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Review

Human diseases with impaired mitochondrial protein synthesis

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ABSTRACT

Mitochondrial respiratory chain deficiencies represent one of the major causes of metabolic disorders that are related to genetic defects in mitochondrial or nuclear DNA. The mitochondrial protein synthesis allows the synthesis of the 13 respiratory chain subunits encoded by mtDNA. Altogether, about 100 different proteins are involved in the translation of the 13 proteins encoded by the mitochondrial genome emphasizing the considerable investment required to maintain mitochondrial genetic system. Mitochondrial protein synthesis deficiency can be caused by mutations in any component of the translation apparatus including tRNA, rRNA and proteins. Mutations in mitochondrial rRNA and tRNAs have been first identified in various forms of mitochondrial disorders. Moreover abnormal translation due to mutation in nuclear genes encoding tRNA-modifying enzymes, ribosomal proteins, aminoacyl-tRNA synthetases, elongation and termination factors and translational activators have been successively described. These deficiencies are characterized by a huge clinical and genetic heterogeneity hampering to establish genotype–phenotype correlations and an easy diagnosis. One can hypothesize that a new technique for gene identification, such as exome sequencing will rapidly allow to expand the list of genes involved in abnormal mitochondrial protein synthesis.

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1. Introduction

Oxidative phosphorylation (OXPHOS), i.e., ATP synthesis and the oxygen-consuming respiratory chain (RC), supplies most organs and tissues with a readily utilizable energy source, being already functional before birth. Consequently, OXPHOS deficiency can theoretically give rise to any symptom, in any organ or tissue, at any age, with any mode of inheritance, due to the twofold genetic origin of OXPHOS components (nuclear DNA and mitochondrial DNA). Mitochondrial OXPHOS deficiencies represent one of the major causes of metabolic disorders with a prevalence estimated at 1/8500 birth [10]. These disorders represent a heterogeneous group of genetic diseases and can be caused by genetic defects in mitochondrial or nuclear DNA. This review will focus on mitochondrial diseases related to impaired translation of the 13 proteins encoded by the mitochondrial DNA.

1.1. The mitochondrial respiratory chain

The mitochondrial OXPHOS catalyzes the oxidation of fuel molecules by oxygen and the concomitant energy transduction into ATP via five complexes, embedded in the inner mitochondrial membrane [19]. Complex I (NADH–coenzyme Q reductase) carries reducing equivalents from NADH to coenzyme Q (CoQ, ubiquinone) and consists of more than 40 different polypeptides. Complex II (succinate–CoQ reductase) carries reducing equivalents from $FADH_2$ to CoQ and contains 4 polypeptides, including the FAD-dependent succinate dehydrogenase and iron–sulfur proteins. Complex III (reduced CoQ–cytochrome c reductase) carries electrons from CoQ to cytochrome c. It contains 11 subunits. Complex IV (cytochrome *c* oxidase, COX), the terminal oxidase of the RC, catalyzes the transfer of reducing equivalents from cytochrome *c* to molecular oxygen. It is composed of 2 cytochromes (a and a_3), 2 copper atoms and 13 different protein subunits.

The mitochondrial OXPHOS is made up of about 100 different proteins. Only 13 of them are encoded by mitochondrial genes and the others by nuclear genes. All complexes of the OXPHOS, except complex II have a double genetic origin. Indeed, 1 to 7 subunits of these complexes are mitochondrially encoded. Moreover, it is hypothesized that several hundreds of nuclear genes are also needed for various functions of the OXPHOS. Therefore, the number of mitochondrial proteins represents more than 3% of all the cellular proteins.

1.2. The mitochondrial DNA

The human mitochondrial DNA (mtDNA) is a 16,569 base pair double stranded circular molecule. Mitochondrion makes a large reticular network and contains several molecules of mtDNA. This

Abbreviations: AARS, aminoacyl-tRNA synthetase; LSFC, Leigh Syndrome French Canadian variant; MLASA, mitochondrial myopathy, lactic acidosis and sideroblastic anemia; MRP, mitochondrial ribosomal proteins; mt, mitochondrial; mtDNA, mitochondrial DNA; OXPHOS, oxidative phosphorylation; PEO, progressive external ophthalmoplegia; RC, respiratory chain; rRNA, ribosomal RNA; SNHL, sensorineural hearing loss; tRNA, transfer RNA

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compact genome lacks introns and contains only one major non-coding region, the displacement or D-loop which contains the promoters for transcription initiation. This genome is present at hundreds to thousands of copies per cell. This molecule contains 13 genes for key OXPHOS subunits. ND1–ND6 are subunits of complex I, cytochrome *b* (cytb) is the only mitochondrially encoded subunit of complex III, COXI–COXIII are subunits of complex IV and ATP6, ATP8 of ATP synthase (complex V). Moreover, mtDNA encodes a large and a small ribosomal RNA (12S rRNA and 16S rRNA) and 22 transfer RNAs (tRNA) scattered along the entire molecule.

The mitochondrion has independent replication, transcription and translation systems. The mitochondrial genome is replicated in two times. The replication starts at the heavy strand replication origin (OH) and extends clockwise around the mtDNA. When the light strand replication origin (OL) is exposed as a single strand, the second strand is then replicated in the opposite direction, starting from OL [11]. Thus, replication is bi-directional but asynchronous. Recently, a new model of mtDNA replication has been proposed in mammals. The mtDNA replication arises from multiple origins and proceeds by a strand-coupled mechanism [58]. The two mtDNA strands are transcribed from specific promoters into polycistronic RNAs, which are further, processed into ribosomal RNAs (rRNA), transfer RNAs (tRNA) and messenger RNAs (mRNA). The mitochondrial mRNAs are translated in the mitochondrial matrix using nuclearly encoded machinery, but following a specific genetic code, different from the nuclear one.

During cell division, mitochondria are randomly partitioned in daughter cells (mitotic segregation). Usually all the mtDNA molecules are identical, but sometimes a mixture of wild type and mutant mtDNA is encountered. This situation is called heteroplasmy, whereas homoplasmy refers to the occurrence of only one type of mtDNA. In heteroplasmic cells, the mtDNA genotype can shift during cell replication. Consequently, some lineages drift toward wild-type mtDNA and become homoplasmic, while others remain heteroplasmic.

The mitochondrial genome is maternally transmitted. The mother transmits her mtDNA to all her progeny, males and females, and her daughters transmit their mtDNA to the next generation. Theoretically, males never transmit their mtDNA.

1.3. The nuclear genes

The majority of mitochondrial proteins are encoded by nuclear genes. Mitochondria contain around 1100–1400 proteins [8] and several hundreds of them are related to RC. These genes encode subunits of the RC, proteins involved in the assembly of the OXPHOS complexes, in synthesis of cofactors, in mtDNA metabolism and maintenance (mtDNA replication, transcription, repair, and dNTP synthesis), in translation of the 13 OXPHOS subunits of mitochondrial origin.

2. The mitochondrial protein synthesis

The mitochondrial mRNA translation allows the synthesis of the 13 OXPHOS subunits encoded by mtDNA. The mammalian mitochondrial protein synthesis apparatus is not completely known. It resembles its prokaryotic counterpart but obviously presents specific characteristics. It is also different from the cytosolic translation machinery and apart few rare examples has a specific machinery.

The mitochondrial genetic code shows several differences from the universal code. AUA codes for methionine and not for isoleucine. UAG is used as stop codon. Finally, UGA serves as codon for tryptophan rather than a stop codon. The mammalian mtDNA contains only 22 tRNA genes that are sufficient to read all codons with a mechanism unique to mitochondrial system. The mitochondrial mRNAs contain very few nucleotide in the 5′-end untranslated (UTR) regions and cap structure.

The proteins encoded by mtDNA are all hydrophobic proteins located in the inner mitochondrial membrane. Mitochondrial mRNA translation has been suggested to take place in a complex bound to the inner membrane through electrostatic force and may also be through protein interaction [27]. At least one inner membrane protein, LETM1, has been suggested to serve as an anchor protein for complex formation with the mitochondrial ribosome [32]. This protein seems also to be involved in Ca^{2+} transport [54]. Yeast Oxa1 protein, which facilitates the cotranslational insertion of the nascent polypeptide chains into the mitochondrial inner membrane, is closely associated to the large ribosomal subunit protein, MrpL40 [22]. It should also be mentioned that translational activator proteins in yeast are integral membrane proteins or bound to the mitochondrial inner membrane.

The mitochondrial ribosomal and transfert RNAs (rRNAs and tRNAs) are encoded by mtDNA but all proteins of the translation machinery are encoded by nuclear genes. The mitochondrial protein synthesis requires ribosomal proteins, ribosomal assembly proteins, aminoacyl-tRNA synthetases, tRNA-modifying enzymes, rRNA methylating enzymes such as TFB1M and several initiation, elongation and termination translation factors. Altogether, about 150 different proteins are involved in the translation of the 13 proteins encoded by the mitochondrial genome emphasizing the considerable investment required to maintain a mitochondrial genetic system.

3. Protein synthesis deficiencies in human

Protein synthesis deficiency can be caused by mutations in any component of the translation apparatus including tRNA, rRNA and proteins. It can therefore present any mode of inheritance. Until now only maternal and autosomal recessive transmission of these deficiencies has been observed. These protein synthesis anomalies result in OXPHOS deficiency affecting theoretically all complexes containing mitochondrially encoded subunits sparing complex II. The aim of this review is to describe the various molecular mechanisms of protein synthesis deficiencies in human. For reviews on mitochondrial protein synthesis in mammals see Refs. [45,49].

3.1. Mitochondrial tRNA mutations

The first mutations affecting mitochondrial mRNA translation were described 20 years ago. The A3243G mutation in the $tRNA^{Leu(UUR)}$ (*MTTL1*) gene is responsible for mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome [17]. MELAS is characterized by onset in childhood with intermittent hemicranial headache, vomiting, proximal limb weakness, and recurrent neurological deficit resembling strokes (hemiparesis, cortical blindness, hemianopsia), lactic acidosis and occasionally ragged red fibers in the muscle biopsy. CT brain scan shows low-density areas (usually posterior) which may affect both white and gray matter but does not always correlate to clinical symptoms or vascular territories The pathogenesis of stroke-like episodes in MELAS has been ascribed to either cerebral blood flow disruption or acute metabolic decompensation in biochemically deficient areas of the brain. Additional mutations in this gene have been reported in association with MELAS or MELAS/myopathy syndrome [38]. This gene is a hotspot for pathogenic mutations.

In the following years more than 150 mutations in tRNAs have been described in association with various clinical presentations (encephalopathy, encephalomyopathy, Leigh syndrome, myopathy, chronic progressive external ophthalmoplegia, Fig. 1). One of the most common is the A8344G missense mutation in the mt $tRNA^{Lys}$ gene that accounts for 80% of Myoclonus Epilepsy with Ragged Red Fibers (MERRF) cases [44]. This disease is characterized by an

encephalomyopathy with myoclonus, ataxia, hearing loss, muscle weakness and generalized seizures. The tRNA^{Ile} gene is the third most commonly mutated tRNA gene. Different mutations of this gene are associated with cardiomyopathy and PEO. These mutations are usually heteroplasmic and maternally inherited. Some of the tRNA gene mutations are restricted to only one family and the pathogenicity of all these mutations has not been always established. The tRNA$^{Leu(UUR)}$, tRNA^{Lys}, and tRNA^{Ile} mutations represent almost half of the known mutations associated with definite and probable pathogenicity [41].

The effect of these mutations on protein synthesis is of variable nature. The 3243A>G MELAS mutation affects the stability of tRNA$^{Leu(UUR)}$ [5]. It also prevents taurine modification in the anticodon. Finally it has been demonstrated that this mutation decreases the stability of the mitochondrial translation products and induces amino acid misincorporation in the mitochondrial translation product demonstrating that the A3243G mutation produces both loss- and gain-of-function phenotypes [40].

3.2. Mitochondrial rRNA mutations

Ribosomal RNA (rRNA) mutations are associated with aminoglycoside-induced deafness. The A1555G mutation in the 12S rRNA gene was first described in a large Arab–Israeli pedigree [34] and subsequently found in many families of various ethnic backgrounds [56]. The incidence of the A1555G mutation varies from 0.6 to 2.5% of the Caucasian clinical population but is higher in Asia (2.9% in China, 3% in Japan, and 5.3% in Indonesia). Surprisingly, 17% of Spanish population with postlingual non-syndromic hearing loss carried this mutation. Usually, the A1555G mutation occurs in homoplasmy, but in some families the heteroplasmic state was identified [14]. Sensorineural hearing loss (SNHL) for this mutation may be triggered by the use of aminoglycosides, and may also occur without exposure to these drugs [53]. In the absence of aminoglycosides, the A1555G mutation produces a variable clinical phenotype among family members [34]. Also, the penetrance differs between families for this mutation. In some pedigrees, most of the individuals carrying the A1555G mutation subsequently develop SNHL, but, in others, the penetrance may be extremely low [56]. These findings indicate that the A1555G mutation itself is not sufficient to produce a clinical phenotype but requires the involvement of modifier factors for the phenotypic expression.

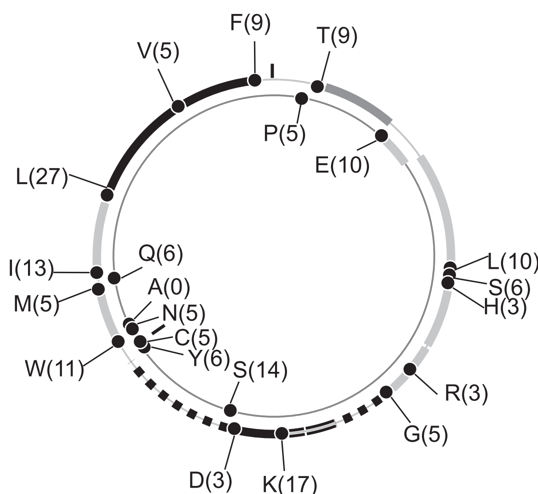

Fig. 1. Mitochondrial DNA strucutre and tRNA mutations. The letters indicate the various tRNA and the numbers between brackets the number of different mutations of each tRNA according to Ref. [38].

3.3. Messenger RNA stability

After processing of the polycistronic RNAs, mRNAs are oligo or polyadenylated at the 3′ termini. This polyadenylation is crucial not only for maintaining global mRNA steady-state levels but also allows to optimize mitochondrial protein synthesis. A homozygous mutation in *MTPAP* gene, encoding the poly(A) RNA polymerase was identified in an Amish family with spastic ataxia that resulted in severely truncated poly(A) tails [13].

3.4. Abnormal tRNA modification

The maturation of transfer RNA (tRNA) involves a number of nucleoside modifications necessary for their proper physiological functioning. This influences both their structural and functional properties, including structure stabilization, amino-acylation and codon recognition. For example, the folding of tRNA^{Lys} into cloverleaf structure and aminoacylation of tRNA^{Ile} are dependant of specific base modifications of the tRNAs [20]. In mammalian mitochondrial tRNAs one nucleotide in 17–18 is modified [20]. Several mitochondrial tRNA modifications have been identified in human but the proteins involved in these modifications are far from being all identified.

PUS1 encodes a pseudouridine synthase that converts uridine into pseudouridine after the nucleotide has been incorporated into RNA of several cytosolic and mitochondrial tRNA. This modification plays an essential role in tRNA function and in stabilizing their secondary and tertiary structures. Pseudouridylation is the most frequently found modification in tRNAs and seems to increase the protein synthesis efficiency. Mutations of this gene have been identified by homozygosity mapping in patients with mitochondrial myopathy, lactic acidosis and sideroblastic anemia (MLASA) [7] (Table 1, Fig. 2). Some patients also had mental retardation and microcephaly. The clinical presentation can be markedly different between patients and it has been suggested that the double localization of PUS1, and its effects on two spatially and functionally separated translational machineries, may account, at least in part, for the variability in the clinical presentations. However, a relatively similar syndrome is related to mutations of the mitochondrial tyrosyl-tRNA synthetase (*YARS2*, see below) suggesting that abnormal cytosolic translation is not the only factor involved in clinical heterogeneity of *PUS1* mutations.

TRMU encodes mitochondria-specific tRNA-modifying enzyme that is required for the 2-thio modification of 5-taurinomethyl-2-thiouridine tRNA-Lys on the wobble position of the anticodon. This gene has been identified as a nuclear modifier able to modulate the phenotypic manifestation of human mitochondrial 12S rRNA mutations associated with deafness. Indeed, the A1555G and C1494T mutations, although primary factors underlying the development of deafness, are not alone sufficient to produce a deafness phenotype [18]. Interestingly, all members of various families carrying both a TRMU A10S replacement and the 12S rRNA mutations exhibited prelingual profound deafness. More recently, linkage analysis and candidate gene sequencing allowed to determine that TRMU mutations result in acute infantile liver failure [59] (Table 1, Fig. 2). Several of these patients died before 1 year of age but part of them surviving the initial acute episode, showed clinical and biochemical resolution of liver failure and had no further episodes. The mitochondrial translation defect observed in the patients could be related from reduced modification of thio-modified mitochondrial tRNAs.

3.5. Abnormal ribosomal proteins

The 55S mammalian mitochondrial ribosome consists of a small (28S) and a large subunit (39S). The small subunit (SSU) contains a 12S rRNA and 30 proteins while the large subunit contains of a 16S rRNA and 48 proteins [24,25]. Both the 12S and the 16S rRNAs are

encoded by the mitochondrial genome but all ribosomal proteins (MRP) are nuclearly encoded. This will obviously require coordinate expression of nuclear and mitochondrial genomes. The protein:RNA ratio in the mitochondrial ribosome is the inverse of that of its prokaryotic counterpart and it was thought for long that the additional and/or larger proteins of the mitochondrial ribosome must compensate for the shortened rRNAs. However, it has been found that the enlarged and additional proteins present in the mitoribosome do not necessarily compensate for the missing rRNA segments but that these proteins occupy new quaternary positions in both subunits of the mitoribosome [43]. Whereas rRNA have catalytic function, ribosomal proteins not only have structural but also biological functions in translation [6].

Up till now, mutations in two mitochondrial ribosomal proteins only have been reported [28,39]. MRPS16 mutation was found in a patient with agenesis of the corpus callosum, muscle hypotonia and hyperlactatemia [28]. MRPS22 mutation results in hypotonia, cardiomyopathy and tubulopathy [39]. A recently reported MRPS22 mutation was found in a patient with brain anomalies, hypertrophic cardiomyopathy and Cornelia de Lange-like phenotype [48] (Table 1, Fig. 2). Both proteins were part of the SSU and their mutations not only result in reduced amounts of the corresponding proteins but also in a partial assembly of the SSU. Indeed another small subunit protein, MRPS11, and the 12S rRNA were decreased in cultured skin fibroblasts of these patients [16] whereas the large subunit was still present despite a non-functional small subunit. Further identification of SSU protein mutations will indicate if other proteins are essential for SSU assembly and probably will help in understanding the normal assembly of the mitochondrial ribosome.

A correct assembly of the mitochondrial ribosome certainly involves several factors but few of them are known. It has been shown in yeast that Afg3/Yta10 *m*-AAA protease, involved in protein quality control, also regulates ribosome assembly by controlling proteolytic maturation of Mrpl32 protein [31]. Loss of function mutations in the human corresponding protein, paraplegin, results in hereditary spastic paraplegia [9].

3.6. Abnormal aminoacyl-tRNA synthetases

To initiate translation, aminoacyl-tRNA synthetases (AARSs) must first catalyze the ligation of specific amino acids to their cognate tRNAs. The correct recognition of amino acids and tRNAs by these enzymes is crucial for the fidelity of protein synthesis. Whereas tRNAs are encoded by mtDNA, AARSs are all encoded by nuclear genes, translated in the cytosol and then imported in the mitochondria. The mitochondria use 20 different AARSs, three of them also acting in the cytosol (GARS, KARS, and QARS). These three enzymes are thus essential for protein synthesis in both cellular locations [1]. Whereas few mutations have been reported in cytosolic AARSs, more and more mutations in mitochondrial AARSs are now reported [1]. GARS and YARS mutations have been reported in autosomal dominant forms of Charcot–Marie–Tooth disease type 2D (CMT2D) and dominant intermediate Charcot–Marie–Tooth disease (DI-CMT) respectively [1]. However, there is no evidence for mitochondrial involvement in these diseases. Mutations of mitochondrial AARSs result in autosomal recessive diseases with onset in the first months of life (Table 1, Fig. 2).

Leukoencephalopathy with brain stem, spinal cord involvement and lactate elevation (LBSL) is an early onset, autosomal recessive disease characterized by cerebellar ataxia, spasticity, and variable cognitive impairment. All patients present a specific brain magnetic resonance imaging (MRI) as well as increased lactate at magnetic

Table 1
Nuclear genes involved in mitochondrial translation deficiency in human.

Gene	Protein	Number of patients	Clinical presentation	Age at onset	Outcome	Reference
tRNA-modifying enzymes						
PUS1	Pseudouridine synthase 1	>4 patients	Sideroblastic anemia + myopathy	6 months–12 years		[7]
TRMU	tRNA 5-methylaminomethyl-2-thiouridylate methyltransferase	7 patients	Liver failure	2–4 months	Death at 3–4 months or recovering	[59]
Ribosomal proteins						
MRPS16	Mitochondrial ribosomal protein S16	1 patient	Agenesis of corpus callosum, hypotonia	Neonat	Death at 2–22 days D3	[28]
MRPS22	Mitochondrial ribosomal protein S22	1 family	Hypotonia, cardiomyopathy	Neonat	Death at 2–22 days	[39]
		1 patient	Brain anomalies, hypertrophic cardiomyopathy, Cornelia de Lange-like	Neonat	Alive at 6 years	[48]
Aminoacyl-tRNA synthetases						
RARS2	Arginyl-tRNA synthetase 2	3 patients/ families	Pontocerebellar hypoplasia	Neonat	Death before 2 years	[15]
DARS2	Aspartyl-tRNA synthetase 2	>30 families	Leukoencephalopathy	3–15 yr		[42]
SARS2	Seryl-tRNA synthetase 2	3 families	Hyperuricemia, pulm hypertesion,renal failure	4 months	Death at 10 months	[4]
YARS2	Lysyl-tRNA synthetase 2	2 families	Sideroblastic anemia + myopathy	Infancy	Death at 18–26 years	[37]
HARS2	Histidyl-tRNA synthetase	1 family	Perrault syndrome (ovarian dysgenesis, sensorineural hearing loss)	2–3 yr		[33]
Elongation factors						
GFM1	mtEFG1	4 patients/ families	Encephalopathy/liver failure	Neonat	Death at before 2 years	[3,12,47,52]
TSFM	mtEFTs	2 patients/ families	Encephalomyopathy/cardiomyopathy	Neonat	Death at 7 weeks	[46]
TUFM	mtEFTu	1 patient	Leukodystrophy	Neonat	Death at 14 months	[52]
Termination factor						
C12orf65		2 families	Leigh syndrome, optic atrophy, ophthalmoplegia	1 years	Alive at 7 and 20 years	[2]
Translation activators						
LRPPRC	Leucine-rich PPR-motif containing protein	55 patients	Leigh Syndrome French Canadian variant (LSFC)	Infancy	Death at 6–69 months	[29]
TACO1	Translational activator of cytochrome c oxidase	1 family	Leigh syndrome	Childhood		[55]

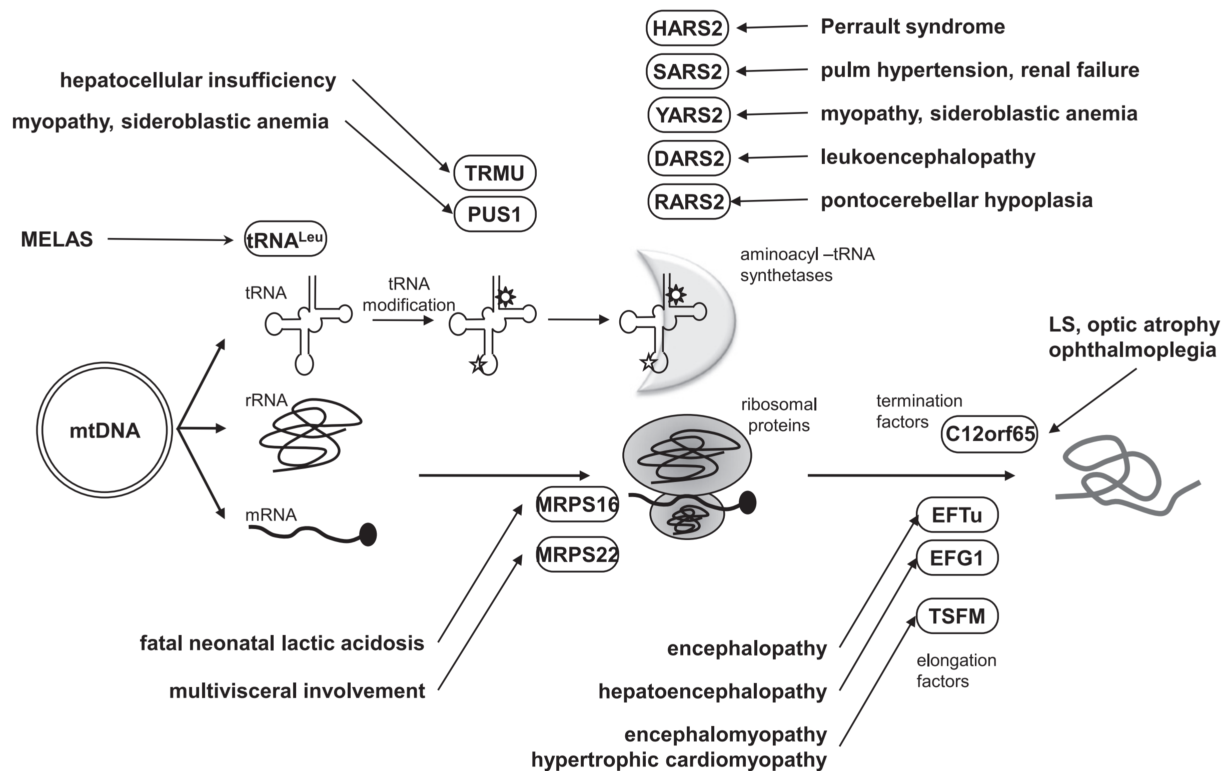

Fig. 2. The schematic steps of mitochondrial protein synthesis. The gene mutations as well as the associated clinical phenotypes are shown. (LS: Leigh syndrome).

resonance spectroscopy (MRS) that was suggestive of mitochondrial dysfunction. By genetic mapping and candidate gene analysis in several unrelated sib pairs, mutations in *DARS2* gene have been identified as a recurrent cause of this syndrome [42]. *DARS2* encodes the mitochondrial aspartyl-tRNA synthetase. The most common mutation is a splice-site mutation in intron 2 that results in the deletion of exon 3, a frameshift (R76SfsX5), and the premature termination of the protein. Whereas the enzyme activity of the mutant proteins expressed in *Escherichia coli* were consistently reduced, no OXPHOS or mitochondrial protein synthesis deficiency could be detected in patients' cells. Numerous patients with a similar clinical presentation and MRI features have then been reported [21,26].

Pontocerebellar hypoplasia (PCH) represents a group of autosomal recessive neurodegenerative disorders with prenatal onset. Six subtypes of pontocerebellar hypoplasia have been identified each of them being characterized by specific additional features. PCH6 is characterized by severe infantile encephalopathy, cerebral atrophy and multiple OXPHOS deficiency and is associated with *RARS2* mutations [15]. *RARS2* encodes the mitochondrial arginyl-tRNA synthetase and the first mutation was identified by homozygosity mapping and gene sequencing. This splicing mutation resulted in reduction of the amount of the mitochondrial $tRNA^{Arg}$ suggesting that this uncharged tRNA become unstable [15]. Additional patients were subsequently reported. MRI findings were similar to those previously published, the patients presented high levels of CSF lactate but OXPHOS enzymes were variably affected [30,35]. Finally, *RARS2* mutations represent a rare cause of PCH as only two patients from a large series of 169 PCH patients presented *RARS2* mutations [30].

YARS2 encodes the tyrosyl-tRNA synthetase and was identified as the disease causing gene in two families with mitochondrial myopathy, lactic acidosis and sideroblastic anemia (MLASA). The clinical presentation of the patients is highly similar to those with *PUS1* mutations but onset of symptoms was at an earlier age for *YARS2* mutations. The same homozygous mutation (F52L) was found in two unrelated consanguineous families of Lebanese origin [37]. The patients presented multiple OXPHOS deficiency in muscle and deficient mitochondrial protein synthesis in myotubes but not in cultured skin fibroblasts. Finally, aminoacylation activity of the mitochondrial tyrosyl-tRNA synthetase showed a 2-fold decrease compared to controls [37].

The HUPRA syndrome is a recently described multisystem fatal mitochondrial disease characterized by HyperUricemia, Pulmonary hypertension, Renal failure and Alkalosis) [4]. The onset of the disease is between 4 and 7 months of age and the patients also present high blood and CSF lactate suggesting a mitochondrial dysfunction. Indeed immunohistochemical staining in muscle biopsy showed COX deficiency and enzyme assays revealed multiple OXPHOS deficiency. Homozygostity mapping in two apparently unrelated families revealed the same *SARS2* mutation. The mitochondrial seryl-tRNA synthetase (SARS2) provides serine aminoacylation to two mitochondrial tRNAs ($tRNA^{Ser\ AGY}$ and $tRNA^{Ser\ UCN}$). The D390G SARS2 mutation resulted in a 10–20% residual amount of $tRNA^{Ser\ AGY}$ whereas $tRNA^{Ser\ UCN}$ amount was in the normal range suggesting that the mutation impairs the ability of the enzyme to acylate $tRNA^{Ser\ AGY}$ and that uncharged tRNA undergoes degradation [4].

Perrault syndrome is a clinically and genetically heterogeneous recessive disease characterized by ovarian digenesis and sensorineural hearing loss. Genetic mapping in a large non-consanguineous family allowed to show that the disease is related to mutations in *HARS2* gene encoding the mitochondrial histidyl-tRNA synthetase [33]. *HARS2* mutations were found in only 1/10 pedigree. In one additional family Perrault syndrome is caused by mutations in *HSD17B4* encoding the 17β-hydroxysteroid dehydrogenase type 4, an enzyme involved in peroxisomal fatty acid beta-oxidation [33]. Why mutations in these different genes result in Perrault syndrome has still to be investigated.

3.7. Abnormal elongation factor

The mitochondrial translation elongation consists of sequential addition of amino acids to the growing polypeptide chain directed by mRNA codons. Our knowledge of mitochondrial translation elongation is essentially derived from studies in bacteria. This process involves in mammals three elongation factors mtEFTu, mtEFTs and mtEFG. mtEFTu associates with all aminoacyl-tRNA substrates thus protecting them from hydrolysis. The aminoacyl-tRNA is then delivered to the aminoacyl-tRNA site (A site) of the ribosome as a ternary complex with mtEFTu and GTP for decoding of mRNA by codon–anticodon interactions in the small ribosomal subunit. GTP hydrolysis on mtEFTu then results in release of mtEFTu·GDP. mtEFTs, a nucleotide exchange protein converts mtEFTu·GDP in active mtEFTu·GTP. The peptide from the peptidyl-tRNA in the P-site of the ribosome moves into the peptidyl transferase center in the large subunit for peptide bound formation. In prokaryotes, mtEFG catalyzes the translocation step in which the deacylated tRNA in the P-site is moved to the exit site (E-site). However, several findings suggest that the E-site is absent from mitochondrial ribosome. Subsequently, the ribosome moves 3 nucleotides relative to the mRNA. The cycle repeats with a new ternary complex entering the A-site [50]. Protein synthesis deficiencies associated with the three mitochondrial elongation factors mtEFTu, mtEFTs and mtEFG have been described. Human mitochondria have two forms of mtEFG factors, mtEFG1 and mtEFG2, that present 35% of identity but mutations in mtEFG1 only have been identified. mtEFG1 has been demonstrated to specifically catalyze translocation, whereas mtEFG2 mediates ribosome recycling and renamed RRF2mt [51]. All patients with mtEFG1 mutations present a severe disease, sometimes with prenatal manifestation such as intrauterine growth retardation, which results in a premature death usually before 2 years of age (Table 1, Fig. 2). Mutations of these genes are relatively rare as systematic studies performed on different series of patients with multiple OXPHOS deficiencies allowed to identify roughly less than 8/100 patients with translation elongation factors mutations [3,12,23,46,47,52]. These translation elongation factor deficiencies resulted in globally decreased mitochondrial translation in cultured skin fibroblasts of patients, some proteins being more severely affected than others. Moreover additional bands which could not be attributed to a specific mtDNA encoded protein are sometimes observed. Mutations of *GFM1* gene, encoding mtEFG1, result in either in liver failure [3,12] or encephalopathy [47,52]. Only one patient with *TUFM* (encoding mtEFTu) mutation has been hitherto reported [52]. The patient had severe infantile macrocystic leukodystrophy with micropolygyria. He also had acute metabolic acidosis, psychomotor regression and axial hypotonia. Surprisingly the same *TSFM* (encoding EFTs) mutation has been found in two unrelated kindred presenting two distinct syndromes (fatal mitochondrial encephalomyopathy for the first patient and hypertrophic cardiomyopathy for the second) [46].

3.8. C12orf65

Several factors are involved in mitochondrial translation termination: the release factor mtRF1a/mtRF1L and the two ribosome recycling factors mtRRF (encoded by MRRF gene) and mtRRF2 (previously named mtEFG2). It should be hypothesized that other yet unknown factors also act as translation termination factors. Indeed, C12orf65 contains the GGQ motif that characterizes the class I release factors (mtRF1, Ict1 [36]) at the active site of the protein that catalyzes the hydrolysis of the ester bond. The precise function of C12orf65 protein has still to be characterized but mutations of this gene were found in patients from two different families with Leigh syndrome, optic atrophy and ophthalmoplegia [2] (Table 1, Fig. 2). Fibroblasts of the patients presented OXPHOS deficiency, abnormal BP-PAGE pattern and deficient mitochondrial mRNA translation. The two unrelated patients presented two different homozygous 1 bp deletions. Both mutations predict the same premature stop codon at position 84 of the amino acid sequence. Overexpression of Ict1 resulted in partial increase of COX activity in a patient's fibroblasts suggesting that C12orf65 and Ict1 may have similar and overlapping functions.

3.9. Translational activators

The mechanisms of mitochondrial protein synthesis regulation are poorly understood in mammals whereas several gene-specific translation activation factors are required in yeast. These yeast translation activators bind to the 5′ UTR sequences of the mRNAs. Mammalian mitochondrial mRNAs lack 5′ UTR and until recently no translation factors were known suggesting that translation regulation involves other mechanisms than in yeast. Identification of some disease causing genes in patients will certainly allow to progressively identify these yet unknown factors (Table 1, Fig. 2).

The *LRPPRC* gene is the causative gene for the Leigh Syndrome French Canadian variant (LSFC) [29]. LRPPRC is a distant homolog of the yeast translational activator Pet309. The protein is supposed to be involved in the stabilization of the mRNAs for COXI and COXIII in mammals without affecting their translation [57].

A specific defect in the synthesis of COXI subunit encoded by mtDNA has been found in a family of late-onset Leigh syndrome and isolated COX deficiency. Genetic mapping and chromosome transfer in a patient's fibroblasts allowed to show that this deficiency resulted from mutation in a new gene, *TACO1* (translational activator of COXI) [55]. Whereas the exact function of TACO1 is not known it has been shown to localize into the mitochondria and is supposed to either function as a multimer or in a complex with another protein(s).

4. Genetic screening of mitochondrial protein synthesis deficiency

The identification of genetic defects of mitochondrial protein synthesis increases rapidly as well as the clinical heterogeneity associated with these deficiencies. The large number of patients with multiple OXPHOS deficiency possibly due to protein synthesis defects as well as the large number of known and possibly unknown genes involved in translation hampers an easy and simple investigation of the patients. Several clinical and laboratory investigations can help to diagnose protein synthesis deficiency but none of them is usually sufficient for a rapid diagnosis.

The clinical presentation of patients is extremely heterogeneous even in a specific subgroup of proteins such as aminoacyl-tRNA synthetases or ribosomal proteins for example. Few patients with the same gene mutations have been described in most cases hampering to establish genotype–phenotype correlations. Moreover, the same clinical features can be related to two different gene mutations (myopathy and sideroblastic anemia related to *PUS1* [7] or *YARS2* [37] mutations) and one specific EFTs mutation can result in at least two distinct phenotypes [46].

Brain MRI images of patients with neurological disease reveal common features such as severe sus-tentorial atrophy and pontine atrophy of the brainstem. This pattern should perhaps be regarded as a suggestive/distinctive feature in mitochondrial protein synthesis defects. Whether these features are specific to translation deficiency has still to be determined. Brain MRI is particularly instrumental for the diagnosis of *DARS2* mutations as all patients presented leukoencephalopathy with brain stem, spinal cord involvement and lactate elevation (LBSL).

A multiple OXPHOS deficiency sparing complex II is observed in most patients. However, some patients with *GFM1* mutations can present isolated complex IV deficiency in muscle or can result in multiple OXPHOS deficiency in fibroblasts but not in muscle [47]. Patients with *DARS2* mutations do not express any deficiency in available tissues such as muscle and fibroblasts [42].

Translation deficiencies are often characterized by abnormal OXPHOS assembly pattern showing low fully assembled complexes I, IV and V. Therefore, BN-PAGE analysis represents a relatively reliable and easy diagnostic tool for these deficiencies. However, BN-PAGE analysis has not been documented in all translation deficiencies hampering to establish if it should be the best diagnosis tool.

Obviously, mitochondrial protein synthesis assay involving [^{35}S]-methionine pulse-chased labeling should represent the gold standard for diagnosis of these defects. It is however relatively expansive and time consuming hampering its use as an easy diagnosis tool. However, this deficiency is sometimes tissue specific as myoblasts but not fibroblasts of patients with *YARS2* mutations display decreased mitochondrial protein synthesis [37].

Finally, due to the short size of the families with protein synthesis deficiencies genetic mapping often cannot be applied.

5. Conclusion

Mitochondrial protein synthesis problems are becoming an important cause of OXPHOS dysfunction. The first mitochondrial MELAS mutation has been described more than 20 years ago [17] and the first nuclear gene mutation (*PUS1*) in 2004 [7]. Then 15 additional nuclear gene mutations have been reported. New techniques for gene identification, such as exome sequencing will rapidly allow to expand the list of genes involved in mitochondrial diseases and especially in the case of abnormal translation. In addition it could also help to determine the modifier genes that could partly account for the clinical variability that is a hallmark of mitochondrial disorders.

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