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Complex I impairment in mitochondrial diseases and cancer: Parallel roads leading to different outcomes☆

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ABSTRACT

Respiratory chain complex I (CI) dysfunctions have been recognized as one of the most frequent causes of mitochondrial neuro-muscular disorders. Moreover, latest reports reveal that CI impairment is a major contributing factor in many other pathological processes, including cancer. In fact, energy depletion, oxidative stress and metabolites unbalance are frequently associated with CI functional and structural alterations. The occurrence of mitochondrial DNA (mtDNA) mutations is a shared feature in neuro-muscular diseases and cancer; however, the two diverging phenotypes arise depending on the mutation type (disassembling *versus* non-disassembling mutations), the mutant load and the cytotype. In this review, we unify our knowledge on CI impairment caused by mutations in structural CI genes and assembly chaperones, both in mitochondrial disorders and cancer, stratifying such mutations based on their functional *versus* structural effects. We summarize shared and specific metabolic consequences of CI dysfunction in these pathologies, which allow us to draw two parallel roads that lead to different clinical outcomes.

This article is part of a Directed Issue entitled: Bioenergetic dysfunction, adaptation and therapy.

1. Introduction

1.1. Complex I structure and function

NADH:ubiquinone oxidoreductase (EC.1.6.5.3) or mitochondrial complex I (CI) is the largest and least understood component of the oxidative phosphorylation system (OXPHOS) (Brandt, 2006). Electron microscopy revealed that CI has an L-shaped structure with a hydrophobic arm embedded in the mitochondrial inner membrane and a peripheral hydrophilic arm that protrudes into the mitochondrial matrix (Radermacher et al., 2006). Recently, the X-ray structure of crystallized CI has been resolved for *Escherichia coli*, *Thermus thermophilus* and for yeast *Yarrowia lipolytica* (Efremov et al., 2010; Efremov and Sazanov, 2011; Hunte et al., 2010). The latter model organism has been chosen since mitochondria of *Saccharomyces cerevisiae* lack CI, but instead have two rotenone-insensitive NADH-oxidoreductases (de Vries and Grivell, 1988; Marres et al., 1991; De Vries et al., 1992). Hatefi and co-workers fractionated the bovine enzyme into three functional parts: (1) a hydrophilic NADH dehydrogenase module that oxidizes NADH; (2) a hydrophilic NADH hydrogenase module, which conducts the electrons *via* iron–sulfur clusters to ubiquinone (UBQ); and (3) a membrane part that acts as a conformation-driven proton pump (see Fig. 1; Ragan and Hatefi, 1986). Human CI is composed of 45 subunits (Carroll et al., 2006), seven of which are encoded by mitochondrial DNA (mtDNA) and constitute the hydrophobic arm, whereas the remaining 38 are encoded by the nuclear genome (nDNA) and are assembled within both the hydrophilic and the hydrophobic arms.

The 14 evolutionarily conserved "core subunits", seven mtDNA- and seven nDNA-encoded, are involved in the electron transfer and proton pumping, whereas the function of the remaining "accessory" or "ancillary" subunits is still unclear (Hirst et al., 2003), albeit

Abbreviations: CI, complex I; CIII, complex III; CIV, complex IV; CV, complex V; DB, decyl-benzoquinone; D-loop, displacement loop; HIF1α, hypoxia inducible factor 1α; LDH, lactate dehydrogenase; LHON, Leber's hereditary optic neuropathy; LS, Leigh syndrome; MELAS, mitochondrial encephalomyopathy lactic acidosis and stroke like syndrome; MERRF, myoclonic epilepsy and ragged red fibers; mtDNA, mitochondrial DNA; FeCN, ferricyanide; nDNA, nuclear DNA; OXPHOS, oxidative phosphorylation; PHDs, prolyl-hydroxylases; PI3K, phosphoinositide3-kinase; ^{31}P-MRS, ^{31}P-magnetic resonance spectroscopy; ROS, reactive-oxygen species; SA, succinic acid; TCA, tricarboxylic acid cycle; UBQ, ubiquinone; α-KG, α-ketoglutarate; $\Delta\psi$, mitochondrial membrane potential.

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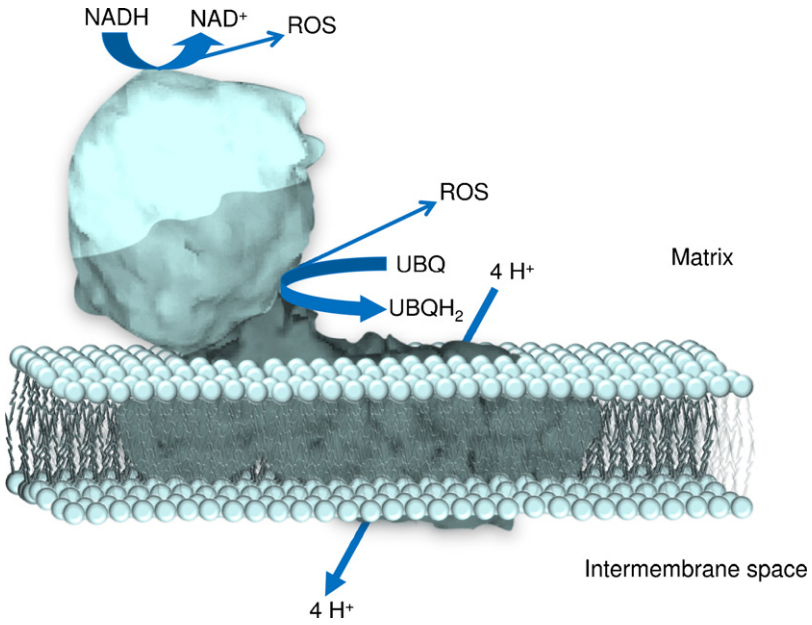

Fig. 1. Complex I structure and function. Three different colors represent the three distinct functional modules. In cyan the NADH dehydrogenase module is indicated (tip of the enzyme), in light blue the NADH hydrogenase module is shown, whereas the grey module represents the membrane arm (embedded in the mitochondrial inner membrane). The proton translocation and the NADH- and UBQ-binding sites are indicated. The latter two represent also the sites of ROS production.

it has been suggested that they may concur to stabilize CI, preventing the generation of reactive-oxygen species (ROS), to regulate the enzymatic activity or to shield the CI from oxidative damage (Chen et al., 2004; Hirst et al., 2003; Hirst, 2011).

CI assembly pathway is a puzzling issue, complicated by the size of the enzyme and by its dual genome control. This dynamic and coordinated process is regulated by the crosstalk between mitochondria and nucleus (Butow and Avadhani, 2004; Ryan and Hoogenraad, 2007). Newly synthesized subunits, encoded by nDNA, are imported in mitochondria and assembled with the highly hydrophobic mtDNA-encoded proteins. Besides structural subunits and prosthetic groups, additional chaperone proteins are required, which are not part of the holoenzyme, but are necessary for the correct assembly of the structural subunits (McKenzie and Ryan, 2010; Nouws et al., 2012; Sugiana et al., 2008). In fact, mutations in genes encoding for CI chaperones have already been demonstrated to dramatically hamper CI formation (Dunning et al., 2007; Nouws et al., 2010; Ogilvie et al., 2005).

It is well known that CI is the first and crucial component of mitochondrial respiratory chain and its function is necessary for the maintenance of cellular redox status (NAD^+/NADH ratio and ROS levels), generation of mitochondrial membrane potential and finally for ATP production (Roestenberg et al., 2012). Electrons derived from NADH oxidation, mainly generated from the tricarboxylic acid cycle (TCA), are transferred to UBQ in a process coupled to proton translocation from the mitochondrial matrix to the intermembrane space, generating a gradient across the membrane, which consists of an electrical ($\Delta\psi$) and a chemical component (ΔpH) (see Fig. 1; Brand and Nicholls, 2011). The electrochemical gradient is the driving force for mitochondrial ATP synthesis by complex V (CV). CI generates ROS as by-products of the electron transfer having two sites (NADH-binding and the UBQ-binding sites) accessible to O_2 where formation of superoxide anion may occur (see Fig. 1; Adam-Vizi and Chinopoulos, 2006; Kussmaul and Hirst, 2006; Hirst et al., 2008; Murphy, 2009).

Functional and structural CI alterations lead to severe mitochondrial dysfunction and, isolated CI deficiency is the most frequent respiratory chain defect found in neuro-muscular mitochondrial disorders. Mutations in nDNA- and mtDNA-encoded genes of both CI structural subunits and assembly chaperones have been recognized as pathogenic (DiMauro and Schon, 2008; McKenzie and Ryan, 2010; Nouws et al., 2010; Zeviani and Carelli, 2007). Alterations in cell survival, apoptosis, calcium homeostasis and mitochondrial morphology and dynamics, due to CI dysfunction, concur to the pathogenic mechanisms of neuro-muscular diseases and also in other processes, such as aging and cancer (Koopman et al., 2005; Lemarie and Grimm, 2011; Visch et al., 2006). In particular, CI may have an active role in the regulation of metabolic remodeling and hypoxia adaptation in cancer, as we will further discuss.

1.2. mtDNA CI-encoded subunits and peculiar features of mitochondrial genetics

Human mtDNA is a double-stranded, circular molecule of 16,569 bp, coding for 13 genes of OXPHOS complex subunits, 22 tRNAs and two rRNAs necessary for intra-organel translation (Anderson et al., 1981). The mitochondrial genome is an extraordinarily compact coding molecule and presents some peculiar features compared to nDNA, such as the lack of introns and intergenic regions, the polycistronic organization of transcripts and the existence of overlapping genes (Montoya et al., 1981). However, mtDNA shows an innate fragility to mutation accumulation (Wallace, 1993), probably due to a less efficient DNA repair system and the lack of non-coding buffering sequences and protective proteins, although a histone-like fuction has been proposed for mitochondrial transcription factor A (Tfam) (Kanki et al., 2004).

Interspersed among protein coding and rRNAs, tRNA genes represent the "punctuation" of the polygenic transcript and identify the signal for cleavage during mitochondrial RNA maturation (Ojala et al., 1981). The two mtDNA strands are defined as heavy (H-) and light (L-) chains based on their nucleotide composition. The replication origin of the H-strand and the site of transcription initiation from opposing H- and L-strand promoters reside within the displacement loop (D-loop), the major regulatory mtDNA region (Clayton, 2000).

Mitochondrial DNA inheritance does not strictly comply with the rules of Mendelian genetics. First of all, mtDNA is maternally