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Review

The power of life—Cytochrome c oxidase takes center stage in metabolic control, cell signalling and survival

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ABSTRACT

Mitochondrial dysfunction is increasingly recognized as a major factor in the etiology and progression of numerous human diseases, such as (neuro-)degeneration, ischemia reperfusion injury, cancer, and diabetes. Cytochrome c oxidase (COX) represents the rate-limiting enzyme of the mitochondrial respiratory chain and is thus predestined for being a central site of regulation of oxidative phosphorylation, proton pumping efficiency, ATP and reactive oxygen species production, which in turn affect cell signaling and survival. A unique feature of COX is its regulation by various factors and mechanisms interacting with the nucleus-encoded subunits, whose actual functions we are only beginning to understand.

Contents

Abbreviations: ATP, adenosine 5′-triphosphate; COX, cytochrome c oxidase; Δp_m, proton motive force; $\Delta\Psi_m$, mitochondrial membrane potential; H_2S, hydrogen sulphur; MPP^+, 1-methyl-4-phenylpyridinium; NO, nitric oxide; NPA, 3-nitropropionic acid; 6-OHDA, 6-hydroxydopamine; ROS, reactive oxygen species; T2, 3,5-diiodo-L-thyronine.

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1. Structural and functional aspects of the mammalian cytochrome c oxidase

Cytochrome c oxidase (COX, complex IV, EC 1.9.3.1.) is the terminal enzyme of the respiratory chain and responsible for reduction of 95% of the oxygen taken up by aerobically growing higher organisms. The dimeric mammalian enzyme is controlled by both nuclear and mitochondrial genomes. Among its 13 subunits per monomer (Tsukihara et al., 1996), 3 are encoded by mitochondrial DNA and 10 by nuclear DNA (Fig. 1; nomenclature of Kadenbach et al., 1983). The mitochondria-encoded COX subunits contain the three almost identical between different species catalytic centers of the enzyme and are essential and sufficient for the catalytic COX activity in eukaryotes and prokaryotes (Babcock and Wikström, 1992; Ferguson-Miller and Babcock, 1996; Ostermeier et al., 1997; Yoshikawa et al., 1998). In both enzymes, subunit II contains the two-copper center Cu_A which is the binding site for cytochrome c. Heme a and the oxygen binding heme a_3/Cu_B centers are located in subunit I. The catalytic functions imply the transfer of electrons from ferrocytochrome c to oxygen, accompanied by the vectorial uptake of protons for the formation of water and the outward translocation of protons building up a proton gradient across the inner mitochondrial membrane as part of the mitochondrial membrane potential ($\Delta\Psi_m$). The proton gradient serves the phosphorylation of ADP and inorganic phosphate to ATP through the F0F1-ATP synthase. Both the proton gradient and ATP can, therefore, be considered as products of the COX reaction. The catalytic activities of the mammalian and bacterial enzymes are similar when studied as isolated enzymes under standard conditions (Hendler et al., 1991). However, large differences in the catalytic activities occur between the two enzymes under more physiological conditions indicating a significant role of nucleus-encoded subunits of the eukaryotic COX complex in electron transport and proton pumping (Kadenbach, 1986; Kadenbach et al., 2000; Ludwig et al., 2001).

2. Regulation of cytochrome c oxidase

Mitochondria are the main producers of ATP in eukaryotic cells and as such they fulfil the cellular energy demand. The control of respiration is explained by the chemiosmotic hypothesis which is also named "respiratory control" and means that the rate of respiration and ATP synthesis is controlled by the intermediate product of oxygen reduction and ATP synthesis. Mitchell (1961) determined the proton motive force Δp_m of the transmembrane proton gradient as a universal principle of energy storage in all organisms. The transmembrane electrochemical potential $\Delta\mu H^+$ consists mainly of the transmembrane electrical potential $\Delta\Psi_m$ and the transmembrane proton gradient ΔpH (Mitchell, 1961). Thus, "respiratory control" is reflected as inhibition of the mitochondrial

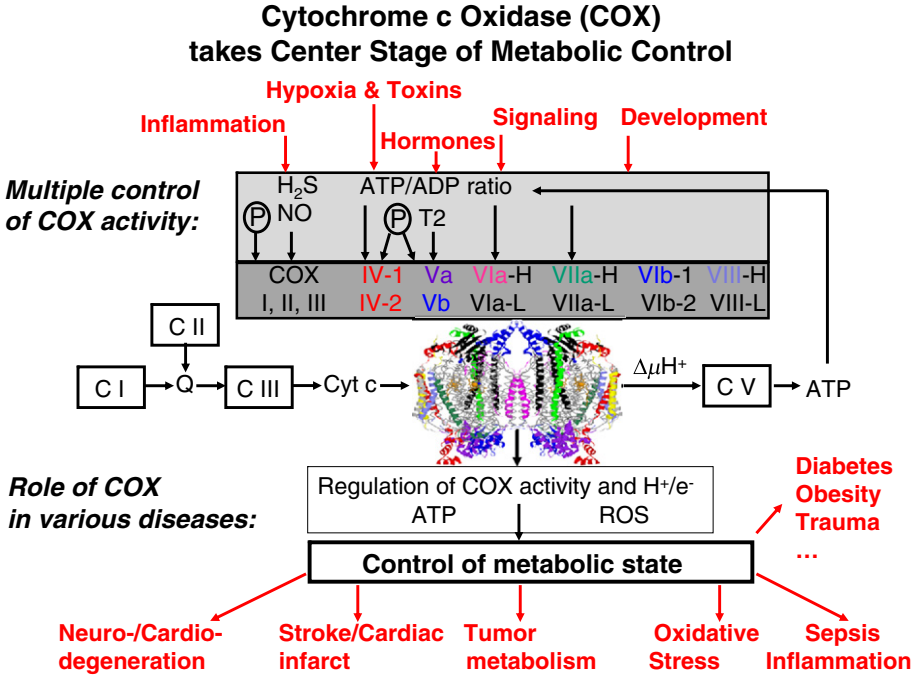

Fig. 1. Schematic representation of cytochrome c oxidase taking center stage of metabolic control. Cytochrome c oxidase (COX) is positioned in the center of the scheme. Crystallographic data of dimeric bovine heart COX (Tsukihara et al., 1996) were taken from PDB entry 1OCC and processed with the software program RASMOL 2.7 (centred; mitochondrial matrix is located at the bottom of the COX crystal structure, the intermembrane space at the top). The three mitochondria-encoded, catalytic subunits in each monomer are represented as peptide backbone traces (grey) with their redox centers highlighted in blue (copper atoms of Cu_A and Cu_B centers) and orange (heme a and a3). The helices of the 10 nucleus-encoded, regulatory subunits are depicted in color (IV—red, Va—purple, VIa—magenta, VIIa—green, VIb—blue, VIII—light-blue). Black arrows pointing from respiratory chain complexes I–III (C I–C III) via ubiquinone (Q) further to cytochrome c (cyt c) and COX indicate the electron transfer, which serves to build up a proton gradient ($\Delta\mu H^+$) across the inner mitochondrial membrane, and which in turn is used to drive the ATP synthase (C V). The produced ATP can be considered as an indirect product of COX catalysis and functions as an allosteric inhibitor of COX activity in a negative feedback reaction (arrow directing to ATP/ADP ratio in the upper panel). Upper panel: Multiple effectors, such as phosphorylation (P), H_2S, NO, ATP/ADP ratio, 3,5-diiodothyronine (T2) resulting from physiological and/or pathological processes (inflammation, hypoxia, exposure to mitochondrial (neuro-) toxins, such as azide, cyanide, cobalt, NPA, 6-OHDA, MPP^+, and hormones (e.g., T2), and signalling or developmental processes) interact with nucleus-encoded regulatory COX subunits (IV–VIII, indicated by black arrows). COX subunits known to be expressed as isoforms (IV, VIa, VIIa, VIb, VIII) are listed and depicted in subunit-specific color. Lower panel: The interaction of effector molecules with COX subunits induces various regulatory mechanisms affecting COX activity and H^+/e^-stoichiometry which in turn influence on the whole respiratory chain with respect to COX being the key and rate-limiting respiratory chain complex. This metabolic control exerted by COX affects ATP and ROS production in the respiratory chain. Subsequently, the metabolic control by COX leads to physiological and/or pathological signalling, protecting from, promoting or inducing diseases, such as neurodegeneration. For further explanations and references, see text.