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Review

Part II: Mouse models of OXPHOS deficiencies caused by defects in regulatory factors and other components required for mitochondrial function

Luisa Iommarini [a], Susana Peralta [b], Alessandra Torraco [c], Francisca Diaz [b,*]

[a] Department of Pharmacy and Biotechnology (FABIT), University of Bologna, Via Irnerio 42, Bologna, Italy
[b] Department of Neurology, University of Miami, Miller School of Medicine, Miami, FL 33136, USA
[c] Unit of Molecular Medicine for Neuromuscular and Neurodegenerative Disease, IRCCS Bambino Gesù, Piazza S. Onofrio 4, 00165 Rome, Italy

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ABSTRACT

Mitochondrial disorders are defined as defects that affect the oxidative phosphorylation system (OXPHOS). They are characterized by a heterogeneous array of clinical presentations due in part to a wide variety of factors required for proper function of the components of the OXPHOS system. There is no cure for these disorders owing to our poor knowledge of the pathogenic mechanisms of disease. To understand the mechanisms of human disease numerous mouse models have been developed in recent years. Here we summarize the features of several mouse models of mitochondrial diseases directly related to those factors affecting mtDNA maintenance, replication, transcription, translation as well to other proteins that are involved in mitochondrial dynamics and quality control which affect mitochondrial OXPHOS function without being intrinsic components of the system. We discuss how these models have contributed to our understanding of mitochondrial diseases and their pathogenic mechanisms.

Contents

* Corresponding author at: 1420 NW 9th Ave, Two Story Labs, Room 230B, Miami, FL 33136, USA. Tel.: +1 305 243 7489.
E-mail addresses: luisa.iommarini2@unibo.it (L. Iommarini), SPeralta@med.miami.edu (S. Peralta), alessandra.torraco@opbg.net (A. Torraco), fdiaz1@med.miami.edu (F. Diaz).

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1. Introduction

Mammalian mitochondrial DNA (mtDNA) is a double-stranded, circular molecule of about 16.5 kb encoding for 37 genes: 13 genes for oxidative phosphorylation (OXPHOS) complex subunits, 22 tRNAs and 2 rRNAs necessary for mitochondrial translation (Anderson et al., 1981). Mitochondrial DNA follows peculiar non-Mendelian genetic rules, including matrilinear transmission, polyploidy, threshold effect and mitotic segregation. Mitochondrial replication, transcription and translation occur in a semi-autonomous fashion, since all the proteins necessary for these processes are encoded by nuclear DNA and imported from the cytoplasm (Falkenberg et al., 2007). The intricate molecular machinery involved in the maintenance, transcription and translation of mtDNA includes several proteins found mutated in human neurological disorders that share a common feature, the presence of mtDNA deletions and/or depletion (Koopman et al., 2012; Spinazzola, 2011). These proteins are either essential for mtDNA replication (POLγ and TWINKLE) and transcription/translation (TFAM, TFB1M, mTERFs, POLRMT, LRPPRC and DARS2) for the correct maintenance of the mitochondrial dNTP pool (TP, TK, ANT1, and RRM2B). In addition, proteins involved in mitochondrial dynamics (MFN1, MFN2, OPA1, and DRP1) and in protein quality control (CLPP, AFG3L2, PARAPLEGIN, OMA1, PHBs, OMI and PARL) are also essential for proper mitochondrial function. In this part of the review miniseries, we summarize the mouse models that recapitulate defects in mtDNA instability, transcription, translation, mitochondrial dynamics, quality control and others. We discuss how these mouse models have contributed to our knowledge of the specific function of these factors and their role in the pathogenic mechanisms of disease of mitochondrial disorders. A summary of these mouse models is found in Fig. 1.

2. Mouse models of proteins involved in mtDNA stability, replication, transcription and translation

The mammalian mtDNA genome must be replicated, transcribed and translated to assure a proper mitochondrial function. Regulation

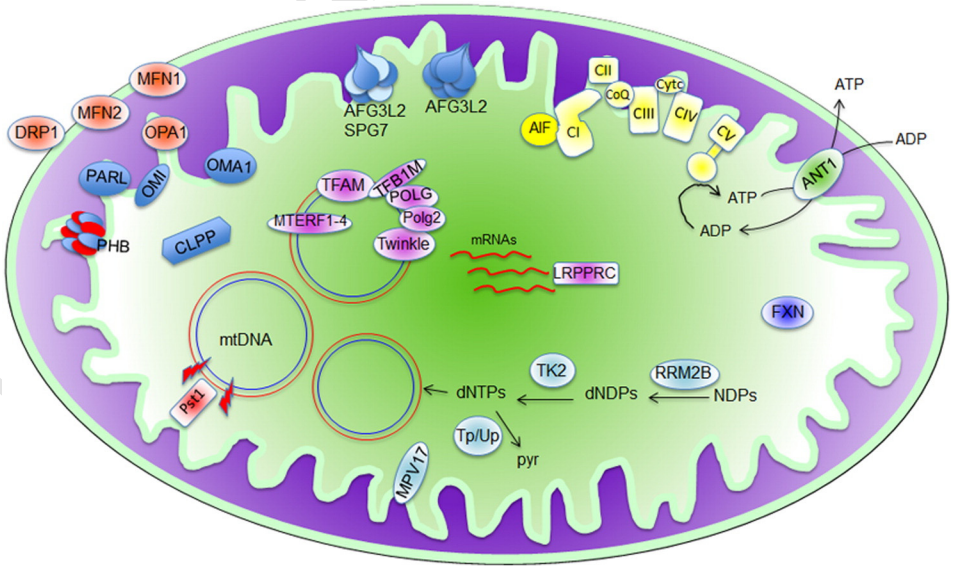

Fig. 1. Mouse models of mitochondrial diseases. Mouse models that affect the oxidative phosphorylation system which is represented in light yellow in the mitochondrial inner membrane. Mouse models affecting mitochondrial dynamics are represented in light orange (MFN1, MFN2, OPA1 and DRP1). Mouse models of proteins involved in mtDNA replication, transcription and translation are represented in light pink (POLG, POLG2, TFAM, TFB1, TWINKLE, MTERFs and LRPPRC). Mouse models of proteins required for dNTP synthesis, and mtDNA synthesis and stability are represented in light blue (RRM2B, TK2, TP, UP and MPV17). Mouse model for mtDNA deletion/depletion caused by double-strand brakes (red bolt) is represented in red (mito-Pst1). Mouse models of protein quality control are represented in blue (CLPP, PHB, PARL, OMI, OMA1, AFG3L2 + SPG7, AFG3L2). Other mouse models (AIF1, ANT1 and FXN). NDPs: nucleotide diphosphates; dNDPs: deoxy-NDPs; dNTPs: deoxy nucleotide triphosphates; Pyr: pyrimidines; mtDNA: mitochondrial DNA. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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