, which provided a unique opportunity to track intra-protein movements of electrical charges within one molecular turnover of the enzyme [1]. Using this method, it was possible to observe in real time generation of the transmembrane electric potential difference ($\Delta\psi$) by bacteriorhodopsin [2], reaction centers [3], and cytochrome bc_1 [4] from photosynthetic bacteria, as well as terminal cytochrome *c* oxidase [5-7] and non-canonical retinal-containing bacterial proteins [8, 9]. Two different approaches are used to study electrogenic mechanism of cytochrome *c* oxidases. The first approach uses photochemical injection of a single electron into the enzyme embedded in a liposome. In this case, tris(2,2'-bipyridyl)ruthenium(II) chloride (RuBpy) acts as a direct photoactivated reducing agent, which forms a complex with the cytochrome *c* binding site in the oxidase near the input Cu_A redox center due to electrostatic interactions [5, 6]. As a result of photoexcitation of RuBpy by a pulsed laser, an electron is transferred from RuBpy* to Cu_A. The oxidized RuBpy is re-reduced by aniline. This approach makes it possible to record time-resolved electrogenic charge transfer during individual one-electron transitions in the catalytic cycle of cytochrome *c* oxidase [7]. In the second approach, laser flash photolysis of a complex of carbon monoxide (CO) with the oxygen-binding high-spin heme a_3 is used to initiate enzymatic reaction in the single-turnover mode. Formation of the CO complex with the partially or completely reduced enzyme occurs under anaerobic conditions. Oxygen (O_2) dissolved in water is then added to the anaerobic cell with the CO-bound oxidase using rapid mixing technique. During decomposition of the CO-oxidase complex triggered by photolysis, O_2 binds to heme a_3 and is reduced by electrons present in the oxidase that is accompanied by generation of $\Delta\psi$ [10]. Thus, the second approach uses combination of the direct electrometric method [1] and the flow-flash method [11]. Terminal quinol oxidases including cytochrome *bd*, which is the subject of this review, do not have a cytochrome *c* binding site. For this reason, the first approach is inapplicable for tracking movement of electric charges inside their protein molecule.

GENERAL CHARACTERISTICS OF CYTOCHROME *bd*

Membrane-bound terminal oxidases of the aerobic respiratory chains of organisms are classified as translocases (enzymes in class EC 7). They catalyze four-electron

Abbreviations: $\Delta\psi$, transmembrane electrical potential difference; Δp, protonmotive force; τ, time constant, reciprocal of rate constant ($t_{1/e}$); H^+/e^-, proton/electron stoichiometry which in the case of *Escherichia coli* respiratory chain means number of protons released into the periplasm per electron used to reduce oxygen to water; RuBpy, tris(2,2'-bipyridyl)ruthenium(II) chloride.

reduction of molecular oxygen to water by ferrocytochrome *c* or quinol (ubiquinol, menaquinol, and possibly plastoquinol) [12, 13]. The catalyzed redox reaction is coupled with generation of Δp (protonmotive force). Δp is an "energy currency" and is used by the cell to synthesize ATP through the mechanism of oxidative phosphorylation [14]. Terminal oxidases are divided into two evolutionarily unrelated superfamilies: heme/Cu-containing oxidases and *bd*-type oxidases also called cytochromes *bd* [15-18]. Unlike the heme-copper oxidases, all biochemically characterized cytochromes *bd* are quinol oxidases, do not contain Cu, and are found only in bacteria and archaea, including pathogens [19-21]. The latter circumstance makes it possible to consider *bd* enzymes as promising therapeutic targets [21, 22]. Since generation of $\Delta\psi$ in the single-turnover mode has been studied so far only in the terminal *bd* oxidases from *Escherichia coli*, we should consider these enzymes in more detail.

Like the electron transport chains of many bacteria, aerobic respiratory chain of *E. coli* is branched. Its terminal region is generally represented by three quinol oxidases: heme-copper cytochrome bo_3 and two cytochromes *bd*, *bd*-I and *bd*-II [23, 24]. Unlike *bd*-type oxidases, cytochrome bo_3 forms Δp by the proton pump mechanism that makes it possible to double pumping stoichiometry: proton/electron (H^+/e^-) [25, 26]. Cytochromes bo_3, *bd*-I, and *bd*-II are encoded by the *cyoABCDE*, *cydABX*, and *appCBX* operons, respectively. *cyoABCDE* is predominantly expressed under high O_2 partial pressure, while *cydABX* is predominantly expressed under microaerobic conditions. The *appCBX* expression is induced during anaerobic growth of *E. coli*, entry of the culture into the stationary phase of growth, and phosphate starvation [24]. Recently, there has been more and more evidence reported that, in addition to functioning as molecular energy transducers, *bd*-type oxidases are involved in other vital processes in the bacterial cell [27-30]. Cytochrome *bd*-I is involved in formation of disulfide bonds during protein folding [31], heme biosynthesis [32], and mechanisms of bacterial resistance to antibiotics [33], peroxynitrite [34], nitrogen monoxide [35-41], and ammonia [42]. Both *bd* oxidases (*bd*-I and *bd*-II) also endow *E. coli* with resistance to cyanide [43], sulfide [43-45], and hydrogen peroxide [46-54].

Three-dimensional structures of both *E. coli bd* enzymes have recently been published (Figs. 1 and 2) [55-58]. Cytochrome *bd*-I was found to contain four subunits (CydA, CydB, CydX, CydY), while cytochrome *bd*-II only three (AppC, AppB, AppX). The CydA, CydB, and CydX subunits are homologous to the AppC, AppB, and AppX subunits, respectively. Two large subunits, CydA/AppC and CydB/AppB, form structural core of the protein. Of the other structural differences between the two *bd* oxidases, it should be noted that the *bd*-II protein incorporated into amphipoles is mainly in the form of a dimer (Fig. 2), while the *bd*-I enzyme exists only as a monomer [57] (Fig. 1). Oxygen channel in cytochrome *bd*-II has a smaller diameter compared to that of cytochrome *bd*-I [57]. In addition, the putative proton-conducting pathway in the *bd*-II enzyme is shorter than in the *bd*-I oxidase [57]. CydA/AppC contains three different hemes acting as redox cofactors: one low-spin hexacoordinate, b_{558}, and two high-spin pentacoordinate, b_{595} and *d*. The heme axial ligands are amino acid

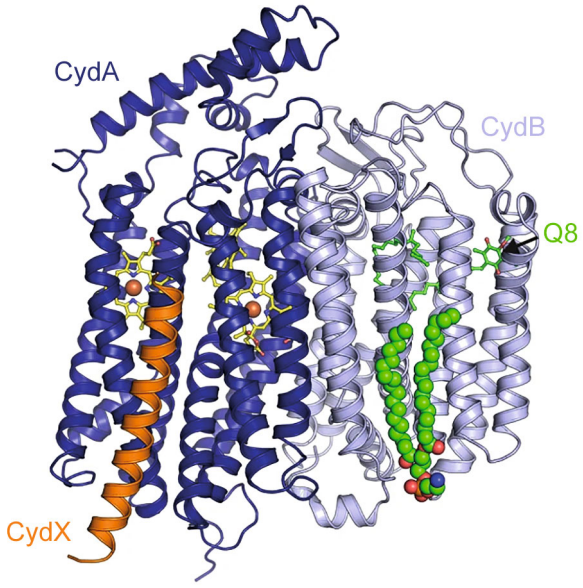

Fig. 1. Three-dimensional structure of *E. coli* cytochrome *bd*-I with 3.3 Å resolution (pdb ID 6RX4). In addition to hemes b_{558}, b_{595}, and *d* associated with the CydA subunit, ubiquinone-8 (Q8) and glycerophospholipid (shown as spherical symbols) associated with the CydB subunit are found in the protein structure. Reprinted from Theßeling et al. [55] under the terms of the Creative Commons Attribution 4.0 International Public License.

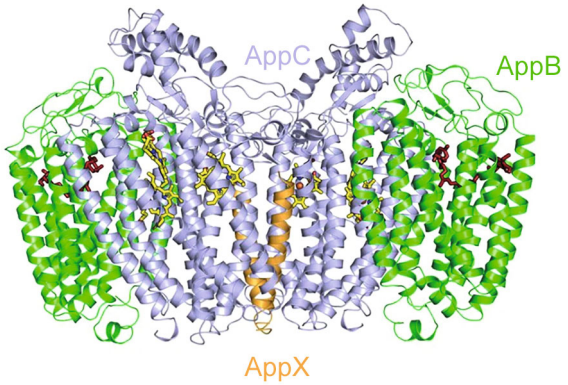

Fig. 2. Three-dimensional structure of *E. coli* cytochrome *bd*-II dimer with 3.0 Å resolution (pdb ID 7OSE). In addition to hemes b_{558}, b_{595}, and *d* associated with the AppC subunit, ubiquinone-8 (shown in red) associated with the AppB subunit is found in the protein structure. Reprinted from Grauel et al. [57] under the terms of the Creative Commons Attribution 4.0 International Public License.

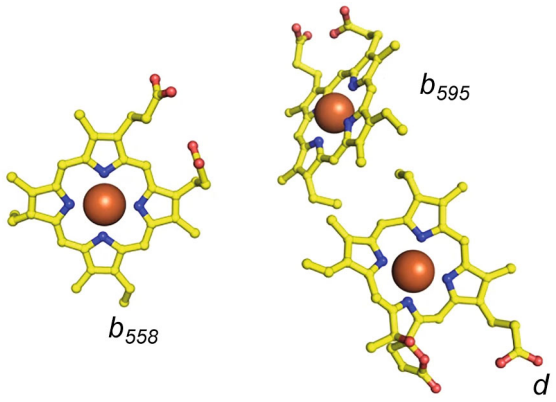

Fig. 3. Triangular arrangement of hemes b_{558}, b_{595}, and d in the CydA subunit of *E. coli* cytochrome *bd*-I. Periplasm: top of the picture, cytoplasm: bottom of the picture. Reprinted from Theßeling et al. [55] under the terms of the Creative Commons Attribution 4.0 International Public License.

residues of the CydA/AppC subunit. These are His186 and Met393 for heme b_{558} and Glu445 for heme b_{595} [55-58]. In cytochrome *bd*-II, the axial ligand of heme *d* is His19 [57-58]. In the case of cytochrome *bd*-I, data on the nature of the heme *d* axial ligand are contradictory. Safarian et al. [56] state that this is also His19, but according to the model of Theßeling et al. [55], such a ligand is Glu99. The hemes in the protein are arranged in a triangle (Fig. 3). Additional structural element in CydA/AppC is the so-called Q-loop. It is located near heme b_{558} and is directly involved in binding of quinol, a lipophilic electron donor. The other large subunit, CydB/AppB, does not contain any metal-containing cofactors. Instead, it carries a tightly bound ubiquinone-8 or demethylmenaquinone-8. This quinone occupies position equivalent to the heme-binding site in CydA/AppC and, probably, plays a role in the protein structure stabilization. Heme b_{558} is the primary electron acceptor upon quinol oxidation. Heme *d* serves as a site for O_2 binding and its subsequent reduction to $2H_2O$ [59, 60]. Heme *d* in cytochrome *bd*-I has an unusually high affinity for O_2, and the resulting oxygenated complex is very stable [61-64]. Functions of heme b_{595} are poorly understood. Excessive distance between the central Fe atoms of hemes b_{595} and *d* (10.9-11.3 Å) most likely does not allow them to form a structural binuclear center similar to that of heme-copper oxidases. However, van der Waals contacts between these hemes are possible since the distance between their edges is much smaller (3.5-3.8 Å) [55-58]. The latter circumstance suggests the possibility of a very fast electron transfer between hemes b_{595} and *d* that was experimentally confirmed [65, 66]. Therefore, these hemes could potentially form a functional diheme center. This assumption is consistent with the data of a number of studies [67-79]. An electron that came from quinol to heme b_{558} is apparently transferred to heme b_{595} and next to heme *d*.

ELECTROGENIC REACTIONS AND CATALYTIC CYCLE OF CYTOCHROME *bd*-I FROM *E. coli*

Use of optical and electrometric methods in combination with flow-flash method made it possible to observe in real time transient formation and decay of the individual intermediates of the catalytic cycle of *E. coli* cytochrome *bd*-I at 21°C [26, 80-83]. The proposed scheme of the catalytic cycle is shown in Fig. 4. In spectroscopic studies, hemoprotein was in detergent micelles, and in electrometric studies, it was incorporated into liposomes. In the experiment, the enzyme was initially converted into a completely reduced state in which heme *d* was bound to CO (**R³–CO**, $b_{558}^{2+}b_{595}^{2+}d^{2+}$–CO). Photolysis of CO from this state of the oxidase leads to the transient appearance of the form of cytochrome *bd*-I not bound to CO (**R³**, $b_{558}^{2+}b_{595}^{2+}d^{2+}$). This transition (**R³–CO→R³**) is not resolved in time in both spectrophotometric and electrometric measurements. In the presence of O_2, a molecule of this diatomic gas binds to heme *d*. As a result, the oxygenated complex, intermediate **A³** ($b_{558}^{2+}b_{595}^{2+}d^{2+}$–$O_2$), is formed. The rate of formation of **A³** is directly proportional to concentration of O_2, with the second-order rate constant to be about 2×10^9 M^{-1} s^{-1} [64, 82]. The **R³→A³** transition is not accompanied by generation of $\Delta\psi$ [26, 82, 83]. **A³** is quickly ($\tau \sim 4.5$ μs) converted into an intermediate, which Belevich et al. first discovered, described, and named as compound **P** [82]. It was found that the **A³→P** transition is also not coupled with generation of $\Delta\psi$ [26, 82, 83]. In contrast to the production of **A³** from **R³**, the rate of formation of compound **P** does not depend on concentration of O_2. During the **A³→P** transition, heme b_{595} undergoes oxidation, heme b_{558} remains in the reduced state, and new oxygen intermediate of heme *d* reveals an unusual absorption maximum at 635 nm [82]. There is still no consensus on chemical structure of the compound **P**. In the original work [82], Belevich et al. suggested that **P** is a true peroxide complex, either a ferryl intermediate with an amino acid radical or a cation radical of the porphyrin ring. According to the more recent report by Paulus et al. [84], compound **P** is a ferryl form of heme *d* with π-cation radical on the porphyrin ring, which is in magnetic interaction with heme b_{595}. It is important to emphasize that Paulus et al. [84] observed formation of compound **P** at 1°C, i.e., under non-physiological conditions. It is possible that the spectral intermediate **P**, appearance of which was registered in real time by Belevich et al. [82], is a mixture of a true peroxide complex ($b_{558}^{2+}b_{595}^{3+}d^{3+}$–O–O–(H)) and a ferryl π-cation radical ($b_{558}^{2+}b_{595}^{3+}d^{*4+} = O^{2-}$), provided that they have similar absorption spectra. At the next stage, **P** is converted (with $\tau \sim 47$ μs) into a non-radical form of the ferryl complex of heme *d* (compound **F**) that is accompanied by oxidation of heme b_{558}. Cat-

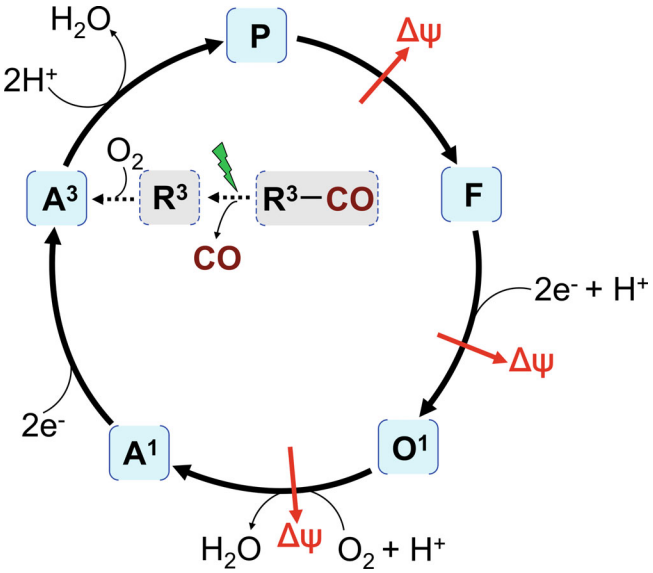

Fig. 4. Catalytic cycle of the *E. coli* cytochrome *bd*-I. Compounds **A³**, **P**, **F**, **O¹**, **A¹** are catalytic intermediates of the enzyme. Compounds **R³** and **R³–CO** are not part of the oxidase catalytic cycle, but can be obtained artificially. Red "arrows of coupling" indicate generation of Δψ at **P→F** and **F→A¹** transitions. Structures of the compounds are discussed in the main text.

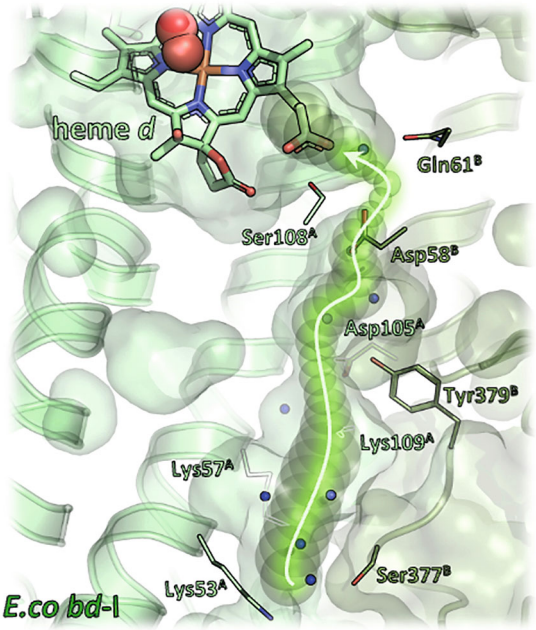

Fig. 5. Proposed proton-conducting pathway in *E. coli* cytochrome *bd*-I. The pathway is lined with side chains of several hydrophilic amino acids and allows transfer of protons from the cytoplasmic side of the membrane to heme *d* propionate. It also contains numerous water molecules (indicated by blue spherical symbols). Reprinted from Friedrich et al. [22] under the terms of the Creative Commons Attribution 4.0 International Public License.

alytic intermediate **F**, most likely, has the structure of $b_{558}^{3+}b_{595}^{3+}d^{4+} = O^{2-}$. The **P→F** transition is associated with generation of Δψ [26, 82, 83].

The *bd*-type oxidase contains three hemes. Therefore, if the isolated enzyme does not contain a bound quinol, then it can be expected that in the completely reduced state it carries three electrons (**R³**). In this case, the reaction of **R³** with O_2 stops at formation of compound **F** [80]. If cytochrome *bd*-I contains a molecule of bound quinol, which is a two-electron donor, its oxidation in the presence of O_2 makes it possible to convert **F** into intermediate **A¹** with τ ~ 0.6-1.1 ms [81, 82]. **A¹** is, probably, the one-electron form of the oxidase with the heme *d* oxycomplex ($b_{558}^{3+}b_{595}^{3+}d^{2+}$–$O_2$). The **F→A¹** transition, like the previous **P→F** transition, is accompanied by generation of Δψ [81, 82]. Whether Δψ is formed at one more particular stage of the catalytic cycle, in the **A¹→A³** transition (Fig. 4), is still unknown.

It was found that under the steady-state conditions in the presence of O_2 and ubiquinol-1, **F** and **A¹** are main catalytic intermediates of the cytochrome *bd*-I (about 40% each) [60]. About 20% of the oxidase is probably in the **O¹** state that is a one-electron form with the oxidized heme *d* ($b_{558}^{2+}b_{595}^{3+}d^{3+}$–OH). The **O¹** state has not been observed in the single-turnover experiments using the flow-flash method [80, 82, 83]. However, it is currently recognized that **O¹** is apparently also a catalytic intermediate of the cytochrome *bd*-I (Fig. 4). It should also be noted that the **R³** form of the enzyme is most likely not its catalytic intermediate [59, 60], however, for the needs of experiment, it can be easily produced artificially.

In 2005, Belevich et al. [81] postulated based on the obtained results existence of an intra-protein proton-conducting pathway for the transfer of H^+ from cytoplasm to the oxygen reductase center of cytochrome *bd*-I. The authors suggested that such movement of H^+ across the membrane, associated with the transfer of an electron from heme b_{558} to hemes b_{595} and *d*, is accompanied by generation of Δψ observed in the experiments [26, 80-83]. Release of H^+ into the periplasmic space during oxidation of quinol by the enzyme also contributes to creation of Δ*p*. 3D structures of the *bd*-I oxidase published in 2019, with resolution of 2.68 Å (pdb ID 6RKO) [56] and 3.3 Å (pdb ID 6RX4) [55], confirmed the hypothesis suggested by Belevich et al. [81]. The structures show a chain of water molecules stretching along a hydrophilic proton-conducting pathway that starts at the cytoplasmic interface between the CydA and CydB subunits and runs perpendicular to the membrane plane towards heme *d*. This proton-conducting pathway includes several hydrophilic amino acid residues (Fig. 5). From the cytoplasmic side, the pathway begins with $Asp119^{CydA}$, then, apparently, it includes $Lys57^{CydA}$, $Lys109^{CydA}$, $Asp105^{CydA}$, $Tyr379^{CydB}$, and, finally, $Asp58^{CydB}$, from which protons are likely delivered to the propionate group of heme *d* [55]. It has been suggested that the conserved hydrophilic residues $Ser108^{CydA}$, $Glu107^{CydA}$, and $Ser140^{CydA}$ also belong to this pathway, facilitating transfer of H^+ from $Asp58^{CydB}$ to the heme *d* propionate [56].

Belevich et al. [81] also hypothesized that the *bd*-I molecule contains two amino acid residues with protonated groups, which are sensitive to the redox state of the high-spin pentacoordinate hemes b_{595} and *d*. Studies of the Glu445Ala and Glu107Leu mutant forms of the *E. coli* cytochrome *bd*-I by electrometry and absorption spectroscopy with microsecond resolution indicate that exactly these highly conserved $Glu445^{CydA}$ and $Glu107^{CydA}$ residues are functionally important [81, 83].

As noted above, $Glu445^{CydA}$ is the axial ligand of the heme b_{595} iron [55, 56]. Its replacement with Ala in the CydA subunit leads to the enzyme inactivation. At the same time, heme b_{595} is retained in the protein but loses its ability to be reduced even in the presence of a strong electron donor, dithionite, added in excess [81]. As in the case of the wild-type cytochrome *bd*-I, the reaction of the reduced Glu445Ala mutant enzyme with oxygen exhibits an initial non-electrogenic stage consisting of the $\mathbf{R^3 \rightarrow A^3}$ and $\mathbf{A^3 \rightarrow P}$ transitions. However, in contrast to the wild-type enzyme, the microsecond phase is not detected in the mutant during $\Delta\psi$ generation. Instead, the mutant form exhibits a slower, smaller electrogenic phase ($\tau \sim 1.3$ ms; amplitude -0.36 mV) followed by a much larger electrogenic transition ($\tau \sim 12.5$ ms; amplitude -1.7 mV). Both electrogenic phases, most likely, reflect the $\mathbf{P \rightarrow F}$ transition in different subpopulations of the Glu445Ala enzyme [81]. Thus, the substitution of Glu445 for Ala strongly inhibits the transmembrane charge transfer associated with oxidation of cytochrome *bd*-I by oxygen.

Similarly, substitution of Glu107 for Leu in the CydA subunit leads to the loss of quinol oxidase activity by cytochrome *bd*-I. The fully reduced mutant form of the Glu107Leu protein ($\mathbf{R^3}$) binds O_2 at about the same rate as the wild-type enzyme. However, formation of the ferryl intermediate (**F**) in the mutant oxidase is believed to be significantly slower compared to the wild-type enzyme. This is evidenced by the results of spectrophotometric experiments, according to which production of the compound **F** has not been observed within the 100-μs time interval in the mutant oxidase, in contrast to the wild-type protein [83]. This conclusion is consistent with the fact that the rate of generation of $\Delta\psi$ (the main phase) by the mutant oxidase is about 350 times slower than the rate measured for the wild-type enzyme [83].

$Glu445^{CydA}$ appears to be protonated during the transition of heme b_{595} from the oxidized to the reduced form, i.e., it serves to compensate for the negative charge of the electron that came to the heme. In the case of heme *d*, $Glu107^{CydA}$ probably plays the same role. According to the published three-dimensional structure of the *E. coli* cytochrome *bd*-I, heme b_{595} is located near the periplasmic surface [55, 56]. Therefore, if H^+ is transferred to $Glu445^{CydA}$ from the periplasmic side of the membrane during the heme b_{595} reduction, this proton is unlikely to be used in the oxygen reductase reaction catalyzed by the enzyme.

CAN CYTOCHROME *bd*-II FROM *E. coli* GENERATE $\Delta\psi$?

Functional studies of the *E. coli* cytochrome *bd*-II are still at the very early stages. Becker et al. [85] reported that the H^+/e^- ratio for the *bd*-II enzyme is 0, i.e., it is an uncoupled quinol oxidase. It is known that cytochromes *bd*-I and bo_3 from *E. coli* are coupled quinol oxidases, with the H^+/e^- values of 1 and 2, respectively [25, 26]. Becker et al. constructed the mutant strain of *E. coli*, MB37, in the respiratory chain of which cytochrome *bd*-II was present but all the primary proton potential generators known at that time, NADH dehydrogenase 1 (NDH-1), cytochrome bo_3, and cytochrome *bd*-I, were absent. The authors calculated H^+/e^- by comparing the values for the specific rates of oxygen consumption and ATP synthesis observed for the MB37 strain and other *E. coli* mutant strains for which the H^+/e^- values had already been measured [85]. Bacterial cells of all the strains were grown under the same conditions, and the rate of ATP synthesis was calculated taking into account the rates of formation of metabolic products – CO_2, acetate, ethanol, and lactate. Unexpectedly, the MB37 strain, which, according to the authors' suggestion, should have the completely uncoupled aerobic respiratory chain, was capable of growing under aerobic conditions on non-fermentable substrates. However, the question arises: how is ATP synthesis ensured in this case? Becker et al. hypothesized [85] that ATP in the MB37 strain is produced exclusively via substrate phosphorylation. In the more recent work, Shepherd et al. [86] suggested that in this mutant strain the proton potential is formed due to functioning of an electrogenic antiporter, which transports an anion of glutamic acid (glutamate) into the cell in exchange for the release of a neutral γ-aminobutyric acid (GABA) from the cell. In this case, GABA in the cell is synthesized from glutamate, and an intracellular proton is consumed during the process.

Borisov et al. [26] found the conclusions of the authors of those two studies [85, 86] unconvincing and experimentally tested whether cytochrome *bd*-II generates Δp. It was found that, under the steady state conditions, both components of Δp – $\Delta\psi$ and ΔpH – are formed due to quinol oxidase activity of cytochrome *bd*-II [26]. The H^+/e^- ratio was measured. As in the case of cytochrome *bd*-I, it turned out to be 1 [26]. It was also shown that the *bd*-II oxidase is able to generate $\Delta\psi$ during a single molecular turnover of the enzyme, presumably, during the $\mathbf{P \rightarrow F}$ and $\mathbf{F \rightarrow A^1}$ transitions [26]. Thus, one can conclude that the *E. coli* cytochrome *bd*-II is the primary generator of Δp.

Therefore, to explain the growth of the *E. coli* MB37 cells under aerobic conditions, alternative mechanisms of ATP formation proposed in [85, 86] are not required.

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