The International Journal of Biochemistry & Cell Biology 48 (2014) 77–84

Contents lists available at ScienceDirect

The International Journal of Biochemistry & Cell Biology

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

Organelles in focus

Mitochondria: Impaired mitochondrial translation in human disease☆

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ARTICLE INFO

Article history:
Received 28 September 2013
Received in revised form
13 November 2013
Accepted 26 December 2013
Available online 8 January 2014

Keywords:
Mitochondrial respiratory chain
Mitochondrial translation
Human mitochondrial disease
Tissue specific presentation
Cytosolic translation

ABSTRACT

Defects of the mitochondrial protein synthesis cause a subgroup of mitochondrial diseases, which are usually associated with decreased activities of multiple respiratory chain (RC) enzymes. The clinical presentations of these disorders are often disabling, progressive or fatal, affecting the brain, liver, skeletal muscle, heart and other organs. Currently there are no effective cures for these disorders and treatment is at best symptomatic. The diagnosis in patients with multiple respiratory chain complex defects is particularly difficult because of the massive number of nuclear genes potentially involved in intra-mitochondrial protein synthesis. Many of these genes are not yet linked to human disease. Whole exome sequencing rapidly changed the diagnosis of these patients by identifying the primary defect in DNA, and preventing the need for invasive and complex biochemical testing. Better understanding of the mitochondrial protein synthesis apparatus will help us to explore disease mechanisms and will provide clues for developing novel therapies.

Organelle facts

- Mitochondrial protein synthesis requires several mitochondrial and nuclear-encoded factors for optimal translation
- The clinical presentation of diseases due to defective mitochondrial protein synthesis is very variable and tissue specific presentations are common
- The reasons behind the tissue specificity are largely unknown
- Besides mitochondrial tRNA mutations and mtDNA deletions or depletion, autosomal recessive mutations have been reported in genes encoding ribosomal proteins, ribosome assembly proteins, mitochondrial aminoacyl-tRNA synthetases, tRNA modifying enzymes and initiation, elongation and termination factors of translation
- Frequent and clinically recognisable genetic causes of human diseases due to impaired mitochondrial translation are caused by mutations in mitochondrial tRNA synthetase and tRNA modifying genes
- The potential interaction between cytosolic and mitochondrial translation requires further investigations

1. Introduction

Mitochondrial diseases affect at least 1 in 5000 of the population and produce diverse clinical phenotypes often presented as multi-systemic disorders (DiMauro et al., 2013; Ylikallio and Suomalainen, 2012; Vafai and Mootha, 2012). In addition to the nucleus, human cells also harbour DNA in the mitochondria (mtDNA), which is essential for cell viability (Tuppen et al., 2010). This small (16.5 kb) genome is found in multiple copies in mitochondria, the subcellular organelles that often constitute more than 20% of the total cell volume. OXPHOS (oxidative phosphorylation) is responsible for the production of ATP by generating a proton gradient across the inner membrane of the mitochondria which is used by the mammalian cells (Greaves et al., 2012). The mitochondrial OXPHOS system comprises around 150 different proteins out of which only 13 polypeptide subunits are encoded by the mtDNA. In addition, the mtDNA encodes the small and large rRNAs, and 22 distinct mitochondrial tRNAs that are necessary for the translation of only the mitochondrial-encoded proteins (Smits et al., 2010; Rötig, 2011; Chrzanowska-Lightowlers et al., 2011). The nuclear-encoded subunits of the respiratory chain (RC) complexes as well as proteins that are inevitable for normal mitochondrial protein synthesis (such as OXPHOS assembly, mtDNA metabolism and maintenance, mitochondrial cofactor biosynthesis, mitoribosomal subunits and assembly factors, regulators of mitochondrial expression and translation, etc.) are encoded by the nuclear genome (nDNA) and synthetised in the cytosol before transported into the organelle (Vafai and Mootha, 2012). The mitochondrial ribosomal proteins assemble with mitochondrial ribosomes 12S rRNA and 16S rRNA to form the mitochondrial ribosome (Pietromonaco et al.,

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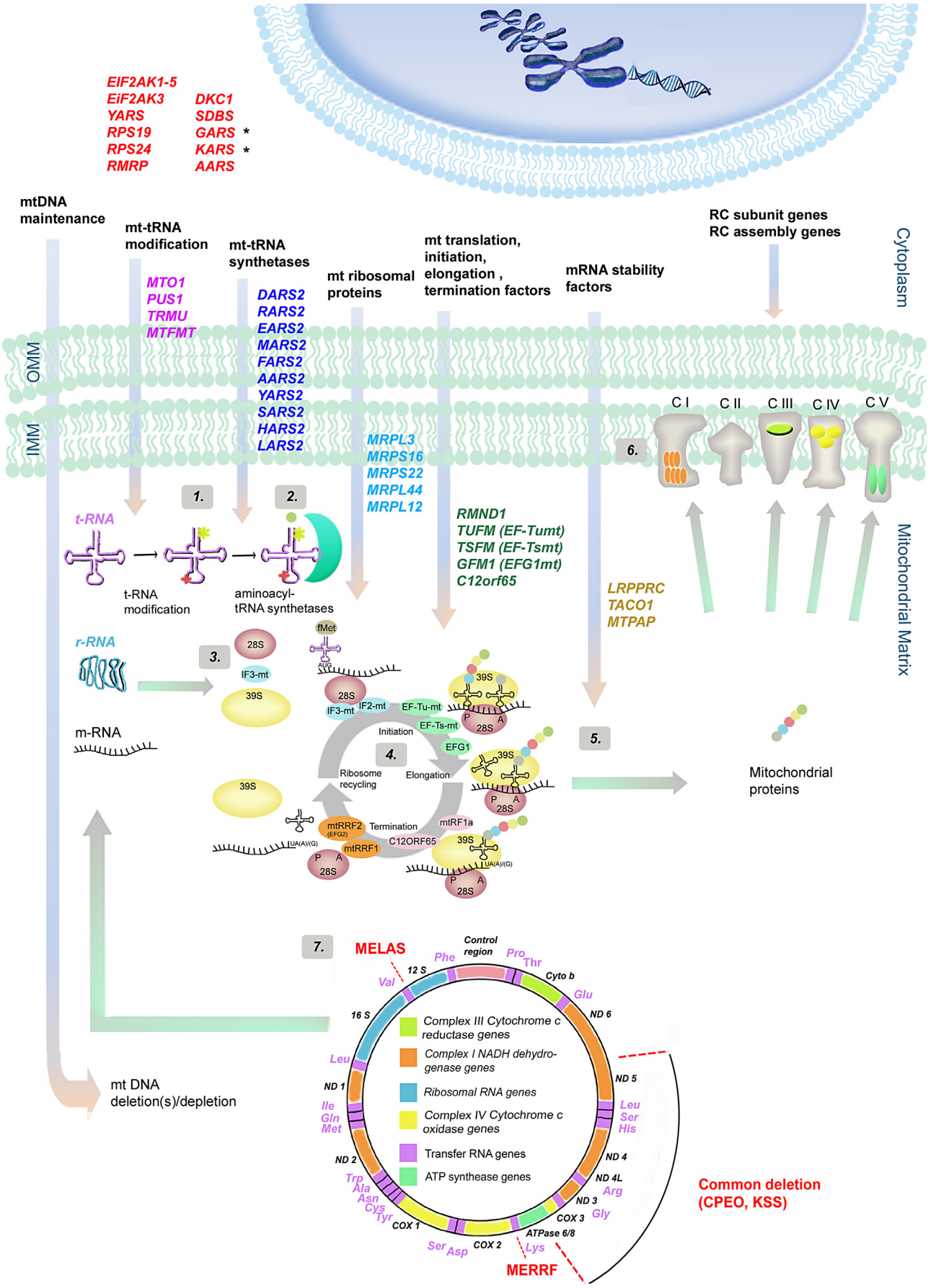
http://dx.doi.org/10.1016/j.biocel.2013.12.011


EIF2AK1-5
EiF2AK3
YARS
RPS19
RPS24
RMRP
DKC1
SDBS
GARS *
KARS *
AARS
mtDNA maintenance
mt-tRNA modification
mt-tRNA synthetases
mt ribosomal proteins
mt translation, initiation, elongation , termination factors
mRNA stability factors
RC subunit genes
RC assembly genes
Cytoplasm
OMM
IMM
MTO1
PUS1
TRMU
MTFMT
DARS2
RARS2
EARS2
MARS2
FARS2
AARS2
YARS2
SARS2
HARS2
LARS2
MRPL3
MRPS16
MRPS22
MRPL44
MRPL12
RMND1
TUFM (EF-Tumt)
TSFM (EF-Tsmt)
GFM1 (EFG1mt)
C12orf65
LRPPRC
TACO1
MTPAP
C I
C II
C III
C IV
C V
6.
Mitochondrial Matrix
1.
2.
t-RNA
t-RNA modification
aminoacyl-tRNA synthetases
r-RNA
3.
28S
IF3-mt
39S
m-RNA
fMet
ATP
IF2-mt
EF-Tu-mt
EF-Ts-mt
Initiation
EFG1
4.
Ribosome recycling
Elongation
Termination
mtRRF2 (EFG2)
mtRRF1
mtRF1a
C12ORF65
P
A
5.
Mitochondrial proteins
7.
MELAS
MERRF
Control region
12 S
16 S
Cyto b
ND 1
ND 2
COX 1
COX 2
ATPase 6/8
COX 3
ND 3
ND 4
ND 4L
ND 5
ND 6
Complex III Cytochrome c reductase genes
Complex I NADH dehydro-genase genes
Ribosomal RNA genes
Complex IV Cytochrome c oxidase genes
Transfer RNA genes
ATP synthease genes
mt DNA deletion(s)/depletion
Common deletion (CPEO, KSS)