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Mini Review

The Role of Mitochondria in Neurodegeneration Development

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Abstract

Mitochondria are highly specialized organelles that are crucial players in cell physiology and pathophysiology. Known as "power-house of the cell", their major function is ATP production, but also regulation of cytosolic calcium homeostasis and ROS generation. Mitochondrial dysfunction is associated with neurodegenerative diseases due to neuronal cells dependence on mitochondria. Parkinson's and Alzheimer's diseases are consequences out of misfolding and aggregation of crucial proteins in the brain - α-synleucin and β-amyloid, which interact with mitochondria in neurons and astrocytes. What is more, in neurodegeneration development, mitochondrial dynamics and quality control were also found interrupted.

Keywords: *Mitochondria; Parkinson's Disease; Alzheimer's Disease; Neurodegeneration; Free Radicals; α-Synleucin; β-Amyloid; Mitophagy; Fission; Fussion; Amyotrophic Lateral Sclerosis; Huntington Disease*

Abbreviations

PD: Parkinson's Disease; AD: Alzheimer's Diseases; βA: β-Amyloid; ROS: Reactive Oxygen Species; mPTP: Mitochondrial Permeability Pores; ALS: Amyotrophic Lateral Sclerosis; HD: Huntington Disease; ER: Endoplasmic Reticulum

Introduction

Mitochondrial dysfunction is associated with neurodegenerative diseases due to neuronal cells dependence on mitochondria [1]. Neurons communicate with each other via synapses. The synaptic transmission provides proper neuronal development, maintenance and brain function. Due to physiological functions of mitochondria to produce ATP and regulate level of cytosolic Ca^{2+}, they are key organelles during brain development and in the adult brain, as ATP and Ca^{2+} are crucial for proper synaptic function [2]. In this review we are going to highlight the role of mitochondrial dysfunction in neurodegenerative disorders development.

Physiological role of mitochondria

Mitochondria are highly specialized organelles that are crucial players in fundamental aspects of cell pathophysiology. Known as "power house of the cell", their major function is ATP production. Beyond energy production, they take part in a generation of reactive oxygen species (ROS), redox molecules and metabolites [3]. Additionally, mitochondria participate in the regulation of Ca^{2+} homeostasis, protecting cells form Ca^{2+} overload [4]. What is more, mitochondria perform regulation of cell signaling, cell death, and biosynthetic metabolism. These multifaceted functions make them crucial organelles in cell physiology as they are cellular stress sensors, and allow cellular adaptations to the environmental changes [3].

Level of mitochondria in cell is regulated by formation of new (biogenesis of mitochondria) and elimination of damaged mitochondria by means of mitophagy. Dysregulation of these processes are reason of react number of diseases including neurodegenerative disorders [2].

Neurodegenerative diseases and mitochondrial function

World's most popular neurodegenerative disorders are Parkinson's (PD) and Alzheimer's diseases (AD). Both diseases are consequences out of misfolding and aggregation of crucial proteins in the brain - α-synuclein and β-amyloid (βA). What is more, these proteins share a common mechanism that involves formation of pores on plasma membrane, deregulation of Ca^{2+} level, mitochondrial dysfunction and oxidative stress. The combination of these factors leads to neuronal cell death [5].

α-synuclein aggregates are a primary structural component of intracellular Lewy bodies in PD, whereas βA is a characteristic for extracellular senile plaques in AD [5]. These deposits of misfolded proteins is a cause of cellular dysregulation and neuronal loss in both disorders [5]. These proteins influence function of mitochondria via reactive oxygen species (ROS) production and calcium signaling, what leads to cell death in the brain [6,7]. Calcium is able to trigger majority of intracellular pathway in all cell types. In neurons it plays fundamental role in synaptic transmission and in neuron-neuron and neuron-glia signaling [8]. Overproduction of ROS leads to oxidative stress which accelerate lipid peroxidation in brain cells [9-11] and is a cause of mitochondrial dysfunction [5].

Effect of β-amyloid on mitochondria is via nitric oxide (NO) production, ROS generation and Ca^{2+} release [11,12]. It induces mitochondrial depolarization by superoxide production from NADH oxidase and by increased Ca^{2+} signal in the matrix [13]. By generation of free radicals and calcium overload, βA activate opening of mPTP (mitochondrial permeability transition pores) which leads to membrane depolarization and inhibits mitochondrial respiration. Moreover, production of superoxide induces damages in DNA and limits mitochondrial respiration substrates [14].

PD's responsible α- synuclein interacts with mitochondria in substantia nigra neurons causing their dysfunction and neuronal loss [15]. It induces mitochondrial depolarization by inhibition of respiratory complex I at electron transport chain [16]. What is more, α-synuclein participate in mitophagy and fission/fusion cycle [17].

Disruption of mitochondrial dynamics and quality control

There are data suggesting that disturbed mitochondrial homeostasis can lead to PD development [2]. Mitochondria quality control is tightly regulated by fission/fusion cycle and mitophagy - selective degradation of mitochondria via autophagic pathway [4]. PD's associated proteins - PINK1 and PARKIN- are crucial for proper mitophagy initiation [2,18]. Multiple studies suggest that popular in PD mutations of genes linked to PARKIN, PINK1 kinase and E3 ubiquitin ligase are a reason of disrupted mitochondrial homeostasis in PD [2]. What is more, the mutations also are to elicit inflammatory response in neurons [1].

Disturbed mitochondrial homeostasis has also been observed in other neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS) and Huntington disease (HD) [2,18]. Altered and aggregated mitochondria were found in motor neurons of ALS patients [19]. Many mutated genes in ALS regulate mitophagy, for instance p62, TBK1 and optineurin. This in a consequence manifests in disturbed ATP production, free radicals generation and disrupted calcium signaling in interaction with the endoplasmic reticulum (ER). Mutations of SOD1 and TDP43 exhibit loss of communication between ER and mitochondria [19]. In addition, mutation on TDP43 results in disrupt transcription of mtDNA that leads to mitochondrial fragmentation and dysfunction [20].

Furthermore, changes in mitochondrial dynamic has been examined in Huntington disease. HD is caused by mutation in a protein of unclear function - Huntingtin (Htt). Nevertheless, there are some studies proving that mutations of Htt effects mitochondria and regulators of mitochondrial trafficking [1,2,21].

The examples of some genetic mutations in neurodegenerative diseases that influence mitochondrial function are presented in table 1.

Disease	Mutated gene	Description of gene	Influence of imitations on mitochondrial function
Alzheimer's disease (AD)	APP	The precursor form of AS In AD oligomeric form of Al3 aggregate to form senile plaques	Elevated apoptotic response, free radical production Abnormal mitochondrial distribution due to altered level of mitochondrial fission and fusion protein Decreased mitochondrial membrane potential and ATP level
	PSI & 2	Component for cleavage of APP to Al3 peptide	Modified mitochondrial motility and activity that leads to changes in brain energetics
Parkinson's disease (PD)	α- synuclein	Function still unclear Significant component of Lewy bodies in PD	Disrupted mitochondrial trafficking Fragmented mitochondria
	PINKI	Kinase localized to mitochondria Crucial protein in fussion/fission cycle	Altered mitochondria! Morphology and mitophagy Increased mitochondria! derived vesicles, activated MitoAP-cytotoxic response
	Parkin	Cytosolic E3 ubiquitin ligase located in the mitochondria Probably inhibiting formation of mitochondria] derived vesicles involved in mitochondrial antigen	Increased mitochondria! derived vesicles formation, activated MitoAP - cytotoxic response Altered mitochondrial morphology and mitophagy Increased oxidative stress
Huntington's disease (HD)	Huntingtin	Cytoplasmic protein, pleiotropic functions in neurons Regulates trafficking of mitochondria, synaptic vesicles	Fragmented mitochondria, altered mitochondrial dynamics Altered mitochondrial fission/fusion protein expression Impaired mitochondria trafficking Disrupted mitochondrial respiration
Amyotrophic Lateral sclerosis (ALS)	SODI	Superoxide dismutase [Cu-Zn], enzyme of antioxidative function	Disrupted mitochondrial trafficking, energy metabolism Reduced calcium-loading capacity in mitochondria Increased cytochrome c release, apoptosis

Table 1: *The influence of genetic mutations in neurodegenerative diseases on mitochondrial function [1,2,22,23].*

Conclusion

Due to many research highlighted above, mitochondrial dysfunction plays a crucial role in pathogenesis of any neurodegenerative diseases. However, many mechanisms are still unclear due to mitochondrial sensitivity to cellular toxins and various forms of stress. Up to this date, these organelles were known to be the powerhouses of the cells, but now they seem to be involved in many more processes. Recent findings about the role of mitochondria in neurodegenerative disorders are just the tip of the iceberg and there are many exciting discoveries ahead [1].

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