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The cytochrome bc_1 complex and the evolution of membrane bioenergetics

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We have previously argued that the use of sodium ion gradient for ATP synthesis is the ancestral modality of membrane bioenergetics and that the Last Universal Cellular Ancestor (LUCA) was unlikely to have proton-dependent energetics [1–4].

The evolutionary primacy of the sodium-dependent membrane bioenergetics contradicts the common belief that the LUCA possessed several proton pumps, such as cytochrome oxidase and quinol: cytochrome c oxidoreductase, which are widespread among bacteria and archaea. To address this conundrum, we analyzed the phylogeny of the quinol: cytochrome c oxidoreductases (cytochrome bc_1 complexes) and showed that the phylogenetic tree of quinol: cytochrome c oxidoreductases did not follow the 16S rRNA tree. We suggest that the common ancestor of the quinol: cytochrome c oxidoreductases evolved within bacteria from a membrane quinone oxidoreductase analogous to the complex II, perhaps in response to the emergence of chlorophyll-based photosynthesis. Different archaeal phyla seem to have acquired different types of quinol: cytochrome c oxidoreductases from bacteria by lateral gene transfer on several independent occasions. A similar scenario has been proposed for the evolution of the cytochrome oxidases [5].

References

[1] A.Y. Mulkidjanian, M.Y. Galperin, K.S. Makarova, Y.I. Wolf, E.V. Koonin, Evolutionary primacy of sodium bioenergetics, Biol. Direct 3 (2008) 13.
[2] A.Y. Mulkidjanian, P. Dibrov, M.Y. Galperin, The past and present of sodium energetics: may the sodium-motive force be with you, Biochim. Biophys. Acta 1777 (2008) 985–992.
[3] A.Y. Mulkidjanian, M.Y. Galperin, E.V. Koonin, Co-evolution of primordial membranes and membrane proteins, Trends Biochem. Sci. 34 (2009) 206–215.
[4] D.V. Dibrova, M.Y. Galperin, A.Y. Mulkidjanian, Characterization of the N-ATPase, a distinct, laterally transferred Na^+-translocating form of the bacterial F-type membrane ATPase, Bioinformatics 26 (2010) 1473–1476.
[5] J. Hemp, R.B. Gennis, Diversity of the heme-copper superfamily in archaea: insights from genomics and structural modeling, Results Probl. Cell Differ. 45 (2008) 1–31.

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Effects of ascochlorin on the yeast *Candida albicans*

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Ascochlorin and ascofuranone are antibiotics produced by the phytopathogenic fungus *Ascochyta viciae*, and both have closely related prenylphenol structures like ubiquinol. Ascofuranone specifically inhibits trypanosome alternative oxidase, and is considered to be a promising candidate as a chemotherapeutic agent against African trypanosomiasis. On the other hand, ascochlorin specifically acts at Q_i and Q_o sites of cytochrome bc_1 complex [1] to inhibit the electron transport. We report the effects of ascochlorin on the pathogenic yeast *Candida albicans*.

Ascochlorin also acted on the cytochrome bc_1 complex to inhibit the cyanide-sensitive respiration of *C. albicans* as well as antimycin A, stigmatellin, and myxothiazol. Further, ascochlorin induces the expression of nuclear-encoded cyanide-resistant alternative oxidase gene, and inhibits the alternative oxidase activity. However, the inhibitory effect was weaker (about 20%) than that of ascofuranone. Interestingly, the amino acid residues of alternative oxidase involved in the inhibitor (or ubiquinol)-binding are completely different from those of cytochrome bc_1 complex. Therefore, ascochlorin inhibits both respiratory electron transports (cyanide-sensitive and cyanide-resistant) in this yeast.

To examine the effects of respiratory inhibitors, *C. albicans* was cultivated using a variety of carbon sources (glucose, acetate, ethanol et al.) at several concentrations. Under all conditions tested, among the respiratory inhibitors, antimycin A showed the most potent inhibition on the aerobic growth, which was slightly increased by the combined addition of ascofuranone. Ascochlorin had a little bit lesser growth inhibition, which was increased in the presence of ascofuranone.

These results suggest that antimycin A induces little alternative oxidase gene expression in spite of its helpful role in the aerobic growth. Although ascochlorin was able to inhibit alternative oxidase activity, this antibiotic induces alternative oxidase gene expression to transport electrons to oxygen, thereby making a contribution to the aerobic energy metabolism in *C. albicans*.

[1] Biochim. Biophys. Acta, 1797, 360–370, 2010.

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Inter- and intra-monomeric communication in the cytochrome bc_1 complex as studied by molecular dynamics simulations

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The cytochrome bc_1 complex (bc_1) acts as a homodimeric proton translocase, as reviewed in [1]. It oxidizes ubiquinol molecules (Q_P) in the catalytic centers *P* via bifurcated reaction and reduces two distinct substrates: the FeS cluster of the Rieske protein and, via the two hemes *b*, the ubiquinone molecule located in another quinone binding site *N* (Q_N), (according to the Mitchell's Q-cycle [2]).

Earlier we have shown that the reaction in the Q_P site is kinetically coupled with the quinone reduction in the Q_N site, so that the relocation of the FeS domain towards its electron acceptor cytochrome c_1 happens only after the ubiquinol formation in the center *N* [3–5]. However, the mechanism of the suggested intra-monomer and