Journal of Experimental and Basic Medical Sciences 2024;5(4):264-270

Review

The Role of the PINK1-Parkin Pathway in Mitophagy and Its Implications in Neurodegenerative Disorders

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ABSTRACT

Mitochondria play a crucial role in cellular biological energy production, regulation of reactive oxygen species, and the synthesis of biological macromolecules. Mitophagy, on the other hand, is responsible for the selective degradation of damaged mitochondria and serves as a vital cellular process for maintaining neuronal homeostasis. Dysfunctional mitophagy leads to a disruption in mitochondrial quality control, which can result in or exacerbate neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and Huntington's disease. The PINK1/Parkin pathway initiates mitophagy through a series of ubiquitin-mediated signaling events in response to mitochondrial damage, promoting the degradation of impaired mitochondria. Disruption of this pathway leads to mitochondrial dysfunction, energy imbalance, oxidative stress, and neuronal degeneration, which are hallmark features of neurodegenerative diseases. Furthermore, impaired mitophagy has been shown to contribute to the pathogenesis of these disorders. In this review, we examine the molecular mechanisms of mitophagy, particularly the PINK1/Parkin pathway, and explore its effects on neurodegenerative diseases.

Keywords: Mitophagy, neurodegeneration, parkin, PINK1.

Mitochondria, the organelle responsible for energy production in the cell, also controls the levels of reactive oxygen species (ROS) and calcium homeostasis. Additionally, they are responsible for regulating the synthesis of large molecules.[1]

When the cell experiences stress conditions, mitochondrial dysfunction can occur, leading to a reduction in the number of mitochondria. A decrease in the number of these organelles can disrupt metabolic pathways, potentially indicating the pathogenesis of various diseases. This, in particular, can contribute to the progression or onset of neurodegenerative diseases.[2-5] In addition to stress conditions, mutations in genes encoding proteins such as leucine-rich repeat kinase 2, parkin (PARK2), PARK7, and PTEN-induced putative kinase 1 (PINK1), which play a role in the mitochondrial quality control system, can also contribute to the development of diseases.[6]

The term mitophagy refers to a specific type of autophagy mechanism. It is the process through which damaged mitochondria are detected and subsequently eliminated, ensuring their selective degradation. This pathway is the most crucial for maintaining neuronal homeostasis. It plays a vital role in cells such as neurons, which have high energy demands and lack the ability to divide.[7]

There is an electrochemical potential energy reservoir formed during energy production on the mitochondrial membrane. The distribution of ions here creates the mitochondrial membrane potential (MMP).[8] When the organelle is damaged, this membrane potential is lost, and this signal becomes the first signal that activates the mitophagy pathway.[9]

The signals that activate the mitophagy pathway are divided into two classes: ubiquitin (Ub)-mediated and receptor-mediated. In the Ub-mediated process, PINK1 kinase and Parkin Ub ligase play a crucial role.[10]

The mechanism works as follows:

(I) After the loss of MMP, the transport of PINK1 to the inner mitochondrial membrane is blocked,

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Cite this article as: Sever T, Erbaş O. The Role of the PINK1-Parkin Pathway in Mitophagy and Its Implications in Neurodegenerative Disorders. JEB Med Sci 2024;5(4):264-270.

doi: 10.5606/jebms.2024.1103

Received : October 16, 2024
Accepted : November 07, 2024
Published online : January 27, 2025

causing it to accumulate on the outer mitochondrial membrane.

(II) The accumulated PINK1 phosphorylates and activates Parkin, which then forms Ub chains and continues sending signals. These signals make the mitochondria more susceptible to damage.[11]

(III) In the final stage, autophagosomes are involved in the process, surrounding the mitochondria and fusing with lysosomes. Through lysosomal enzymes, the mitochondria are broken down and recycled.[10] This mechanism is considered a fundamental cellular pathway for maintaining mitochondrial quality control in neurons and preserving neuronal homeostasis.[12]

PINK1

PINK1 is a short-lived serine/threonine kinase composed of 581 amino acids. It has structural domains, including a serine/threonine kinase region, an N-terminal mitochondrial targeting sequence, a C-terminal autoregulatory region, and transmembrane domains.[13]

Under physiological conditions, PINK1 protein is maintained at low levels. Upon translocation to the mitochondria, it undergoes proteolytic processing in the mitochondrial targeting sequence and transmembrane regions, activating it. When full-length (63 kDa), it is delivered to the mitochondria through outer mitochondrial membrane translocase complexes and inner mitochondrial membrane translocase complexes. It is cleaved at the inner mitochondrial membrane, converting into its active form of 52 kDa. It is then released into the cytosol, where it is degraded by the ubiquitin-proteasome system.[14,15] In the case of mitochondrial damage, errors occur in the cleavage processes of PINK1, and since PINK1 cannot be cleaved and translocated to the inner membrane, it begins to accumulate on the outer mitochondrial membrane.[16,17] Here, the stabilized PINK1 becomes a signal. Accumulated PINK1 phosphorylates the Ub-like region of Parkin, activating it. Once Parkin is activated, the mitophagy mechanism is initiated.[18] Active parkin ubiquitinates mitochondrial proteins, marking them and the mitochondrion itself for degradation. This collaboration forms the PINK1/Parkin pathway.[19]

The PINK1/Parkin pathway preserves mitochondrial health along axons in neurons. To achieve this, PINK1 is locally synthesized and transported with the mitochondria, allowing the mitophagy process to be carried out in distal regions as well.[20]

PARKIN

As previously mentioned, parkin is an E3 ubiquitin ligase that functions downstream of PINK1. It consists of 465 amino acids and contains multiple domains. It includes a ubiquitin-like domain at its N-terminus and a RING-between-RING fingers at its C-terminus.[21]

Parkin primarily ubiquitinates various targets, including key outer mitochondrial proteins. This ubiquitination process marks these proteins for degradation, contributing to the selective removal of damaged mitochondria through mitophagy.[22] Parkin has the capacity to perform monoubiquitination and polyubiquitination, creating ubiquitin chains. It has been found to interact with various E2 ubiquitin-conjugating proteins. Additionally, it is thought to regulate its own degradation by self-ubiquitinating through chains called K6-linked ubiquitin.[23]

The human Parkin protein contains a total of 35 cysteine residues and 8 bound Zn2+ ions. The ligase activity is primarily based on the RING1 domain, which catalyzes the transfer of ubiquitin.[24,25]

Deubiquitinase enzymes such as USP30 or USP2, when localized to the mitochondria, can inhibit mitophagy, and this can sometimes block the process. However, inhibition of USP30 or USP15 can correct this defect and restore mitophagy, even in the absence of parkin.[26]

PINK1/PARKIN PATHWAY AND NEURODEGENERATIVE DISORDERS

Neurodegenerative disorders are heterogeneous disorders that can be triggered by mitochondrial dysfunctions. They are characterized by the continuous loss of specific neuronal populations and circuits within the nervous system.[27]

Mitochondria are not defined as stable structures because they are continuously influenced by various dynamic processes. The regulation of mitochondrial function depends on the collaboration of many proteins involved in these processes, and any disruptions that occur can lead to mutations that may cause the onset of various diseases.[28]

The brain can regulate oxygen consumption and redox capacity. Under physiological conditions, ROS are necessary in small amounts for neuron development and function. However, the brain's high oxygen consumption rate, combined with low levels of glutathione and glutathione peroxidase, results

in low antioxidant defense mechanisms, making it highly sensitive to the effects of oxidative stress. Additionally, the brain contains multiple unsaturated fatty acids that are prone to oxidation, and there is almost no catalase, an enzyme known for ROS clearance, in the brain. For these reasons, the brain is highly vulnerable to oxidative damage.[29]

Mitochondria are responsible for regulating cellular metabolism and controlling ROS in neurons. The mechanisms that maintain the health of these organelles are crucial. Dysfunction of the mitophagy mechanism, which preserves mitochondrial functionality and removes unhealthy mitochondria, leads to an imbalance in energy homeostasis in neurons, increased oxidative stress, and cellular degeneration. This condition can severely affect the functions of the nervous system.[30]

The rapid increase in mitochondrial degradation promotes the removal of damaged or dysfunctional mitochondria from the cell. As a result, the burden on healthy organelles increases, further disrupting cellular functions. This condition can trigger mitophagy-mediated neuronal death.[31]

Endoplasmic reticulum (ER) stress is defined as the accumulation of misfolded proteins in the ER lumen. In response to mild ER stress, cells increase their protein-folding capacity. However, when this mechanism fails, cells initiate the autophagy process.[32] Mitochondrial dysfunction and impaired mitophagy are two interrelated features of aging. They are considered to be either causes or risk factors for common neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD).[33] In these diseases, a decrease in the levels of PINK1 and parkin proteins is observed, leading to disruptions in the process of removing damaged mitochondria.[34]

Inflammation

The relationship between mitochondrial dysfunction and inflammation is quite strong. Immune cells involved in the proinflammatory response (microglia, dendritic cells, lymphocytes, etc.) are typically associated with increased anaerobic respiration activity. Macrophages and T cells, on the other hand, are dependent on mitochondrial oxidative phosphorylation metabolism, and metabolic remodeling in these cells is critical.[36]

Microglia are innate immune cells of the central nervous system (CNS). They play a role in maintaining CNS homeostasis and development from the embryonic stage through adulthood.[37] They can also play a role in the pathogenesis of certain CNS disorders in some cases.[38] Mitochondrial ROS is the most important regulatory factor for the inflammatory response of microglia.[39] These stimuli can trigger inflammatory functions, such as increased ROS production through cytokines released by activated microglia. In this way, they can act as both responders and triggers of neuroinflammation, contributing to the pathogenesis of various CNS diseases.[40]

Mitochondria, in cooperation with the ER, can act as a MitoSensor in DNA and RNA detection. As a result, the DNA released from damaged mitochondria triggers an immune response. This feature has been evolutionarily conserved and plays a critical role in immune response strategies.[41]

Parkinson's Disease

Parkinson's disease, a neurodegenerative disorder, is characterized by well-known symptoms such as tremors, rigidity, and postural instability. Similar symptoms are observed in both genetic and familial forms of the disease. The pathology of PD involves the loss of dopaminergic (DA) neurons in the substantia nigra, a brain region that serves as the primary source of dopamine production. Additionally, surviving neurons exhibit Lewy bodies, which are intracellular inclusions composed of aggregated alpha-synuclein proteins.[42] The accumulation of alpha-synuclein in the substantia nigra can be mitigated through the overexpression of the parkin gene.[43]

Mutations in the PINK1 and parkin genes are particularly associated with early-onset PD.[44] PINK1 and parkin mutations can interact with other genetic mutations, leading to a more severe disease phenotype. Individuals with biallelic PINK1/Parkin mutations exhibit higher levels of circulating cell-free mitochondrial DNA (mtDNA) compared to age-related PD.[45,46] Inflammation resulting from the release of mtDNA is considered a biomarker for PINK1/Parkin-associated PD.[46]

Knockout of the PINK1 or Parkin genes in mouse models alone has not been sufficient to cause Parkinsonism. However, when these mice possess a genetic background with a high level of mitochondrial DNA mutations, it has resulted in the loss of DA neurons.[47] In models with parkin deficiency, it has been observed that the loss of DA neurons is mediated by the cGAS-stimulator of interferon genes (STING1) pathway, which is a part of the cellular immune system. Additionally, a correlation has been identified between plasma levels of free

mitochondrial DNA and the inflammation marker IL-6 in patients with PINK1-mutant and parkin-mutant PD. It has been determined that in PINK1 knockout mice, the activation of STING proteins is required for the onset of inflammation.[48,49]

With brain aging, the activity of the PINK1/Parkin pathway has been found to increase, and this increase is more pronounced in neurodegenerative diseases such as PD and AD. In familial PD and similar disorders, pS65-ubiquitin-positive structures, which serve as a biomarker during the activation of the PINK1/Parkin pathway, are concentrated in the substantia nigra pars compacta region. Interestingly, pS65-ubiquitin can be detected in newly formed Lewy bodies and even in cells without these inclusions; however, it is absent in mature Lewy bodies.[50,51] This suggests that the PINK1/Parkin pathway may be activated early in the pathogenesis of sporadic PD.

The research conducted by Fang et al.[52] on mitochondrial dysfunction associated with PD and alpha-synuclein toxicity revealed that the knockout of the USP30 gene triggers mitophagy and provides protection against alpha-synuclein. This finding suggests that targeting USP30 to restore mitophagy and enhance neuroprotection in the absence of parkin could be a potential therapeutic strategy.

Alzheimer's Disease

Alzheimer's disease is the most well-known age-related neurodegenerative disorder. This disease generally manifests in two forms: early-onset and late-onset. Familial AD is caused by mutations in the APP, PS1, and PS2 genes. These cases are characterized by slow, progressive, and irreversible degeneration. Ultimately, this process leads to mental impairment and, eventually, death. In late-onset AD, various factors play a role. One of these factors is mitochondrial dysfunction.[53-56]

Mitochondrial dysfunction is a common feature in AD and includes changes such as mtDNA damage, impaired mtDNA expression, increased mtDNA mutations, and decreased mtDNA copy numbers. Additionally, increased oxidative damage reduced mitochondrial axonal transport, and disruptions in mitochondrial dynamics are also observed.[55-57] In AD, physical interactions between mitochondria and amyloid-beta (Aβ) are observed along with respiratory anomalies and energy hypometabolism in neurons, similar to those seen in PD. Mitochondrial dysfunctions, which are more prominent in the early stages, highlight the role of these interactions in the pathogenesis of AD.[58-62]

The accumulation of dysfunctional mitochondria in neurons leads to a decrease in ATP levels and an increase in ROS production, exacerbating mitochondrial damage. This, in turn, causes abnormal processing of APP and pTau, contributing to the formation of Aβ plaques and neurofibrillary tangles, which are characteristic features of AD.[60] In addition to its direct toxic effects on neurons, Aβ increases the neurons' sensitivity to harmful factors such as free radicals and oxidative stress, which contribute to the progression of AD.[61]

In brain regions affected by AD, more pS65-Ub structures are observed compared to age-matched controls, similar to PD. When comparing AD brains with different levels of tau or Aβ pathology, pS65-Ub structures show a strong correlation with tauopathy but do not show correlation independently with Aβ pathology.[63] It has been shown in several studies that the absence of parkin or PINK1 leads to an increase in tauopathy or Aβ pathology.[64] On the other hand, overexpression of parkin or PINK1, or activation of mitophagy with small molecules, partially suppresses the development of these pathologies and is considered a potential therapeutic approach to prevent the progression of neurological disorders.[65] In contrast, in experiments conducted with *Drosophila*, Lee et al.[66] did not observe a reduction in mitophagy in flies lacking parkin or PINK1.

Huntington's Disease

Huntington's disease is caused by a mutation in the HTT gene. It is a genetically inherited, autosomal dominant neurodegenerative disease that primarily affects medium-spiny neurons. This mutation leads to motor dysfunctions such as abnormal voluntary and involuntary movements, as well as psychiatric and cognitive impairments.[67] Mutant HTT (mHtt) interacts with glyceraldehyde 3-phosphate dehydrogenase, a protein that normally regulates cellular functions, leading to mitochondrial damage and a reduction in mitophagy. Additionally, it impairs the ability of autophagosomes to recognize and clear damaged organelles.[68]

In HD mouse models, it has been observed that harmful proteins are not efficiently cleared by autophagosomes, resulting in a reduction of mitophagy.[69] In an experiment conducted in *Drosophila*, mHtt expression disrupted mitochondrial morphology, but overexpression of PINK1 corrected these abnormalities, improving neuronal integrity and survival rates.[70] Additionally, it has been shown that overexpression of PINK1 partially corrected

mitophagy defects in striatal cells, which are located in the striatum, a region significantly affected by HD and playing a key role in learning and reward mechanisms.[69,71]

In conclusion, errors in the PINK1/Parkin pathway can affect the mitophagy mechanism and lead to neurodegeneration. In PD, the accumulation of α-synuclein and mutations in the PINK1 and parkin genes reveal the interactions between genetic factors and mitochondrial quality control mechanisms, contributing to neurodegeneration. Similarly, in AD, mitochondrial DNA damage and reduced mitophagic activity exacerbate Aβ and tau pathology, strengthening the link between mitochondrial dysfunction and neurodegeneration. The findings suggest that PINK1/Parkin-mediated mitophagy may have a protective response in AD. In HD, the toxic effects of mutant huntingtin protein disrupt mitochondrial dynamics and autophagic processes, leading to disease progression.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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