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Review

Respiratory chain supercomplexes: Structures, function and biogenesis

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ABSTRACT

Over the past sixty years, researchers have made outmost efforts to clarify the structural organization and functional regulation of the complexes that configure the mitochondrial respiratory chain. As a result, the entire composition of each individual complex is practically known and, aided by notable structural advances in mammals, it is now widely accepted that these complexes stablish interactions to form higher-order supramolecular structures called supercomplexes and respirasomes. The mechanistic models and players that regulate the function and biogenesis of such superstructures are still under intense debate, and represent one of the hottest topics of the mitochondrial research field at present. Noteworthy, understanding the pathways involved in the assembly and organization of respiratory chain complexes and supercomplexes is of high biomedical relevance because molecular alterations in these pathways frequently result in severe mitochondrial disorders. The purpose of this review is to update the structural, biogenetic and functional knowledge about the respiratory chain supercomplexes and assembly factors involved in their formation, with special emphasis on their implications in mitochondrial disease. Thanks to the integrated data resulting from recent structural, biochemical and genetic approaches in diverse biological systems, the regulation of the respiratory chain function arises at multiple levels of complexity.

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Abbreviations: MRC, mitochondrial respiratory chain; CoQ, coenzyme Q or ubiquinone; cyt*c*, cytochrome *c*; SC, supercomplex; CI-CIV, respiratory chain complexes I to IV; $CIII_2$, dimeric CIII; CV, ATP synthase; BN-PAGE, blue native gel electrophoresis; EM, electron microscopy.

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1. Introduction

Recent investigations have shed light into the sophistication surrounding the biogenesis of the oxidative phosphorylation (OXPHOS) system. In mammals, the OXPHOS system is formed by five multiprotein enzyme complexes and two mobile electron carriers embedded in the inner mitochondrial membrane. The first four enzyme complexes (CI-CIV) comprise the mitochondrial respiratory chain (MRC), which facilitates electron transfer from reducing equivalents to molecular oxygen coupled to the generation of a proton gradient across the inner membrane that will be used by the ATP synthase (complex V) to drive ATP synthesis. In addition to their structural subunits, the biogenesis of these five hetero-oligomeric enzymatic complexes requires an extensive number of ancillary factors to coordinate subunits maturation, incorporation of prosthetic groups and assembly into the holoenzymes. The discovery that some MRC enzymes physically interact to form a variety of supramolecular structures called supercomplexes (SCs) and respirasomes, and the existence of SC-specific assembly factors involved in their assembly, has put the spotlight on the structural and functional properties of the SCs, and on the regulatory pathways involved in their biogenesis. It is currently debated whether SCs play a relevant functional role in cellular bioenergetics, in the formation of reactive intermediates, or in the stabilization of the individual MRC complexes. Since genetic alterations in MRC subunits and assembly factors often lead to severe encephalomyopathies and neurodegenerative disorders, a full understanding of the structural organization and biosynthetic regulation of the MRC is essential to understand the molecular mechanisms underlying mitochondrial pathology. In this review we will explore the current knowledge on mammalian respiratory SCs, integrating the historical perspective with the most recent structural findings, and putting this information in the context of mitochondrial disease.

2. Mitochondrial respiratory chain, a long-lasting journey

2.1. Composition and function of the respiratory chain

The production of adenosine 5′-triphosphate (ATP), the key energy source of the cell, through aerobic substrate oxidation is the main function of the mitochondrial metabolism. In the late 50s, several redox enzymes and prosthetic groups responsible for the classic mitochondrial electron transfer chain were defined [1] followed by their reconstitution in the early 60 s [2]. The overall respiratory chain activity was postulated as a sequential transfer of electrons between four major multi-enzymatic complexes dispersed in the inner mitochondrial membrane (IMM): NADH dehydrogenase:ubiquinone oxidoreductase (complex I, CI), succinate:ubiquinone oxidoreductase (complex II, CII), ubiquinol:cytochrome *c* oxidoreductase or cytochrome *bc1* complex (complex III, CIII), and cytochrome *c* oxidase (complex IV, CIV). In addition, the electron transfer was ensured by the diffusion of two mobile components acting as co-substrates: the lipophilic ubiquinone, also designated as coenzyme Q (CoQ), embedded in the membrane lipid bilayer, and the hydrophilic heme protein cytochrome *c* (cyt*c*) located on the external surface of the IMM [3,4]. Altogether, these components form the mitochondrial respiratory chain (MRC) where cellular respiration takes place. Organic nutrients are catabolized into small electron donor molecules, $NADH_2$ and $FADH_2$, which transfer the electrons to CI and CII, respectively. CoQ uptakes the electrons from both sources, transferring them to dimeric CIII ($CIII_2$), then to cyt*c* and finally to CIV, that yields the electrons to molecular oxygen. This electron flux is coupled to a proton pump from the matrix to the intermembrane space through complexes I, III and IV, which generates an electrochemical gradient across the IMM that provides the necessary free energy for the ATP synthase (complex V, CV) to synthesize ATP through the mechanism known as oxidative phosphorylation [5].

2.2. Models for the structural organization of the respiratory chain

Despite the well-known functional relevance of the respiratory chain, the structural organization of its components remains unclear.

2.2.1. Solid-state model

The pioneering spectrophotometric studies of Chance and Williams represented the MRC as a solid state assembly of prosthetic groups that carry out sequential redox reactions in a protein matrix [1]. The evidences in favour of this “rigid” or “solid-state model” were based on the isolation of CI-CIII and CII-CIII active units in a stoichiometric molar ratio of 1:1 during intermediate purification steps of the individual enzymes, that were interpreted as secondary enzymatically active complexes [6]; and on the reconstitution of a “repeating unit of electron transfer” containing all MRC complexes from bovine heart mitochondria [7]. This model implied the notion of permanently-bound CoQ to the MRC units. Accordingly, vesicle reconstitution experiments showed stoichiometric associations between CI and $CIII_2$ at high protein concentrations with no exchange between free and bound ubiquinone, i.e., no ‘CoQ-pool’ behaviour [8]. Only when sufficient lipid was added the CoQ-pool behaviour was restored, but this was interpreted as the movement of complex-associated CoQ rather than of free CoQ [9]. Later studies in *Saccharomyces cerevisiae* provided evidence that CoQ and cyt*c* only diffused freely along the membrane upon the addition of chaotropic agents, suggesting that the respiratory chain in yeast also behaves as one functional unit that at least comprises complexes III and IV with bound CoQ and cyt*c* [10].

2.2.2. Liquid-state model

The general vision gradually evolved into a “random collision”, “fluid” or “liquid-state” model, proposed by Hackenbrock and co-workers, that pictured all membrane proteins and redox components that catalyse electron transport and ATP synthesis in constant and independent diffusional motion, where electron transfer to

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