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Mitochondrial genetic diseases

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Abstract

Purpose of review—Mitochondrial diseases are individually uncommon, but collectively pose a significant burden on human health. Primary mitochondrial disease is caused by defects in the mitochondrial DNA-encoded genes or in nuclear genes whose products are imported into the mitochondrion. Great strides have been made in determining the cause of mitochondrial disorders, but the clinical ability to diagnose these conditions lags behind because of phenotypic overlap between distinct genetic entities and the complexity and invasiveness of standard diagnostic testing. In this review, we evaluate new findings in mitochondrial genetics, recent developments in mitochondrial disease diagnostic testing, and emerging ideas for mitochondrial disease therapies.

Recent findings—Clinical cohort studies have revealed important themes in patient care relative to manifestations of mitochondrial disease. Significant strides have also been made toward creating embryos free from the risk of maternally inherited mitochondrial DNA-based disease. Several new genetic causes of both nuclear and mitochondrial DNA-based diseases have been identified in the past year. In addition, novel insights have emerged from basic studies of mitochondrial biology that hold promise for the development of targeted mitochondrial disease therapies.

Summary—Research on mitochondrial biology and disease continues to improve the clinical capacity to diagnose the heterogeneous group of mitochondrial diseases that afflict the pediatric population. This research also provides a framework for future approaches to devise effective mitochondrial disease therapies.

Keywords

diagnosis; mtDNA; nDNA; respiratory chain; therapy

Introduction

Since the first identification of mitochondrial DNA mutations associated with disease in 1988, there has been an explosion in the recognition of distinct nuclear and mitochondrial genetic causes of mitochondrial disease. Due to an improved understanding of mitochondrial pathology, the recognized incidence has escalated and the minimal prevalence of mitochondrial disease is now estimated at 1 in 5000 across all ages. Affected children present across nearly all pediatric disciplines, with a predominance of neurologic, muscular, cardiac, gastrointestinal, and ophthalmologic manifestations. While the diagnostic

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evaluation of suspected primary mitochondrial disease has embraced the rapidly changing landscape of genetic information, the overall diagnostic yield remains low for the highly heterogeneous group of mitochondrial disorders that are caused by mutations across two genomes. Strictly speaking, no cures for mitochondrial disease are known. Indeed, clinically available therapies currently remain limited to symptomatic management and prophylactic antioxidant and vitamin cofactor cocktails. In this context, we review outstanding mitochondrial disease research contributions published over the past year.

Studies of clinical mitochondrial disease cohorts

Mitochondrial disease can variably affect a wide range of systems. Here, we outline recent progress among several different clinical cohorts of mitochondrial disease.

Ophthalmologic manifestations

While ophthalmologic manifestations are common in mitochondrial disease, their relative frequency is unclear. A retrospective study of 59 patients with a mean age of 11 years old and confirmed pathogenic mtDNA mutations found that 81% had ophthalmologic manifestations [1]. In order of descending frequency, these included refractive errors, optic atrophy, reduced eye motility, low visual acuity, ptosis, severe external ophthalmoplegia, nystagmus, strabismus, and photophobia. A total of 28% of patients had abnormal macula and/or peripheral retinal pigmentation. Retinal dystrophy was present in 37% of patients evaluated by electroretinogram, including patients with Kearns–Sayre syndrome, Leigh syndrome, MELAS, MERRF, LHON, and myopathy. As ophthalmologic manifestations are present in the majority of mitochondrial disease patients, regular ophthalmologic examinations are warranted in all patients with mitochondrial disease.

Gastrointestinal pseudo-obstruction

A retrospective study of 80 patients with chronic intestinal pseudo-obstruction (CIPO), a rare disorder caused by intestinal dysmotility without fixed obstructive lesions, found mitochondrial defects in 19% of the study cohort [2]. Five patients had mutations in the thymidine phosphorylase gene, two had mutations in tRNA-Leu(UUR), and five had mutations in the DNA polymerase gamma gene. No genetic defect was detected in three patients with mitochondrial disorders. Mitochondrial CIPO patients were distinguished by very poor nutritional status that frequently required long-term parenteral nutrition as well as poor prognosis, extra-digestive symptoms, neurologic complications, and a high incidence of premature death. Although gastrointestinal dysmotility is common in primary mitochondrial disease, this study suggests that all patients with CIPO should be evaluated for mitochondrial defects.

Coenzyme Q_{10} deficiency

The primary coenzyme Q_{10} (CoQ_{10}) deficiencies are a rare group of mitochondrial diseases with the potential for effective treatment by supplemental CoQ_{10}. Nonetheless, any type of mitochondrial disease diagnosis is commonly accompanied by a recommendation to begin lifelong CoQ_{10} supplementation. The incidence of secondary CoQ_{10} deficiency in primary mitochondrial disease due to other genetic causes is unclear. A multicenter trial was performed to measure muscle CoQ_{10} content by HPLC quantitation among clinically heterogeneous patients having mitochondrial myopathy [3]. CoQ_{10} deficiency was identified in 37% of patients, including nine with pathogenic mtDNA mutations. These data confirm the value of considering CoQ_{10} supplementation in patients with mitochondrial myopathy.

Mitochondrial DNA-related research

Mutations in mtDNA account for up to approximately one-third of pediatric-onset and two-thirds of adult-onset mitochondrial diseases.

Methods for preventing maternal transmission of mtDNA mutations

With the prevalence of mitochondrial disease recognized to be in the order of 1 in 5000 and the incidence of asymptomatic carriers of low levels of heteroplasmic mtDNA pathogenic mutations to occur in the order of 1 in 250 live births, much attention has recently been focused on preimplantation genetic methodologies to reduce transmission of inherited mtDNA mutations [4–6]. As mtDNA is maternally transmitted, mtDNA-based disease might be preventable by nuclear transfer techniques in the setting of in-vitro fertilization. Transfer of the pronucleus between a fertilized human zygote and an enucleated egg results in minimal carry-over of donor zygote mtDNA and is compatible with onward development to the blastocyst stage *in vitro* [7]. Another group developed a preclinical model of mtDNA genome replacement in mature, nonhuman, primate (*Macaca mulatta*) oocytes [8]. Their approach involved spindle–chromosomal complex transfer to an enucleated recipient egg. The reconstructed oocytes could support normal fertilization, embryo development, and production of healthy offspring. No spindle donor mtDNA was identified in the three offspring created. Thus, pronuclear transfer between zygotes, as well as spindle replacement, may offer novel reproductive options to prevent maternally inherited mtDNA disease transmission. However, ethical and practical considerations remain, given the complexity of individual cases and the uncertainty surrounding future heteroplasmic loads and resulting disease burden in different tissues of offspring born following such procedures [5].

Benign cytochrome c oxidase deficiency

Most childhood-onset mitochondrial diseases are progressive and have a severe, if not fatal, outcome. There is a peculiar exception known as ‘benign cytochrome *c* oxidase deficiency myopathy.’ Infants with this condition present with profound hypotonia and lactic acidosis, appearing similar to other children with congenital lactic acidosis. Remarkably, however, affected children with this rare form of mitochondrial respiratory chain (RC) complex IV deficiency will spontaneously recover if they survive beyond the first few months of life. A homoplasmic m.14674T>C mt-tRNA(Glu) mutation was identified in 17 patients from 12 families with this condition [9]. Thus, a simple molecular test can now distinguish infants with mitochondrial myopathy who have a good prognosis.

Newly recognized mitochondrial disorders caused by mutations in nuclear genes

Much of the burden of pediatric mitochondrial disease is due to mutations in nuclear genes whose products localize to the mitochondrion. New forms of mitochondrial disease with nuclear origin are continually described, and the last year has seen several new examples of associations between nuclear mutations and mitochondrial diseases (Table 1).

Novel defects in proteins having supporting roles for respiratory chain function

Duncan and colleagues used homozygosity mapping to map a defect in CoQ_{10} biosynthesis in a proband with profound lactic acidosis in the newborn period [10]. The defect in *COQ9* was studied in yeast, where a mutation homologous to that in the patient was sufficient to eliminate respiratory growth. The approach to genetic discovery in this study was noteworthy, as the investigators used homozygosity by descent in an ostensibly nonconsanguineous family to identify small candidate regions that were cross-referenced to genes involved in CoQ_{10} synthesis. In an equally impressive feat of genetic discovery, SNP

mapping of an affected pedigree with progressive Leigh syndrome in combination with micro-cell-mediated transfer of chromosome fragments was used to identify mutations in a new mitochondrial translation factor, translation activator of cytochrome c oxidase 1 (*TACO1*) [11]. Studies of the identified gene in yeast and patient cells suggested that *TACO1* is a specific activator of translation for a mitochondrial complex IV subunit (COXI), thus representing a novel pathogenic mechanism for mitochondrial disease.

Novel defects in nuclear-encoded subunits and assembly factors of respiratory chain complexes

Several disorders were described that directly affected electron transport complex formation or stability. Mutations in *NDUFAF3* were identified in three families with undiagnosed complex I deficiency. The importance of these mutations was illustrated by both complementation analysis and demonstration of an interaction between *NDUFAF3* and another complex I assembly gene, *NDU-FAF4*, which had previously been associated with mitochondrial disease due to complex I deficiency [12]. The first patient with a mutation in the structural complex V subunit, *ATP5E*, was also reported. This child had neonatal lactic acidosis, developmental delay, and methylglutaconic aciduria, features reminiscent of those seen in patients with mutations in two other subunits of complex V, *TMEM70* and *ATP12* [13].

Cytogenetically visible or comparative hybridization detectable aberrations in the nuclear genome have been linked to mitochondrial disorders. An unusual, homozygous, contiguous deletion that included a complex I assembly factor and a gene involved in fatty acid synthesis was linked to a fatal multisystem disorder in a dysmorphic child with lactic acidosis [14]. The mitochondrial complex I assembly factor gene encompassed by this deletion, *NDUFAF2*, has been previously associated with mitochondrial cytopathies. This study illustrates the importance of pursuing microarray-based genomewide copy number analysis in complex cases that include suspected mitochondrial disease phenotypes.

Novel diagnostic approaches for mitochondrial disease

The diagnosis of mitochondrial disease requires a multifaceted approach, including a range of genetic testing as well as biochemical analyses.

Mitochondrial DNA depletion syndromes

Improvements in the speed, specificity, and sensitivity of mitochondrial testing are keys to improving diagnostic success rates. An extensive retrospective evaluation of a large cohort of patients who had been screened for mitochondrial DNA depletion syndromes (MDS) yielded valuable guidelines for interpretation of mtDNA copy number data in various tissues. The study confirmed that blood and fibroblast-derived DNA had limited utility for reliable detection of mtDNA depletion. Analyses performed in liver, and to a lesser extent in muscle, gave the most clinically relevant results [15]. Of note, liver mtDNA quantitation detected abnormalities in patients with *TK2* mutations, which have been traditionally linked to depletion within muscle. These data imply that liver samples are the gold standard for MDS evaluations, regardless of the phenotype.

Biochemical and imaging studies of the mitochondrial electron transport chain

Enzymatic analyses of muscle samples are a standard evaluation of mitochondrial function, although obtaining proper tissue samples for analysis can be a practical barrier to their performance. The orbicularis oculi muscle can easily be collected during routine blepharoplasty or ptosis surgery (common in the patient population with mitochondrial disease), circumventing the need for a standard muscle biopsy of quadriceps muscle. One

study used this source to achieve accurate diagnoses in 9 of 10 patients, reducing patient morbidity and diagnostic cost [16]. On a cautionary note, however, the utility of enzymatic studies, often considered ‘gold standard’ in mitochondrial disease, was found to be limited in some classes of disease [17]. A retrospective analysis of muscle biopsies performed in patients with tRNA point mutations showed that abnormalities in respiratory chain enzyme activity were no more frequent than would have been expected due to chance. Using a different approach, Jonckheere and colleagues developed a low labor-intensive method for studying oxygen consumption using fluorescence-based detection in digitonin-permeabilized fibroblasts [18].

Blue native gel in-vitro separation of electron transport complexes has been used to identify structural lesions in electron transport complexes, often aiding in the diagnostic evaluation when specific blue native findings correlate with particular causes of disease. A study of patients who formed abnormal subcomplexes of complex V showed that an unusually high number of these patients had mtDNA lesions rather than nuclear defects [19]. On a larger scale the ability to infer mitochondrial failure from diagnostic imaging can facilitate disease diagnosis. However, a retrospective study of MRI imaging suggested that imaging may have no discriminatory value in distinguishing patients with primary mitochondrial disease from those without [20].

Genetic analyses of mitochondrial disorders

When consideration is given to sequencing mtDNA to detect point mutations, the most clinically affected tissue, usually muscle or liver, is typically recommended for analysis, since blood cells may not contain the pathogenic mutation. Fortunately, recent research suggests mtDNA sequence analysis in urine may be as accurate as tissue-based detection in some conditions. Heteroplasmic load of the common m.3243A>G mutation in uroepithelial cells closely correlated with that in clinically affected tissues and was found to be stable over time, indicating the utility of assaying this noninvasive source of mtDNA [21].

Another sequencing technology that will play an expanding role in mitochondrial disease evaluation is massively parallel or ‘next-generation’ sequencing. The promise and pitfalls of this technology were described in a study of two patients harboring previously known nuclear gene mutations whose blood DNA was reanalyzed by sequencing of the entire mitochondrial genome and targeted nuclear genes of interest [22]. Causative mutations were identified in both cases, although a large number of extraneous polymorphisms were also detected. These sequence variants will typically require clinical interpretation in the setting of diagnostic uncertainty, imposing a significant burden on clinical diagnostic laboratories and managing physicians. The superior capability of massively parallel sequencing to reliably identify low-level mtDNA mutation heteroplasmy is also now clear, which greatly exceeds the detection range of conventional Sanger sequencing [22].

Novel treatment approaches to mitochondrial disease

Given the heterogeneity of mitochondrial disease causes, a multifaceted approach will be necessary to effectively treat diverse disease manifestations.

Modifiers of mitochondrial pathways

RC function is regulated in part by protein phosphorylation. This appears to result from a mitochondrial signaling pathway that includes soluble adenylyl cyclase (mt-sAC). mt-sAC modulates RC activity, particularly at complex IV or cytochrome *c* oxidase (COX). Researchers have recently demonstrated in both cultured cells and COX-deficient animals that the mt-SAC pathway modulates mitochondrial biogenesis [23]. mt-SAC upregulation normalizes production of reactive oxygen species and mitochondrial biogenesis to restore

mitochondrial function. Thus, manipulation of mitochondrial signaling pathways may offer a novel means to treat COX deficiency.

Another pathway that may have therapeutic relevance for primary mitochondrial disease is the PPAR-γ signaling pathway. Expression profiling in a mouse model of Friedrich's ataxia (FRDA) identified transcriptional signatures consistent with increased lipogenesis in skeletal muscle and altered fiber-type composition in heart, processes known to be regulated by the PPAR-γ pathway [24]. Modulation of the PPAR-γ pathway *in vitro* affects frataxin levels, suggesting that PPAR-γ modulation may be a therapeutic target in FRDA. Further importance of the PPAR signaling family to mitochondrial function was suggested by an investigation of PGC-1-related coactivator (PRC) [25]. Silencing of PRC inhibited respiratory growth, reduced expression of RC protein subunits, lowered complex I and IV activity, and led to diminished ATP production. These data support a role for PRC in the integration of pathways directing mitochondrial respiratory function and cell growth. Recent work in cellular and animal models of mitochondrial disease further demonstrated that increased mitochondrial biogenesis can boost residual OXPHOS capacity and prevent bioenergetic crisis [26]. Indeed, beneficial effects of endurance exercise in a mouse model of mitochondrial myopathy were recently shown to be mediated by increased muscle PGC-1 α. Exercised animals had increases in mitochondrial biogenesis, residual respiratory capacity, lifespan, and ATP levels, as well as delayed onset of myopathy [27].

Antioxidant therapies

Mitochondrial diseases cause impaired cellular redox balance and increased oxidant stress. Recently, researchers demonstrated that glutathione level may be a useful biomarker to detect redox imbalance in mitochondrial disorders [28]. Glutathione levels were low in T lymphocyte subsets, monocytes, and neutrophils from mitochondrial patients at baseline, but normalized when patients were treated with antioxidant supplements. Such redox testing may provide a relatively noninvasive means to monitor mitochondrial disease status and response to therapies. Additional evidence to support a useful role for antioxidants in primary mitochondrial dysfunction was provided by 6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid (Trolox) treatment of fibroblasts from complex I-deficient patients [29]. Treatment with Trolox normalized membrane potential, increased ER calcium, and enhanced the bradykinin-induced increase in cellular calcium concentration. These data highlight not only the occurrence of increased reactive oxygen species levels in complex I deficiency, but the therapeutic value of antioxidant therapy. Similarly, a case report of a Leigh syndrome patient demonstrated improvements in brainstem function, particularly respiratory function, following the treatment with a CoQ_{10} derivative, idebenone [30]. Finally, butin, a flavonoid that scavenges superoxide and hydroxyl radicals, decreased mitochondrial reactive species accumulation, balanced intracellular calcium levels, and improved mitochondrial energy production in a Chinese hamster lung fibroblast cell line exposed to hydrogen peroxide [31]. Taken together, these studies suggest that the mitochondrial-targeted antioxidants may have an important role in the treatment of primary mitochondrial RC dysfunction.

Nutritional therapies for mitochondrial depletion syndromes (MDS)

MDS, only uncovered in the beginning of this decade, have been the subject of considerable research but as yet have no effective treatments. A study of three siblings with MDS due to *MPV17* mutations suggested that avoidance of fasting by regular carbohydrate feedings or the provision of intravenous glucose could improve liver function and clinical outcomes [32]. There was surprisingly little risk in this treatment strategy, as exemplified by a lack of lactic acidemia after glucose loading. In contrast to carbohydrate restriction strategies occasionally used in the management of mitochondrial disease patients, these data suggest

that some may benefit from similar nutritional therapies used in patients with other inborn errors of metabolism. In particular, this report suggests that appropriate care may include the provision of high-level carbohydrates during acute illness.

Conclusion

Mitochondrial disorders continue to present significant challenges to physicians and scientists. Despite decades of research, complete understanding of the genetic origins of mitochondrial disease remains elusive. The clinical overlap between patients with similar genetic defects complicates the diagnostic search in individual patients. Therapies remain symptom-driven, rather than curative. Nonetheless, ongoing research increases understanding with each passing year, as we move incrementally closer to the goal of developing effective treatments for the heterogeneous group of mitochondrial diseases.

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Table 1
Recently identified nuclear-encoded mitochondrial disease genes

Nuclear gene	Clinical phenotype	Gene role
COQ9 [10]	Neonatal lactic acidosis Hypertrophic cardiomyopathy	CoQ_{10} biosynthetic enzyme
TACO1 [11]	Leigh syndrome	Mitochondrial translation
NDUFAF3 [12]	Leigh syndrome	Complex I assembly factor
ATP5E [13]	Neonatal lactic acidosis	Complex V assembly factor