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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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References

[1] Baloyannis SJ. Mitochondrial alterations in Alzheimer's disease. Journal of Alzheimer's Disease. 2006;**9**(2):119-126

[2] Wang X, Wang W, Li L, Perry G, Lee HG, Zh'u X. Oxidative stress and mitochondrial dysfunction in Alzheimer's disease. Biochimica et Biophysica Acta. 2014;**1842**(8):1240-1247

[3] Schapira AHV. Mitochondria in the aetiology and pathogenesis of Parkinson's disease. The Lancet Neurology. 2008;**7**(1):97-109

[4] Browne SE. Mitochondria and Huntington's disease pathogenesis: Insight from genetic and chemical models. Annals of the New York Academy of Sciences. 2008;**1147**(1):358-382

[5] Damiano M, Galvan L, Déglon N, Brouillet E. Mitochondria in Huntington's disease. Biochimica et Biophysica Acta. 2010;**1802**(1):52-61

[6] Orrell RW, Schapira AHV. Mitochondria and amyotrophic lateral sclerosis. International Review of Neurobiology. 2002;**53**:411-426

[7] Dutta R, McDonough J, Yin X, et al. Mitochondrial dysfunction as a cause of axonal degeneration in multiple sclerosis patients. Annals of Neurology. 2006;**59**(3):478-489

[8] de Barcelos IP, Troxell RM, Graves JS. Mitochondrial dysfunction and multiple sclerosis. Biology. 2019;**8**(2):37

[9] Rezin GT, Amboni G, Zugno AI, Quevedo J, Streck EL. Mitochondrial dysfunction and psychiatric disorders. Neurochemical Research. 2009;**34**(6):1021-1029

[10] Chrzanowska-Lightowlers ZMA, Lightowlers RN. How much does a disrupted mitochondrial network influence neuronal dysfunction? EMBO Molecular Medicine. 2019;**11**(1):e9899

[11] Area-Gomez E, Guardia-Laguarta C, Schon EA, Przedborski S. Mitochondria, OxPhos, and neurodegeneration: Cells are not just running out of gas. The Journal of Clinical Investigation. 2019;**129**(1):34-45

[12] DiMauro S. Mitochondrial encephalomyopathies--fifty years on: The Robert Wartenberg lecture. Neurology. 2013;**81**:281-291

[13] DiMauro S. Mitochondrial diseases. Biochimica et Biophysica Acta (BBA) - Bioenergetics. 2004;**1658**(1-2):80-88

[14] Taylor RW, Turnbull DM. Mitochondrial DNA mutations in human disease. Nature Reviews. Genetics. 2005;**6**(5):389

[15] Frazier AE, Thorburn DR, Compton AG. Mitochondrial energy generation disorders: Genes, mechanisms, and clues to pathology. Journal of Biological Chemistry. 2019;**294**(14):5386-5395

[16] Skladal D, Halliday J, Thorburn DR. Minimum birth prevalence of mitochondrial respiratory chain disorders in children. Brain. 2003;**126**:1905-1912

[17] Gorman GS, Schaefer AM, Ng Y, Gomez N, Blakely EL, Alston CL, et al. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. Annals of Neurology. 2015;**77**:753-759

[18] Müller-Höcker J. Mitochondria and ageing. Brain Pathology. 1992;**2**(2):149-158

[19] Fang EF, Scheibye-Knudsen M, Chua KF, Mattson MP, Croteau DL,

Bohr VA. Nuclear DNA damage signaling to mitochondria in ageing. Nature Reviews. Molecular Cell Biology. 2016;**17**(5):308-321

[20] Breitenbach M, Rinnerthaler M, Hartl J, et al. Mitochondria in ageing: There is metabolism beyond the ROS. FEMS Yeast Research. 2014;**14**(1):198-212

[21] Wallace DC, Fan W. Energetics, epigenetics, mitochondrial genetics. Mitochondrion. 2010;**10**:12-31

[22] Marchi S, Patergnani S, Missiroli S, et al. Mitochondrial and endoplasmic reticulum calcium homeostasis and cell death. Cell Calcium. 2018;**69**:62-72

[23] Abeti R, Abramov AY. Mitochondrial Ca2+ in neurodegenerative disorders. Pharmacological Research. 2015; **99**:377-381

[24] Sattler R, Xiong Z, Lu WY, MacDonald JF, Tymianski M. Distinct roles of synaptic and extrasynaptic NMDA receptors in excitotoxicity. The Journal of Neuroscience. 2000;**20**(1):22-33

[25] Green DR, Reed JC. Mitochondria and apoptosis. Science. 1998;**281**(5381):1309-1312

[26] Fan TJ, Han LH, Cong RS, Liang J. Caspase family proteases and apoptosis. Acta Biochimica et Biophysica Sinica Shanghai. 2005;**37**(11):719-727

[27] Friedlander RM. Apoptosis and caspases in neurodegenerative diseases. The New England Journal of Medicine. 2003;**348**(14):1365-1375

[28] Antonsson B, Martinou J-C. The Bcl-2 protein family. Experimental Cell Research. 2000;**256**(1):50-57

[29] Hashimoto M, Rockenstein E, Crews L, Masliah E. Role of protein aggregation in mitochondrial dysfunction and neurodegeneration in Alzheimer's and Parkinson's diseases. Neuromolecular Medicine. 2003;**4**(1-2):21-36

[30] Wang X, Su BO, Siedlak SL, Moreira PI, Fujioka H, et al. Amyloid-β overproduction causes abnormal mitochondrial dynamics via differential modulation of mitochondrial fission/ fusion proteins. Proceedings of the National Academy of Sciences. 2008;**105**(49):19318-19323

[31] Lee HK, Cho YM, Kwak SH, Lim S, Park KS, Shim EB. Mitochondrial dysfunction and metabolic syndrome-looking for environmental factors. Biochimica et Biophysica Acta. 2010;**1800**(3):282-289

[32] Cain AJ. An easily controlled method for staining mitochondria. Journal of Cell Science. 1948;**3**(6):229-231

[33] Roels F. Cytochrome c and cytochrome oxidase in diaminobenzidine staining of mitochondria. The Journal of Histochemistry and Cytochemistry. 1974;**22**(6):442-444

[34] Neto BA, Carvalho PH, Santos DC, Gatto CC, Ramos LM, et al. Synthesis, properties and highly selective mitochondria staining with novel, stable and superior benzothiadiazole fluorescent probes. RSC Advances. 2012;**2**(4):1524-1532

[35] Santel A, Fuller MT. Control of mitochondrial morphology by a human mitofusin. Journal of Cell Science. 2001;**114**(5):867-874

[36] Yi M, Weaver D, Hajnócky G. Control of mitochondrial motility and distribution by the calcium signal: a homeostatic circuit. The Journal of Cell Biology. 2004;**167**(4):661-672

[37] Wang X, Schwarz TL. The mechanism of Ca2+−dependent regulation of kinesin-mediated mitochondrial motility. Cell. 2009;**136**(1):163-174

[38] Rizzuto R, Bernardi P, Pozzan T. Mitochondria as all-round players of the calcium game. The Journal of Physiology. 2000;**529**:37-47

[39] Claude A, Fullam EF. An electron microscope study of isolated mitochondria: Method and preliminary results. The Journal of Experimental Medicine. 1945;**81**(1):51

[40] Sun MG, Williams J, Munoz-Pinedo C, et al. Correlated three-dimensional light and electron microscopy reveals transformation of mitochondria during apoptosis. Nature Cell Biology. 2007;**9**(9):1057-1065

[41] Lea PJ, Hollenberg MJ. Mitochondrial structure revealed by high-resolution scanning electron microscopy. The American Journal of Anatomy. 1989;**184**:245-257

[42] Patten DA, Wong J, Khacho M, Soubannier V, Mailloux RJ, et al. Slack OPA1-dependent cristae modulation is essential for cellular adaptation to metabolic demand. The EMBO Journal. 2014;**33**:2676-2691

[43] Xu Y, Sutachan JJ, Plesken H, Kelley RI, Schlame M. Characterization of lymphoblast mitochondria from patients with Barth syndrome. Laboratory Investigation. 2005;**85**:823-830

[44] Chan DC. Fusion and fission: Interlinked processes critical for mitochondrial health. Annual Review of Genetics. 2012;**46**:265-287

[45] Frezza C, Cipolat S, Martins de Brito O, Micaroni M, Beznoussenko GV, et al. OPA1 controls apoptotic cristae remodeling independently from mitochondrial fusion. Cell. 2006;**126**:177-189

[46] Neupert W, Herrmann JM. Translocation of proteins into mitochondria. Annual Review of Biochemistry. 2007;**76**:723-749

[47] Gilkerson RW, Selker JM, Capaldi RA. The Cristal membrane of mitochondria is the principal site of oxidative phosphorylation. FEBS Letters. 2003;**546**:355-358

[48] Perkins GA, Renken CW, van der Klei IJ, Ellisman MH, Neupert W, Frey TG. Electron tomography of mitochondria after the arrest of protein import associated with Tom19 depletion. European Journal of Cell Biology. 2001;**80**:139-150

[49] Mannella CA, Marko M, Buttle K. Reconsidering mitochondrial structure: New views of an old organelle. Trends in Biochemical Sciences. 1997;**22**:37-38

[50] Baloyannis SJ. Mitochondrial alterations in Alzheimer's disease. Journal of Alzheimer's Disease. 2006;**9**:119-126

[51] Chang DTW, Reynolds IJ. Mitochondrial trafficking and morphology in healthy and injured neurons. Progress in Neurobiology. 2006;**80**(5):241-268

[52] Sheng ZH. Mitochondrial trafficking and anchoring in neurons: New insight and implications. The Journal of Cell Biology. 2014;**204**(7):1087-1098

[53] Hollenbeck PJ, Saxton WM. The axonal transport of mitochondria. Journal of Cell Science. 2005;**118**(23):5411-5419

[54] Grafstein B, Forman DS. Intracellular transport in neurons. Physiological Reviews. 1980;**60**:1167-1283

[55] Hollenbeck PJ. The pattern and mechanism of mitochondrial transport in axons. Frontiers in Bioscience. 1996;**1**:91-102

[56] Langford GM, Kuznetsov SA, Johnson D, Cohen DL, Weiss DG. Movement of axoplasmic organelles on actin filaments assembled on acrosomal processes: Evidence for a barbed-end-directed organelle motor. Journal of Cell Science. 1994;**107**:2291-2298

[57] Bridgman PC. Myosin-dependent transport in neurons. Journal of Neurobiology. 2004;**58**:164-174

[58] Errea LO, Moreno B, González FA, García-Roves PM, Villoslada P. The disruption of mitochondrial axonal transport is an early event in neuroinflammation. Journal of Neuroinflammation. 2015;**12**:152

[59] Ghafourifar P, Mousavizadeh K, Parihar MS, Nazarewicz RR, Parihar A, Zenebe WJ. Mitochondria in multiple sclerosis. Frontiers in Bioscience. 2008;**13**:3116-3126

[60] Nikic I, Merkler D, Sorbara C, Brinkoetter M, Kreutzfeldt M, Bareyre FM, et al. A reversible form of axon damage in experimental autoimmune encephalomyelitis and multiple sclerosis. Nature Medicine. 2011;**17**:495-499

[61] Sorbara CD, Wagner NE, Ladwig A, Nikic I, Merkler D, Kleele T, et al. Pervasive axonal transport deficits in multiple sclerosis models. Neuron. 2014;**84**:1183-1190

[62] McFarland R, Taylor RW, Turnbull DM. A neurological perspective on mitochondrial disease. Lancet Neurology. 2010;**9**:829-840

[63] Wallace DC. Mitochondrial diseases in man and mouse. Science. 1999;**283**(5407):1482-1488

[64] Finsterer J. Central nervous system manifestations of mitochondrial disorders. Acta Neurologica Scandinavica. 2006;**114**(4):217-238

[65] Calabrese V, Scapagnini G, Stella AG, Bates TE, Clark JB. Mitochondrial involvement in brain function and dysfunction: Relevance to aging, neurodegenerative disorders and longevity. Neurochemical Research. 2001;**26**(6):739-764

[66] Ng YS, Turnbull DM. Mitochondrial disease: Genetics and management. Journal of Neurology. 2016;**263**(1): 179-191

[67] Islam MT. Oxidative stress and mitochondrial dysfunction-linked neurodegenerative disorders. Neurological Research. 2017;**39**(1):73-82

[68] Baloyannis SJ. Mitochondria: Strategic point in the field of Alzheimer's disease. Journal of Alzheimers and Neurodegenerative Diseases. 2016;**2**:004

[69] Baloyannis SJ. What has electron microscopy contributed to Alzheimer's research? Future Neurology. 2015;**10**(6):515-527

[70] Greaves LC, Reeve AK, Taylor RW, Turnbull DM. Mitochondrial DNA and disease. The Journal of Pathology. 2012;**226**:274-286

[71] Parikh S, Goldstein A, Koenig MK, Scaglia F, Enns GM, Saneto R, et al. Diagnosis and management of mitochondrial disease: A consensus statement from the mitochondrial medicine society. Genetics in Medicine. 2015;**17**(9):689-701

[72] Morava E, van den Heuvel L, Hol F, et al. Mitochondrial disease criteria: Diagnostic applications in children. Neurology. 2006;**67**:1823-1826

[73] Minczuk M, Papworth MA, Miller JC, Murphy MP, Klug A. Development of a single-chain, quasi-dimeric zinc-finger nuclease for the selective degradation of mutated human mitochondrial DNA. Nucleic Acids Research. 2008;**36**:3926-3938

[74] Yarham JW, Al-Dosary M, Blakely EL, Alston CL, Taylor RW, Elson JL, et al. A comparative analysis approach to determining the pathogenicity of mitochondrial tRNA mutations. Human Mutation. 2011;**32**:1319-1325

[75] Hussein E. Non-myeloablative bone marrow transplant and platelet infusion can transiently improve the clinical outcome of mitochondrial neurogastrointestinal encephalopathy: A case report. Transfusion and Apheresis Science. 2013;**49**:208-211

[76] Spendiff S, Reza M, Murphy JL, Gorman G, Blakely EL, Taylor RW, et al. Mitochondrial DNA deletions in muscle satellite cells: Implications for therapies. Human Molecular Genetics. 2013;**22**:4739-4747

[77] Kerr DS. Review of clinical trials for mitochondrial disorders: 1997-2012. Neurotherapeutics. 2013;**10**:307-319

[78] Nightingale H, Pfeffer G, Bargiela D, Horvath R, Chinnery PF. Emerging therapies for mitochondrial disorders. Brain. 2016;**139**(6):1633-1648

[79] Baloyannis SJ, Baloyannis JS. Mitochondrial alterations in Alzheimer's disease. Neurobiology of Aging. 2004;**25**:405-406