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Review

Mitochondrial diseases

Salvatore DiMauro *

Department of Neurology, 4-420 College of Physicians and Surgeons, Columbia University, 630 West 168th Street, New York, NY 10032, USA

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Abstract

By convention, the term ‘‘mitochondrial diseases’’ refers to disorders of the mitochondrial respiratory chain, which is the only metabolic pathway in the cell that is under the dual control of the mitochondrial genome (mtDNA) and the nuclear genome (nDNA). Therefore, a genetic classification of the mitochondrial diseases distinguishes disorders due to mutations in mtDNA, which are governed by the relatively lax rules of mitochondrial genetics, and disorders due to mutations in nDNA, which are governed by the stricter rules of mendelian genetics.

Mutations in mtDNA can be divided into those that impair mitochondrial protein synthesis in toto and those that affect any one of the 13 respiratory chain subunits encoded by mtDNA. Essential clinical features for each group of diseases are reviewed.

Disorders due to mutations in nDNA are more abundant not only because most respiratory chain subunits are nucleus-encoded but also because correct assembly and functioning of the respiratory chain require numerous steps, all of which are under the control of nDNA. These steps (and related diseases) include: (i) synthesis of assembly proteins; (ii) intergenomic signaling; (iii) mitochondrial importation of nDNA-encoded proteins; (iv) synthesis of inner mitochondrial membrane phospholipids; (v) mitochondrial motility and fission.

Keywords: Mitochondrial disease; Respiratory chain; mtDNA mutation; nDNA mutation

‘‘Translational research’’ is the latest buzzword, which has to be used in every grant application to entice reviewers. Beyond faddism, however, even the most basic of researcher hopes that his/her findings will ultimately benefit patients. In this spirit, it seems appropriate that the proceedings of the EBEC Meeting, dedicated to bioenergetics, be concluded by an overview of mitochondrial diseases. Indeed, the term ‘‘mitochondrial diseases’’ refers specifically to defects of the mitochondrial respiratory chain, the bioenergetic pathway *par excellence* [1].

Mitochondrial myopathies were described in the early 1960s, when systematic ultrastructural and histochemical studies revealed excessive proliferation of normal- or abnormal-looking mitochondria in muscle of patients with weakness or exercise intolerance [2,3]. Because, with the modified Gomori trichrome stain, the areas of mitochondrial accumulation looked purplish (Fig. 1), the abnormal fibers were dubbed ‘‘ragged-red fibers’’ (RRF) and came to be considered the pathological hallmark of mitochondrial disease [4]. However, it soon became apparent that in many patients with RRF, the myopathy is associated with symptoms and signs of brain involvement, and the term ‘‘mitochondrial encephalomyopathy’’ was introduced. It also became clear that lack of RRF in the biopsy does not exclude a mitochondrial etiology, as exemplified by Leigh syndrome (LS), an encephalopathy of infancy or childhood invariably due to mitochondrial dysfunction but almost never accompanied by RRF. The first biochemical evidence of a mitochondrial dysfunction—loose coupling of oxidation and phosphorylation—was reported in 1962 by Luft et al. [5] in a young woman with non-thyroidal hypermetabolism (Luft syndrome).

These disorders are especially interesting from the genetic point of view because the respiratory chain is the only metabolic pathway in the cell that is under the dual control of the mitochondrial genome (mtDNA) and the nuclear genome (nDNA). Therefore, a genetic classification of the

* Tel.: +1-212-305-1662; fax: +1-212-305-3986.
E-mail address: sd12@columbia.edu (S. DiMauro).

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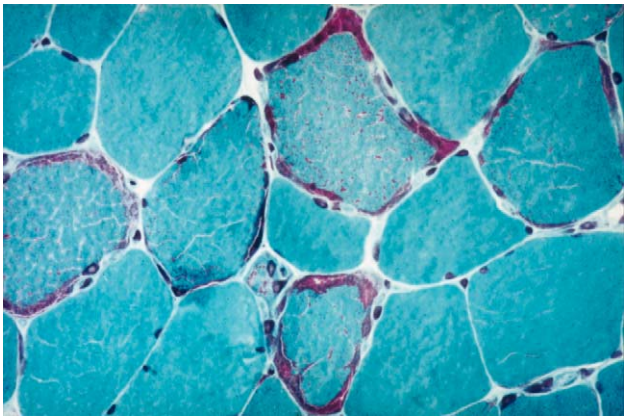

Fig. 1. Ragged-red fibers (RRF) revealed by the modified Gomori trichrome stain. Abnormal accumulations of mitochondria appear as reddish blotches, mostly at the periphery of muscle fibers (courtesy of Dr. Eduardo Bonilla, Columbia University).

mitochondrial diseases distinguishes disorders due to mutations in mtDNA, which are governed by the laxer rules of mitochondrial genetics, and disorders due to mutations in nDNA, which are governed by the stricter rules of mendelian genetics (Table 1).

1. Diseases due to mutations in mtDNA

Of the approximately 80 proteins that make up the respiratory chain, 13 are encoded by mtDNA and all others are encoded by nDNA. As indicated by the different colors in Fig. 2, complex II, coenzyme Q, and cytochrome *c* are exclusively encoded by nDNA. In contrast, complexes I, III, IV, and V contain some subunits encoded by mtDNA: seven for complex I (ND1–ND4, ND4L, ND5, and ND6), one for complex III (cytochrome *b*), three for complex IV (COX I–COX III), and two for complex V (ATPase6 and ATPase8).

Human mtDNA is a 16.569-kb circular, double-stranded molecule, which contains 37 genes: 2 rRNA genes, 22 tRNA genes, and 13 structural genes encoding the respiratory chain subunits listed above. In the course of evolution, mtDNA has lost much of its original autonomy and now is the slave of nDNA, which encodes numerous factors needed for mtDNA trascription, translation, and replication. Since 1988 (the birthdate of mitochondrial molecular pathology [6,7]), the circle of mtDNA has become crowded with pathogenic mutations (Fig. 3), and the principles of mitochondrial genetics should, therefore, be familiar to the practicing physician.

Table 1
Genetic and biochemical classification of the mitochondrial diseases

Genome	Gene	[mtDNA]	Biochemistry	Clinical phenotype
mtDNA		single Δ	⇓ prot. synth.	KSS; ocular myopathy; PS
	$tRNA^{Leu(UUR)}$		⇓ prot. synth.	MELAS
	$tRNA^{Lys}$		⇓ prot. synth.	MERRF
	other tRNAs		⇓ prot synth.	multiple phenotypes
	ATPase6		⇓ ATP synth.	NARP/MILS
	ND1, ND4, ND6		⇓ complex I	LHON
	ND1, ND4		⇓ complex I	myopathy[a]
	Cyt b		⇓ complex III	myopathy[a]
	COX III		⇓ complex IV	myopathy[a]
nDNA				
	NDUF		⇓ complex I	LS
	SDHA		⇓ complex II	LS
	BCS1L		⇓ complex III	GRACILE
	SURF1		⇓ complex IV	LS
	SCO1		⇓ complex IV	hepatoencephalomyopathy
	SCO2		⇓ complex IV	cardioencephalomyopathy
	COX10		⇓ complex IV	nephroencephalomyopathy
	COX 15		⇓ complex IV	cardioencephalomyopathy
	ATP 12		⇓ complex V	fatal infantile multisystemic
	TP	multiple Δ	⇓ _	MNGIE
	ANT1	multiple Δ	⇓ prot. synth.	adPEO-plus[b]
	Twinkle	multiple Δ	⇓ prot. synth.	adPEO-plus[b]
	POLG	multiple Δ	⇓ prot. synth.	ad/arPEO-plus[b]
	dGK	depletion	⇓ prot. synth.	hepatocerebral syndrome
	TK2	depletion	⇓ prot. synth.	myopathy; SMA
	TAZ		⇓ cardiolipin	Barth syndrome
	OPA1		⇓ mit. Motility	ad optic atrophy

Abbreviations and symbols: Δ, deletion; KSS, Kearns–Sayre syndrome; PS, Pearson syndrome; MELAS, Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; LS, Leigh syndrome; MILS, maternally inherited LS; GRACILE, growth retardation, aminoaciduria, cholestasis, lactacidosis, early death; adPEO, autosomal dominant progressive external ophthalmoplegia; arPEO, autosomal recessive PEO; SMA, spinal muscular atrophy. [mtDNA] indicates changes of mtDNA secondary to nDNA mutations (defects of intergenomic signaling).

[a] Mutations in cyt b and COX genes can also cause multisystemic diseases.

[b] Plus refers to proximal weakness, neuropathy, psychiatric disorders, parkinsonism.

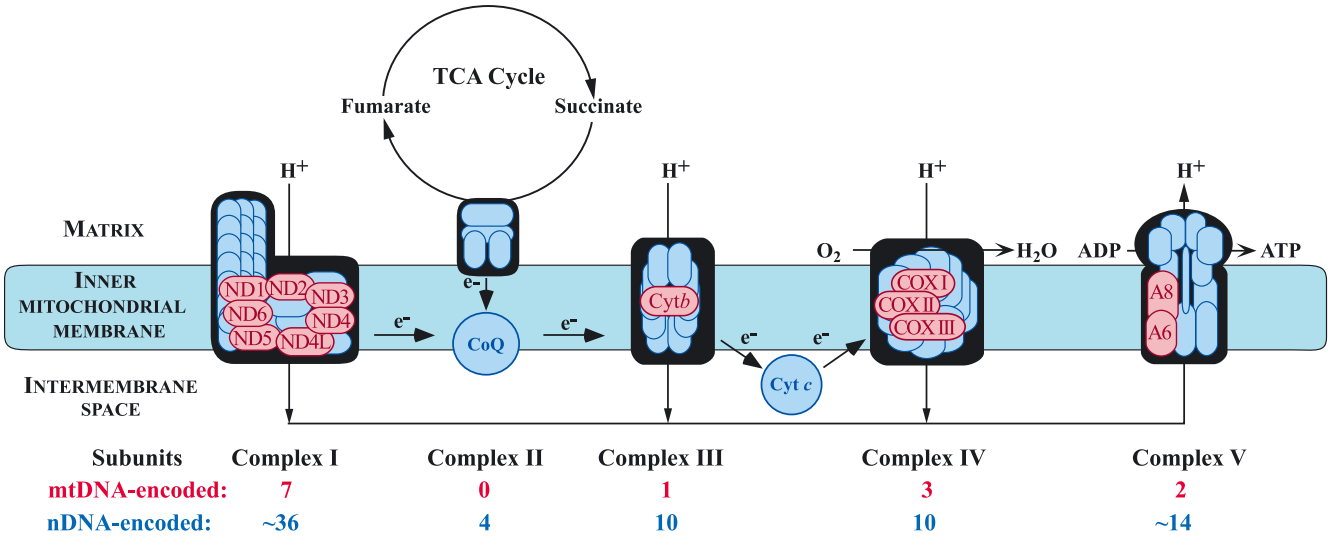

Fig. 2. Scheme of the respiratory chain, showing the mtDNA-encoded subunits in red and the nDNA-encoded subunits in blue. As electrons (e^-) flow along the electron transport chain, protons (H^+) are pumped from the matrix into the intermembrane space through complexes I, III, and IV. Protons then flow back into the matrix through complex V, producing ATP.

(i) *Heteroplasmy and threshold effect*. Each cell contains hundreds or thousands of mtDNA copies, which, at cell division, distribute randomly among daughter cells. In normal tissues, all mtDNA molecules are identical (homoplasmy). Deleterious mutations of mtDNA usually affect some but not all mtDNAs within a cell, a tissue, or an individual (heteroplasmy). The clinical expression of a pathogenic mtDNA mutation is largely determined by the relative proportion of normal and mutant mtDNA genomes in different tissues. A minimum critical number of mutant mtDNAs is required to cause mitochondrial dysfunction in a particular organ or tissue, resulting in a mitochondrial disease (threshold effect).

(ii) *Mitotic segregation*. At cell division, the proportion of mutant mtDNAs in daughter cells may shift and the phenotype may change accordingly. This phenomenon, called mitotic segregation, explains how certain patients with mtDNA-related disorders may actually manifest different mitochondrial diseases at different stages of their lives.

(iii) *Maternal inheritance*. At fertilization, all mtDNA derives from the oocyte. Therefore, the mode of transmission of mtDNA and of mtDNA point mutations (single deletions of mtDNA are usually sporadic events) differs from mendelian inheritance. A mother carrying a mtDNA point mutation will pass it on to all her children (males as well as females), but only her daughters will transmit it to their progeny. A disease expressed in both sexes but with no evidence of paternal transmission is strongly suggestive of a mtDNA point mutation. A recent surprising report cast doubts on the rule of maternal inheritance [8], but two simultaneous papers [9,10] and a further study from the "surprisers" [11] reiterated the general validity of maternal inheritance.

The best way for the clinician to chart his course toward a diagnosis in the clinical morass of mitochondrial diseases is to use a classification that combines genetic and biochemical criteria (Table 1). From the genetic point of view, there are two major categories, disorders due to defects of mtDNA and disorders due to defects of nDNA. Mutations in mtDNA can be divided into those that impair mitochondrial protein synthesis in toto (e.g. tRNA or rRNA genes mutations and rearrangements), and those that affect one of the 13 respiratory chain subunits encoded by mtDNA.

1.1. Defects in mitochondrial protein synthesis

1.1.1. mtDNA rearrangements

Single deletions of mtDNA have been associated with three usually sporadic conditions [12]: (i) Pearson syndrome (PS), a rapidly fatal disorder of infancy characterized by sideroblastic anemia and exocrine pancreas dysfunction; (ii) Kearns–Sayre syndrome (KSS), a multisystem disorder with onset before age 20 of impaired eye movements (progressive external ophthalmoplegia, PEO), pigmentary retinopathy, and heart block. Frequent additional signs include ataxia, dementia, endocrine problems (diabetes mellitus, short stature, hypoparathyroidism). Lactic acidosis, elevated cerebrospinal fluid (CSF) protein (over 100 mg/dl), and RRF in the muscle biopsy are typical laboratory abnormalities. (iii) PEO with or without proximal limb weakness, often compatible with a normal life span. Deletions vary in size and location, but a "common" deletion of 5 kb is frequently seen in patients and in aged individuals. (Fig. 3).

Duplication of mtDNA can occur in isolation or together with single deletions and have been seen in patients with KSS or with diabetes mellitus and deafness. Duplications and duplications/deletions (as well as the associated phenotypes) are rare and usually transmitted by maternal inheritance.

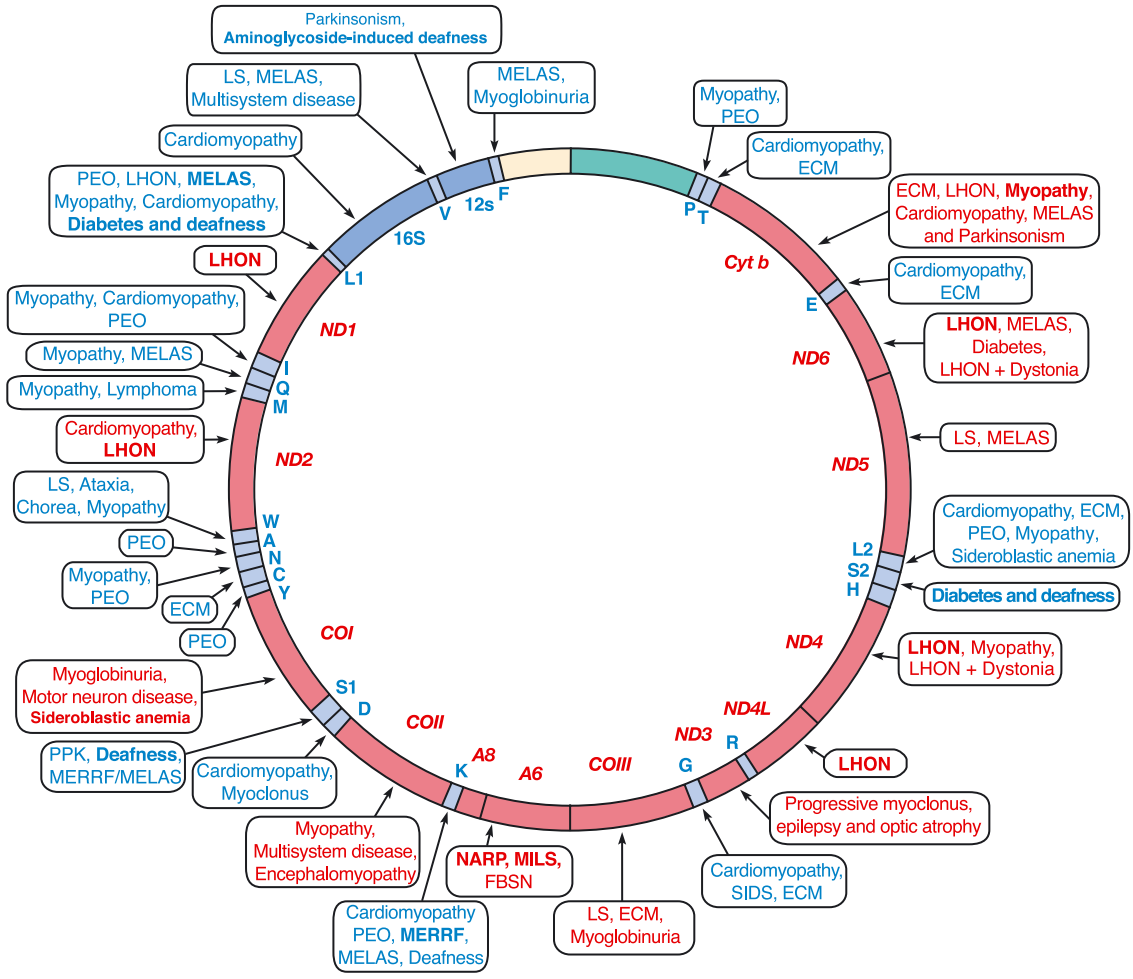

Fig. 3. Morbidity map of the human mitochondrial genome as of January 1, 2004. The map of the 16.569-kb mtDNA shows differently shaded areas representing the protein-coding genes for the seven subunits of complex I (ND), the three subunits of cytochrome oxidase (COX), cytochrome *b* (Cyt b), and the two subunits of ATP synthetase (A8/6), the 12S and 16S ribosomal RNAs (12S, 16S), and the 22 transfer RNAs (tRNA) identified by one-letter codes for the corresponding amino acids. Diseases due to mutations that impair mitochondrial protein synthesis are shown in blue; diseases due to mutations in protein-coding genes are shown in red. Reproduced from Ref. [1], with permission. Abbreviations: FBSN, familial bilateral striatal necrosis; KSS, Kearns–Sayre syndrome; LHON, Leber's hereditary optic neuropathy; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged-red fibers; MILS, maternally inherited Leigh syndrome; NARP, neuropathy, ataxia, retinitis pigmentosa; PEO, progressive external ophthalmoplegia.

1.1.2. mtDNA point mutations

Point mutations have been identified in mtDNA from patients with a variety of disorders, most of them maternally inherited and multisystemic, but some sporadic and tissue-specific (Fig. 2). Among the maternally inherited encephalomyopathies, two syndromes are more common.

The first is MELAS (*m*itochondrial *e*ncephalomyopathy, *l*actic *a*cidosis, and *s*troke-like episodes), which usually presents in children or young adults after normal early development [13]. Symptoms include recurrent vomiting, migraine-like headache, and stroke-like episodes causing cortical blindness, hemiparesis, or hemianopia. MRI of the brain shows "infarcts" that do not correspond to the distribution of major vessels. The most common mtDNA mutation is A3243G in the $tRNA^{Leu(UUR)}$ gene, but about a dozen other mutations have been associated with MELAS, some of which are in protein-coding genes.

The second syndrome is MERRF (*m*yoclonus *e*pilepsy with *r*agged *r*ed *f*ibers), characterized by myoclonus, seizures, mitochondrial myopathy, and cerebellar ataxia [14]. Less common signs include dementia, hearing loss, peripheral neuropathy, and multiple lipomas. Three mtDNA mutations, all in the $tRNA^{Lys}$ gene (A8344G, T8356C, G8363A), have been associated with MERRF. Only one patient with a bona fide MERRF syndrome harbored a mutation in a different tRNA: G611A in the $tRNA^{Phe}$ gene [15].

Not surprisingly, syndromes associated with tRNA mutations can affect every system in the body, including the eye (optic atrophy; retinitis pigmentosa; cataracts); hearing (neurosensory deafness); the endocrine system (short stature; diabetes mellitus; hypoparathyroidism); the heart (hypertrophic cardiomyopathies; conduction blocks); the gastrointestinal tract (exocrine pancreas dysfunction; intestinal pseudo-obstruction; gastroesophageal reflux); and the

kidney (renal tubular acidosis). Any combination of the symptoms and signs listed above should raise the suspicion of a mitochondrial disorder, especially if there is evidence of maternal transmission.

1.2. Defects of protein-coding genes

Also in this category, two syndromes are more common. The first syndrome comes in two flavors: (i) NARP (*n*europathy, *a*taxia, *r*etinitis *p*igmentosa) usually affects young adults and causes retinitis pigmentosa, dementia, seizures, ataxia, proximal weakness, and sensory neuropathy; (ii) *m*aternally *i*nherited *L*eigh *s*yndrome (MILS) is a more severe infantile encephalopathy with characteristic symmetrical lesions in the basal ganglia and the brainstem. Both conditions are due to mutations at nt-8993 of the ATPase6 gene [16]. The mutations also come in two flavors, T8993G and T8993C, the T-to-G transversion being both clinically and biochemically more deleterious than the T-to-C change [17]. In addition, the T8993G mutation provides an excellent example of the pathogenic importance of mutation load: when the degree of heteroplasmy is moderate (around 70%), the clinical expression is NARP, a subacute or chronic disease of young adults, but when the degree of heteroplasmy is very high (about 90%), the clinical expression is a rapidly progressive encephalopathy of infancy or childhood, Leigh syndrome [18].

The second syndrome, LHON (*L*eber's *h*ereditary *o*ptic *n*europathy) is characterized by acute or subacute loss of vision in young adults, more frequently males, due to bilateral optic atrophy [19]. About a dozen different mtDNA point mutations in structural genes have been associated with LHON, but only three appear to be pathogenic even when present in isolation (primary mutations) and all three affect genes of complex I (ND genes). These are G11778A in ND4, G3460A in ND1, and T14484C in ND6. The exquisite vulnerability of the optic nerve in LHON and the predominance of affected males remain to be explained and call into question additional genetic or environmental factors.

Interestingly, point mutations in mtDNA protein-coding genes often escape the rules of mitochondrial genetics in that they affect single individuals and single tissues, most commonly skeletal muscle [20] (Fig. 2). Thus, patients with exercise intolerance, myalgia and sometimes recurrent myoglobinuria may have isolated defects of complex I, complex III, or complex IV, due to pathogenic mutations in genes encoding ND subunits, COX subunits, and especially cytochrome *b* [21]. The lack of maternal inheritance and the involvement of muscle alone suggest that mutations arose de novo in myogenic stem cells after germ-layer differentiation (''somatic mutations'').

Given how crowded the ''morbidity map'' of mtDNA is (Fig. 2), we can legitimately ask whether we are scraping the bottom of the barrel in this area. My answer is a resounding ''no'' for the following reasons: (i) new mtDNA mutations are still being identified; (ii) accepted pathogenetic concepts are being challenged, including the invariably innocent nature of homoplasmic mutations and the high mutational load required for pathogenicity; (iii) dogmas of mitochondrial genetics are being cracked, including—as mentioned above—the strict maternal inheritance of mtDNA; (iv) the functional and pathogenic importance of mtDNA haplotypes is under intense investigation [22,23]; (v) unusual clinical phenotypes are associated with mtDNA mutations, such as autistic spectrum disorders [24]; (vi) the detailed pathogenesis of different encephalopathies is still unclear.

2. Diseases due to mutations in nDNA

Disorders due to mutations in nDNA are very numerous not only because most respiratory chain subunits are nucleus-encoded, but also—and more importantly—because correct structure and functioning of the respiratory chain requires many steps, all of which are under the control of nDNA. These steps include:

(i) nuclear factors are needed for the proper assembly of respiratory chain complexes. Mutations in these ancillary proteins have been associated with numerous disorders, notably Leigh syndrome.
(ii) mtDNA integrity and replication requires nDNA-encoded factors and there has been rapid progress in our understanding of the molecular basis of disorders of intergenomic signaling, including syndromes associated with multiple mtDNA deletions and mtDNA depletion.
(iii) transport of nDNA-encoded proteins from the cytoplasm into mitochondria. Hereditary defects in this complex machinery can cause mitochondrial diseases, although only relatively few such disorders have been documented.
(iv) the respiratory chain is embedded in the lipid bilayer of the inner mitochondrial membrane, which is more than a mere scaffold. Alterations of this lipid milieu can cause disease, as illustrated by altered synthesis of cardiolipin in Barth syndrome.
(v) mitochondria move around the cell, divide by fission, and fuse with one another. Disorders of these essential functions can also cause disease, as illustrated by autosomal dominant optic neuropathy.

2.1. Mutations in genes encoding subunits or ancillary proteins of the respiratory chain

As noted above, mtDNA encodes only 13 subunits of the respiratory chain, while nDNA encodes all subunits of complex II, most subunits of the other four complexes, as well as CoQ10 and cytochrome *c*. Although most of the progress in the first decade of the ''molecular era'' has been

in mtDNA-related disorders, attention has shifted towards mendelian defects of the respiratory chain. These can affect respiratory chain complexes directly or indirectly.

Direct "hits" are mutations in gene encoding respiratory chain subunits, including subunits of complex I [25] and of complex II [26]. These have been associated mostly with autosomal recessive forms of Leigh syndrome. Apparently primary coenzyme Q10 (CoQ10) deficiency can cause three major syndromes, a predominantly myopathic disorder with recurrent myoglobinuria, a predominantly encephalopathic disorder with ataxia and cerebellar atrophy, and a generalized form [27]. Presumably, the different presentations reflect mutations in different biosynthetic enzymes, but this remains to be documented. Diagnosis is important because all patients with CoQ10 deficiency respond to CoQ10 supplementation.

Indirect "hits" are mutations in genes encoding proteins that are not components of the respiratory chain, but are needed for the proper assembly and function of respiratory chain complexes. This "murder by proxy" scenario is best illustrated by mendelian defects of COX (complex IV). Mutations in five ancillary proteins, SURF1, SCO2, SCO1, COX10, and COX15, have been associated with COX-deficient Leigh syndrome [28–30] or other multisystemic fatal infantile disorders, in which encephalopathy is accompanied by cardiomyopathy [31,32] (SCO2, COX15), nephropathy [33] (COX10), or hepatopathy [34] (SCO1). Mutations in a complex III assembly protein, BCS1L, have also been associated with Leigh-like syndromes [35] and with a lethal infantile disorder dubbed GRACILE (*g*rowth *r*etardation, *a*minoaciduria, *c*holestasis, *i*ron overload, *l*actacidosis, and *e*arly death) [36,37]. The newest addition to this group of disorders is a defect of complex V due to mutations in the assembly protein ATP12, associated with congenital lactic acidosis and a fatal infantile multisystemic disease involving brain, liver, heart, and muscle [38].

This is a burgeoning field of research with important theoretical and practical implications. From an investigative point of view, these disorders are teaching us a lot about the structural and functional complexity of the respiratory chain. At a more practical level, identification of mutations in these genes renders prenatal diagnosis available and suggests approaches to therapy, such as copper administration to infants with mutations in SCO2, a protein involved in copper homeostasis in complex IV [39,40].

2.2. Defects of intergenomic signaling

As noted above, the mtDNA is highly dependent for its proper function and replication on numerous factors encoded by nuclear genes. Mutations in these genes cause mendelian disorders characterized by qualitative or quantitative alterations of mtDNA [41,42].

Examples of qualitative alterations include autosomal dominant or autosomal recessive *multiple deletions of mtDNA*, usually accompanied clinically by progressive external ophthalmoplegia (PEO) plus a variety of other symptoms and signs [43]. Four of these conditions have been characterized at the molecular level. Mutations in the gene for thymidine phosphorylase (*TP*) are responsible for an autosomal recessive multisystemic syndrome called MNGIE (*m*itochondrial *n*eurog*a*stro*i*ntestinal *e*ncephalomyopathy) [44,45]. Mutations in the gene encoding one isoform of the adenine nucleotide translocator (*ANT1*) have been identified in some, but not all, patients with autosomal dominant PEO [46]. Interestingly, both types of mutations affect mitochondrial nucleotide pools and may have similar pathogenic mechanisms. Mutations in a gene called *Twinkle*, a helicase, are associated with autosomal dominant PEO [47], whereas mutations in the gene encoding polymerase γ (*POLG*) may cause either autosomal dominant or autosomal recessive PEO, sometimes associated with psychiatric problems or parkinsonism [48,49].

Examples of quantitative alterations of mtDNA include severe or partial expressions of *mtDNA depletion*, usually characterized clinically by congenital or childhood forms of autosomal recessively inherited myopathy or hepatopathy [50,51]. Although skeletal muscle and liver seem to be the main target tissues, other tissues are often affected in both conditions, including kidney (renal tubular acidosis) and the central nervous system (CNS). CNS involvement often simulates spinal muscular atrophy (SMA) and mtDNA depletion should be considered in children with SMA phenotype but without mutations in the SMN gene [52,53]. Mutations in two genes, both involved in mitochondrial nucleotide homeostasis, have been associated with mtDNA depletion syndromes, although they do not explain all cases. Mutations in the gene encoding thymidine kinase 2 (*TK2*) are often seen in patients with myopathic mtDNA depletion syndromes [52,54], whereas mutations in the gene encoding deoxyguanosine kinase (*dGK*) predominate in patients with hepatic or multisystemic mtDNA depletion syndromes [55,56].

2.3. Defects of mitochondrial protein importation

Mitochondrial proteins synthesized in the cytoplasm are provided with mitochondrial targeting signals that direct them to the appropriate compartment within the organelle. Transport across outer and inner membranes requires a battery of factors, including docking proteins, chaperonins, and proteases, and it involves unfolding and refolding of the protein to be translocated [57]. Several mutations in targeting sequences have been documented, preventing individual proteins to reach their destination. In contrast, few genetic defects are known that impair the general transport machinery, presumably because the resulting upheaval in mitochondrial function would not be compatible with life [58]. However, at least two disorders have been associated with mutations in components of the transport machinery.

The first is an X-linked disease, the deafness-dystonia syndrome (Mohr–Tranebjaerg syndrome), which is characterized by neurosensory hearing loss, dystonia, cortical blindness, and psychiatric symptoms, and is due to mutations in the *TIMM8A* gene, which encodes the deafness-dystonia protein (DDP1), an intermembrane space component of the transport machinery [59].

The second is an autosomal dominant form of hereditary spastic paraplegia due to mutations in the chaperonin HSP60 [60].

2.4. Alterations of the lipid milieu of the inner mitochondrial membrane

This situation is exemplified by Barth syndrome (BTHS), an X-linked recessive disorder characterized by mitochondrial myopathy, cardiopathy, growth retardation, and leucopenia [61]. The tafazzin (*TAZ*) gene responsible for this disorder encodes a family of proteins (‘‘tafazzins’’) that are homologous to phospholipid acyltransferases [62]. Analysis of phospholipids in target tissues from patients with BTHS and *TAZ* mutations, patients with BTHS-like syndromes without *TAZ* mutations, and both normal and disease controls showed decreased cardiolipin in all tissues from genetically proven BTHS patients only [63,64]. Cardiolipin was affected selectively and other phospholipids were normal, and the molecular composition of cardiolipin was altered in all tissues from BTHS patients.

2.5. Alterations of mitochondrial motility or fission

Mitochondria are dynamic organelles propelled within the cell, sometimes long-distance (think of mitochondria traveling to the apical end of a motor nerve from the neuronal soma in the anterior horn of the spinal cord) by energy-requiring dynamins along cytoskeletal microtubular rails [65]. Mutations in a gene encoding a dynamin-related guanosine triphosphatase (*OPA1*) have been associated with an autosomal dominant form of optic atrophy resulting in early-onset blindness, the mendelian counterpart of LHON [66,67]. In monocytes from these patients, morphology has shown that mitochondria were clumped together rather than being uniformly distributed throughout the cytoplasm.

2.6. Late-onset neurodegenerative diseases and aging

While there is little question that mitochondrial dysfunction (*oxidative stress*) has a role both in the pathogenesis of late-onset neurodegenerative disorders, including Parkinson disease (PD), Huntington disease (HD), Alzheimer disease (AD), and amyotrophic lateral sclerosis (ALS), and in the pathogenesis of what has been called ‘‘the most common disease of all’’, aging, the relative contributions of the nuclear genome, the mitochondrial genome, and of environmental factors remain to be defined and probably vary in different conditions. Discussing this area of ‘‘mitochondrial medicine’’ is beyond the scope of this minireview, and the reader is referred to several comprehensive recent reviews [68–72].

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