Volume 327, number 2, 131–136 FEBS 12743 July 1993

Minireview

Comparison of ubiquinol and cytochrome *c* terminal oxidases

An alternative view

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Received 11 May 1993; revised version received 7 June 1993

There have been numerous instances in the recent literature where the properties of ubiquinol and cytochrome *c* terminal oxidases are compared. Here we specifically examine the cytochrome bo_3-type ubiquinol oxidase from *Escherichia coli* and the cytochrome aa_3-type cytochrome *c* oxidases. A second redox-active copper site (Cu_A) is present only in the cytochrome *c* oxidases and the physiological electron donors for the two enzymes are different (ubiquinol-8 vs. ferrocytochrome *c*). In our opinion, these differences are significant and most likely indicate that distinct turnover mechanisms are operative in the two enzymes.

Ubiquinol oxidase; Cytochrome oxidase; Electron transfer; Proton pumping

1. INTRODUCTION

In a recent review [2], it was postulated that a variety of ubiquinol and cytochrome *c* oxidases form a superfamily of heme-copper oxidases. Following the example of this review, we classify the cytochrome bo_3 (*Escherichia coli*), cytochrome ba_3 (*Acetobacter aceti*) and cytochrome aa_3 (*Bacillus subtilis* and *Sulfolobus acidocaldarius*) complexes in the family of ubiquinol oxidases and the cytochrome aa_3 (mitochondrial version and similar bacterial enzymes), cytochrome ba_3 (*Thermus thermophilus*), and cytochrome caa_3 (*T. thermophilus*, *Bacillus cereus*, *Bacillus stearothermophilus*, thermophilic bacillus PS3, and *B. subtilis*) complexes in the family of cytochrome *c* oxidases (Table I). All of these oxidases appear to have a similar heme–copper dioxygen activating center. The major difference between the two families is obviously the different substrates (quinol vs. ferrocytochrome *c*) but it also appears that most, if not all, of the quinol oxidases are missing the Cu_A site found in the cytochrome *c* oxidases. Since the *E. coli* cytochrome bo_3 complex and the aa_3-type cytochrome *c* oxidase complexes are the best characterized enzymes in their respective families, we center on these two enzymes in the discussion which follows. However, it is not fair to compare the bacterial *E. coli* cytochrome bo_3 complex with the mammalian aa_3-type oxidases as the latter oxidases are significantly more evolved containing at least 13 polypeptides [3]. Thus, in the comparisons which follow, the aa_3-type cytochrome *c* oxidase from bacterial sources is emphasized, though data from more complex organisms are included where appropriate.

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Contribution No. 8798 from the Division of Chemistry and Chemical Engineering, California Institute of Technology.

In order to maintain clarity in our comparison of terminal oxidases, we have followed the lead of Puustinen and Wikström [1] in the nomenclature of heme structures. Isolated heme structures are indicated by upper-case letters (hemes A, B, C, O), whereas when the corresponding hemes are within their natural proteinaceous surroundings, the term cytochrome is applied and italic lower-case letters are used (cytochromes *a*, *b*, *c*, *o*). A further distinction is sometimes necessary when the heme macrocycle itself of a particular cytochrome is under discussion. So whereas the term cytochrome encompasses the heme and immediate surrounding protein matrix thus identifying a general region of the protein (for example, 'reduction potential of cytochrome *a*'), the term heme and italic lower-case letters (hemes *a*, *b*, *c*, *o*) is used when the heme macrocycle is being referred to (for example, 'the ligation of heme *a*'). In addition, the low-spin heme which is unreactive towards extraneous ligands is denoted without subscript, yet following the classical terminology of the mitochondrial cytochrome *c* oxidase complex, the O_2-binding heme is denoted with the subscript 3 (hemes a_3 and o_3).

2. BIOPHYSICAL CHARACTERISTICS

There are several recent reviews comparing the bo_3- and aa_3-type oxidase complexes [4–6]. For completeness, we summarize the main conclusions. The *E. coli* cytochrome bo_3 ubiquinol oxidase complex and cytochrome aa_3-type cytochrome *c* oxidase complexes catalyze the four electron reduction of dioxygen to water by utilizing electrons from ubiquinol-8 and ferrocytochrome *c*, respectively. In addition, these proteins cou-

ple part of the free energy of dioxygen reduction to the endergonic vectorial translocation of protons across the membrane in which they reside (Fig. 1). Other similarities between the two terminal oxidases include: (1) subunit sequence similarity [7]; (2) the presence of one low-spin (six-coordinate) and one high-spin (five-coordinate) heme [8,9]; (3) exchange coupling between the high-spin heme and a copper ion (binuclear site) in their resting states; and (4) heme-heme interaction and alignment of these hemes with respect to the membrane bilayer normal [4,10,11]. Nevertheless, there are notable differences between the two proteins including: (1) one heme B and one heme O (bo_3) versus two heme A's (aa_3); (2) one (bo_3) versus two (aa_3) redox active copper ions (the cytochrome bo_3 complex lacks the unusual $g = 2$ EPR signal found in the cytochrome aa_3 complex, which is attributed to the Cu_A site); and (3) the different substrates, i.e. ubiquinol-8 (bo_3) versus ferrocytochrome c (aa_3) [4,12,13]. We now discuss these similarities and differences in greater depth.

3. SEQUENCE SIMILARITIES

The purified cytochrome bo_3 complex contains stoichiometric amounts of four, possibly five, polypeptides [14] which are encoded by the *cyo*ABCDE operon. The *cyo*B gene product corresponds to subunit I (COI) of the aa_3-type oxidases and is by far the most homologous subunit. In fact, for this subunit, there exists 37% sequence identity between the cytochrome bo_3 and the *Paracoccus denitrificans* cytochrome aa_3 complexes [7] (40% identity with the subunit I sequence of the bovine heart cytochrome c oxidase complex [2]). Site-directed mutagenesis studies have shown that the histidines ligating the redox centers in subunit I (the two hemes and Cu_B) are conserved in the two terminal oxidases [15–17]. In addition, the amino acid sequence around the ligands of the binuclear site is highly conserved [18,19]. In conjunction with the biophysical studies noted above, these sequence similarities suggest that subunit I of the two oxidases are likely to be structurally similar. This structural similarity indicates that the dioxygen chemistry of the two enzymes is likely to be very similar if not identical. Thus, one may think of the 'catalytic core' (i.e. subunit I and its associated redox centers) as a highly conserved motif for dioxygen activation and reduction. However, note that recent data reveal different proton transfer characteristics during dioxygen reduction for the two enzymes [20].

The homology between the other subunits of the two enzyme complexes is not nearly so high as that for the respective subunit I sequences. Subunit II (the *cyo*A gene product) of the cytochrome bo_3 complex lacks the four putative ligands for Cu_A in cytochrome aa_3 complexes (two cysteines and two histidines all four of which are invariant in the known cytochrome aa_3 complex sequences) but otherwise has a similar hydropathy profile. Not surprisingly, conserved residues which have been implicated in the binding of cytochrome c to the aa_3-type oxidases (Asp-158, Glu-198; bovine numbering) are absent in the subunit II sequence of the cytochrome bo_3 complex. Sequence identity between subunit II of the *P. denitrificans* cytochrome aa_3 and cytochrome bo_3 complexes is only 10%. The *cyo*C gene product (subunit III) shows slightly greater sequence identity with COIII (23%) yet two putative transmembrane helices found at the N-terminus of COIII are missing in subunit III of the cytochrome bo_3 complex. The coun-

Table I

Comparison of ubiquinol and cytochrome c terminal oxidases

Type	Number of subunits	Number of coppers	Cu_A present[a]	Species	Reference(s)
Ubiquinol oxidases					
bo_3[b]	4–5	1	no	*Escherichia coli*	7,14,42
ba_3	4	1	no	*Acetobacter aceti*	43
aa_3	4	1	no	*Bacillus subtilis*	44,45
aa_3	1–3	2–3	no	*Sulfolobus acidocaldarius*	46,47,48,49
Cytochrome c oxidases					
aa_3[c]	3–13	2–3	yes		
ba_3	4[d]	2	yes	*Thermus thermophilus*	50
caa_3	2–4	2–3	yes	*T. thermophilus*	51,52
				Bacillus cereus	53
				Bacillus stearothermophilus	54
				Thermophilic bacillus PS3[e]	55,56
				B. subtilis	57

[a] The presence or absence of a Cu_A site has not been definitely confirmed in all cases. A best guess is made based on the present literature.
[b] This enzyme is expressed as a cytochrome oo_3 complex with little difference in activity in various overexpressing strains [42].
[c] The aa_3-type cytochrome c oxidase has been isolated from many organisms, from bacteria to mammals. See ref. 58 for a review.
[d] The cytochrome ba_3 complex was originally reported to contain one subunit but other investigators report four subunits [59].
[e] The PS3 enzyme is expressed as a cytochrome cao_3 complex with a 2-fold higher V_{max} under air-limited conditions [60].

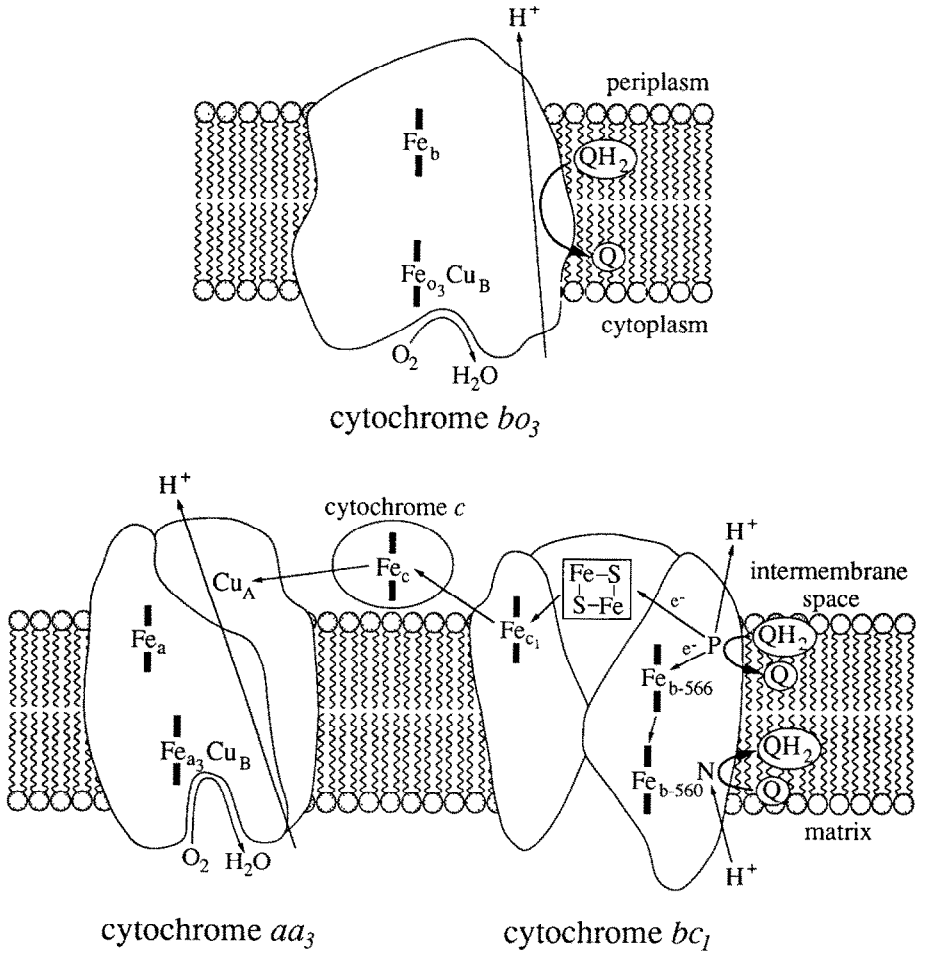

Fig. 1. Schematics of the electron transfer and proton translocation functions of the cytochrome bo_3, cytochrome aa_3 and cytochrome bc_1 complexes. Ubiquinol oxidation occurs at center P (P) of the cytochrome bc_1 complex and ubiquinone reduction occurs at center N (N).

terparts of *cyo*D and *cyo*E are found in the operons of bacterial aa_3-type oxidases but the homology is minimal [7,21]. In bacteria, COIV (corresponding to the gene product of *cyo*D) has been identified chemically only for the aa_3-type oxidase complex of PS3 [22,23]. A polypeptide analog of the *cyo*E gene product has not been found in purified cytochrome aa_3 complexes from bacteria.

4. THE UNDERLYING QUESTION

The reduced homology between the *cyo*ACDE gene products and the polypeptide counterparts of the aa_3-type oxidases relative to the extensive similarities between the largest polypeptides of the respective enzyme complexes leads us to the basic premise which we wish to address in this discussion: Do the structural differences in the remaining subunits serve merely to accommodate the different electron donors, or do they additionally reflect altered electron transfer mechanisms which result in unique physiological capabilities with respect to control of both electron transfer pathways and electron transfer mechanisms? Further, is the linkage between the various electron transfer events and the proton translocation capabilities of the respective enzymes, as well as the control of this linkage, affected by the structural differences of the two oxidases? In order to answer these questions, we first attempt to assess the magnitude of the difference in structure required to accommodate the two different electron donors for the bo_3- and aa_3-type oxidases.

5. THE SUBSTRATE BINDING SITES

The physiological substrate for the aa_3-type oxidases is the redox protein ferrocytochrome *c* (MW ~ 12 kDa), a water-soluble one-electron donor whereas that for the bo_3-type oxidases is the organic cofactor ubiquinol-8 (MW < 1 kDa), a very hydrophobic two-electron donor. The difference in size between the two substrates indicates that the binding domain for these electron donors on their respective proteins is expected to be much different with regards to size and shape. Thus, the binding domain for ferrocytochrome *c* is envisioned to be a negatively charged surface patch on the oxidase

complex [24] whereas ubiquinol-8 is expected to bind in a small hydrophobic pocket within the protein matrix. These structural differences, while significant, can be easily accommodated by appropriate sequence changes.

According to transient electron transfer studies, the primary electron input site in the aa_3-type oxidases is the Cu_A site [25–27]. This redox site is thought to be in the cytoplasmic domain of the enzyme complex [28]. Additionally, it is noteworthy, that Cu_A is the only redox site found in subunit II [29] and cytochrome *c* binding residues have been localized on this subunit [30–32]. Thus, Cu_A appears appropriately situated to act as an intermediary acceptor of electrons from aqueous ferrocytochrome *c*, subsequently donating electrons to the hemes and Cu_B in the more hydrophobic recesses of the enzyme in the membrane. In contrast, ubiquinol-8 is expected to be localized in the hydrophobic interior of the membrane bilayer. Thus, the binding domain for ubiquinol-8 is expected to be in a different three-dimensional location on the enzyme complex relative to the binding domain for ferrocytochrome *c*. This analysis implies that Cu_A may serve merely to funnel the electron into the 'catalytic core.' Since ubiquinol-8 can approach closer to the hemes and Cu_B in subunit I, the intermediary electron acceptor, Cu_A, becomes unnecessary. There is an alternative viewpoint, however, which we will discuss later.

6. ELECTRON TRANSFER PATHWAYS

Perhaps the most significant difference between the ferrocytochrome *c* and ubiquinol-8 substrates is that the former is a one-electron donor and the latter is a two-electron donor. This difference is relevant to the present analysis because it likely indicates different electron transfer mechanisms which in turn may reflect disparities in functional capabilities of the respective enzymes. The electron transfer between ferrocytochrome *c* and the aa_3-type oxidases is an outer-sphere process which merely requires that the two redox proteins approach within a given distance and in the correct orientation (i.e. the binding may be fleeting). On the other hand, one expects ubiquinol-8 to bind fairly strongly to the bo_3-type oxidases. More accurately, the ubisemiquinone-8 species must have a high affinity for the enzyme complex. The reason is, of course, that the semiquinone intermediate is a highly reactive species that must be stabilized by the enzyme complex in order to prevent non-productive electron transfer. We note that there is no precedent in biology for concerted two-electron transfer between an *unbound* quinol and a redox protein. It is possible for concerted two-electron transfer to proceed from a *bound* ubiquinol, however. For example, concerted inner-sphere electron transfer to the binuclear center is possible. Since the binuclear center is the site of dioxygen reduction, we consider it unlikely to be able to accommodate a bulky ubiquinol molecule in addition to the dioxygen intermediates. Thus, a situation in which electron transfer proceeds first to cytochrome *b* followed by subsequent electron transfer to the binuclear center appears more likely. Note that in this latter scenario, the oxidation of ubiquinol-8 cannot be concerted since ferricytochrome *b* is a one-electron acceptor. One might postulate two rapid one-electron transfers through cytochrome *b*, yet an evalution of the reduction potentials of ubiquinone and the cytochrome bo_3 complex indicates that this is probably not a feasible model.

Whereas the midpoint potentials of the four redox centers in the aa_3-type oxidases are all between ~ 250 and ~ 400 mV, the corresponding potentials for the cytochrome bo_3 complex are distributed over a much wider range. There is some disagreement in the literature, but recent data indicate that the room temperature midpoint potentials for cytochrome *b*, cytochrome o_3 and Cu_B are about 60, 220 and 400 mV, respectively [33,34]. The most obvious explanation for the requirement of the lower redox potential cytochromes *b* and o_3, especially the former, relative to cytochromes *a* and a_3, respectively, is the different redox potentials of the electron donors to the protein complexes. Ubiquinone has been estimated to have a midpoint reduction potential of about 60 mV in the inner mitochondrial membrane [35] while cytochrome *c* has a midpoint potential of about 250 mV [36]. Thus, cytochrome *b* appears to be well suited to be the primary electron acceptor from ubiquinol. One should remember, however, that the 60 mV midpoint reduction potential for ubiquinone is an average potential of the ubiquinone/ubisemiquinone and ubisemiquinone/ubiquinol couples. The former couple has the lower midpoint potential and the absolute difference between these couples is at least 80 mV [37] but could be as much as ~ 400 mV [38] depending on the protonation state of the ubisemiquinone intermediate. Thus, it is unlikely that cytochrome *b* can accept the first electron from ubiquinol (midpoint reduction potential for ubisemiquinone → ubiquinol is ≥ ~ 100 mV). On the other hand, the two electrons from ubiquinol may reduce the cytochrome bo_3 complex via a split electron transfer pathway (reminiscent of the Q cycle in the cytochrome bc_1 complex), the first electron going to the binuclear site and the second going to cytochrome *b* (Fig. 2). Note that in this scenario, the midpoint potentials of the donor and acceptor are more closely matched, as in the cytochrome bc_1 complex [38], promoting efficient electron transfer.

7. PROTON TRANSLOCATION MECHANISMS

In light of the above discussion, it is clear that some of the electron transfer mechanisms in the bo_3-type oxidases are necessarily different from those in the aa_3-type oxidases. The pertinent question to ask at this juncture, then, is whether these alternative mechanisms affect the

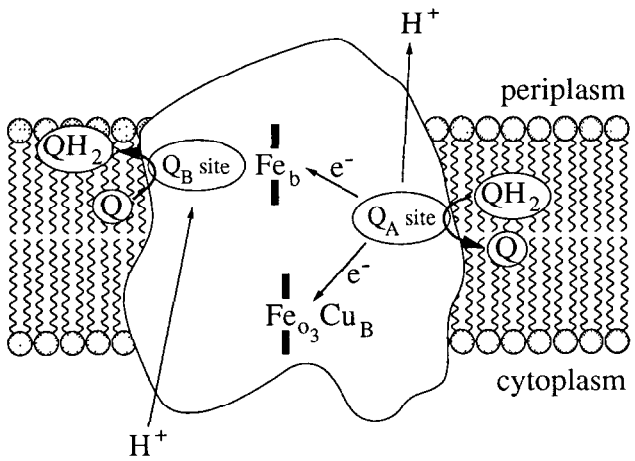

Fig 2. Schematic of a possible Q-loop mechanism in the cytochrome bo_3 complex. The Q_A site is like center P in the cytochrome bc_1 complex and the Q_B site is like center N. See text for details

functional capabilities of the enzyme in any significant way. For example, both enzyme complexes have been shown to catalyze the active transport of protons across the membrane in which they reside. Is the coupling mechanism between dioxygen reduction and proton translocation similar or different for the two enzymes, and if different, how so? For the translocation process to be identical, one would expect the binuclear center or cytochrome *a/b* to be the site of redox linkage. It is our opinion that the binuclear site is not the site of redox linkage, since the dioxygen chemistry occurs at the binuclear center, and the electron transfer between heme a_3/o_3 and Cu_B is likely very fast ruling out efficient coupling between electron transfer and the conformational changes that accompany the proton pump [39]. This leaves the low-spin heme as the site of redox linkage if the enzymes have similar proton translocation mechanisms. On the other hand, the two oxidases could have radically different proton translocation mechanisms. We note that the different proton transfer characteristics seen during dioxygen reduction for the two enzymes [20] support a scenario which invokes alternative translocation mechanisms. For example, the Cu_A site could somehow be involved in proton translocation in the aa_3-type oxidases, and a redox loop mechanism involving two ubiquinone/ubiquinol binding sites similar to that proposed for the cytochrome bc_1 complex could be operative in the bo_3-type oxidases (Fig. 2). Note that the cytochrome bo_3 complex combines the electron transfer processes of both the cytochrome bc_1 and aa_3 complexes (Fig. 1). Thus, to us, it is an attractive notion that the bo_3-type oxidases combine features from both the bc_1-(ubiquinone/ubiquinol redox loop) and aa_3-type oxidases (dioxygen chemistry). In this respect, the cytochrome bo_3 complex is similar to the cytochrome bc_1/cytochrome *c*/cytochrome aa_3 supercomplexes isolated from *P. denitrificans* [40] and PS3 [41] the latter complexes being the more evolved enzymes. Note that a redox loop mechanism necessarily requires two ubiquinone/ubiquinol binding sites (a testable proposal). Finally, we emphasize that these arguments may also apply to other less well characterized enzymes which lack a Cu_A site and exhibit quinol oxidase activity such as the cytochrome aa_3 ubiquinol oxidases from *B. subtilis* and *S. acidocaldarius* and the cytochrome ba_3 ubiquinol oxidase (originally termed cytochrome a_1) from *A. aceti* (Table I).

8. CONCLUSIONS

This discussion reveals that while the bo_3- and aa_3-type terminal oxidases are similar in some respects, other processes may in fact be quite different. Thus, it would be imprudent to assume, based on a few similarities, that the proteins are similar in all respects or that the differences are minor; such a view might lead us astray or inhibit us from designing appropriate experiments to decipher the function of these enzymes. While it is useful to point out similarities between proteins, we note that it is often the study of differences that yields greater insight. We hope that the issues brought up in this discussion serve to stimulate investigations directed at understanding the function of these exciting terminal oxidases.

Acknowledgements This work was supported by Grant GM22432 from the National Institute of General Medical Sciences, U. S. Public Health Service (SIC). SMM and MHBS are recipients of National Research Service Predoctoral Awards and MHBS is a recipient of an Albert L Raymond Fellowship.

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