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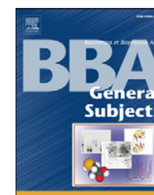

Review

Modelling biochemical features of mitochondrial neuropathology ☆

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Background: The neuropathology of mitochondrial disease is well characterised. However, pathophysiological mechanisms at the level of biochemistry and cell biology are less clear. Progress in this area has been hampered by the limited accessibility of neurologically relevant material for analysis.

Scope of review: Here we discuss the recent development of a variety of model systems that have greatly extended our capacity to understand the biochemical features associated with mitochondrial neuropathology. These include animal and cell based models, with mutations in both nuclear and mitochondrial DNA encoded genes, which aim to recapitulate the neuropathology and cellular biochemistry of mitochondrial diseases.

Major conclusions: Analysis of neurological tissue and cells from these models suggests that although there is no unifying mode of pathogenesis, dysfunction of the oxidative phosphorylation (OXPHOS) system is often central. This can be associated with altered reactive oxygen species (ROS) generation, disruption of the mitochondrial membrane potential ($\Delta\Psi_m$) and inadequate ATP synthesis. Thus, other cellular processes such as calcium (Ca^{2+}) homeostasis, cellular signaling and mitochondrial morphology could be altered, ultimately compromising viability of neuronal cells.

General significance: Mechanisms of neuronal dysfunction in mitochondrial disease are only just beginning to be characterised, are system dependent and complex, and not merely driven by energy deficiency. The diversity of pathogenic mechanisms emphasises the need for characterisation in a wide range of models, as different therapeutic strategies are likely to be needed for different diseases. This article is part of a Special Issue entitled Frontiers of Mitochondrial Research.

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1. Introduction

Mitochondrial disease is highly variable in its presentation, potentially affecting any organ, in isolation or combination, at any age, with any severity [1]. Similarly, the genetic basis of the disease is complex. Mutations have been characterised in over 100 genes, encoded either by the nuclear genome (nDNA) and inherited in a Mendelian manner, or by the mitochondrial genome (mtDNA) and inherited through the maternal lineage only [1,2]. Mutations inherited through the mtDNA are further complicated in that each cell typically contains thousands of copies of the mtDNA genome [3]. Accordingly, mutations of this type are often inherited in a heteroplasmic manner, where the cell contains a mixture of wild-type and mutant mtDNA. Disease may only manifest in such cases when the mutant load exceeds a certain threshold.

Mitochondrial disease, although diverse in presentation, typically affects the more metabolically active tissues and organs, most notably the brain [1,2,4]. Common neurological symptoms of mitochondrial disease include developmental delay or regression, optic atrophy, hearing loss, ataxia, seizures and stroke [5]. That the disease frequently manifests as a neurological disorder of the central nervous system (CNS) is perhaps not so surprising considering that the human brain comprises only 2% of our body weight and yet accounts for 20% of oxygen consumption [6]. This underscores the high dependence of the CNS on energy supply from the mitochondrial oxidative phosphorylation (OXPHOS) system (Fig. 1), the chain of mitochondrial protein complexes that creates an electrochemical gradient of protons, ultimately driving ATP synthesis [7]. Just how and where the brain spends this very large energy budget is still contentious, but is central to understanding the specificity of mitochondrial diseases. It is likely though that most energy is consumed in the dual process of firing action potentials and repackaging neurotransmitters [8]. Neurons however are not the only cell type in the brain with an appetite for energy. Astrocytes, for example, are the most common cell type in the brain, and are intricately linked to neurons for proper function [9]. They are also reported to be highly metabolically active, not merely suppliers of glutamate and lactate to neurons, but potentially also receiving some of these same products back from neurons to drive OXPHOS, and propagating signals of their own [9–13].

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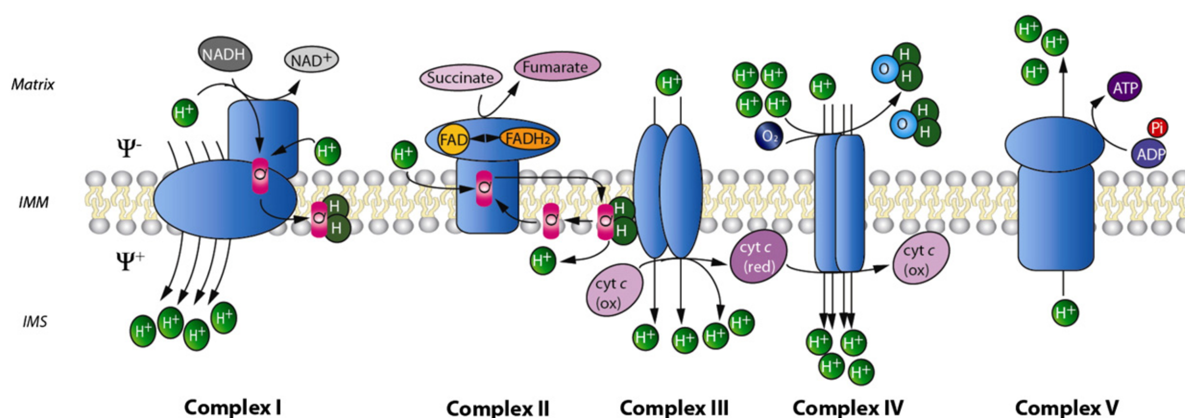

Fig. 1. The OXPHOS system. The mitochondrial OXPHOS system (blue) pumps H^+ protons (green) across the IMM and into the IMS at complexes I, III and IV to maintain the $\Delta\Psi_m$. Electrons enter OXPHOS by oxidation of NADH at CI and succinate at CII; they are transferred by the mobile electron carrier Q to CIII and then via cyt *c* to CIV, where they are used to reduce molecular oxygen to form water. CV utilises the electrochemical gradient, and couples proton flow through the complex with ATP synthesis from ADP and inorganic phosphate. Abbreviations: cyt *c*, cytochrome *c*; IMM, inner mitochondrial membrane; IMS, intermembrane space; OMM, outer mitochondrial membrane; ox, oxidised; Pi, inorganic phosphate; Q, ubiquinone; QH_2, ubiquinol; red, reduced; Ψ, charge.

Although the clinical manifestations of mitochondrial disease have generally been well characterised, the difficulty in obtaining relevant fresh neurological tissue has limited our understanding of the biochemical features at a cellular level. To this end, a number of animal and cellular model systems of primary mitochondrial dysfunction that mimic neurological mitochondrial disorders have recently been generated (Fig. 2). Additionally, a number of model systems have been generated that mimic disorders where mitochondrial dysfunction may be secondary but appears to be central to neurological pathogenesis (Fig. 2).

Such models have provided the opportunity to further our understanding of the neuropathology of disease involving mitochondrial dysfunction, through biochemical characterisation of mitochondrial function and structure. Perhaps the most fruitful of these models to date has been the mouse. Mouse models have provided the opportunity to characterise neurological biochemistry *in vivo* in the mouse brain (Fig. 2, Table. 1 and extended in Supplementary Table. 1), as well as *in vitro* (Fig. 2, Table. 2), utilising primary cell cultures of neurologically relevant cell types such as neurons and glial cells.

These mouse models have faithfully recapitulated aspects of common mitochondrial disorders with neurological involvement. For example, the *Ndufs4* (nuclear encoded) knockout (KO) mouse models exhibit key features of Leigh syndrome (LS), such as bilateral lesions in the brain stem, ataxia, increased serum lactate, blindness and breathing abnormalities [14–17]. More recently, the mtDNA-encoded *mt-Nd4* and *mt-Nd6* transgenic mouse models were shown to develop optic atrophy, similar to patients with Leber's hereditary optic neuropathy (LHON) [18,19]. It is of note that the generation of any model system with mtDNA-encoded mutations, not least in mouse, has been a great challenge to the field. Restraining such advances are the lack of genetic tools available to manipulate mtDNA, along with the further complication that the mode of inheritance is not Mendelian in nature and mtDNA can exist in either a heteroplasmic or homoplasmic state as discussed above.

Until recently, mouse models have been restricted to nuclear gene defects due to technical difficulties in introducing mitochondrial DNA (mtDNA) mutations into germ cells. Here, cybrid technology — the fusion of an enucleated patient cell with a host cell whose mtDNA has been chemically ablated — has provided the opportunity to model biochemical dysfunction in neuronal-like cells with a broad range of pathogenic mtDNA mutations [20,21] (Fig. 2, Table. 2).

Although yet to be fully exploited, further transforming our capacity to study a wide variety of mitochondrial disease-causing mutations is induced pluripotent stem (iPS) cell technology (Fig. 2, Table. 2) [22]. The technique is characterised by the cellular transfection of four key transcription factors that, when expressed simultaneously in mouse or human cells, can confer pluripotency. These pluripotent cells can subsequently be induced to differentiate into the cell type of choice, such as the neurologically relevant neurons and astrocytes.

In addition to studies of classical or primary mitochondrial disorders, there are also a number of models that mimic disorders where secondary mitochondrial dysfunction appears to contribute to disease pathogenesis. These include: the *Sod1* (nuclear encoded) transgenic mice with large scale death of motor neurons, as seen in patients with amyotrophic lateral sclerosis (ALS) [23–26]; and a number of cellular and mouse models which seek to recapitulate Friedreich's Ataxia (FA), albeit with varying degrees of success [27–32].

Biochemical studies of mitochondrial disease in model systems have often focused on primary defects that directly affect the mitochondrial OXPHOS system (Fig. 1). The OXPHOS system plays a central role in maintaining a host of mitochondrial processes [7] by pumping protons across the inner mitochondrial membrane (IMM) and into the intermembrane space (IMS) to create an electrical and chemical gradient of protons, the mitochondrial membrane potential ($\Delta\Psi_m$) (Table. 2) [3]. The $\Delta\Psi_m$ drives a number of critical cellular functions, chiefly the synthesis of ATP by complex V (CV) [33]. Other critical processes dependent on the $\Delta\Psi_m$ include: modulating rates of superoxide production from CI and CIII [34]; regulating mitochondrial ultrastructure [35]; maintaining cellular calcium homeostasis [36]; and acting as a regulator of cell death pathways [37]. Regulation, however, does not always occur in a straightforward linear relationship. Cellular calcium, for example, is not just regulated by mitochondria, but itself regulates mitochondrial function [38]. This review focuses on the interplay between each of these mitochondrial processes, as modeled in both animal and cellular systems of mitochondrial disease, and how this may contribute to disease pathogenesis.

2. Dysfunction of OXPHOS

The OXPHOS system is comprised of five-multi subunit complexes (CI - V) embedded in the IMM, collectively encoded for by 12 mtDNA and 74 nDNA genes (Fig. 1) [7]. The system oxidises the reduced coenzymes NADH and $FADH_2$ at CI and II respectively. Liberated electrons are then passed along the OXPHOS complexes via ubiquinone (Q) to CIII, which shuttles the electrons to CIV via cytochrome *c* (cyt *c*), where finally the electrons are donated to molecular oxygen (O_2) to form water (H_2O). Electron transport is coupled to proton pumping at CI, III and IV, which take protons from the mitochondrial matrix, and deposit them in the mitochondrial intermembrane space to maintain the $\Delta\Psi_m$. The fifth OXPHOS complex, CV, utilises the $\Delta\Psi_m$ by mechanically coupling the

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