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Minireview

Mitochondrial complex I deficiency of nuclear origin I. Structural genes

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ABSTRACT

Complex I (or NADH–ubiquinone oxidoreductase), is by far the largest respiratory chain complex with 38 subunits nuclearly encoded and 7 subunits encoded by the mitochondrial genome. Its deficiency is the most frequently encountered in mitochondrial disorders. Here, we summarize recent data obtained on architecture of complex I, and review the pathogenic mutations identified to date in nuclear structural complex I genes. The structural *NDUFS1*, *NDUFS2*, *NDUFV1*, and *NDUFS4* genes are mutational hot spot genes for isolated complex I deficiency. The majority of the pathogenic mutations are private and the genotype–phenotype correlation is inconsistent in the rare recurrent mutations.

Contents

Abbreviations: CI, complex I; OXPHOS, oxidative phosphorylation; $NADH,H^+$, reduced nicotinamide adenine dinucleotide.

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1. Introduction

As mitochondria are widespread throughout the organism, a respiratory chain deficiency can theoretically give rise to any symptom, in any organ or tissue, at any age and with any mode of inheritance, owing to the dual genetic origin of respiratory chain enzymes (nuclear and mitochondrial DNA) [1]. In 2004, Thorburn et al. defined a minimum birth prevalence of 13.1/100 000 or 1/7634 for primary OXPHOS disorders with onset at any age [2]. The figure sharply rises if including secondary defects putatively occurring in a number of neurological neurodegenerative diseases and aging.

Complex I (CI), or NADH:ubiquinone oxidoreductase, is the largest of the five OXPHOS complexes [3]. This multi-enzymatic complex, which is composed in mammals of 38 nuclearly-encoded subunits and 7 subunits encoded by the mitochondrial genome [4], catalyzes electron transfer from NADH through the respiratory chain, using the lipid-soluble ubiquinone as an electron acceptor [5]. With a stoichiometry of four protons to two electrons ($4H+/2e-$), it contributes about 40% of the proton motive force that drives adenosine 5′-triphosphate (ATP) synthesis by ATP synthase [6,7]. This and the large number of genes coding for its many subunits and for assembly proteins might explain why deficiency of CI represents the most frequent (40%) of the human mitochondrial hereditary disorders of oxidative phosphorylation [8,9]. The clinical phenotypes observed in patients with early onset diseases are often devastating, with a rapid progression, and death within a few years after birth. No successful therapy is currently available. It is therefore important to locate the genetic causes of these diseases to offer at least the possibility of adequate genetic counseling and prenatal diagnostics [10]. However, mutations in the mitochondrial DNA and CI nuclear genes appear to account for less than half of all patients with CI deficiency [11], with a systematic screening of all mitochondrially encoded CI subunits conducting to the detection of pathogenic mutations in 20% of CI deficient children [12]. A recent study conducted to the identification of pathogenic mutations in 21.7% of a cohort of 60 CI deficient patients without molecular diagnosis: pathogenic mutations were identified in the mitochondrial DNA in only 3 patients (5%) while mutations in CI-associated nuclear genes, mainly CI structural genes, were discovered in 10 patients (16.7%) [13].

In this review, we intend to summarize the recent data obtained on architecture of CI and to report on the pathogenic nuclear mutations in structural CI genes, identified to date as being responsible for isolated CI deficiency.

2. The nuclear-encoded complex I subunits

2.1. Composition, architecture and functional aspects of complex I

2.1.1. Complex I catalytic-core subunits and functional modules

Studies have first focused on prokaryotic CI, as it represents the minimal form of the enzyme [14,15]. It comprises 14 subunits, sufficient to perform all bioenergetic functions, carrying all redox centers, flavin mononucleotide (FMN), and 8–9 iron–sulfur clusters (named N1a to N6b), involved in electron transfer through the complex. These 14 "central" subunits found in prokaryotic and eukaryotic CI fall in two different categories: 7 mitochondrial DNA-encoded subunits are highly hydrophobic with predicted transmembrane helices, and 7 nuclearly-encoded subunits contain all binding motifs for the substrate, NADH, and for redox prosthetic groups. Central CI subunits are organized in three well defined functional modules: the electron input module or *N module* that oxidizes NADH, the electron output module or *Q module* that reduces ubiquinone, and the *P module* that translocates protons across the membrane [3]. Electrons from NADH enter the N module (comprising the *Homo sapiens* NDUFV1, NDUFV2, NDUFS1 subunits) of CI through FMN, which is non-covalently bound to the NDUFV1 subunit. FMN serves as a two-to-one electron converter and feed single electrons into a "wire" composed of the iron–sulfur clusters N3 (bound to NDUFV1), N1b, N4, and N5 (all of them bound to NDUFS1). The binuclear cluster N1a, which is in the NDUFV2 subunit, is unlikely to participate directly in the electron transfer from FMN to ubiquinone, but might act as an antioxidant electron carrier [5]. The Q module (comprising the NDUFS2, NDUFS3, NDUFS8, and NDUFS7 subunits) accepts electrons from the iron–sulfur clusters of the N module and transfers them via 3 more iron–sulfur clusters (N6a and N6b, bound to NDUFS8; N2, bound to NDUFS7) to ubiquinone. The iron–sulfur cluster N2 is the immediate electron donor to ubiquinone [16].The hydroxyl group of tyrosine-144 in NDUFS7, which is in close proximity to iron–sulfur cluster N2, is involved in binding of the quinone head group within a broad cavity formed by the NDUFS7 and the NDUFS2 subunits [17]. Proton pumping is mediated by the membrane-embedded P module, comprising the seven mitochondrial DNA-encoded CI subunits (ND1, ND2, ND3, ND4, ND4L, ND5, ND6). The ND2, ND4 and ND5 subunits seem to have evolved from Na^+/H^+ antiporters [3].

2.1.2. Complex I "supernumerary" subunits

In addition to these 14 "central" subunits, mitochondrial CI of eukaryotes contains up to 32 additional "accessory" or "supernumerary" subunits, presumably not associated directly with energy conservation process [3,5]. Roles in preventing ROS generation and protection against oxidative damage by shielding redox groups from reaction with oxygen, in binding of the CI to the membrane, and in the stabilization of the enzyme by forming a scaffold around the core subunits have been suggested. Also, more specific functions in the regulation of activity or the assembly of other subunits into the holocomplex have been implied. For example, phosphorylation of the NDUFS4 subunit in murine and human cell cultures is associated with stimulation of the NADH–ubiquinone oxidoreductase activity of the complex and promotes import/maturation in mitochondria of this nuclear-encoded protein [18]. Another marked example is the NDUFA13 subunit, which is involved in distinct biochemical processes. The NDUFA13 protein, also named GRIM-19, for Gene associated with Retinoid-Interferon induced Mortality 19 protein, was first postulated to be a cell death-promoting protein [19]. Alterations of the *NDUFA13* gene were then reported in thyroid Hürthle cell tumors [20]. It was also shown that a viral RNA product encoded by human cytomegalovirus interacts with GRIM-19 and CI, that stabilizes the inner mitochondrial membrane potential ($\Delta\psi m$), sustains ATP production and protects infected cells from rotenone-induced apoptosis [21]. The functional domains of NDUFA13 were further dissected by generating a number of deletion, truncation, and point mutants: disruption of $\Delta\psi m$ by NDUFA13 mutants enhanced the cell's sensitivity to apoptotic stimuli [22]. Direct interaction between NDUFA13 and STAT3 (signal transducer and activator of transcription 3) followed by inhibition of STAT3 transcriptional activity were further demonstrated [23]. Constitutive activation of STAT3 is common in many human and murine cancer cells, and its activation leads to cellular transformation. STAT3 pathway inhibitors have been reported to suppress cancer growth. Analysis of the expression of STAT3 downstream molecules confirmed that *in vitro* GRIM-19 overexpression treatment of constitutively activated STAT3 cancer cells significantly reduced STAT3-dependent transcription [24].

2.1.3. Complex I topology and architecture

CI has an L-shaped overall architecture with 2 arms of approximately equal length: it comprises a membrane arm, embedded in the inner mitochondrial membrane, and a peripheral arm, which protrudes into the mitochondrial matrix. With mild chaotropic detergents, intact CI can be resolved into 4 subcomplexes: Iα, Iβ, Iγ and Iλ [25]. A schematic representation of CI is given in Fig. 1.

Subcomplex Iα consists of the hydrophilic peripheral arm *plus* part of the hydrophobic membrane arm, as subcomplex Iβ contains