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Research Article

ROLE OF MITOCHONDRIAL OXPHOS DYSFUNCTION IN THE DEVELOPMENT OF NEUROLOGICAL DISEASES

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Abstract

Oxidative phosphorylation (OXPHOS) is an enzyme metabolic pathway that oxidizes nutrients to release chemical energy stored in the form of ATP (adenosine triphosphate). This process consists of five protein complexes I-V and takes place in the mitochondria. Several previous studies have stated that failure in this role has an effect on reducing the development of neurological diseases. The previous studies showed increasing the synaptic activity in the nervous system will increase mitochondrial division also and the failure of this process induced apoptosis and death of the nervous system. Failure of the OXPHOS process is associated with mutations in nuclear DNA or in mitochondrial DNA (mtDNA). Factors causing mtDNA damage, namely the absence of his tone proteins that bind mtDNA which should be able to protect mtDNA against free radicals, in mtDNA there is no DNA repair mechanism and mtDNA is located in the inner mitochondrial membrane adjacent to the site of ROS production (highly toxic).

Keywords: Neuron, OXPHOS, Mutation.

INTRODUCTION

The forms of diseases of the nervous system are very varied and require complex treatment, and most of these diseases are incomplete or even the causes and mechanisms and effective therapy are not understood [1,2].It happened because there are so many causes for disorders of the nervous system (multiple causes) that prevention or therapy becomes difficult, even nearly impossible[3]. The previous studies tried to find out more about disorders of the nervous system, it would be better to focus on the cellular level because the cellular level is vital for the development, cell metabolism and bioenergy of the nervous system[4,5]. Cell metabolism has a great influence on the development of cells, such as nerve cells [6,7]. Disturbances in cell metabolism (a lack of ATP) will have implications for the work of a cell itself and mitochondria, as a source of energy production, play an important role in supplying energy to metabolizing cells, resulting in damage or failure of mitochondria in organizing energy production (mtDNA and nDNA), in ha, this dysfunction in mitochondrial oxidative phosphorylation (OXPHOS) affects the metabolism of these cells, including in the nervous system [8,9].

The importance of mitochondria in neurons

Cell regulation of the number and size of mitochondria is controlled by division and fusion mechanisms. These process are especially important in neurons that aim to produce large amounts of energy[10]. Neurons are made up of thousands of mitochondria, which carry out their work like a formation of wires. Increased synaptic activity will increase mitochondrial division and failure of function in this process will induce apoptosis and death of the neuron system. However, the effects of this fission and fusion will lead to the production of reactive oxygen species (ROS), which will affect the development of neurodegenerative diseases[11]. Energy production for the body, cell mitochondria must produce a number of ATP through oxidative carbohydrates, fatty acids and amino acids, which is known as the process of oxidative phosphorylation [12,13]. Oxidative Phosphorylation (OXPHOS) occurs via the electron transport chain (ETC), which takes place in the inner mitochondrial membrane[14]. ETC is composed of complex I (NADH ubiquinone oxidoreductase), II (ubiquinone succinate oxidoreductase), III (ubiquinone cytochrome c oxidoreductase) and IV (cytochrome c oxidase); ATP is further produced by F1F0-ATP synthase, also known as complex V, which is a component of the OXHOS system but not part of the ETC[15,16]. It is not only do muscle cells have lots of mitochondria and ATP, but also the brain also needs a lot of ATP. Interestingly, neurons are completely dependent on the OXPHOS system to produce ATP because neurons cannot carry out the process of glycolysis to produce ATP even when there is limited amount of OXPHOS [17,18]. Failure of the OXPHOS process is associated with mutations in nuclear DNA or in mitochondrial DNA or can even occur as a result of damage to both, there is a complex relationship between mutations of the two components, such as mutations in nDNA may result in mtDNA damage and dysfunction, and vice versa

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mtDNA mutations can result of variations in nDNA expression[1,19]. The diagnosis of mitochondrial disease is associated with mutations in mtDNA and nDNA. Both mutations, nDNA and mtDNA, occur due to an increase in reactive oxidative species, or the production of toxic ROS[20,21]. Mitochondrial DNA is responsible for coding for proteins that affect OXPHOS so that mtDNA damage can cause interference with respiration and ROS production, and then lead to second mtDNA mutations, which will further cause damage to DNA and proteins that affect OXPHOS dysfunction[22,23]. Factors causing mtDNA damage, namely the absence of histone proteins that bind mtDNA which should be able to protect mtDNA against free radicals, in mtDNA there is no DNA repair mechanism and mtDNA is located in the inner mitochondrial membrane adjacent to the site of ROS production (highly toxic). However, mtDNA is also protected by a nucleid envelope structure consisting of mitochondrial proteins mtSSB and TFAM which protect against oxidative damage [12,24].

Diseases of the nervous system: Mutations of mtDNA and DNA

Diseases of the nervous system that occur at a young age result from OXPHOS dysfunction directly in mtDNA and nDNA mutations. The diseases are:

MELAS, is a maternally inherited disease from the mother's mitochondria and is characteristic of stroke. Manifestations of MELAS include vision imbalance, motor disabilities and dementia. The majority of MELAS sufferers show an A to G mtDNA mutation in the 3234 nucleotide of the MT-TL1 gene which encodes the transfer RNA for the amino acid leucine [25,26].

MERRF, is a mitochondrial disease with a variable clinical phenotype. This disease arises due to mutations at nucleotide 8344 in the MT-TK gene which codes for tRNA in mtDNA. Patients with MERRF usually exhibit myoclonic epilepsy, ataxia, and myopathy [8,27].

NARP, occurs due to point mutations at m.8399 T > C and m.8993 T > G in the mtDNA gene MT-ATPase6. This point mutation leads to breakdown of OXPHOS during ATP synthesis and increased ROS production [22,28].

Friedreich's Ataxia (FRDA), is an autosomal recessive disease associated with mitochondrial dysfunction as a result of a deficiency in the iron-sulfur cluster resulting from mutations in the nDNA coding for frataxin. In FRDA patients, homozygous expansion of the FRDA gene is seen with the initial intron in the form of a GAA repeat, which is responsible for coding frataxin, a mitochondrial protein for heme synthesis, formation of iron-sulfur clusters, and iron detoxification. Patients with FRDA are diagnosed with the phenotype of ataxia, spasticity and axonal sensory neuropathy, including early degeneration of sensory neuron [29,30].

Leigh Syndrome, This nervous system disease is associated with nDNA mutations in the structure and non-structure of the OXPHOS gene, where mutation points occur located in the MT-ATPase6 gene, which converts thymine to guanine at nucleotide 8993, substitution of leucine to arginine at the amino acid position 156 in ATP 6 protein. Interestingly, LS patients with the T8993G mutation show different symptoms from the T8993C mutation [31,32,33].

LHON, occurs as a result of more than 20 different mtDNA mutations, but most usually result from a 3-part mutation encoding the protein complex 1: m.3460 G >A, m.11778 G>A, or m.14484 T>C [34,35]. In addition to diseases caused by mutations in mtDNA and nDNA, OXPHOS damage and dysfunction can also occur due to the production of ROS which are highly toxic causing several diseases, such as Parkinson's Disease (PD) with decreased dopamine neurons in the substantia nigra pars compactica (SNpc) and development of proteinases including what are known as Lewy bodies on dopamine neurons (DA)[16,36]. Decreased Purkinje cells have also been reported in patients with neurodegeneration. Symptoms in people with PD can include tremor, rigidity, bradykinesia, and postural instability[37]. So far the cause of PD is still not known with certainty, it can occur due to genetic mutations in the Parkin and PINK1 proteins, or both which result in mitochondrial damage through the process of autophagy, but there are also PD that are not related to mutations[38,39]. Furthermore, the discovery of mtDNA deletions in the substantia nigra in PD patients is thought to contribute to neuronal death in this area. [40,41].

Alzheimer's Disease, occurs as a result of hippocampal neurons showing increased levels of mtDNA and cytochrome c oxidase in the cytosol, which play a role in the decline of hippocampal neurons[42]. There is also a decrease in membrane potential and a reduction in ATP [43,44].

Huntington's Disease, results from multiple CAG replications in the Huntington gene. This results in the onset of decreased motor function and even cognitive imbalance. Preliminary studies demonstrated that the peroxisome proliferator-activated gamma coactivator-1α (PGC-1α) receptor plays an important role in the biogenesis of controlling neuronal mitochondrial numbers[45,46]. Researchers also demonstrated that overexpression of PGC-1α induces mitochondrial loss[47].

Amyotrophic lateral sclerosis Occurs due to mutation of the superoxide dismutase 1 (SOD1) gene which is responsible for the conversion of superoxide to oxygen and hydrogen peroxide[48,49,50].

Conclusion

The development of research in the cellular-mocular field shows that not only mutations in nuclear DNA play a role in the emergence of genetic diseases, mutations in mtDNA that regulate and produce ATP also contribute to genetic diseases. world of health to develop therapies related to mitochondrial diseases.

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