Biochimica et Biophysica Acta 1787 (2009) 529–532

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbabio

TMEM70 protein — A novel ancillary factor of mammalian ATP synthase

Josef Houštěk [a,*], Stanislav Kmoch [b], Jiří Zeman [c]

[a] Department of Bioenergetics, Institute of Physiology, Academy of Sciences of the Czech Republic, Vídeňská 1083, 142 20 Prague 4-Krč, Czech Republic
[b] Institute of Inherited Metabolic Disorders, 1st Faculty of Medicine, Charles University, Czech Republic
[c] Department of Pediatrics, 1st Faculty of Medicine, Charles University, Prague, Czech Republic

ARTICLE INFO

Article history:
Received 11 August 2008
Received in revised form 21 November 2008
Accepted 26 November 2008
Available online 6 December 2008

Keywords:
Mitochondrial disease
ATP synthase
Biogenesis
TMEM70

ABSTRACT

An increasing number of patients with nuclear genetic defects of mitochondrial ATP synthase have been identified in recent years. They are characterized by early onset, lactic acidosis, 3-methylglutaconic aciduria, hypertrophic cardiomyopathy and encephalopathy and most cases have a fatal outcome. Patient tissues show isolated defect of the ATP synthase complex and its content decreases to ≥30% of normal due to altered enzyme biosynthesis and assembly. Gene mapping and complementation studies have identified mutations in *TMEM70* gene encoding a 30kD mitochondrial protein of unknown function as the cause of the disease. An altered synthesis of this new ancillary factor in ATP synthase biogenesis was found in most of the known patients with decreased ATP synthase content. As revealed by phylogenetic analysis, TMEM70 is specific for higher eukaryotes.

1. Introduction

Within the last few years, a growing number of human mitochondrial diseases, due to nuclear genetic defects of mitochondrial oxidative phosphorylation (OXPHOS) complexes, have been diagnosed and an increasing number of affected genes have been identified. They code for structural subunits or helper proteins that are essential for assembly of the OXPHOS complex, subunit processing or biosynthesis of specific cofactors [1].

Up to now, nuclear genetic defects could be found in isolated disorders of all mitochondrial respiratory chain complexes but the number of affected genes clearly does not correspond to the structural complexity of the individual OXPHOS complexes or with numerous, complex-specific ancillary proteins essential for their biogenesis. This holds true particularly for complex I, NADH dehydrogenase, which is not present in *S. cerevisiae*, that has provided the most significant genetic "background information" for mammalian mitochondrial genomics, but is also true for complex IV — cytochrome *c* oxidase, and complex V — F_OF_1 ATP synthase. In cytochrome *c* oxidase (COX), 19 ancillary factors have been described in yeast, 16 of which have their homologues in humans [2]. Out of these, SURF1, SCO1, SCO2, COX10 and COX15 have been found to be responsible for COX deficiency, either because of mutation in the factor or its absence [3]. Although the COX complex contains 10 nuclear encoded subunits, only one of them, COX6B1, has been recently found to be responsible for COX dysfunction leading to human disease [4]. Even less is known about the pathogenesis of ATP synthase, where only nuclear gene for the F_1-assembly factor ATP12 has so far been associated with an isolated enzyme deficiency [5].

In some cases, the search for the genes responsible for dysfunction of the mitochondrial respiratory chain complex has led to the discovery of a new, previously unknown mitochondrial protein. For example, the *LRPPRC* (leucine-rich pentatricopeptide repeat cassette) gene, specific for higher eukaryotes and responsible for the Leigh syndrome French Canadian (LSFC) variant of COX deficiency, was identified by integrative genomics [6]. However, a large number of OXPHOS diseases still remain unexplained and a better knowledge of the mammalian mitochondrial proteome is of key importance for identification of disease-causing genes. Some 1451 human mitochondrial proteins encoded by 1080 genes have been predicted by recent studies based on integrative genomics which combined 8 independent approaches parameters using a naive Bayes classifier implemented with a Maestro computer program [7]. Most of them were further validated by mass spectrometry of purified mitochondrial proteins from different tissues and by GFP tagging [8]. These powerful strategies predicted a number of new mammalian mitochondrial proteins including 19 assembly factors for mitochondrial complex I and directly enabled identification of candidates for novel mitochondrial disease-causing genes, as for example MPV17 in the case of mtDNA depletion syndrome [9] or C8orf38 in infantile lethal complex I deficiency [8].

2. ATP synthase biogenesis

Mammalian F_OF_1-ATP synthase is a heterooligomeric mitochondrial complex made up of 16 different subunits [10]. The catalytic F_1

Abbreviations: ATP synthase, F_OF_1-ATP synthase; F_1-catalytic part of ATP synthase, F_O-membrane sector part of ATP synthase; COX, cytochrome *c* oxidase; mtDNA, mitochondrial DNA; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species

* Corresponding author. Tel: +42 2 4106 2434; fax: +42 2 4106 2149.
E-mail address: houstek@biomed.cas.cz (J. Houštěk).

0005-2728/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbabio.2008.11.013

factor is composed of subunits α, β, γ, δ, and ε and of a loosely attached IF1 inhibitor protein; F_1 is connected by two stalks to the membrane-embedded F_O portion which functions as a proton channel and consists of an additional ten subunits, a, b c, d, e, f, g, OSCP, A6L, and F6. Subunits a and A6L (subunits 6 and 8) are mtDNA encoded; all other subunits are coded for by the nuclear DNA.

The current concept of ATP synthase biogenesis stems from evolutionary divergent models such as bacterial, yeast and mammalian cells. Indeed, yeast served as a momentous model for the elucidation of ATP synthase biogenesis and assembly in eukaryotes, however, several basic differences exist between the yeast and the mammalian enzyme. In addition to subunits 6 and 8, the yeast mitochondrial genome encodes subunit 9 (subunit c); the yeast subunit 6 is synthesized in a precursor form and the intron–exon organization of the yeast mtDNA leaves an additional space for transcriptional regulation.

Eukaryotic ATP synthase is formed stepwise and enzyme assembly begins with formation of the F_1 catalytic part which then associates with subunits c and the other F_O subunits [11]. The two mtDNA encoded subunits, 6 and 8, appear to be added, at least in the mammalian enzyme, during the last stage of enzyme assembly [12,13].

The biogenesis of eukaryotic ATP synthase is dependent on the mutual action of several helper proteins, which serve chaperone-type functions, specific to the assembly of ATP synthase. Moreover, there are other proteins that govern the expression of ATP synthase genes at different levels (Table 1). This process is well known in yeast [11,14–16]) which requires several factors involved in F_1 assembly (ATP11, ATP12, FMC1) and F_O assembly (ATP10, ATP23). In addition other factors are involved in mRNA stability, translation and processing of mtDNA encoded subunits (NCA1-3, NAM1, AEP1-3 ATP22, ATP25) (Table 1). In mammalian mitochondria, only functional homologues of ATP11 and ATP12, have been found [11,17,18], i.e. the F_1 chaperons interacting with subunits β and α. Both are absolutely essential for assembly of the functional $\alpha_3\beta_3$ heterooligomer. Due to the above mentioned differences in organization and expression of the mitochondrial genome in yeast, all other ancillary factors described in *S. cerevisiae* are missing in higher eukaryotes. The only exception might be the recently identified *ATP23* gene [14,19] which encodes a 32 kDA metalloprotease of the inner mitochondrial membrane, having chaperone activity in the intermembrane space. ATP23 has two functions in yeast, processing of the subunit 6 precursor and association of the subunit 6 with subunit 9 oligomer. There exists a mammalian ortholog of ATP23 which contains a HEXXH motif of the protease active site, but its function is unknown, also because the mammalian subunit a lacks the precursor. On the one hand it is thus understandable why most of the known yeast auxiliary proteins for ATP synthase biogenesis are absent in mammals, on the other hand the multisubunit heterooligomer structure of ATP synthase complex is equally complicated in lower and higher eukaryotes, and it is possible that additional mammalian assembly factors may exist.

Table 1
Ancillary proteins involved in the biogenesis of yeast and mammalian ATP synthase (based on [11,14–16,19,36])

Genes	Yeast	Mammals	Target	Function
ATP11	+	+	F_1 subunit β	Chaperone
ATP12	+	+	F_1 subunit α	Chaperone
FMC1	+	−	Atp12p/F_1 subunit α	Co-chaperone
TMEM70	−	+	?	?
NAM1	+	−	Subunit 6 and 8	mRNA processing
AEP3, *NCA2*, *NCA3*	+	−	Subunit 6 and 8	mRNA stability/ translation
ATP22	+	−	Subunit 6	Translation
ATP10	+	−	Subunit 6	Chaperone
ATP23	+	?	Subunit 6	Processing/assembly
NCA1, *ATP25*	+	−	Subunit 9	mRNA stability
AEP1, *AEP2*/*ATP13*	+	−	Subunit 9	Translation

3. Nuclear genetic defects of ATP synthase biogenesis

ATP synthase is the key enzyme in ATP production in mammalian cells and its dysfunction represents a serious problem in energy supply for vital functions. Mitochondrial diseases due to isolated defects of ATP synthase belong to the most severe metabolic disorders and typically affect newborns and small children. This holds true for mtDNA defects as well as for nuclear genetic defects which represent distinct types of mitochondrial diseases, from both a biochemical and a clinical point of view.

Maternally transmitted ATP synthase dysfunction can be caused by mtDNA heteroplasmic missense mutations in *ATP6* [20–22], altered splicing of *ATP6-COX3* mRNA [23,24], or a premature stop codon in *ATP8* [25] gene. The enzyme subunits are usually present in near-normal amounts but in many cases BlueNative electrophoresis has revealed a reduced content of the assembled ATP synthase complex and accumulation of incomplete F_OF_1 subcomplexes. ATP synthase is affected by altered protonophoric function of the membrane F_O sector and intra-enzyme coupling of H^+-transport and ATP synthase catalytic activity [26]. The utilization of an electrochemical proton gradient for ATP synthesis is highly depressed and, as a result, the cell suffers from energetic deprivation but also from increased ROS synthesis, as demonstrated in 8993T/G homoplasmic cybrids [27]. Patients with the *ATP6* mutations mostly show CNS involvement and they present with neuropathy, ataxia, and retinitis pigmentosa (NARP), maternally inherited Leigh syndrome (MILS), or bilateral striatal necrosis, while hypertrophic cardiomyopathy has been found in the case of *ATP8* mutation [25].

A completely different type of mitochondrial disorders are isolated defects of ATP synthase of nuclear genetic origin (OMIM 604273), that are autosomal recessive [28]. They are characterized by a severely decreased content of an otherwise structurally and functionally normal enzyme resulting from impaired biosynthesis of the ATP synthase complex, which appears to be associated with the initial stage of enzyme biogenesis, the assembly of the F_1 catalytic part [28]. Patient's cells have diminished ability to synthesize ATP and due to the altered discharge of the mitochondrial proton gradient, mitochondria of ATP synthase-deficient patients show elevated level of membrane potential which, in turn, activates mitochondrial ROS production [29,30].

Within the last several years increasing numbers of patients with nuclear genetic ATP synthase defects has been found; mostly presenting with early onset lactic acidosis, cardiomyopathy, variable CNS involvement and 3-methylglutaconic aciduria [13,31]. In 2004 the search for the disease-causing gene(s) resulted in the identification of a homozygous missense mutation in the third exon of the *ATP12* gene which replaced tryptophan 94 with arginine. The mutation was found in a patient with severe encephalopathy and it was confirmed that the primary defect was in the assembly of the F_1 catalytic part of ATP synthase, due to dysfunction of one of the F_1 specific assembly factors [5]. Nevertheless, this case turned out to be rather atypical and neither the *ATP11*, nor the *ATP12* genes have been mutated in number of other diagnosed cases [31], in which also no mutations could be found in the ATP synthase subunit genes.

4. TMEM 70 — novel factor in ATP synthase biogenesis

Further attempts to uncover the pathogenic mechanism have been made to test whether the ATP synthase deficiency could be caused by the lack of ATP11 or ATP12 assembly factors or by limited availability of one or more structural subunits, in a similar fashion as low expression of subunit c downregulates ATP synthase in thermogenic

brown adipose tissue mitochondria [32–34]. Microarray transcription profiling has been performed in 13 cases with ATP synthase deficiency using both tailored and commercial oligonucleotide DNA microarrays. However, the results did not show any pronounced downregulation of ATP synthase subunits or other known ATP synthase-related genes [35]. Therefore, to identify the affected disease causing gene(s), linkage analysis and homozygosity mapping of selected index patients from several unrelated families was performed using Affymetrix GeneChip Mapping 250K arrays. The observed homozygosity profiles were intersected with whole genome expression profiles determined in patient fibroblast (Agilent 44kArray). As a result, gene *TMEM70* on chromosome 8 was identified as a highly probable candidate, and subsequently shown to be mutated [36].

Pathogenicity of TMEM70 mutations was confirmed in complementation experiments where fibroblasts from ATP synthase-deficient patients were transfected with wild type *TMEM70* cDNA cloned into the pEF-DEST51 expression vector [36] (Fig. 1A). As a result, the cellular content of ATP synthase subunits as well as the content of intact ATP synthase complex were restored (Fig. 1B) thus demonstrating that the absence-dysfunction of TMEM70 proteins was the primary cause of the disease. Complementation studies further showed that wtTMEM70 also restored oligomycin sensitive ATPase activity, ADP-stimulated respiration and mitochondrial ATP synthesis. Consequently, the mitochondria in *wtTMEM70*-complemented fibroblasts also recovered the ADP-induced decrease in membrane potential in substrate-supplemented, digitonin-permeabilised fibroblasts [36].

The *TMEM70* gene consists of three exons and encodes a 260 amino acid protein of unknown function. In all genotyped cases, a substitution (c.317–2A>G) was found, located in the splicing site of intron 2, which leads to aberrant splicing and loss of the *TMEM70* transcript, thus preventing synthesis of the protein. Further analysis of known cases with isolated ATP synthase deficiency revealed the presence of a homozygous c.317-2A>G mutation in 23 cases and one compound heterozygote patient with the second *TMEM70* mutation (c.118_119insGT) [36]. Out of all the cases analyzed, there was only one case where *TMEM70*, *ATP11* and *ATP12* were all found to be unmutated, indicating that an additional gene must be involved in ATP synthase deficiency.

Practically all patients with the *TMEM70* mutation were of Roma/Gypsy origin, but consanguinity has only been reported in a few cases. Estimation of consanguinity and/or degree of relationship between individual families and patients, from genotyping data available from Czech and Slovak families, suggests that the parents from the individual families may be relatives of the 3rd–6th generation. Based on this information and considering the fact that we analyzed the majority of patients known and available to us, it appears that isolated ATP synthase deficiency is a defect occurring frequently in the Roma population due to the founder allele effect. This fact however does not exclude the possibility that in the other populations the same defect may results from other mutations in the TMEM70 gene (as P27 in ref [36]).

5. TMEM 70 function and evolution

TMEM70 was identified by integrative genomics as one of the novel genes encoding mitochondrial proteins and GFP-tagged TMEM70 has been shown to be localized in mitochondria [7]. Although its exact function is not known at present, it is clear that TMEM70 represents a novel type of ancillary factor involved in the biogenesis of ATP synthase. Assuming that *TMEM70* mutations completely inhibit production of the TMEM70 protein, this factor may not be absolutely essential for ATP synthase biosynthesis, as a small amount of ATP synthase is always present in affected tissues [28], similarly to the COX deficiency due to the absence of the SURF1 assembly factor [37], where also residual amounts of the normal COX complex are found. BlueNative and two-dimensional electrophoretic analysis of fibroblasts and tissues from TMEM70 patients revealed the presence of traces of free F_1 ATPase, in addition to small amounts of full size ATP synthase complexes, but no larger F_OF_1 subassemblies [28]. Interestingly, in patient fibroblasts after complementation with *wtTMEM70*, the restoration of the ATP synthase complex was associated with the disappearance of unassembled F_1 (Fig. 1B, C), indicating that TMEM70 may be involved in the assembly of F_1 or in F_1 interaction with some of the F_O subunits.

TMEM70 protein contains a conserved DUF1301 domain and two putative transmembrane regions indicating that TMEM70 can be a membrane-associated protein. Using phylogenetic analysis, we found *TMEM70* homologues in genomes of multicellular eukaryotes and plants, but surprisingly not in yeast or fungi [36]. The only single-cell organism exception was the choanoflagellate protozoan *Monosiga brevicollis*, but the degree of homology was very weak.

6. Conclusions

There are two nuclear genes, which when mutated cause isolated deficiency of human ATP synthase. Both of them code for helper proteins involved in enzyme biogenesis. While the first, the rarely mutated F_1 α-

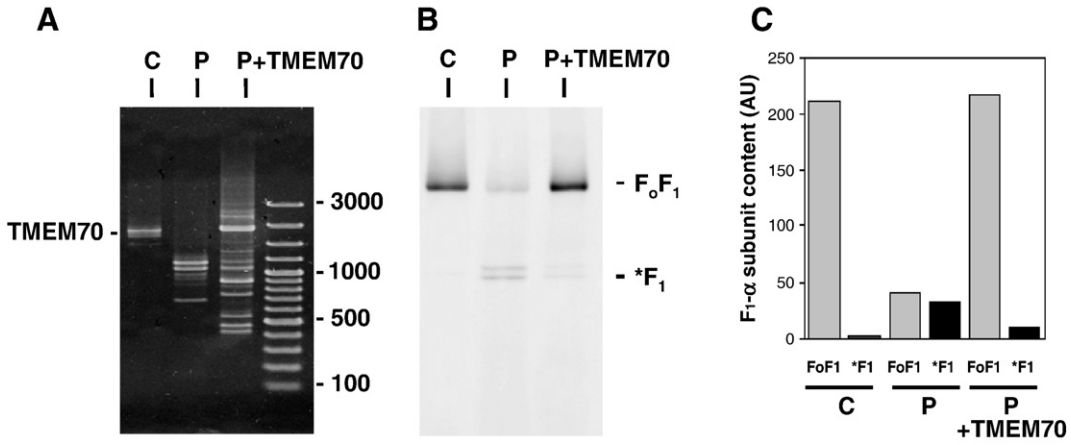

Fig. 1. Complementation of ATP synthase deficient fibroblast with wtTMEM70. (A) *TMEM70* cDNA analysis in fibroblasts from control (C), patient (P) and patients' fibroblasts stably transfected with TMEM70-pEF-DEST51 (P + TMEM70), (B) BlueNative-PAGE analysis of lauryl maltoside-solubilised mitochondria isolated from fibroblasts of C, P and P + TMEM70, immunodetection was performed with monoclonal anti-F_1 α subunit antibody (1 μg/ml, MS502, MitoSciences) and IRDye®-labeled secondary antibodies using an Odyssey Infrared Imager (LiCor Biosciences). (C) Relative content of fully assembled F_OF_1 ATP synthase complex (F_OF_1) and of F_1-subassembly (*F_1) in C, P and P + TMEM70, data were quantified from B using Aida 2.11 Image Analyzer software (Raytest).

specific ATP12 is an essential eukaryotic assembly factor, the second factor, TMEM70, is only present in higher eukaryotes and it appears to be responsible for a vast majority of cases of ATP synthase deficiency of nuclear genetic origin, at least in the Roma population.

Acknowledgements

This work was supported by the Grant Agency of the Ministry of Health of the Czech Republic (9759-4) and Ministry of Education, Youth and Sports of the Czech Republic (AV0Z 50110509, 1M0520 and MSM 0021620806).

References

[1] E.A. Shoubridge, Nuclear genetic defects of oxidative phosphorylation, Hum. Mol. Genet. 10 (2001) 2277–2284.
[2] J.M. Herrmann, S. Funes, Biogenesis of cytochrome oxidase-sophisticated assembly lines in the mitochondrial inner membrane, Gene 354 (2005) 43–52.
[3] P. Pecina, H. Houstkova, H. Hansikova, J. Zeman, J. Houstek, Genetic defects of cytochrome c oxidase assembly, Physiol. Res. 53 (Suppl. 1) (2004) 213–223.
[4] V. Massa, E. Fernandez-Vizarra, S. Alshahwan, E. Bakhsh, P. Goffrini, I. Ferrero, P. Mereghetti, P. D'Adamo, P. Gasparini, M. Zeviani, Severe infantile encephalomyopathy caused by a mutation in COX6B1, a nucleus-encoded subunit of cytochrome c oxidase, Am. J. Hum. Genet. 82 (2008) 1281–1289.
[5] L. De Meirleir, S. Seneca, W. Lissens, I. De Clercq, F. Eyskens, E. Gerlo, J. Smet, R. Van Coster, Respiratory chain complex V deficiency due to a mutation in the assembly gene ATP12, J. Med. Genet. 41 (2004) 120–124.
[6] V.K. Mootha, P. Lepage, K. Miller, J. Bunkenborg, M. Reich, M. Hjerrild, T. Delmonte, A. Villeneuve, R. Sladek, F. Xu, G.A. Mitchell, C. Morin, M. Mann, T.J. Hudson, B. Robinson, J.D. Rioux, E.S. Lander, Identification of a gene causing human cytochrome c oxidase deficiency by integrative genomics, Proc. Natl. Acad. Sci. U. S. A. 100 (2003) 605–610.
[7] S. Calvo, M. Jain, X. Xie, S.A. Sheth, B. Chang, O.A. Goldberger, A. Spinazzola, M. Zeviani, S.A. Carr, V.K. Mootha, Systematic identification of human mitochondrial disease genes through integrative genomics, Nat. Genet. 38 (2006) 576–582.
[8] D.J. Pagliarini, S.E. Calvo, B. Chang, S.A. Sheth, S.B. Vafai, S.E. Ong, G.A. Walford, C. Sugiana, A. Boneh, W.K. Chen, D.E. Hill, M. Vidal, J.G. Evans, D.R. Thorburn, S.A. Carr, V.K. Mootha, A mitochondrial protein compendium elucidates complex I disease biology, Cell 134 (2008) 112–123.
[9] A. Spinazzola, C. Viscomi, E. Fernandez-Vizarra, F. Carrara, P. D'Adamo, S. Calvo, R.M. Marsano, C. Donnini, H. Weiher, P. Strisciuglio, R. Parini, E. Sarzi, A. Chan, S. DiMauro, A. Rotig, P. Gasparini, I. Ferrero, V.K. Mootha, V. Tiranti, M. Zeviani, MPV17 encodes an inner mitochondrial membrane protein and is mutated in infantile hepatic mitochondrial DNA depletion, Nat. Genet. 38 (2006) 570–575.
[10] I.R. Collinson, J.M. Skehel, I.M. Fearnley, M.J. Runswick, J.E. Walker, The F1F0-ATPase complex from bovine heart mitochondria: the molar ratio of the subunits in the stalk region linking the F1 and F0 domains, Biochemistry 35 (1996) 12640–12646.
[11] S.H. Ackerman, A. Tzagoloff, Function, structure, and biogenesis of mitochondrial ATP synthase, Prog. Nucleic Acid Res. Mol. Biol. 80 (2005) 95–133.
[12] L.G. Nijtmans, P. Klement, J. Houstek, C. van den Bogert, Assembly of mitochondrial ATP synthase in cultured human cells: implications for mitochondrial diseases, Biochim. Biophys. Acta 1272 (1995) 190–198.
[13] J. Houstek, A. Pickova, A. Vojtiskova, T. Mracek, P. Pecina, P. Jesina, Mitochondrial diseases and genetic defects of ATP synthase, Biochim. Biophys. Acta 1757 (2006) 1400–1405.
[14] X. Zeng, W. Neupert, A. Tzagoloff, The metalloprotease encoded by ATP23 has a dual function in processing and assembly of subunit 6 of mitochondrial ATPase, Mol. Biol. Cell 18 (2007) 617–626.
[15] X. Zeng, A. Hourset, A. Tzagoloff, The saccharomyces cerevisiae ATP22 gene codes for the mitochondrial ATPase subunit 6-specific translation factor, Genetics 175 (2007) 55–63.
[16] X. Zeng, M.H. Barros, T. Shulman, A. Tzagoloff, ATP25, a new nuclear gene of saccharomyces cerevisiae required for expression and assembly of the Atp9p subunit of mitochondrial ATPase, Mol. Biol. Cell 19 (2008) 1366–1377.
[17] Z.G. Wang, P.S. White, S.H. Ackerman, Atp11p and Atp12p are assembly factors for the F1-ATPase in human mitochondria, J. Biol. Chem. 276 (2001) 30773–30778.
[18] A. Pickova, M. Potocky, J. Houstek, Assembly factors of F1Fo-ATP synthase across genomes, Proteins 59 (2005) 393–402.
[19] C. Osman, C. Wilmes, T. Tatsuta, T. Langer, Prohibitins interact genetically with Atp23, a novel processing peptidase and chaperone for the F1FO-ATP synthase, Mol. Biol. Cell 18 (2007) 627–635.
[20] Y. Tatuch, B.H. Robinson, The mitochondrial DNA mutation at 8993 associated with NARP slows the rate of ATP synthesis in isolated lymphoblast mitochondria, Biochem. Biophys. Res. Commun. 192 (1993) 124–128.
[21] J. Houstek, P. Klement, J. Hermanska, H. Houstkova, H. Hansikova, C. van den Bogert, J. Zeman, Altered properties of mitochondrial ATP-synthase in patients with a T−>G mutation in the ATPase 6 (subunit a) gene at position 8993 of mtDNA, Biochim. Biophys. Acta 1271 (1995) 349–357.
[22] E.A. Schon, S. Santra, F. Pallotti, M.E. Girvin, Pathogenesis of primary defects in mitochondrial ATP synthesis, Semin. Cell. Dev. Biol. 12 (2001) 441–448.
[23] S. Seneca, M. Abramowicz, W. Lissens, M.F. Muller, E. Vamos, L. de Meirleir, A mitochondrial DNA microdeletion in a newborn girl with transient lactic acidosis, J. Inherit. Metab. Dis. 19 (1996) 115–118.
[24] P. Jesina, M. Tesarova, D. Fornuskova, A. Vojtiskova, P. Pecina, V. Kaplanova, H. Hansikova, J. Zeman, J. Houstek, Diminished synthesis of subunit a (ATP6) and altered function of ATP synthase and cytochrome c oxidase due to the mtDNA 2 bp microdeletion of TA at positions 9205 and 9206, Biochem. J. 383 (2004) 561–571.
[25] A.I. Jonckheere, M. Hogeveen, L.G. Nijtmans, M.A. van den Brand, A.J. Janssen, J.H. Diepstra, F.C. van den Brandt, L.P. van den Heuvel, F.A. Hol, T.G. Hofste, L. Kapusta, U. Dillmann, M.G. Shamdeen, J.A. Smeitink, R.J. Rodenburg, A novel mitochondrial ATP8 gene mutation in a patient with apical hypertrophic cardiomyopathy and neuropathy, J. Med. Genet. 45 (2008) 129–133.
[26] G. Sgarbi, A. Baracca, G. Lenaz, L.M. Valentino, V. Carelli, G. Solaini, Inefficient coupling between proton transport and ATP synthesis may be the pathogenic mechanism for NARP/Leigh syndromes resulting from the 8993T>G mutation in mtDNA, Biochem. J. 395 (2006) 493–500.
[27] M. Mattiazzi, C. Vijayvergiya, C.D. Gajewski, D.C. DeVivo, G. Lenaz, M. Wiedmann, G. Manfredi, The mtDNA T8993G (NARP) mutation results in an impairment of oxidative phosphorylation that can be improved by antioxidants, Hum. Mol. Genet. 13 (2004) 869–879.
[28] J. Houstek, P. Klement, D. Floryk, H. Antonicka, J. Hermanska, M. Kalous, H. Hansikova, H. Hout'kova, S.K. Chowdhury, T. Rosipal, S. Kmoch, L. Stratilova, J. Zeman, A novel deficiency of mitochondrial ATPase of nuclear origin, Hum. Mol. Genet. 8 (1999) 1967–1974.
[29] J. Houstek, T. Mracek, A. Vojtiskova, J. Zeman, Mitochondrial diseases and ATPase defects of nuclear origin, Biochim. Biophys. Acta 1658 (2004) 115–121.
[30] T. Mracek, P. Pecina, A. Vojtiskova, M. Kalous, O. Sebesta, J. Houstek, Two components in pathogenic mechanism of mitochondrial ATPase deficiency: energy deprivation and ROS production, Exp. Gerontol. 41 (2006) 683–687.
[31] W. Sperl, P. Jesina, J. Zeman, J.A. Mayr, L. Demeirleir, R. Vancoster, A. Pickova, H. Hansikova, H. Houst'kova, Z. Krejcik, J. Koch, J. Smet, W. Muss, E. Holme, J. Houstek, Deficiency of mitochondrial ATP synthase of nuclear genetic origin, Neuromuscul. Disord. 16 (2006) 821–829.
[32] J. Houstek, U. Andersson, P. Tvrdik, J. Nedergaard, B. Cannon, The expression of subunit c correlates with and thus may limit the biosynthesis of the mitochondrial F0F1-ATPase in brown adipose tissue, J. Biol. Chem. 270 (1995) 7689–7694.
[33] U. Andersson, J. Houstek, B. Cannon, ATP synthase subunit c expression: physiological regulation of the P1 and P2 genes, Biochem. J. 323 (1997) 379–385.
[34] T.V. Kramarova, I.G. Shabalina, U. Andersson, R. Westerberg, I. Carlberg, J. Houstek, J. Nedergaard, B. Cannon, Mitochondrial ATP synthase levels in brown adipose tissue are governed by the c-Fo subunit P1 isoform, FASEB J. 22 (2008) 55–63.
[35] A. Cizkova, V. Stranecky, R. Ivanek, H. Hartmannova, L. Noskova, L. Piherova, M. Tesarova, H. Hansikova, T. Honzik, J. Zeman, P. Divina, A. Potocka, J. Paul, W. Sperl, J.A. Mayr, S. Seneca, J. Houstek, S. Kmoch, Development of a human mitochondrial oligonucleotide microarray (h-MitoArray) and gene expression analysis of fibroblast cell lines from 13 patients with isolated F1Fo ATP synthase deficiency, BMC Genomics 9 (2008) 38.
[36] A. Čížková, V. Stránecký, J. Mayr, M. Tesařová, V. Havlíčková, J. Paul, R. Ivánek, A. Kuss, H. Hansíková, V. Kaplanová, M. Vrbacký, H. Hartmannová, L. Nosková, T. Honzík, Z. Drahota, M. Magner, K. Hejzlarová, W. Sperl, J. Zeman, J. Houštěk, S. Kmoch, TMEM70 mutations cause isolated ATP synthase deficiency and neonatal mitochondrial encephalocardiomyopathy, Nat. Genet. 40 (2008) 1288–1290.
[37] V. Tiranti, K. Hoertnagel, R. Carrozzo, C. Galimberti, M. Munaro, M. Granatiero, L. Zelante, P. Gasparini, R. Marzella, M. Rocchi, M.P. Bayona-Bafaluy, J.A. Enriquez, G. Uziel, E. Bertini, C. Dionisi-Vici, B. Franco, T. Meitinger, M. Zeviani, Mutations of SURF-1 in Leigh disease associated with cytochrome c oxidase deficiency, Am. J. Hum. Genet. 63 (1998) 1609–1621.