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Review

Energy-converting respiratory Complex I: On the way to the molecular mechanism of the proton pump

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This work is dedicated to the memory of Michael Verkhovsky, whose ideas and studies it is based upon.

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ABSTRACT

In respiring organisms the major energy transduction flux employs the transmembrane electrochemical proton gradient as a physical link between exergonic redox reactions and endergonic ADP phosphorylation. Establishing the gradient involves electrogenic, transmembrane H^+ translocation by the membrane-embedded respiratory complexes. Among others, Complex I (NADH:ubiquinone oxidoreductase) is the most structurally complex and functionally enigmatic respiratory enzyme; its molecular mechanism is as yet unknown. Here we highlight recent progress and discuss the catalytic events during Complex I turnover in relation to their role in energy conversion and to the enzyme structure.

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Abbreviations: *cyt*, cytochrome; E_h, apparent redox potential; E_m, midpoint redox potential; EPR, electron paramagnetic resonance; eT, electron transfer; N, negatively charged membrane side, facing bacterial cytoplasm or mitochondrial matrix; P, positively charged membrane side, facing bacterial periplasm or mitochondrial intermembrane space; *pmf*, proton-motive force; pT, proton transport; Q, quinone; QH_2, quinol; ROS, reactive oxygen species; TMS, transmembrane segment; UQ, ubiquinone; UQH_2, ubiquinol; $\Delta\mu_{H^+}$, standard transmembrane electrochemical potential of protons; $\Delta\tilde{\mu}_{H^+}$, transmembrane electrochemical potential of protons; $\Delta\tilde{\mu}_{Na^+}$, transmembrane electrochemical potential of sodium ions; $\Delta\psi$, transmembrane electric potential; ε, protein dielectric constant; τ, apparent time constant.

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1. Introduction: mitochondrial and bacterial respiratory chains

Cell respiration is the most efficient energy-transforming system in mitochondria and in many respiring bacteria. The process couples the highly exergonic electron transfer (oxidation of respiratory substrates) to the highly endergonic formation of ATP from ADP and phosphate (often referred to as "ATP synthesis"; oxidative phosphorylation) and some other types of cellular work. The two general principles of the process are the following:

(i) The source of energy for metabolism is the redox reaction between the electron donor and acceptor. The vast majority of electron donors (respiratory substrates) are derived from photosynthetically formed reduced organic compounds, e.g. carbohydrates; for the aerobic life, the almost universal electron acceptor is molecular oxygen;
(ii) The physical link between redox and phosphorylation parts of the process is the transmembrane electrochemical potential of protons, $\Delta\tilde{\mu}_{H^+}$ (proton-motive force, or *pmf*; in certain special cases in bacteria, also the gradient of Na^+ ions, $\Delta\tilde{\mu}_{Na^+}$). The $\Delta\tilde{\mu}_{H^+}$ is established as a result of transmembrane translocation of H^+ by the respiratory complexes (Complexes I, III, and IV) and consumed by H^+- (or Na^+-) motive ATP synthase. Since the electrogenic nature of proton translocation, both electric ($\Delta\psi$ [mV]) and chemical (pH gradient, $59 \times \Delta$pH [mV] at +20 °C) components contribute to $\Delta\tilde{\mu}_{H^+}$. Although the two forms are thermodynamically convertible, the primary form is, however, the electric potential established between the two aqueous compartments separated by the lipid bilayer membrane; the formation of ΔpH requires work against buffering capacity of both transmembrane compartments.

About 90% of ATP production in the cell comes from oxidative phosphorylation coupled to cell respiration. Textbook values for oxidation of 1 molecule of glucose in mammalian mitochondria give 38 ATP molecules, 34 of which are formed by oxidative phosphorylation. (The real values may be slightly less due to the revised mechanistic H^+/P or P/e^- ratios for H^+-ATPase Watt et al., 2010; Wikström and Hummer, 2012.) Note that in respiring bacteria the stoichiometries may differ significantly due to the variation in the mechanistic H^+/P ratio of H^+-ATPase (Steigmiller et al., 2008; Lau and Rubinstein, 2012).

Most of the redox energy entering aerobic metabolism is supplied via NADH produced by the Krebs cycle (but also, to a lesser degree, from fatty acid oxidation, protein degradation, and glycolysis). The midpoint redox potential (E_m) values for glucose and NADH differ only slightly (see Table 1), so almost all energy is preserved in the form of NADH (contribution from $FADH_2$ and succinate is negligible, in comparison, from the point of view of energy conservation). Energy provided from the oxidation of NADH by oxygen is given by the difference between the respective E_m of the electron acceptor and donor[1]:

$$\Delta E_m \approx (+820\,\text{mV}) - (-320\,\text{mV}) = +1140\,\text{mV}$$

(pH 7, 1 atm O_2). The respective standard free energy drop for this reaction is given by

$$\Delta G^\circ(\text{kJ/mol}) = -n \times 0.0961 \times \Delta E_m(\text{mV})$$

or

$$\Delta G^\circ(\text{meV}) = -n \times \Delta E_m(\text{mV})$$

where n is the stoichiometric number of electrons participating in the reaction. For the oxidation of one NADH molecule by O_2, $\Delta G^\circ = -119$ kJ/mol (Table 1). Taking into account the experimentally measured value of ATP production in mitochondria (~2.27 ATP per NADH Hinkle, 2005), this gives 52.5 kJ/mol per ATP molecule (a typical literature value for the formation of 1 ATP molecule from ADP and P_i under "average" cellular condition is 57 kJ/mol). For the lossless (ideal) electrochemical coupling, the electrogenic, transmembrane H^+ translocation driven by a redox reaction with standard free energy ΔG° causes standard electrochemical potential:

$$|\Delta\mu_{H^+,\max}|(\text{mV}) = \frac{|\Delta G^\circ|}{n}(\text{meV}) \equiv |\Delta E_m|(\text{mV})$$

giving 1.14 V for the oxidation of one NADH molecule by O_2. At physiological conditions the value may differ due to the concentration ratio factors:

$$\Delta G = \Delta G^\circ - 59 \times lg\frac{[\text{electron donor}^{\text{reduced}}]}{[\text{electron donor}^{\text{oxidized}}]} + 59 \times lg\frac{[\text{electron acceptor}^{\text{reduced}}]}{[\text{electron acceptor}^{\text{oxidized}}]},$$

or

$$|\Delta\tilde{\mu}_{H^+,\max}|(\text{mV}) = \frac{|\Delta G|}{n}(\text{meV}) \equiv |\Delta E_h|(\text{mV})$$

and for the oxidation of NADH it is less than the standard value; however, keeping in mind that the electrical contribution in $\Delta\tilde{\mu}_{H^+}$ predominates, the transmembrane electric potential is still rather large. Pure lipid is excellent electrical insulator; the resistance of a typical artificial bilayer lipid membrane is ~1 GΩ. Being directly applied across the lipid bilayer membrane (average thickness, defined as the distance between the acyl carbonyl groups, is 36 Å) such $\Delta\psi$ supplies electric field of ~290 kV × cm^{-1}. However, in biological membranes containing many membrane-embedded or membrane-associated proteins, the tolerance of the bilayer to electric field, though dependent on the source of lipid, is typically much weaker. For example, in mitochondria or *Escherichia coli* cells, a typical maximum $\Delta\psi$ value sustained by the membrane ranges from 220 to 250 mV. At higher voltage the membrane loses its integrity and its conductivity sharply rises leading to a short-circuit and electrical damage. This poses a problem of efficient generation and use of the electric field coupled to the respiratory redox process; an obvious solution is to split the whole voltage span (1.14 V) into several, mechanistically coupled voltage generators, each of which can only generate smaller field. The latter principle is indeed realized in the real respiratory chain (Rich and Maréchal, 2010; Jastroch et al., 2010; Nicholls, 2010).

Mitochondrial respiratory electron transfer chain (Fig. 1) consists of three enzymes catalyzing linear, sequential electron transfer (eT) from NADH through ubiquinol (UQH_2) and cytochrome (cyt) *c*

[1] All redox potentials quoted are expressed versus normal hydrogen electrode (NHE) scale.

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