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Minireview

Strategies for treating mitochondrial disorders: An update

Mauro Scarpelli [a], Alice Todeschini [b], Fabrizio Rinaldi [b], Silvia Rota [b], Alessandro Padovani [b], Massimiliano Filosto [b,*]

[a] Section of Neurology, Department of Neurological and Movement Sciences, University of Verona, Verona, Italy
[b] Clinical Neurology, Section for Neuromuscular Diseases and Neuropathies, University Hospital "Spedali Civili", Brescia, Italy

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ABSTRACT

Mitochondrial diseases are a heterogeneous group of disorders resulting from primary dysfunction of the respiratory chain due to both nuclear and mitochondrial DNA mutations. The wide heterogeneity of biochemical dysfunctions and pathogenic mechanisms typical of this group of diseases has hindered therapy trials; therefore, available treatment options remain limited.

Therapeutic strategies aimed at increasing mitochondrial functions (by enhancing biogenesis and electron transport chain function), improving the removal of reactive oxygen species and noxious metabolites, modulating aberrant calcium homeostasis and repopulating mitochondrial DNA could potentially restore the respiratory chain dysfunction.

The challenge that lies ahead is the translation of some promising laboratory results into safe and effective therapies for patients.

In this review we briefly update and discuss the most feasible therapeutic approaches for mitochondrial diseases.

Contents

1. Introduction

Mitochondria are sub-cellular organelles involved in supplying cellular energy and in other critical cell processes such as adaptive thermogenesis [1], ion homeostasis [2], innate immune responses [3], reactive oxygen species (ROS) production [4] and programmed cell death (apoptosis) [5].

Since the first report more than 50 years ago when a mitochondrial defect was detected in a single patient with hypermetabolism [6], the field of mitochondrial diseases (MD) has evolved into the discipline of mitochondrial medicine with its own epidemiological and genetic rules. Mitochondrial disorders are now considered to be among the most common inherited diseases. Based on a study carried out in the northeast of England, one in 10,000 people are clinically affected by a mitochondrial DNA-related disorder, and one in 6000 individuals are considered at risk [7]. Within the next few years, the application of new technologies such as whole-exome sequencing is expected to result in a huge expansion of the number of nuclear genes that will be

* Corresponding author at: Clinical Neurology, University Hospital "Spedali Civili", Pz.le Spedali Civili 1, 25100 Brescia, Italy. Fax: +39 030 3384086.
E-mail address: massimiliano.filosto@unibs.it (M. Filosto).

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found defective in patients with MD [8], increasing incidence even more.

MD result from a primary dysfunction of the respiratory chain due to both nuclear and mitochondrial DNA involvement (nDNA and mtDNA, respectively). Mutations typically manifest with reduction of enzyme function in one or more of the five respiratory chain complexes and subsequent deficiency in ATP synthesis [9]. When the respiratory chain is compromised, the reducing equivalents (NADH and $FADH_2$) and pyruvate accumulate in the cytosol. Excess in cytosolic pyruvate is converted to lactate by lactate dehydrogenase, thereby accounting for the increased lactic acid found in many MD [10].

Although the vast majority of oxidative phosphorylation (OXPHOS) mutations impair the cell production of ATP, in some cases OXPHOS damage may leave ATP synthesis intact. Cell models of disease indicate a remarkable capacity for preservation of ATP production through enhanced glycolysis [11–13]. For these reasons, other pathological mechanisms could contribute to the tissue damage, such as overproduction of ROS [14] and induction of autoimmune responses [15].

Despite remarkable progress in defining the genetic factors triggering MD, full comprehension of their pathogenesis remains elusive [16]. This is part of the explanation why this group of disorders is still faced with limited therapeutic options. In addition, the definition of clear clinical biomarkers as well as a wide multicenter collaboration in order to include adequate patient populations should be of critical importance for obtaining rigorous and well-designed studies [17].

Current treatment is most often supportive and may include vitamin cofactors, nutritional manipulations, and exercise [18]. To date, only small controlled clinical trials have been performed, with the primary outcome most often focused on improving muscle strength and/or endurance, biochemical defects and quality of life [18]. Much of the evidence used to support specific treatments comes from single case reports, but there also have been a number of small quasi-randomized trials and open-labeled case series. In a recent meta-analysis, no clear evidence supporting any intervention in mitochondrial disorders was found, and authors concluded that further research is needed to establish the role of a wide range of therapeutic approaches [19].

However, there are several exciting strategies in a development stage aimed to overcome the initial mitochondrial defect and alleviate its up- and downstream effects. Some of them have already been tested in cell cultures or animal models; others, i.e. enzyme replacement therapy and bone marrow transplantation, are at late stages of pre-clinical analysis or, in some cases, available in clinical practice [20,21].

Gene therapy and strategies aimed to correct, bypass and avoid the transmission of the molecular defect to the offspring are taking more and more space and efforts in these years, with extremely promising results [20,21]. We will not discuss in detail here these approaches and we refer the reader to excellent reviews recently published in this field [22–25].

It is important to mention that an increased number of different diseases present with a so called "secondary" mitochondrial dysfunction or involves mitochondria in their pathogenesis [26–28].

Nevertheless, the focus of this review is on primary MD due to a respiratory chain defect, for which we briefly update and discuss the emerging pharmacological options of treatment, paying attention both to currently available and future strategies. A mention to pyruvate dehydrogenase (PDH) deficiency and ethylmalonic encephalopathy deficiency given their close relationship with the mitochondrial respiratory chain, will also be done.

2. Therapeutic approaches

2.1. Enhancement of mitochondrial biogenesis

In recent years, the enhancement of overall mitochondrial biogenesis has emerged as an exciting therapeutic perspective.

OXPHOS requires the function of five enzyme complexes (complexes I–IV and ATP synthase), consisting of more than 89 structural subunits (13 of them encoded by mtDNA, and the rest by nuclear genes). The proper function of OXPHOS requires coordinated expression, transport and assembly of these subunits, and the vast majority of these additional essential proteins are encoded by nDNA as well [10,29].

The transcriptional coactivators PGC (peroxisome proliferator-activated receptor g coactivator)-1a, PGC-1b and PRC (PGC-related coactivator) have been identified as activators of a signaling cascade that, by involvement of several transcription factors including the nuclear receptors peroxisome proliferator-activated receptors (PPARs), NRF-1 and -2 (nuclear respiratory factors) and ERRa (estrogen-related receptor alpha), result in the expression of a large number of nuclear genes involved in mitochondrial respiration and biogenesis [30–33].

The PGC pathway also directly regulates mtDNA through the modulation of TFAM (transcription factor A, mitochondrial), the mtDNA packaging and transcription factor [31].

In accordance to that, the up-regulation of PGC-1a signaling could increase the total number of mitochondria within cells, thereby restoring mitochondrial bioenergetics to near normal levels, assuming that a nuclear mutation causing respiratory deficiency saves at least some residual OXPHOS function [32].

Bezafibrate is a PPAR pan-agonist and an activator of PGC-1a and has been demonstrated to improve respiration of OXPHOS defective cells in culture [32].

Particularly, the effect of bezafibrate was investigated in cells with *SCO2* mutations [34]. *SCO2* belongs to a group of cytochrome *c* oxidase (COX) assembly genes, and its mutations cause COX deficiency and impaired copper metabolism, resulting in a fatal infantile cardioencephalomyopathy [35]. Supplementation with copper salts rescues the defect in patients' cells [36]. Casarin et al. studied the effect of bezafibrate and copper in cells with *SCO2* mutations, and showed that the two compounds were only marginally effective when administered individually, whereas the combined treatment achieved complete rescue of COX activity [34].

However, bezafibrate has been used in two COX-defective models, the *Surf1* −/− associated with mild COX deficiency and no clinical phenotype, and the *ACTA-Cox15* −/− associated with profound COX deficiency and severe mitochondrial myopathy; in both of them neither stimulation of mitochondriogenesis nor induction of mitochondrial respiratory chain enzyme activities was observed, whereas a bezafibrate-associated toxicity was shown in these mice [37].

In the same animal models, administration of the AMP-dependent kinase (AMPK) agonist 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR), which potentially increases PGC-1a activity, corrected COX deficiency [37]. Recently, AICAR was found to improve growth and ATP content, to increase mitochondrial biogenesis without altering mitochondrial membrane potential ($\Delta\psi$) and to decrease ROS production, suggesting that the strategy to increase the mitochondrial mass represents a very interesting potential treatment for MD [37,38].

Sirtuins, the mammalian orthologs of the yeast *silent information regulator* (*Sir*) *2* gene, are important regulators of several proteins and represent targets able to activate the mitochondrial biogenesis. Activation of Sirtuin1, a NAD^+-dependent protein deacetylase, increases mitochondrial biogenesis and function, by enhancing mitochondrial respiratory chain activities and transcription of genes related to OXPHOS. The modulation of NAD^+ bioavailability, increasing the formation throughout supplementation with nicotinamide riboside, a natural NAD^+ precursor, or reducing the consumption by inhibiting the poly(ADP-ribose) polymerases, represents a new exciting target for therapy of MD. Very robust results have been obtained in different mouse models of mitochondrial myopathy, and the hope is that these promising results can be rapidly translated in humans [39,40].

In recent years, increasing evidence for a role of estrogens, estrogens receptors and estrogen-related receptors in regulating mitochondrial