Chapter

Introductory Chapter: Mitochondrial Alterations and Neurological Disorders

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1. Introduction

Mitochondria (from Greek mito, μίτος, thread; and chondrion, χόνδριον, thick granule) are principal cell organelles, which participate in a wide spectrum of essential cellular functions, being the main energy providers for living eukaryotic cells, especially for neurons and glia, which are characterized by high metabolic activity and energy consumption.

Thus, it is expectable that mitochondrial dysfunction, having pleotropic effect on the cell, may play a crucial role in a substantial number of serious neurological disorders including Alzheimer's disease (AD) [1, 2], Parkinson's disease (PD) [3] Huntington's disease [4, 5], amyotrophic lateral sclerosis (ALS) [6], multiple sclerosis (MS) [7, 8], as well as some of the major psychiatric diseases [9], given that both, neurons and glia, are particularly sensitive and vulnerable to energy decline [10].

Mitochondria hypothesis of those devastating diseases advocates reasonably in favor of the important role that mitochondrial dysfunction may play in the early stages of neurodegeneration by inducing energy deficiency and oxidative stress [11].

However, the majority of the mitochondrial diseases, being maternally inherited, which are designated as mitochondrial encephalomyopathies [12], are closely connected either with the impairment of nucleus-to-mitochondria signaling or with mutations in mtDNA or nuclear genome that affect seriously the mitochondrial respiratory function even from the initial steps of the life [13], inducing defective oxidative phosphorylation (OXPHOS).

2. The genetic background of mitochondrial dysfunction

It is well known that mitochondria, as very specific organelles, include several copies (2–10 copies) of their own DNA (mtDNA), which consists of a 16.5 kb circular DNA molecule, being particularly prone to mutation [14]. mtDNA encodes for 37 genes, 13 of them encoding 13 polypeptides, which all are major components of OXPHOS complexes I, III, IV, and V, along with 22 tRNAs and 2 rRNAs, which play an essential role for the expression of the 13 subunits [15].

Mutations in mtDNA may be related to 25% of childhood-onset diseases [16] and to 75% of adult-onset ones [17], depending on the existing homoplasmy or heteroplasmy. In addition, the accumulation of mtDNA mutations can also induce or facilitate the aging process [18], since a common phenomenon in mammalian aging is the substantial decrease of electron transfer in mitochondria [19, 20].

3. Biological consequences of mitochondrial dysfunction

The mitochondria in addition to energy production compose also reactive oxygen species (ROS), which control redox status and intracellular Ca2+ levels and may induce apoptosis, by activating the mitochondrial permeability transition pore (mtPTP) [21]. In addition, mitochondria play a very important role in neuronal and glial calcium homeostasis due to their high capacity to accumulating Ca2+ [22].

Resting neurons contain usually minimal Ca2+ that can be increased by the activation of NMDA glutamate receptors, which induce a massive entry of Ca^{2+} into neurons, resulting in its high accumulation in the mitochondria [23]. Continuous activation of NMDA receptors would therefore induce Ca^{2+} overload of the mitochondria with the tragic consequence of the cell apoptosis, which frequently occurs as an epilogue of the excitotoxicity [24].

The apoptosis consists of a wide spectrum of biological phenomena [25] including the release of caspase activators [26], the alterations of the electron transport system, the change of mitochondrial transmembrane potential, the disruption of the cellular oxidation-reduction equilibrium, and the activation of the pro-apoptotic Bcl-2 family proteins [27, 28].

In the majority of the mitochondria-related neurological disorders, the functional or morphological alteration of the mitochondrial may be induced by increased ROS production, abnormal protein aggregates (Ab, tau) [29, 30], mutations in genes encoded by the mitochondrial and nuclear genome, and exposure of the cell to toxic factors [31].

4. The morphology of mitochondria in health and disease

Cell mitochondria could be visualized in light microscopy in properly fixed material by means of a number of special staining reactions [32–34]. It is observed that their size generally ranges from 0.5 to 1 micron in diameter, being changeable due to frequent divisions and fusions, which are controlled by mitofusin activity [35]. The shape of the mitochondria is also continuously changed due to their impressive active motility, controlled by calcium signal [36, 37], given that they are in constant flux, especially in brain's areas of high energy consumption in order to contribute in energy supply and to participate in the intracellular signaling actively [38].

Electron microscopy has been contributing greatly in the study of mitochondria in health and disease [39, 40]. Each mitochondrion in healthy condition is surrounded by a limiting double membrane and includes numerous longitudinal or tubular invaginations called mitochondrial cristae that are folds of the inner layer of the double membrane [41], which is four times greater than the outer one.

The cristae are mostly arranged perpendicularly to the long axis of the organelle, exhibiting a high morphological variability according to metabolic demands of the cell [42], being frequently lamellar, tubular, or triangle-shaped. In the majority of the mitochondria, the cristae are arranged parallel to one another inside a structureless matrix, which is clearly seen among the cristae.

Cardiolipin seems to play a crucial role in the morphology of cristae, since the disruption of cardiolipin biosynthesis induces obvious alteration of the cristae morphology [43]. In addition, Opa1, which is a GTPase, demonstrating dynamin-like properties, plays a substantial role in the modulation of the cristae structure and in their remodeling during mitochondrial fusion and fission [44] and apoptotic process [45]. The cristae have a high protein content [46], being also the principal site of the oxidative phosphorylation [47].

Electron microscope tomography, revealing the three-dimensional appearance of the cristae, shows that they are connected with the inner mitochondrial membrane by a narrow, tubular opening, characterized as "crista junction" (CJ), which is associated with protein import [48] and mitochondrial inner compartmentalization [49].

In neurodegeneration such as in Alzheimer's disease, mitochondrial cristae are disrupted even from the initial stages of the disease, and concentric patterns of cristae membranes are frequently seen [50].

5. Mitochondrial trafficking and concentration

Mitochondria, like many other cell organelles, are oriented and positioned properly in neurons and glia in order to be able to fulfill the energy demands of the cells perpetually. Thus, neurons, axons, dendrites, and synapses, which are characterized by high ceaseless activity, have intensive mitochondrial motility and impressive concentrations [51], via various trafficking patterns [52].

Axonal transport of mitochondria [53] requires microtubules (MTs) [54, 55] or actin filaments in axons [56], which facilitate the movement of the mitochondria in areas of high metabolic demands and increased energy consumption [57]. It is noticed that disruption of axonal transport of mitochondria occurs as an early phenomenon in cases of neuroinflammation [58], including multiple sclerosis [59–61].

6. Clinical expression of mitochondrial dysfunction

A considerable number of syndromes have been described with marked neurological phenomena in the spectrum of mitochondrial disorders [62]. The severity of the clinical manifestation of mitochondrial dysfunction varies considerably, given that there exists a threshold in the degree of mitochondrial deficiency for the clinical expression of the disease [63, 64]. Thus, the symptoms and clinical phenomena are continuously aggravated, in the majority of the cases of mitochondrial diseases, as the age of the patients advances [65]. It is reasonable to accept that organs with high energy demand would be more seriously affected by the mitochondrial dysfunction than others with low level of energy necessity. Thus the brain, the skeletal muscles, and the heart have a typical involvement in adolescence and adulthood, though multi-system manifestation is not also an uncommon phenomenon, especially in childhood.

Many clinical syndromes have been described that are associated with mitochondrial dysfunction including encephalomyopathy, stroke-like episodes, myoclonic epilepsy, neuro-gastrointestinal phenomena, cranial or peripheral neuropathy, ataxia, retinitis pigmentosa, chronic progressive external ophthalmoplegia which are associated frequently with lactic acidosis, mental retardation, or progressive mental decline [66].

In addition, oxidative stress, due to mitochondrial dysfunction, plays a principal role, as causative factor, in the neurodegeneration [67] and in Alzheimer's disease particularly [68, 69], and it is considered as been among the potential risk factors for the neurometabolic and neoplastic diseases, as well as obesity [70].

Molecular genetic testing on one hand and muscle biopsy on the other hand for the histochemical investigation in light microscopy and the ultrastructural study in electron microscopy of the muscle tissue are essential diagnostic procedures for approaching the diagnosis of mitochondrial disorders [71]. In addition, biochemical testing in blood, urine, and spinal fluid associated with neuroimaging [72]

would be useful diagnostic procedures in following in time the progression of mitochondrial diseases [71].

7. The final escape

A final escape from the labyrinth of mitochondrial-related neurological disorders is extremely difficult and less pragmatic under the present circumstances. Prospectively, an efficient treatment could be based on a stable modulation of mtDNA heteroplasmy [73], whereas gene therapy, gene transfer, and tRNA-targeted therapeutic attempts [74] as well as stem cell therapy for nuclear DNA mutations [75, 76] are very promising therapeutic endeavors with substantial medical and scientific value [77, 78].

In addition, an efficient and easy to apply treatment of mitochondrial dysfunction would open new bright horizons in the therapy of the inflammatory and neurodegenerative disorders [79], being beneficial in the amelioration of the quality of life of a substantial number of seriously suffering human beings.

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