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Exploring membrane respiratory chains☆

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ABSTRACT

Acquisition of energy is central to life. In addition to the synthesis of ATP, organisms need energy for the establishment and maintenance of a transmembrane difference in electrochemical potential, in order to import and export metabolites or to their motility. The membrane potential is established by a variety of membrane bound respiratory complexes. In this work we explored the diversity of membrane respiratory chains and the presence of the different enzyme complexes in the several phyla of life. We performed taxonomic profiles of the several membrane bound respiratory proteins and complexes evaluating the presence of their respective coding genes in all species deposited in KEGG database. We evaluated 26 quinone reductases, 5 quinol:electron carriers oxidoreductases and 18 terminal electron acceptor reductases. We further included in the analyses enzymes performing redox or decarboxylation driven ion translocation, ATP synthase and transhydrogenase and we also investigated the electron carriers that perform functional connection between the membrane complexes, quinones or soluble proteins. Our results bring a novel, broad and integrated perspective of membrane bound respiratory complexes and thus of the several energetic metabolisms of living systems. This article is part of a Special Issue entitled 'EBEC 2016: 19th European Bioenergetics Conference, Riva del Garda, Italy, July 2–6, 2016', edited by Prof. Paolo Bernardi.

1. Introduction

In vertebrates, energy is generated in mitochondria by the process of oxidative phosphorylation. During the oxidation of nutrients such as glucose, amino acids or fatty acids, reduced metabolites with low reduction potentials, such as NADH or succinate, are produced in the mitochondrial matrix. These reduced metabolites provide electrons to the respiratory chain, placed in the inner mitochondrial membrane, which are conducted through several electron carriers and protein complexes containing redox centers with progressively higher reduction potential, until the final electron acceptor, O_2. According to the Chemiosmotic hypothesis, postulated by Peter Mitchell in 1961, the free-energy obtained by the reactions performed by respiratory complexes is used to translocate protons from the mitochondrial matrix to the intermembrane space, in order to create a transmembrane difference in electrochemical potential[1] [1]. The energy stored by this electrochemical potential is subsequently used by ATP synthase for the synthesis of adenosine triphosphate (ATP), by transhydrogenase for the reduction of $NADP^+$ by NADH and by transporters to import or export metabolites.

Abbreviations: ACIII, Alternative Complex III; ADH, Alcohol dehydrogenase; ALDH, Aldehyde dehydrogenase; AMO, Ammonia monooxygenase; AOX, Alternative oxidase; CISM, Complex Iron-Sulfur Molybdoenzyme; DAADH, D-amino acid dehydrogenase; DHODH, dihydroorotate dehydrogenase; DmsABC, DMSO reductase; DMSO, dimethyl sulfoxide; Dsr, dissimilatory sulfite reductase; ETF-QO, electron transfer flavoprotein:quinone oxidoreductase; Fdn-N, Formate dehydrogenase-N; GADH, D-glyceraldehyde dehydrogenase; GLDH, Glycerol dehydrogenase; G3PDH, Glycerol-3-phosphate dehydrogenase; HCO, heme–copper oxygen reductase; HDR, heterodisulfide reductase; HiPIP, High-Potential Iron–sulfur Protein; LQO, Lactate:quinone oxidoreductase; MQ, menaquinone; mPPase, membrane-bound pyrophosphatase; Mtr, Methyltetrahydromethanopterin-coenzyme M methyltransferase; mGDH, membrane-bound Glucose dehydrogenase; MQO, malate:quinone oxidoreductase; Nap, periplasmic nitrate reductase; Nar, nitrate reductase; NDH-2, type II NADH:quinone oxidoreductase; Nhc, nine-heme cytochrome; NOR, nitric-oxide reductase; NQR, Na^+-translocating NADH:quinone oxidoreductase; Nrf, cytochrome *c* nitrite reductase; OAD, oxaloacetate decarboxylase; PhsABC, Thiosulfate reductase; pMMO, particulate membrane-associated methane monooxygenase; Pnt, membrane-bound nicotinamide nucleotide transhydrogenase; PP, pyrophosphate; PPOR, protoporphyrinogen IX:quinone oxidoreductase; PQ, plastoquinone; PQO, pyruvate:quinone oxidoreductase; PRODH, L-Proline: quinone oxidoreductase; Qmo, quinone-interacting membrane-bound oxidoreductase complex; PsrABC, polysulfide reductase; QRC, quinone reductase complex; Rnf, ion-translocating ferredoxin:NAD^+ oxidoreductase or ferredoxin:methylphenazine oxidoreductase; SDH, succinate dehydrogenase; SLDH, D-sorbitol dehydrogenase; SQR, sulfide:quinone oxidoreductase; TMAO reductase, quinol:trimethylamine N-oxide oxidoreductase; TQO, Thiosulfate:quinone oxidoreductase; TtrABC, tetrathionate reductase; UQ, ubiquinone.

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[1] For practicality, from now on, we will refer to the transmembrane difference in electrochemical potential as membrane potential.

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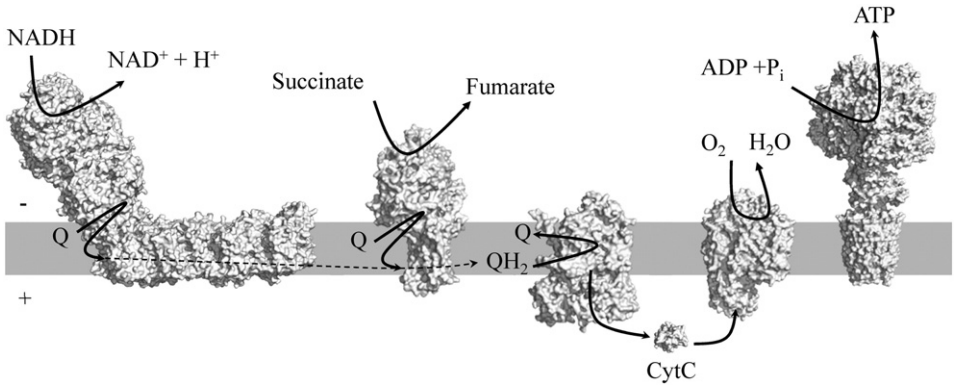

Fig. 1. Mitochondrial respiratory chain. Schematic representation of the classic mitochondrial respiratory complexes. The electron donors, NADH and Succinate, are oxidized by Complexes I and II, respectively, with concomitant reduction of quinone to quinol. Complex III oxidizes quinol and reduces cytochrome *c*. Complex IV oxidizes cytochrome *c* and reduces oxygen to water. Complexes I, III and IV contribute to the establishment of the transmembrane difference in electrochemical potential by translocating protons across the membrane. This membrane potential is used by Complex V for the synthesis of ATP (+ and – indicate the positive and negative sides of the transmembrane difference in electrochemical potential, respectively).

1.1. Mitochondrial respiratory chains in mammals

The canonical respiratory chain of mammals consists of four multisubunit protein complexes, Complexes I, II, III and IV and of the mobile electron carriers: ubiquinone and cytochrome *c* (Fig. 1). Electrons obtained from the oxidation of NADH enter the respiratory chain at the level of Complex I (NADH:ubiquinone oxidoreductase). This enzyme catalyzes the two electron oxidation of NADH and the reduction of ubiquinone to ubiquinol, coupled to the translocation of possibly four protons from the mitochondrial matrix to the intermembrane space, contributing in this way to the establishment of the membrane potential. Mitochondrial Complex I consists of 14 core subunits and 30 accessory subunits [2]. Complex II (succinate:quinone oxidoreductase or succinate dehydrogenase, SDH) is constituted by four subunits and catalyzes the two-electron oxidation of succinate to fumarate with the reduction of ubiquinone to ubiquinol [3]. This reaction is not coupled to charge translocation. Besides Complexes I and II, at least three other single subunit enzymes in mammalian mitochondria feed electrons to the quinone/quinol pool without involving proton translocation across the membrane: Electron transfer flavoprotein:ubiquinone oxidoreductase (ETF-QO), which oxidizes electron transfer flavoprotein (ETF) and mediates the electron transfer between different mitochondrial flavoprotein dehydrogenases and the quinone/quinol pool [4]; glycerol-3-phosphate dehydrogenase (G3PDH), which catalyzes the oxidation of glycerol-3-phosphate, and dihydroorotate dehydrogenase (DHODH), involved in pyrimidine biosynthesis [5]. Complex III (ubiquinol:cytochrome *c* oxidoreductase or cytochrome bc_1 complex) catalyzes the electron transfer from ubiquinol to cytochrome *c*, coupled to the translocation of two protons per oxidized ubiquinol across the inner mitochondrial membrane, contributing directly to the generation of the membrane potential [5]. In mitochondria of mammals, Complex III contains 11 subunits [6]. The final step in the mammalian mitochondrial respiratory chain is the transfer of electrons from reduced cytochrome *c* to O_2, forming 2 H_2O molecules. This four electrons reaction is catalyzed by Complex IV (cytochrome *c* oxidase, or cytochrome *c*:oxygen oxidoreductase), which pumps $4H^+$ per 4 e^- across the membrane [7]. Mitochondrial Complex IV is composed of two catalytic subunits and 11 additional subunits [5].

1.2. Non mammal mitochondrial respiratory chains—plants, fungi and protists

The classic electron transport chain in plant mitochondria is similar to that of animal mitochondria: it comprises the four core complexes, Complexes I, II, III and IV. Complex I is composed of up to 50 subunits, 17 of which are different from the mammalian homologue [8–9]. One of those distinct components was identified as a carbonic anhydrase [10]. Complex II is composed of four subunits and other additional proteins of unknown function in plants [8]. Ubiquinol produced by Complexes I and II is oxidized by Complex III, ubiquinone:cytochrome *c* oxidoreductase or cytochrome bc_1 Complex [11]. Plant Complex IV also shows supplementary proteins [8].

Plants' electron transfer chain also includes an alternative oxidase (AOX), which catalyzes the reduction of oxygen to water directly from quinol oxidation and without proton translocation across the membrane. The expression of AOX is manifested by the ability of plants to respire in the presence of cyanide, a potent inhibitor of Complex IV [9]. Additionally, several dehydrogenases can directly transfer electrons to ubiquinone such as alternative NAD(P)H dehydrogenases (type II NADH:quinone oxidoreductase, NDH-2), G3PDH and ETF-QO [8–9].

Mitochondrial electron transport chains of fungi and protozoa also contain protein complexes similar to those of the classic mammalian mitochondrial chain, Complexes I, II, III and IV [12–14]. Most fungal mitochondria have the classic respiratory chain, but some fungi, such as *Saccharomyces cerevisiae*, lack Complex I [15]. Instead, these fungi have genes encoding NDH-2s [16]. Also usually, fungi have additional components, such as AOX [17–18]. Fungal parasites, like obligate intracellular Microsporidians, lack genes for energy metabolism and are strictly dependent on the host for energy. They uptake ATP from their host cells via ADP/ATP translocases located in their plasma membranes [19]. Several filamentous fungi are able to survive in anoxic conditions, being capable to produce ATP using nitrogen or sulfur as final electron acceptor [20–21]. *Fusarium oxysporum*, from the Ascomycetes phylum has the ability to reduce nitrate to nitrous oxide, in a process coupled to ATP synthesis in the mitochondria, which is catalyzed by nitrate reductase, nitrite reductase and nitric oxide reductase [20,22]. *F. oxysporum* is also able to reduce inorganic sulfur to hydrogen sulfide by a NADH-dependent sulfur reductase [21]. Some anaerobic fungi, such as *Neocallimastix patriciarum*, lack mitochondria. Instead, they possess hydrogen and ATP-generating organelles called hydrogenosomes [23].

Protists may experience different environments and are able to live as free living organisms, parasites or symbionts of multicellular eukaryotes. For example, the free living aerobic amoeboflagellate *Naegleria gruberi* possesses the canonical mitochondrial respiratory enzymes and in addition it has NDH-2 and AOX [24]. *Euglena gracilis*, a single-celled flagellate protist, has typical eukaryotic mitochondria but includes lactate:quinone oxidoreductase (LQO) and AOX [25–26]. In *Pygsuia biforma*, an amoeba-like organism, ETF-QO, G3PDH and AOX are components of its respiratory chain [27]. A number of pathogenic protist species from low oxygen habitats, including *Trichomonas vaginalis*, *Giardia intestinalis* and *Entamoeba histolytica*, lack typical mitochondria [28–31]. For example, *T. vaginalis* instead of mitochondria contains hydrogenosomes, which produce hydrogen as an end product

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