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Human Mitochondrial Complex I in Health and Disease

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The oxidative phosphorylation (OXPHOS) system of the mitochondrion uses the products of ~60 nuclear genes and 13 mitochondrial genes to generate cellular ATP. These proteins are organized into five large complexes—electron transport chain complexes I–IV and ATP synthetase (complex V) (Hatefi 1985)—of which complex I, or nicotinamide adenine dinucleotide (NADH):ubiquinone oxidoreductase, is the largest. Studies of the bovine heart have identified at least 35 complex I nuclear gene products, together with 7 mitochondrially encoded proteins (Walker 1992; Skehel et al. 1998). In the past year, our knowledge of the human complex I genes and gene products has made substantial progress. Here we review recent insights into these components and their roles in health and disease.

Complex I, which is embedded in the inner mitochondrial membrane (IMM), serves to dehydrogenate NADH and to shuttle electrons to coenzyme Q. This electron transport generates a proton gradient across the IMM, which provides the proton-motive force that is used in ATP synthesis. The total human complex consists of ⩾42 subunits, 7 encoded by the mitochondrial genome and the remainder by the nuclear genome (Smeitink et al. 1998*b*). The coordinated interactions between the nucleus and the mitochondrion that build and maintain this vital multiple-subunit protein complex remain poorly understood. As of last year, however, all 35 known human nuclear-encoded cDNAs for complex I proteins had been characterized (Loeffen et al. 1998*b;* Smeitink et al. 1998*b*), thanks, in part, to the work of Walker (1992), who characterized the homologous complex from cattle, and also, in part, to the increasing power of genomic methods that are readily available through public databases. On the basis of the genetic information available from prokaryotes and lower eukaryotes, we expect that knowledge about this intriguing complex will expand rapidly in coming years. For the many individuals with inherited defects in complex I function, these advances offer the prospect of efficient diagnosis, reliable genetic counseling and prenatal diagnostics, better understanding of the cellular consequences of complex I deficiency, and, ultimately, treatment strategies more rational than those currently available.

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Nuclear Genes of Human Complex I

The exact protein composition of complex I has not been studied in detail in mitochondria from whole human organs; however, work with bovine heart tissue has thus far identified 35 nuclear-encoded subunits (Walker 1992; Skehel et al. 1998), including 3 flavoproteins (FPs), 7 iron-sulfur proteins (IPs), and 24 hydrophobic proteins (HPs) (Galante and Hatefi 1979); a recently identified 17.2-kD subunit (Skehel et al. 1998) has not yet been placed in any of these three groups. FP and IP proteins from cattle, bacteria, and fungi protrude from the IMM into the mitochondrial matrix (Grigorieff 1998; Guenebaut et al. 1998). This protruding "arm" includes the NDUFV1 protein, which binds and transfers electrons to NADH, as well as many proteins of the IP group, which carry out intra- and intersubunit electron transfer. The final electron acceptor for complex I, ubiquinone, is predicted to bind one or more of these proteins, but no such interaction has yet been identified. The HP fraction, embedded in the lipid bilayer of the IMM, contains most of the nuclear-encoded proteins and all seven mitochondrially-encoded proteins. This fraction seems to mediate proton translocation from the mitochondrial matrix into the intermembrane space (Belogrudov and Hafeti 1994).

Table 1 summarizes the present molecular data regarding the human nuclear-encoded complex I subunits. Presently, the complete gene structure is known for 6 of the 35 genes and chromosomal localization is known for 26 of 35 (Emahazion and Brookes 1998; Emahazion et al. 1998). A small form of complex I, consisting of 14 subunits, is found in *Escherichia coli* (Weidner et al. 1993). In this bacterium, all complex I genes are organized as an operon, called "*Nuo*" after the NADH:ubiquinone oxidase. In most eukaryotes, homologues of *NuoB–NuoG* and *NuoI* are nuclear genes. Comparative

Table 1

Human Complex I Nuclear Genes: Present Knowledge

Gene Group and Gene	cDNA Sequence	nDNA Sequence	Chromosomal Localization	Leader Sequence	Biochemical Function
Flavoprotein:					
NDUFV1 (*NuoF*)	+	+	11q13	+	NADH binding, electron transfer
NDUFV2 (*NuoE*)	+	+	18p11.2-p11.21	+	Electron transfer
NDUFV3	+	+	21q22.3	+	
Iron-sulfur:					
NDUFA5	+	−	7q31.33		
NDUFS1 (*NuoG*)	+	−	2q33-34	+	Electron transfer
NDUFS2 (*NuoD*)	+	−	…	+	
NDUFS3 (*NuoC*)	+	−	11p11.11	+	
NDUFS4	+	−	5q11.1	+	Phosphorylation
NDUFS5	+	−	1p34.2-p33		
NDUFS6	+	−	5pter-p15.33	+	
Hydrophobic:					
NDUFA1	+	+	Xq24-25		
NDUFA2	+	−	5q31.2		
NDUFA3	+	−	…		
NDUFA4	+	−	…		
NDUFA6	+	−	21q13.1		
NDUFA7	+	−	19p13.2		Ubiquinone binding?
NDUFA8	+	−	9q33.2-34.11		
NDUFA9	+	−	…	+	
NDUFA10	+	−	12p	+	
NDUFAB1	+	−	16p12.3-12.1		Acylcarrier protein motif
NDUFB1	+	−	14q31.3		
NDUFB2	+	−	7q34-35	+	
NDUFB3	+	−	…		
NDUFB4	+	−	…		
NDUFB5	+	−	…	+	
NDUFB6	+	−	9p13.2		
NDUFB7	+	−	19p13.12-13.11		
NDUFB8	+	−	10q23.2-23.33	+	
NDUFB9	+	+	8p24.21		
NDUFB10	+	−	16p13.3		
NDUFS7 (*NuoB*)	+	−	19p13	+	Electron transfer
NDUFS8 (*NuoI*)	+	+	11q13.1-13.3	+	Electron transfer
NDUFC1	+	−	4q28-28.3		
NDUFC2	+	−	…		
Unknown:					
17.2 kD	+		…		

NOTE.—*E. coli* homologues of human complex I genes are indicated in parentheses in the first column. For primary data, see Walker (1992), Emahazion and Brookes (1998), Emahazion et al. (1998), Loeffen et al. (1998*b*), Skehel et al. (1998), Smeitink et al. (1998*b*), and Lin et al. (1999). Ellipses (…) = unknown.

studies show that the number of nuclear-encoded complex I subunits increases with the evolutionary complexity of the organism. The seven human nuclear-encoded counterparts of the *E. coli* Nuo proteins, namely, NDUFV1 and 2, NDUFS1–3, and NDUFS7 and 8, would be predicted to carry out essential aspects of complex I function, and we began our mutational analysis of human patients with the genes for these subunits.

Nuclear-Mitochondrial Interactions

Except for complex II, in which all four known structural genes are nuclear, all components of the OXPHOS system are under the control of both the mitochondrial and nuclear genomes. This poses a regulatory challenge that is unique in human cell biology. The control of mitochondrial gene expression is relatively well known (Shadel and Clayton 1997; Clayton 1998), but regulation of the nuclear-encoded genes and coordination of the two genomes are not. Fortunately, work in model systems, including the fungus *Neurospora crassa* (Belogrudov and Hatefi 1994), has begun to address the regulation of transcription and translation of these genes, as well as intracellular signaling, complex assembly, and stochiometry.

The regulatory regions of several genes encoding complex I proteins have been characterized. We recently found a consensus motif in the human *NDUFV1* gene

for binding the transcription factor nuclear respiratory factor II (Schuelke et al. 1998). This binding sequence motif has also been detected in other nuclear genes for mitochondrial proteins, including those for cytochrome c oxidase and for the β subunits of ATP-synthetase and of the mitochondrial transcription factor. Moyes et al. (1998) speculate that these genes respond in a modular fashion to physiological change.

The transport of nuclear-encoded complex I gene products to and through the IMM is poorly understood. Transport of the complex I preproteins across the mitochondrial outer membrane is presumed to occur via a dedicated import machinery, called "Tom" for translocase of the outer membrane (Dekker et al. 1998). This multiple-subunit machinery contains receptors and a general import pore. Recently, Hill et al. (1998) showed that Tom40, one of the eight Tom proteins, forms a cation-selective conductance channel that binds to mitochondrial-targeting sequences on the cytoplasmic face of the mitochondrion and transports them across the membrane. At least 15 of the known nuclear-encoded complex I gene products, including all of the subunits shared with the *E. coli* complex, contain classic mitochondrial-targeting leader sequences, but *cis*-acting targeting sequences have not been defined for the remaining proteins. Alternatively, internal targeting sequences may be present in these proteins; Sirrenberg et al. (1998) recently discovered a pathway in yeast for the mitochondrial transport of proteins containing internal signals.

The matrix arm and the membrane portion of complex I form independently and are joined in the course of assembly. In *N. crassa,* the membrane arm itself is formed from two smaller modules, which assemble through the action of two specific chaperones (Kuffner et al. 1998). The functions of the components of the OXPHOS system, particularly human and yeast cytochrome c oxidase, also appear to be mediated by nuclear-encoded factors, namely, the SURF1 protein and its yeast homologue Shy1 (Duhig et al. 1998; Tiranti et al. 1998; Zhu et al. 1998). No such chaperones or accessory factors are yet known for human complex I.

Complex I subunit mRNA expression appears to be ubiquitous in human tissues, and the brain, heart, skeletal muscles, and kidneys accumulate these mRNAs at high levels. Among these mRNAs, only the NDUFB6 message is expressed most strongly in the kidney (Smeitink et al. 1998*a*), suggesting that mutations in *NDUFB6* may cause distinctive phenotypes. So far, no mutations in *NDUFB6* have been found in people with isolated complex I deficiency.

Isolated Human Complex I Deficiency

Mitochondriocytopathies occur with an estimated incidence of 1 per 10,000 live births, and isolated complex I deficiency is one of those most frequently encountered (Robinson 1998). The first clinical symptoms of complex I deficiency, presenting either at birth or in early childhood, seem to result from brain dysfunction, sometimes combined with defects in other energy-consuming organs, such as the skeletal muscle and the heart. For this reason, complex I deficiencies are grouped among the mitochondrial encephalomyopathies. Robinson (1998) categorized complex I–deficient patients into three major clinical groups. The most common presentation is Leigh syndrome (Leigh 1951), with cardiomyopathy occurring in ~40% of Leigh syndrome patients (Morris et al. 1996; Rahman et al. 1996). A second category often seen is fatal neonatal lactic acidosis. A relatively uncommon third group comprises patients who present with hepatopathy and tubulopathy with very mild symptoms, such as exercise intolerance, or with cardiomyopathy and cataracts. In our experience, the majority of patients with complex I deficiency die before the age of 5 years of a multisystem disorder, usually Leigh syndrome or a Leigh-like syndrome. In contrast to the patients described by Robinson (1998), none of our patients with cardiomyopathy or cataract showed isolated complex I deficiency (Sengers et al. 1975; Smeitink et al. 1989). Furthermore, none of the 40 patients with whom we have worked who exhibited isolated complex I deficiency in their cultured fibroblasts or myocytes appear to fit into Robinson's third category (J. L. C. M. Loeffen, J. A. M. Smeitink, J. M. Trijbels, A. J. Janssen, R. T. P. Triepels, R. C. A. Sengers, and L. P. van den Heuvel, unpublished data).

Since the elucidation of the complete human mitochondrial genome, mutational analysis of mtDNA has attracted much attention as a way to explore the underlying cause of isolated complex I deficiency. The most frequently observed pathological mtDNA mutations are found in the genes for mitochondrial tRNAs for leucine (*T3271C, A3243G*) and lysine (*A8344G, T8356C*) and in the protein-encoding subunits ND1 (*T4160A, G3460A*), ND4 (*G11778A*), and ND6 (*T14484C, G14459A*) (Wallace 1992; Zeviani et al. 1998). Since the underlying genetic defect can be ascribed to mutations in mtDNA in only ~5% of complex I–deficient patients (Liang and Wong 1998), we focused our attention on mutational analysis of nuclear complex I genes and selected a group of 20 patients with isolated complex I deficiency in whom the enzyme deficiency was confirmed in more than one tissue. Since maternal inheritance was not evident in this group, the known mitochondrial DNA mutations associated with complex I deficiency could be excluded. We started our search for mutations in subunits highly conserved during evolution. Mutational analysis of eight nuclear genes encoding proteins of complex I revealed mutations in five of our patients and two additional siblings (Loeffen et al. 1998*a;* van den Heuvel et al. 1998; Schuelke et al. 1999; Triepels

Table 2

Nuclear Gene Mutations in Patients with Isolated Complex I Deficiency

Affected Gene (Mutation[s])	Sex/Age (mo)[a]	Symptoms at Presentation	Course of Illness	Lactic Acid Concentration			MRI Findings[c]	Age at Death/ Postmortem Findings[d]
				Blood	Urine	CSF[b]		
NDUFS4 (5-bp duplication)	M/8	Vomiting, failure to thrive, hypotonia	Progressive	Normal	Normal	Normal	Atrophy, basal ganglia abnormalities	16 mo
NDUFS8 (P79L, R102H)	M/<1	Feeding difficulties, hypotonia, episodic apnea and cyanosis	Progressive, moderate hypertrophic cardiopathy	Increased	Increased	Increased	Atrophy, symmetrical hypodensities	11 weeks (LS confirmed)
NDUFS7 (V122M)	M/26	Feeding problems, dysarthria, ataxia	Progressive	Normal	Normal	Sl. incr.	Symmetrical hypodensities	3.5 years (LS confirmed)
NDUFS7 (V122M)	M/11	Vomiting	Progressive after infection (3.4 years)	Normal	Normal	Normal	Symmetrical hypodensities	5 years (LS confirmed)
NDUFV1 (R59X, T423M)	M/5	Vomiting, strabismus, hypotonia	Progressive, myoclonic epilepsy	Increased	Normal	Increased	Atrophy	14 mo
NDUFV1 (R59X, T423M)	M/7	Vomiting, strabismus, hypotonia	Progressive, myoclonic epilepsy	Increased	Normal	Increased	Atrophy	17 mo
NDUFV1 (A341V)	F/6	Infantile myoclonic epilepsy	Progressive	Normal	Normal	Increased	Atrophy, progressive macrocystic leucodystrophy	Alive at age 10 years

[a] Age at presentation.
[b] CSF = cerebrospinal fluid; Sl. incr. = slightly increased.
[c] MRI = magnetic resonance imaging.
[d] LS = Leigh syndrome.

et al., in press). Interestingly, none of our subjects carry mutations in any of the 18 complex I subunit genes we have studied that are not conserved with *E. coli*. We are continuing to search for mutations in the remaining complex I structural genes in this group of patients. On the basis of precedent from *N. crassa* (Kuffner et al. 1998), it is possible that some of these individuals will carry mutations in genes that are required for the folding or assembly of complex I proteins.

The currently known mutations and clinical features of our complex I–deficient patients are summarized in table 2. Six patients had a progressive and ultimately fatal multisystemic disorder in which cerebral dysfunction was the most prominent clinical sign; one is alive at 10 years of age but is severely handicapped. Increased lactic acid concentration, considered to be one of the hallmarks of a mitochondriocytopathy, was certainly not present in all body fluids routinely investigated. Strikingly, one patient showed no lactic acid elevation, not even after a series of provocative tests. We assume, on the basis of past experience with mtDNA studies, that the inheritance pattern of most children with enzymatic complex I deficiency is autosomal recessive.

Outstanding Questions

The cloning of the nuclear genes and cDNAs that encode the human complex I components should make prenatal and postnatal diagnosis of complex I deficiency possible, although the large number of nuclear and mitochondrial genes involved is still somewhat daunting. Chip technology will certainly increase our diagnostic abilities in the near future. At present, extensive mutational detection studies of nuclear genes are performed only after the common mtDNA mutations have been excluded.

Before the emerging molecular data can be put to use to benefit families with complex I deficiency, we badly need answers to several fundamental questions. First, until detailed protein studies of the complex have been performed with human cells, the total number of the human complex I nuclear genes will remain uncertain. Quite recently, Walker's group, which had just reported the identity of the 42d complex I subunit (Skehel et al. 1998), announced the presence of a 43d subunit in bovine heart. Furthermore, the stochiometry of this multiprotein subunit complex has not been explored in humans, nor have any studies addressed possible differences between cell types in the composition of the complex, which could account for variable clinical presentation of this mitochondrial encephalomyopathy. In addition, very limited information is available about the expression, intracellular transport, and assembly of the subunits of the complex, all steps that might be impaired in individuals deficient in OXPHOS. Insights into these medically relevant biosynthesis issues may come from detailed studies of bacteria and fungi, as was seen recently with the identification of the *SURF1* gene in cytochrome c oxidase–deficient patients with Leigh syndrome (Tiranti et al. 1998; Zhu et al. 1998). Finally, the metabolic and general physiological effects of aberrant complex I function will need to be explored if rational therapeutic strategies are to be developed.

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