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Review

Mitochondrial Diseases Part I: Mouse models of OXPHOS deficiencies caused by defects in respiratory complex subunits or assembly factors

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ABSTRACT

Mitochondrial disorders are the most common inborn errors of metabolism affecting the oxidative phosphorylation system (OXPHOS). Because of the poor knowledge of the pathogenic mechanisms, a cure for these disorders is still unavailable and all the treatments currently in use are supportive more than curative. Therefore, in the past decade a great variety of mouse models have been developed to assess the *in vivo* function of several mitochondrial proteins involved in human diseases. Due to the genetic and physiological similarity to humans, mice represent reliable models to study the pathogenic mechanisms of mitochondrial disorders and are precious to test new therapeutic approaches. Here we summarize the features of several mouse models of mitochondrial diseases directly related to defects in subunits of the OXPHOS complexes or in assembly factors. We discuss how these models recapitulate many human conditions and how they have contributed to the understanding of mitochondrial function in health and disease.

Contents

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1. Introduction

Mitochondria have a crucial role in energy production in eukaryotic cells, providing the primary energy source in the cells, ATP, by the oxidative phosphorylation system (OXPHOS). This system is composed of five functionally coupled multi-protein complexes (CI-CV) embedded in the inner mitochondrial membrane and of two mobile electron carriers, coenzyme Q (CoQ_{10}) and cytochrome *c* (Cyt*c*). The OXPHOS system couples the electron flow and proton translocation across the mitochondrial inner membrane generating the electrochemical gradient necessary for ATP synthesis.

The OXPHOS complexes are composed of subunits encoded by the nuclear DNA (nDNA) and the mitochondrial DNA (mtDNA). The exception of the dual genetic origin is complex II, which is entirely encoded by the nDNA. Hence, the biosynthesis of the OXPHOS complexes requires coordination on the expression of both nuclear and mitochondrial-encoded proteins, import of those proteins encoded in the nucleus to the mitochondria and the assembly and addition of prosthetic groups. This biosynthetic process requires a series of chaperones better known as assembly factors, which tend to be specific for each complex and do not form part of the final enzyme (Fernandez-Vizarra et al., 2009).

Defects in the OXPHOS system result in a heterogeneous group of pathologies and metabolic syndromes, commonly known as "mitochondrial diseases". Mitochondrial disorders can rise from mutations either in nDNA or mtDNA resulting in a compromised ATP synthesis and/or chronic oxidative stress. The most affected organs are those with high energy demands such as the heart, skeletal muscle and brain, but also other tissues may be affected, partially explaining the broad clinical spectrum that includes neurodegeneration and/or muscular weakness in children and adults (DiMauro and Schon, 2008). To date, hundreds of mutations, either point mutations or large-scale rearrangements, have been found in the mtDNA (www.mitomap.org) and more than 1000 nuclear genes have been involved in disease-causing mutations (MitoCarta human inventory, Broad Institute). Of these nDNA mutations identified, besides those encoding for subunits of the respiratory complexes, many are related to their respective assembly factors (Diaz et al., 2011).

Because of the numerous genes involved in the development of the disease; the dual genetic control; the wide variety of the clinical symptoms and the variable onset of the disease, finding a diagnosis for a mitochondrial disease is often challenging.

Effective treatments for mitochondrial disorders are still unavailable, mostly due to the poor knowledge of the pathogenic mechanisms underlying these diseases. For this reason, in the last decade, an effort has been made by the scientific community to develop mouse models to improve our knowledge of the pathophysiology of mitochondrial disorders and to provide a platform for testing therapeutic interventions. Due to the extensive information and number of models created in the last few years, we decided to create a miniseries review comprised of three parts. Part I (this chapter) focuses on those mice models directly related to components of the OXPHOS system, mitochondrial complexes subunits and assembly factors necessary for proper respiratory complexes biogenesis. Part II of the review miniseries focuses on the defects caused by mutations in factors that are not part of the OXPHOS system but are required for its function such as those factors involved in mtDNA maintenance, replication, transcription, translation, mitochondrial dynamics and mitochondrial protein quality control. Part III of the review miniseries focuses on the therapeutic interventions that have been tested on several of the mouse models described in parts I and II. We summarized the main features of the animal models and described how they recapitulate human pathogenic phenotypes and how they have advanced our knowledge on the pathological mechanisms of disease. Fig. 1 summarizes the animal models described in this chapter for each respiratory complex including structural subunits and assembly factors.

2. Mouse models of complex I deficiency

Mammalian complex I (CI or NADH: ubiquinone oxidoreductase) is the largest enzyme of the OXPHOS system with an estimated size of 1 MDa. It is an L-shape multi-protein complex and consists of at least 44 subunits, 38 of which are encoded by the nuclear DNA and the rest by the mitochondrial genome (Hirst et al., 2003). CI deficiency is the most frequent cause of mitochondrial defects. The majority of the mutations affect genes encoding for structural subunits, but lately, a growing number of genes, encoding for assembly factors of the enzyme, have been found mutated in patients with severe neurological diseases (Mckenzie and Ryan, 2010; Pagniez-Mammeri et al., 2012). Isolated CI defects are associated with a wide variety of clinical phenotypes ranging from Leigh syndrome (LS) or infantile subacute necrotizing encephalomyelopathy, fatal infantile lactic acidosis, leukodystrophy, cardiomyopathy, hepatopathy, tubulopathy and optic neuropathy (Bugiani et al., 2004; Ngu et al., 2012; Ogilvie et al., 2005; Swalwell et al., 2011). Such diversity of phenotypes makes even more urgent the need for generating mouse models mirroring the broad spectrum of clinical outcomes to study pathogenic mechanisms in detail and to design specific therapies. Table 1 shows a summary of the various mouse models with defects in complex I.

2.1. Ndufs4

NDUFS4 encodes a small protein of about 18 kDa, essential for CI assembly and stability. It is inserted at a late stage of CI biogenesis (Antonicka et al., 2003c; Lazarou et al., 2007) and mutations in this gene are responsible of LS or Leigh-like disease (Bénit et al., 2003; Budde et al., 2000; Petruzzella et al., 2001; van den Heuvel et al., 1998). The first *Ndufs4* knockout (KO) mouse was created by ablating the floxed exon 2 in the germ line using the *Mox2-Cre* transgenic mice (Kruse et al., 2008). The *Ndufs4*$^{-/-}$ mice developed a Leigh-like phenotype characterized by ataxia, blindness, retarded growth rate and lethargy leading to premature death at about 7 weeks of age. CI abundance and activity were variably reduced in several tissues, being almost undetectable in the liver and in the central nervous system (CNS). In contrast, CI-dependent oxygen consumption in the KO mouse was reduced to about 50% of control levels in the skeletal muscle (Kruse et al., 2008). This marked variation in CI levels in different tissues suggested that the *Ndufs4*$^{-/-}$ mice may have died from the loss of neuronal function during development. To test this hypothesis, a