ISSN 2616-5791 Vol.4, Issue 12: 88-95, DOI: 10.25236/AJMHS.2023.041212

Advances in the Study of the Relationship between Mitochondrial Damage and Neurodegenerative Diseases

Wei Wenqing[1,a,*], Du Kejun[1,b], Yao Jinyu[2,c], Liu Ying[1,d]

[1]*Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712046, China*
[2]*Hechuan District Center for Disease Control and Prevention, Chongqing, 401519, China*
[a]*1936144853@qq.com*, [b]*256563017@qq.com*, [c]*3515654319@qq.com*, [d]*97082069@qq.com*
[*]*Corresponding author*

Abstract: *Mitochondria are essential organelles in almost all cells (except erythrocytes) and are required for key processes such as bioenergy production, biosynthesis of reactive oxygen species, control of calcium homeostasis and triggering of cell death. Disruption of any of these processes can severely affect cellular function, especially neuronal function. Both hereditary and sporadic neurodegenerative diseases are inevitably accompanied by dysfunction of one or more key mitochondrial processes such as fusion, fission, reactive oxygen species production and energy generation. Mitochondrial damage plays an important role in the development of the neurodegenerative diseases amyotrophic lateral sclerosis, Parkinson's disease and Alzheimer's disease. Therefore, this paper reviews the literature on mitochondrial injury and neurodegenerative diseases in recent years and provides an overview of them to provide a referable basis for subsequent clinical studies.*

Keywords: *Mitochondrial damage; neurodegenerative disease; correlation; research progress*

1. Introduction

Neurodegenerative diseases are a heterogeneous group of disorders in which the nervous system functions abnormally due to abnormalities or deficits in neuronal or myelin function. Common ones include Alzheimer's disease and Parkinson's disease, muscular dystrophy lateral sclerosis and Huntington's disease. The main clinical manifestations are loss of cognitive function and impairment of motor behaviour, with progressive aggravation of symptoms, and the incidence increases with age. The mechanisms of neurodegenerative diseases are not yet fully understood. Mitochondria are multifaceted organelles that power key neuronal functions. One of the most important functions of the mitochondrion is to provide energy in cellular oxidative respiration, and its homeostasis is maintained by both number and function. When glucose metabolism is impaired or single-electron transport is affected by genetic or exogenous factors resulting in abnormal function or number of respiratory chain complexes, this may lead to inhibition of electrochemical gradients and subsequent energy failure, leading to neurodegenerative Diseases. The thirteen proteins required by the electron transport chain complex are encoded by mtDNA. mtDNA is particularly sensitive to oxidative stress due to its proximity to sites of oxidative metabolism, lack of histone protection, and limited pathways for damage repair. Mitochondrial dynamics encompasses the processes of mitochondrial fission and fusion, transport, biosynthesis and degradation, and autophagy. Mitochondria adjust the morphology, number and function of mitochondria through fission and fusion to adapt to cellular needs and maintain homeostasis in numbers. Mitochondrial dysfunction causes a decrease in the activity of key respiratory enzymes and a subsequent increase in ROS levels. When ROS are produced in excess, hydroxyl radicals are formed, causing oxidative damage to polyunsaturated fatty acids in biological membranes, proteins, enzymes, and nucleic acids, altering their structure and function, and thus affecting the above biological processes. Neuronal mitochondria are more vulnerable to oxidative stress because of the high oxygen demand of neuronal cells, high lipid content, relatively high content of unsaturated fatty acids, which are more sensitive to oxidative activity, and low levels of antioxidant enzymes. Whereas in many pathological conditions, mitochondrial dysfunction may be due to increased oxidative stress, which can stimulate post-translational modifications (PTMs) of mitochondrial proteins and/or oxidative damage to mitochondrial DN and lipids, although the brain accounts for only 2% of body weight, it receives 15% of cardiac output and accounts for 20% of systemic oxygen consumption [1]. In addition, Nrf2 regulates oxidative stress, mitochondrial

ISSN 2616-5791 Vol.4, Issue 12: 88-95, DOI: 10.25236/AJMHS.2023.041212

biogenesis, and mitochondrial autophagy in various organs, periphery, and central nervous system of the human body, whereas increasing evidence suggests that altered expression of Nrf2 is closely associated with aging and neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, stroke, and multiple sclerosis, and that it plays a crucial role [2].

2. Brain Diseases Associated with Mitochondrial Damage

2.1. Mitochondrial damage and Alzheimer's disease

Alzheimer's disease is defined as a cognitive disorder that is pervasive enough to interfere with a person's ability to work or complete daily activities, with the main histological features including large numbers of amyloid plaques containing amyloid beta (aβ) protein and neurogenic fibrillary tangles (NFTs) consisting of hyperphosphorylated tau protein. Temporal lobe and medial parietal cortex are frequently associated with brain atrophy and reduced glucose utilisation, which dominates the posterior regions of the brain, at least in the early stages [3]. The pathogenesis of Alzheimer's disease is currently unknown, but the mitochondrial cascade hypothesis suggests that mitochondria-associated alterations of the endoplasmic reticulum membrane (MAM) and MPTP are key factors in the pathogenesis of Alzheimer's disease. One of the most widely accepted hypotheses, put forward by Hardy and Allsop in 1991, is that misprocessing of amyloid β precursor protein (APP) and the deposition of pathogenic Aβ fragments are the the main driver of the progressive neuronal and synaptic loss behind cognitive decline [4]. Aβ is a 4 kDa fragment of amyloid precursor protein, a larger precursor molecule widely produced by brain neurons, blood vessels, and blood cells (including platelets), and to a lesser extent astrocytes. β-secretase (β-APP cleavage enzyme-1) is found in the extracellular structural domain of the amyloid precursor protein and the γ- secretase cleaves two subsequent protein hydrolysis of APP at intramembrane sites to produce Aβ Alterations in mitochondrial physiology have been found in Alzheimer's disease, but it is not clear whether they are an early event in the progression of the disease associated with amyloidosis or other disorders in the clinic. A recent study showing mitochondria-related experiments using APP/PS1 mice showed imbalances in mitochondrial dynamics in the cerebral cortex and hippocampus of these mice, representing very early events in disease progression. It was demonstrated in cellular models that these imbalances are the result of Aβ accumulation, which ultimately induces an increase in mitophagy, a mechanism for selectively removing damaged mitochondria through autophagy. With increased mitophagy, Aβ independently increased autophagy in APP/PS1 mice. Thus, mitochondrial dysfunction may be an early feature of Alzheimer's disease associated with amyloid overload [5]. Whereas the amyloidogenic pathway produces Aβ of various fragment sizes (mainly 38 to 43 amino acids), the most common Aβ isoforms produced in the amyloidogenic pathway are Aβ1-40 and Aβ1-42, the latter of which are particularly susceptible to aggregation into soluble Aβ oligomers (AβOs) or insoluble Aβ protofibrils, which can generate Aβ plaques in the brain. It has been shown that the presence of mitochondrial abnormalities and their association with oxidative damage labelled by 8-hydroxyguanosine and nitrotyrosine can be determined in patients with Alzheimer's disease using mitochondrial DNA in situ hybridisation (mtDNA), immunocytochemistry for cytochrome oxidase, and morphometrics from electron micrographs of biopsy specimens, the results of which show that the same neurons in Alzheimer's disease show increased oxidative damage. Thus, based on this result, Aβ accumulation is thought to be associated with dysregulation of mitochondrial homeostasis k and disruption of its electron transport chain complex. Also early experiments have shown [6] that mitochondrial dysfunction is usually characterised by impaired mitochondrial membrane potential (MMP), reduced ATP production and decreased mitochondrial mass. In addition, insulin is an important growth factor that regulates cell growth, energy utilisation, mitochondrial function, autophagy, oxidative stress, synaptic plasticity and cognitive function. Insulin and its downstream signalling molecules are mainly localised in the cerebral cortex and hippocampus. The major molecules involved in impaired insulin signalling include IRS, PI3K, Akt and GSK-3β, and activation or inactivation of these major molecules plays a role in aberrant insulin signalling or insulin resistance through increased or decreased phosphorylation. Thus, insulin resistance is thought to be a major cause of the development of AD features such as neuroinflammation and oxidative stress. And several studies have also suggested a strong link between diabetes and AD, which is attributed to an impaired insulin signalling pathway.

2.2. Mitochondrial damage and Parkinson's

A growing body of evidence suggests that the etiology of Parkinson's is multifactorial, involving

ISSN 2616-5791 Vol.4, Issue 12: 88-95, DOI: 10.25236/AJMHS.2023.041212

complex interactions between genetic and environmental factors. A large body of evidence from human tissue, genetic and toxin-induced animal and cellular models suggests that mitochondrial dysfunction plays a central role in the pathophysiology of Parkinson's disease, and that mitochondrial dysfunction due to defects in bioenergetics, alterations in mitochondrial DNA, production of reactive oxygen species, abnormalities in calcium homeostasis, and abnormalities in mitochondrial dynamics and quality control are associated with the potential mechanisms of neuronal cell death in Parkinson's disease. A recent study by Gonzalez-Rodriguez and colleagues in Nature [7] found that MCI dysfunction is sufficient to cause progressive Parkinson's disease due to mitochondrial dysfunction involved in Parkinson's disease with MPTP and rotenone, both of which block MCI function and produce irreversible Parkinson's-like symptoms, and that postmortem Parkinson's disease patients' brains show MCI deficits. By reviewing the improved size and analysis of PD GWAS data and recent advances in mitochondrial disease genetics, this study comprehensively assessed the role of mitochondrial function-related genes in sporadic Parkinson's, in which a tumour-specific multigene risk rating was computed and demonstrated that cumulative small effect variants in the major and minor gene lists were significantly associated with an increased risk of Parkinson's [8]. In addition, mitochondrial toxins cause Parkinson's disease by autosomal recessive inheritance of the Parkinson's genes Parkin, PTEN-inducible kinase 1 and DJ-1 encoding proteins involved in the mitochondrial pathway. The remaining studies confirm that additional evidence for mitochondrial dysfunction comes from autosomal dominant Parkinson's models caused by mutations in α-synuclein (SNCA) and leucine-rich repeat kinase 2 (LRRK2) [9]. It has also been shown [10] that the PINK1/Parkin pathway is thought to be the most common cause of early-onset Parkinson's, and that many of the mutations associated with Parkinson's disease lead to mitochondrial dysfunction including abnormal mitochondrial dynamics, disturbances in mitochondrial calcium-ion homeostasis, and abnormalities of mitochondrial splitting and merging, which lead to decreased mitochondrial function, mitochondrial oxidative stress, and mitochondria-related cell death, and some mutations also affect mitochondrial interactions with other organelles, further exacerbating the progression of Parkinson's disease. More importantly, Parkinson's disease patients have structural and functional mitochondrial abnormalities, including defects in oxidative phosphorylation, reduced ATP synthesis, and reduced mitochondrial membrane potential. Mitochondrial dynamics and mitochondrial autophagy are also affected, leading to abnormal accumulation of mitochondria and decreased ability to remove damaged mitochondria. Therefore, abnormal mitochondrial function may be an important feature in the pathogenesis of Parkinson's disease, and further study of the relationship between mitochondria and Parkinson's disease is important for revealing the pathogenesis of the disease and finding a cure.

2.3. Mitochondrial damage and Huntington's disease

Huntington's disease is a neurodegenerative disorder caused by pathological amplification of CAG repeat sequences within the Huntington's gene, resulting in amplification of polyglutamine in the encoded protein. Degeneration initially occurs in the caudate nucleus and striatum and progresses to involve the cerebral cortex, with typical clinical manifestations including progressive motor dysfunction and dementia. The underlying mechanisms leading to the pathology have not been identified and the disease pathogenesis may be multifactorial. It has been shown [10] that heat shock transcription factor 1 accumulates in the mitochondria of Huntington's disease cell model, YAC128 mouse model and human striatal-like organoids derived from Huntington's disease-induced pluripotent stem cells, and that overexpression of mitochondrial-targeted HSF1 (mtHSF1) in the striatum leads to neurodegeneration and Huntington's disease-like behaviour in mice. The pathogenesis of mtHSF1 may be that mtHSF1 promotes mitochondrial fission by activating the phosphorylation of the S616 site of dynamin 1. In addition, mtHSF1 inhibits the formation of single-stranded DNA-binding protein 1 oligomers, which leads to mitochondrial DNA deletion. And it has been pointed out in previous studies [11] that mitochondrial dysfunction is closely related to redox changes in Huntington's disease. Mutant Huntington's proteins can directly interact with mitochondrial proteins, such as the endosomal translocase 23 (TIM23), disrupting mitochondrial proteostasis and promoting reactive oxygen species production and Huntington's disease progression. In addition, aberrant brain and muscle redox signalling can lead to altered metabolic homeostasis and dyskinesia in HD, which can be ameliorated by the mitochondria-targeted antioxidant mito-quinone or the SIRT1 activator resveratrol, improving mitochondrial biogenesis and function. In addition, inefficient clearance of damaged mitochondria is thought to be one of the pathogenic mechanisms in neurodegenerative diseases such as Huntington's disease. In contrast, mutant HTT disrupts transcription, interferes with immune and mitochondrial function, and undergoes aberrant post-translational modifications. It is toxic and, at the DNA level, somatic CAG repeat amplification in vulnerable cells affects the disease process. In animal experiments, some researchers have cleared mHTT from the brains of adult mice, and their results showed that while neurodegeneration

ISSN 2616-5791 Vol.4, Issue 12: 88-95, DOI: 10.25236/AJMHS.2023.041212

increased CSF mHTT concentrations, mHTT was also present in the CSF of mice without neurodegeneration, and the study also found that mHTT secretion by CNS cells and lytic-like clearance of extracellular interstitial space contributed to mHTT in the CSF. Thus, the results of this study support passive release and active clearance of mHTT in CSF, suggesting that its treatment-induced changes may represent a combination of target contact and neuronal preservation. In contrast, recent studies on mutant Huntington's protein (mHtt) and mitochondria have revealed that mHtt interacts with mitochondrial dividing protein power-related protein 1 (DRP1) to enhance the enzymatic activity of the gtpase DRP1, which induces excessive mitochondrial fracture and aberrant distribution, leading to defective mitochondrial axonal transport and selective synaptic degeneration [12]. On the other hand [13], lower concentrations of reactive oxygen species are essential for normal cell signalling, whereas higher concentrations and prolonged exposure to reactive oxygen species cause damage to cellular macromolecules such as DNA, lipids and proteins, ultimately leading to necrosis and apoptotic cell death. The normal functioning of the central nervous system is completely dependent on the chemical integrity of the brain. In addition to this, it has been found that neuronal membranes are rich in polyunsaturated fatty acids, which are highly sensitive to reactive oxygen species, whereas HTT RNA levels or protein species can be used as a biomarker, also Huntington proteins play an important role as measured from biological systems or pathways, and mitochondrial autophagy prevents the accumulation of damaged mitochondria in the presence of pathogenic protein oligomers, protein mutations, stress, or injury. In addition to Htt, other SUMO ligases, enzymes, mitochondrial and autophagy components play important roles in disease progression. Vitamins play a crucial in role in the development of Huntington's disease, e. g., vitamin C deficiency reduces antioxidant levels, enhances oxidative stress, and disrupts glucose cycling; vitamin B5 deficiency disrupts acetylcholine and hormone synthesis in the brain. Whereas others have proposed [14] that melatonin, an endogenous free radical scavenger synthesised by neuronal mitochondria, decreases with aging and neurodegeneration, and that reduced levels of melatonin impair mitochondrial homeostasis, leading to mitochondrial DNA (mtDNA) release and activation of cytoplasmic DNA-mediated neuronal inflammatory responses. In brain and primary cortical neurons of melatonin-deficient arylalkylamine n-acetyltransferase (AANAT) knockout mice, mitochondrial oxidative stress is increased, mitochondrial membrane potential is reduced, and mtDNA release is increased.

2.4. Mitochondrial damage and other neurodegenerative diseases

The main feature of amyotrophic lateral sclerosis is the degeneration of motor neurons in the anterior horn of the spinal cord and the brain, leading to progressive muscle weakness, muscular dystrophy and respiratory failure. The pathogenic mechanisms of motor neuron degeneration are complex and include RNA toxicity, excitotoxicity, destabilisation of proteins, defects in axonal transport, oxidative stress and mitochondrial dysfunction. Among them, the change of reactive oxygen species and its induced mitochondrial damage and the initiation of apoptotic process are one of the important factors in the pathogenesis of amyotrophic lateral sclerosis, which ultimately causes motor neuron dysfunction and neurodegenerative pathological changes. Early scholars, Sasaki et al [15], in their study of the lumbar spine (L1-L5) in patients with amyotrophic lateral sclerosis, found the presence of aggregated black mitochondria in the neurons of the anterior horn of the spinal cord. The mitochondria in the soma of these neurons appeared to be swollen with markedly increased cristae, or multiple layers of cristae even stacked into filamentous structures. In in vivo models of amyotrophic lateral sclerosis, structural damage to mitochondria and breaks in the network usually occur early in the pathogenesis, suggesting that altered mitochondrial morphology may be a direct cause rather than a consequence of neurodegeneration. Abnormal aggregation of SOD1 protein in the cytoplasm, abnormal mitochondrial function, and altered levels of reactive oxygen species were found in fibroblasts from amyotrophic lateral sclerosis patients with mutations in the SOD1 gene, and the results suggest that endogenous excess reactive oxygen species may have a toxic effect on the mitochondria, revealing the importance of antioxidant systems [16]. Whereas several studies have shown that reduced activity of mitochondrial respiratory chain complexes I, II, III and IV are detected in skeletal muscle and spinal cord of patients with amyotrophic lateral sclerosis [17]. In addition, it has been noted that excess reactive oxygen species can lead to single-strand breaks in mtDNA, disrupting its structure and function and affecting downstream transcription and translation processes; it can also induce mutations in mtDNA, leading to oxidative modifications and the formation of base oxidation products with mutagenic effects, resulting in impaired ATP production and increased levels of reactive oxygen species, which at high levels can further trigger nucleic acid mutations [18]. Finally, uncontrolled mPTP opening is a key factor in promoting mitochondrial ROS generation. It has been shown that cyclophilin D promotes mPTP opening [19]. Xiao et al [20] examined the expression of cyclophilin D in skeletal muscle mitochondria of G93A mice before and after the onset of the disease,

ISSN 2616-5791 Vol.4, Issue 12: 88-95, DOI: 10.25236/AJMHS.2023.041212

and the relative level of cyclophilin D in skeletal muscle mitochondria of 2-month-old G93A mice (before the onset of the disease) was unchanged compared with that of WT mice, whereas that of 4-month-old mice (after the onset of the disease) showed a significant increase. Increased significantly. This study suggests that the expression level of cyclophilin D in mitochondria correlates with the stage of the disease, and that cyclophilin D may play an important role in the progression of amyotrophic lateral sclerosis by regulating the opening of mPTP and influencing the generation of reactive oxygen species.

3. Treatment of mitochondrial diseases

3.1. Western medical treatment

3.1.1. Targeted therapy

At present, gene-targeted therapy for mitochondria is mainly divided into physical methods, chemical methods, biological methods, and gene editing methods. Physical methods penetrate the cell membrane through mechano-physical methods, transferring exogenous DNA directly into the cell and randomly diffusing into the mitochondria [21]. The advantage is that the target gene is directly transferred into the cytoplasm without the need to carry a special carrier, and the disadvantage is that the efficiency is relatively low and the cell can be damaged during the physical penetration process. The chemical method is to change the chemical properties of the target DNA so that it can cross the cell membrane and then target into the mitochondria [22]. In addition, there are studies exploring the use of novel biological materials such as biopeptides to target the target gene into the mitochondria [23]. Gene editing methods are used to reduce the amount of mutant mtDNA in the cell by targeting the gene editing system constructed from instrumental enzymes to be transported to the mitochondria, so that the mutant mtDNA will be cleaved, broken, and then automatically removed by the mitochondria. At the same time, the mitochondria will synthesise new mtDNA, causing the proportion of normal mtDNA in the cell to rise, thus counteracting the effects of the mutant mtDNA, and the cell function will have a chance to be restored. Currently, there have been studies using the gene editing technologies ZFN and TALENs to successfully reduce the amount of mutant mtDNA that leads to mitochondrial disease in animals [24], which is the first time that mitochondrial DNA has been edited in animals using gene editing technology, and it is a major breakthrough in the research on the treatment of mitochondrial disease.

3.1.2. Other approaches

Mitochondrial transplantation replacement therapy is considered an effective treatment, and Masuzawa et al. demonstrated that mitochondrial transplantation increased total tissue ATP content and increased expression of mitochondrial proteins and precursor metabolites that support energy production and cellular respiration. In addition, improved angiogenesis, prevention of apoptosis and enhanced recovery of cardiac function were demonstrated. In addition, it has been shown that intrathecal injection of HTT-lowering agents dose-dependently reduces cerebrospinal fluid mHTT in HD patients, and the mechanism of action may be that HTT enters the cerebrospinal fluid by both passive release and active secretion, and is subsequently cleared by the analogous lymphatic cleavage, a finding of great significance for interpreting treatment-induced changes of cerebrospinal fluid mHTT in clinical trials of Huntington's disease. In contrast, in recent years, hydrophilic bile acids, particularly taurine deoxycholic acid, have shown important antiapoptotic and neuroprotective effects, and a large body of experimental and clinical evidence suggests that they may act as disease modifiers in neurodegenerative diseases. Preclinical studies have shown that taurine deoxycholic acid acts not only by modulating and inhibiting the apoptotic cascade, but also by attenuating oxidative stress, protecting mitochondria, producing anti-neuroinflammatory effects, and acting as a chemical chaperone to maintain protein stability and proper folding. Coenzyme Q10, on the other hand, is a lipid molecule that acts as an electron-moving carrier in the electron transport chain and also contains antioxidant properties. Coenzyme Q10 supplementation plays a key role in the treatment of mitochondrial diseases, and coenzyme Q10 and its synthetic analogue, Idebenone, are mainly used in the treatment of various neurodegenerative diseases. Pharmacological activation of permethrin is protective in models of neurodegenerative and metabolic diseases, and during endoplasmic reticulum stress, permethrin activation triggers insufficient mitochondrial perfusion and prevents premature apoptotic fragmentation of mitochondria. Permethrin activation also increases the formation of mitochondrial cristae and the assembly of respiratory supercomplexes, which enhances the cell's atp-generating capacity, thus permethrin enhances mitochondrial quality control during stress by promoting the expression of mitochondrial chaperone proteins and proteases, increasing mitochondrial biogenesis and mitochondrial autophagy, which leads to the renewal of the mitochondrial network [25].

ISSN 2616-5791 Vol.4, Issue 12: 88-95, DOI: 10.25236/AJMHS.2023.041212

3.2. Traditional Chinese Medicine (TCM) treatments

3.2.1. Chinese medicine treatment

Ginseng is a famous Chinese herb in China with a long history of clinical application and occupies a very important position in traditional Chinese medicine. Ginsenoside Rd, the active compound in ginseng, is known to have a broad-spectrum pharmacological effect on reducing nerve damage that can lead to neurological disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, depression, cognitive disorders, and cerebral ischemia.

3.2.2. Acupuncture

The clinical effectiveness of acupuncture on neurodegenerative diseases has been widely confirmed, since ancient times, Alzheimer's disease has been the concern of various medical practitioners, the Chinese medicine refers to it as "dementia", "stupidity", " Chinese medicine refers to it as "dementia", "stupidity", "dullness", etc. Medical practitioners through the ages have attributed its pathogenesis to the reduction of the medulla oblongata and the loss of use of the divine mechanism. The newly released "Research Report on the Status of Alzheimer's Disease in China" shows that the follow-up rate of Alzheimer's disease is low, and although the need for lifelong medication has been recognised by most of the patients interviewed, the price, efficacy, and side effects of the drugs lead to a low adherence to the medication rate of the patients. Acupuncture, as an economical and convenient traditional Chinese medicine therapy with few side effects, has been proven to be clinically effective for AD and has high patient compliance in the literature [26]. Acupuncture can significantly improve cognitive dysfunction and psycho-behavioural phenomena in patients with mild-to-moderate Alzheimer's disease [27], and the combination of acupuncture with medication is better than Western medicine alone in improving cognitive function and daily living ability in patients with Alzheimer's disease [28]. In addition, acupuncture therapy has been shown to be advantageous for the improvement of Parkinson's symptoms, and studies have shown that acupuncture therapy is better than the drug-only group in improving the motor dysfunction of Parkinson's patients [29], and can assist in the improvement of Parkinson's patient's gait, muscle stiffness, and the efficacy of Parkinson's concomitant non-motor symptoms such as cognitive dysfunction, dysphagia, anxiety, depression, sleep disorders, constipation, and other non-motor symptoms. Amyotrophic lateral sclerosis belongs to the category of "impotence" in traditional Chinese medicine, and the effective rate of needle and medicine combination treatment of amyotrophic lateral sclerosis is significantly higher than that of drug treatment alone [30]. The combination of acupuncture and traditional Chinese medicine can also improve the clinical symptoms of Huntington's disease [31]. Acupuncture is effective in the prevention and treatment of neurodegenerative diseases and has been widely used in clinical practice, but its specific mechanism has not been clarified, and currently, its mitochondrial autophagy regulation mechanism has attracted much attention.

4. Summary

Mitochondria, as the core functional apparatus of intracellular energy metabolism, are the basis for maintaining normal physiological activities of cells with normal morphology, quantity and quality, while mitochondrial damage mechanisms such as impaired mitochondrial energy metabolism, mutations in mitochondrial DNA, altered mitochondrial dynamics, Ca2+ overloading, and mitochondrial dysfunction may play an important role in the progression of neurodegenerative diseases. As the number of people suffering from neurodegenerative diseases is increasing year by year worldwide, elucidating the role of mitochondrial damage in neurodegenerative diseases and searching for possible targets for the prevention and treatment of neurodegenerative diseases are of great significance in improving the quality of patients' survival.

References

[1] Mohammed Akbar, Musthafa Mohamed Essa, Ghazi Daradkeh, et al. Mitochondrial dysfunction and cell death in neurodegenerative diseases through nitroxidative stress [J]. Brain Research, 2016, 1637:34-55.

[2] Kumar Vishal, Kundu Satyabrata, Singh Arti, et al. Understanding the role of histone deacetylase and their inhibitors in neurodegenerative disorders: Current targets and future perspective [J]. Current neuropharmacology, 2021, 20(1):158-178.

[3] Guy M. McKhann, David S. Knopman, Howard Chertkow, et al. The diagnosis of dementia due to

ISSN 2616-5791 Vol.4, Issue 12: 88-95, DOI: 10.25236/AJMHS.2023.041212

Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease [J]. Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 2011, 7(3):263-269.

[4] Sharma Chanchal, Kim Sehwan, Nam Youngpyo, et al. Mitochondrial Dysfunction as a Driver of Cognitive Impairment in Alzheimer's Disease [J]. International Journal of Molecular Sciences, 2021, 22(9):4850-4850.

[5] de la Cueva Macarena, Antequera Desiree, Ordoñez Gutierrez Lara, et al. Amyloid-β impairs mitochondrial dynamics and autophagy in Alzheimer's disease experimental models [J]. Scientific Reports, 2022, 12(1):10092-10092.

[6] Tillement L, Lecanu L, Papadopoulos V. Alzheimer's disease: effects of beta-amyloid on mitochondria [J]. Mitochondrion. 2011, 11(1):13-21.

[7] González Rodríguez Patricia, Zampese Enrico, Stout Kristen A., et al. Disruption of mitochondrial complex I induces progressive parkinsonism [J]. Nature, 2021, 599(7886):650-656.

[8] Kimberley J. Billingsley, Ines A. Barbosa, Sara Bandrés-Ciga, et al. Mitochondria function associated genes contribute to Parkinson's Disease risk and later age at onset [J]. NPJ Parkinson's Disease, 2019, 5(1):1-9.

[9] Harbauer Angelika B, Hees J Tabitha, Wanderoy Simone, et al. Neuronal mitochondria transport Pink1 mRNA via synaptojanin 2 to support local mitophagy [J]. Neuron, 2022, 110(9):1516-1531.e9.

[10] Norat Pedro, Soldozy Sauson, Sokolowski Jennifer D., et al. Mitochondrial dysfunction in neurological disorders: Exploring mitochondrial transplantation [J]. npj Regenerative Medicine, 2020, 5(1):22-22.

[11] Liu Chunyue, Fu Zixing, Wu Shanshan, et al. Mitochondrial HSF1 triggers mitochondrial dysfunction and neurodegeneration in Huntington's disease [J]. EMBO molecular medicine, 2022, 14(7):e15851-e15851.

[12] Sawant Neha, Morton Hallie, Kshirsagar Sudhir, et al. Mitochondrial Abnormalities and Synaptic Damage in Huntington's Disease: a Focus on Defective Mitophagy and Mitochondria-Targeted Therapeutics [J]. Molecular neurobiology, 2021, 58(12):1-28.

[13] Caron Nicholas S, Banos Raul, Yanick Christopher, et al. Mutant huntingtin is cleared from the brain via active mechanisms in Huntington disease [J]. The Journal of neuroscience : the official journal of the Society for Neuroscience, 2020, 41(4):780-796.

[14] Jauhari Abhishek, Baranov Sergei V, Suofu Yalikun, et al. Melatonin inhibits cytosolic mitochondrial DNA-induced neuroinflammatory signaling in accelerated aging and neurodegeneration [J]. The Journal of clinical investigation, 2021, 131(9):3124-3136.

[15] Sasaki Shoichi, Iwata Makoto. Mitochondrial alterations in the spinal cord of patients with sporadic amyotrophic lateral sclerosis [J]. Journal of neuropathology and experimental neurology, 2007, 66(1):10-16.

[16] Liu Wenchao, Liu Tao, Liu Zhihui et al. Detection the mutated protein aggregation and mitochondriai function in fibroblasts from amyotrophic lateral sclerosis patients with SOD1 gene mutations [J]. National Medical Journal of China, 2016, 96(25):1982-1986.

[17] Delic Vedad, Kurien Crupa, Cruz Josean, et al. Discrete mitochondrial aberrations in the spinal cord of sporadic ALS patients [J]. Journal of neuroscience research, 2018, 96(8):1353-1366.

[18] Kumar Manoj, Pathak Dhananjay, Kriplani Alka, et al. Nucleotide variations in mitochondrial DNA and supra-physiological ROS levels in cytogenetically normal cases of premature ovarian insufficiency [J]. Archives of gynecology and obstetrics, 2010, 282(6):695-705.

[19] Baines Christopher P, Kaiser Robert A, Purcell Nicole H, et al. Loss of cyclophilin D reveals a critical role for mitochondrial permeability transition in cell death [J]. Nature, 2005, 434(7033):658-662.

[20] Yajuan Xiao, Chehade Karam, Jianxun Yi, et al. ROS-related mitochondrial dysfunction in skeletal muscle of an ALS mouse model during the disease progression [J]. Pharmacological Research, 2018, 138:25-36.

[21] Yasuzaki Yukari, Yamada Yuma, Ishikawa Takuya, et al. Validation of Mitochondrial Gene Delivery in Liver and Skeletal Muscle via Hydrodynamic Injection Using an Artificial Mitochondrial Reporter DNA Vector [J]. Molecular pharmaceutics, 2015, 12(12):4311-4320.

[22] Yuma Yamada, Takuya Ishikawa, Hideyoshi Harashima, et al. Validation of the use of an artificial mitochondrial reporter DNA vector containing a Cytomegalovirus promoter for mitochondrial transgene expression [J]. Biomaterials, 2017, 136:56-66.

[23] Chuah Jo-Ann, Matsugami Akimasa, Hayashi Fumiaki, et al. Self-Assembled Peptide-Based System for Mitochondrial-Targeted Gene Delivery: Functional and Structural Insights [J]. Biomacromolecules, 2016, 17(11):3547-3557.

[24] Bacman Sandra R, Kauppila Johanna H K, Pereira Claudia V, et al. MitoTALEN reduces mutant

ISSN 2616-5791 Vol.4, Issue 12: 88-95, DOI: 10.25236/AJMHS.2023.041212

mtDNA load and restores tRNAAla levels in a mouse model of heteroplasmic mtDNA mutation [J]. Nature medicine, 2018, 24(11):1696-1700.
[25] Almeida Liliana M, Pinho Brígida R, Duchen Michael R, et al. The PERKs of mitochondria protection during stress: insights for PERK modulation in neurodegenerative and metabolic diseases [J]. Biological reviews of the Cambridge Philosophical Society, 2022, 97(5):1737-1748.
[26] Jia Yujie, Meng Dan, Sun Menglu, et al. Clinical Observation of Sanjiao Acupuncture on Mild to Moderate Alzheimer's Disease: A Randomized Controlled Trial [J]. Liaoning Journal of Traditional Chinese Medicine, 2017, 44(9): 1911-1914.
[27] Liu Ke, Miao Linqing, Jiang, et al. Clinical Research Situation and Analysis of Acupuncture Compared with Western Medicine in Improving Cognitive Impairment and Behavioral and Psychological Symptoms in Patients with Alzheimer's Disease [J]. Modernization of Traditional Chinese Medicine and Materia Medica-World Science and Technology, 2021, 23(6): 2105-2115.
[28] Zhao Ying. Clinical study on the treatment of mild-to-moderate Alzheimer's disease by acupuncture in the Duchenne vein [D]. Harbin: Heilongjiang University of Traditional Chinese Medicine, 2021.
[29] Sheng Gang, Guo Zhen. Acupuncture in Treating 38 Cases of Parkinson's Disease [J]. Western Journal of Traditional Chinese Medicine, 2018, 31(10):108-110.
[30] Meng Bin, Tian Jing. Clinical Observation of Tong Du Wen Yang Needling for Amyotrophic Lateral Sclerosis [J]. Shanghai Journal of Acupuncture and Moxibustion, 2017, 36(2): 134-137.
[31] Guo Xiaocong, Yang Dianhui, Fan Yingkong. A case of Huntington's disease treated with acupuncture combined with traditional Chinese medicine by Prof Yang Dianhui [J]. Journal of Sichuan of Traditional Chinese Medicine, 2017, 35(6): 152-153.