# Mitophagy Regulates Neurodegenerative Diseases

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Mitochondria are the primary source of cellular energy regulating cellular metabolism and physiology. To maintain cellular metabolism and homeostasis, damaged or unwanted mitochondria should be eliminated through mitophagy, a form of mitochondrial quality control process. Mitophagy is a highly selective autophagy process that eliminates dysfunctional or redundant mitochondria through multiple regulatory pathways in a ubiquitin-dependent or -independent manner. Since the term “mitophagy” was first coined by Dr. Lemasters in 2005, accumulating scientific evidence reveals that the accumulation of damaged mitochondria is one of the causal factors for various human diseases including neurodegenerative and cardiovascular diseases as well as cancers. Among all the cell types affected by mitochondrial dysfunction, neurons are vulnerable to mitochondrial damage due to their high energy demand.

Keywords: mitophagy ; neurodegenerative diseases ; Parkinson’s disease ; Alzheimer’s disease ; Huntington’s disease

## 1. Aging

Mitochondria play an essential role in the process of aging. The function of mitochondria decreases, and mitochondrial DNA mutations accumulate with aging. In the process of aging, the feature of dysfunctional mitochondria includes decreasing the content of mitochondria, changing the morphology of mitochondria, reducing the efficiency of the electron transport chain, and increasing ROS production. The mitochondrial quality control system, especially mitophagy, decreases with the deepening of aging. These changes are accompanied by the occurrence and development of diseases. Due to the high energy consumption of neurons, mitochondria are particularly important for their function, indicating that aging is a significant risk factor for neurodegenerative diseases.

In recent studies, the induction of mitophagy and degeneration of $NAD^+$ in Werner syndrome (WS) patients, which is an autosomal recessive accelerated aging disease and caused by mutations in the gene encoding the Werner (WRN) DNA helicase, has been observed [1]. The main clinical symptoms include cancer, juvenile cataracts, dyslipidemia, premature atherosclerosis, and insulin resistance diabetes. $NAD^+$ supplementation can significantly relieve the accelerated aging process in Caenorhabditis elegans and Drosophila melanogaster models of WS [1]. Through the mechanism study, the $NAD^+$ effect is achieved through DCT-1 and ULK-1 dependent mitophagy [1]. Cardiovascular aging is another very important aging event in which the regulation of mitochondrial homeostasis is involved [2]. Many studies have shown that mitophagy plays an important role in the anti-cardiovascular aging process in recent years. Heat shock protein 27 (HSP27), a small heat shock protein involved in the responses to oxidative stress, heat shock, and hypoxic/ischemia injury [3], can induce mitophagy and antioxidant function to reduce the degree of heart aging [4]. Another study demonstrated that double knockout of Akt2 and AMPK induced cardiac aging in 12-month-old mice, which was most likely achieved by reducing autophagy and mitophagy levels because more p62, lower LC3B II and LC3B I ratios, and lower level of mitophagy receptors associated with aging including PINK1, Fundc1, etc. were observed in double knockout Akt2 and AMPK mice [5]. Harman’s free radical theory is the commonly accepted aging theory at present [6][7]. This theory assumes that the decrease in cellular longevity is caused by the increase in reactive oxygen species. Recent studies have shown that mitochondria are the main source of ROS and the main target of ROS-mediated damage [8]. ROS is a by-product of mitochondrial respiration. With aging, mitochondria function decreases, and more ROS are accumulated, leading to the damage of mitochondria and mtDNA. These phenomena suggest that increasing mitophagy and restoring mitochondrial function can prevent and treat vascular and cardiac aging-related dysfunction.

Although growing studies have shown that there is a strong relationship between mitophagy and aging, the reason for the decline in mitophagy with aging is not clear. With aging, ROS accumulation may lead to the oxidation of many proteins related to mitophagy function including PINK1, Parkin, LC3, etc. The oxidation of protein will reduce its function, which may lead to mitophagy dysfunction. S-nitrosylation is a critical post-translational regulation of most proteins, which attaches a nitrogen monoxide group to the thiol side chain of cysteine [9]. Recent studies have shown that it may play an important role in aging and neurodegenerative diseases [10]. S-nitrosoglutathione reductase (GSNOR) is an important enzyme regulating S-nitrosylation. Its activity gradually decreases with aging, and leads to mitophagy related protein such

as Drp1 and Parkin S-nitrosylation, thus affecting the function of mitophagy [11]. Another study on Alzheimer's disease (AD) revealed that the S-nitrosylation transfer reaction mediated by UCH-L1, Cdk5, and Drp1 may play an important role in the occurrence and development of AD [10]. These results indicate that with the development of aging, post-translational modification may play a critical role in the dysfunction of proteins, which affects the physiological process, especially mitophagy.

In addition, skeletal muscle aging is also related to mitophagy. Sarcopenia refers to the loss of muscle mass and function with aging, and its molecular mechanism is not clear. However, an increasing body of evidence has shown that it is related to decreased autophagy levels, especially mitophagy. Mitochondrial dysfunction and fragmentation exist in aging muscles, which indicates that the regulation of mitochondrial homeostasis is unbalanced. Some studies have reported that NIX, PINK1, and Parkin levels are enhanced in aging muscles, suggesting that mitophagy as an anti-aging process is activated with aging [12][13][14]. Although mitophagy can remove damaged mitochondria and restore mitochondria health, with the deepening of the aging process, the related functional proteins of mitophagy are oxidized, resulting in the weakening of function, which is not enough to clear the damaged mitochondria, thus accelerating the aging. Exercise is thought to be a way to enhance mitophagy. Studies have shown that Parkin plays an important role in exercise-induced mitophagy [13], suggesting that Parkin, as a regulatory protein of mitophagy, participates in the process of mitophagy in skeletal muscle and plays an critical role in the aging of skeletal muscle. These studies indicate that the induction of mitophagy has a significant effect on the treatment of aging-related diseases. A clinical trial on Urolithin A (UA) shows that UA, as a safe and effective inducer of mitophagy, plays an important role in skeletal muscle health, providing more evidence for the treatment of premature aging-related disease by the induction of mitophagy [15].

## 2. Parkinson's Disease

Parkinson's disease (PD) is a prevalent neurodegenerative disorder primarily characterized by loss of dopaminergic neurons in the substantia nigra and accumulation of mutational alpha-synuclein. This was first described by James Parkinson in 1917 [16]. The precise mechanism of PD is unclear, but considerable evidence suggests that damage in mtDNA, redundant ROS, and dysfunctional mitophagy potentially regulates the occurrence of PD [17][18]. Accumulation of mitochondrial DNA (mtDNA) mutations caused by reactive oxygen species (ROS) results in mitochondrial dysfunction, thereby enhancing ROS production [19]. Mitophagy, a crucial mitochondrial quality control process, regulates mitochondrial function for neuron health [20]. Accumulation of damaged and dysfunctional mitochondria has been observed in Parkinson's disease, suggesting that mitochondrial network homeostasis is impaired in PD patients [21][22]. Furthermore, PINK1 knockout mice revealed a progressive loss of dopaminergic neurons in the substantia nigra [23]. This suggests that the disorder of the mitophagy process is potentially and strongly associated with PD (**Table 1**).

**Table 1.** Genes related to neurodegenerative diseases and mitophagy.

| Gene | Protein | Function in Mitophagy | Disease | Reference |
|---|---|---|---|---|
| ***PARK6*** | **PINK1** | **Kinase, involved in the regulation of several mitophagy related proteins** | **PD, AD, HD** | [24][25] |
| ***PARK2*** | **Parkin** | **Selectively recognize and eliminate damaged mitochondria from the cell** | **PD, AD, HD** | [25][26] |
| ***SNCA*** | **Alpha-synuclein** | **Located on the mitochondria through its *N*-terminal, lead to mitochondrial damage and dysfunction** | **PD** | [27] |
| ***DJ-1*** | **Protein DJ-1** | **Regulate mitophagy and ATP produce** | **PD** | [28] |
| ***GBA*** | **Glucocerebrosidase** | **Ensure normal function of lysosome and influence mitochondrial morphology and dynamics** | **PD** | [27][29] |
| ***DRP1*** | **Dynamin-related protein 1** | **Mediate mitochondrial fission** | **PD, AD, HD** | [30] |
| ***OPA1*** | **Optic atrophy 1** | **Mediate mitochondrial fusion** | **PD, AD, HD** | [31] |
| ***MFN1*** | **Mitofusin 1** | **Mediate mitochondrial fusion** | **PD, AD, HD** | [32] |
| ***VCP*** | **Valosin-containing protein** | **Accumulation of VCP can induce superabundant mitophagy** | **HD** | [33] |
| ***Rhes*** | **Ras homolog enriched in striatum** | **Up-regulate mitophagy via NIX receptor** | **HD** | [34] |
| ***OPTN*** | **Optineurin** | **Mediates the formation of autophagosome** | **ALS** | [35] |

| Gene | Protein | Function in Mitophagy | Disease | Reference |
|---|---|---|---|---|
| *TBK1* | TANK-binding kinase 1 | Mediate the engulfment of damaged mitochondria | ALS | [36] |

PINK1-Parkin pathway mutations inhibit mitophagy, which is directly related to PD occurrence [37]. PINK1 is highly expressed in organs or tissues with high energy demand including the brain, heart, and muscles. Moreover, Parkin is expressed in various types of tissues, which perhaps shows its complex functions [38]. Parkin mutations related to PD prevent the recruitment of Parkin to mitochondria and the accumulation of damaged mitochondria. This enhances ROS production, thereby promoting PD pathologies [26]. Moreover, mitochondrial disturbance of fission and fusion caused by alpha-synuclein can be rescued via PINK1 and Parkin co-expression [39]. Additionally, the NIX-mediated mitophagy pathway independently restores mitophagy in the PD patient cell lines without functional PINK1 and Parkin [40]. On the other hand, USP30 is identified as a deubiquitinase for mitophagy regulation negatively. Overexpression of USP30 inhibits mitophagy by removing ubiquitin on damaged mitochondria [41]. Several USP30 inhibitors are under development for the treatment of PD [42]. Despite PINK1/Parkin pathway dysfunction being a major contribution to PD pathologies, more studies have shown other genes that influence mitophagy involved in PD. DJ-1 is a mitochondrial location redox sensor. Loss of DJ-1 leads to mitochondrial fragmentation that may affect mitophagy. Mutation of DJ-1 causes a recessive form of PD [43][44]. Mutation of LRRK2, a large multidomain protein, influences mitophagy via regulating the PINK1/Parkin pathway, causing an autosomal dominant form of PD [45][46][47]. These findings suggest that mitochondrial dysfunction is strongly related to PD pathogenesis, and induction of mitophagy rescuing mitochondrial biogenesis may ameliorate PD pathology.

Notably, most PD patients are classified as sporadic patients, whereas only less than 10% of PD cases are diagnosed as familial PD. Among familial PD patients, important mutations in DJ-1 and GBA are implicated in maintaining normal mitochondrial function [28][29]. Although the biogenesis of these two categories is different, a significant difference between both groups for clinical profile or motor symptoms cannot be observed [48]. Since the pathogenic cause of PD is complicated and is still unknown, an effective strategy that can radically cure PD remains unavailable [49]. By eliminating dysfunctional mitochondria and degrading abnormal structural proteins, mitophagy is a potential strategy for PD treatment.

## 3. Alzheimer’s Disease

Alzheimer’s disease (AD) is the most common neurodegenerative disease; its symptoms include memory loss and cognitive impairments. Dysfunctional mitochondria accumulation, damaged synapse, disease-defining amyloid-β (Aβ) oligomers, and intracellular neurofibrillary tangles (NFTs) are the fundamental pathological hallmarks of AD [50][51].

A series of evidence suggests that amyloid deposition is a common pathological hallmark in numerous neurodegenerative diseases including AD; an excessive aggregation of amyloid-beta impairs neurons, causing their death [52]. Besides, amyloid precursor protein-derived *C*-terminal fragments (APP-CTFs) accumulating in AD patients and AD mouse models trigger mitochondrial damage and mitophagy failure in an Aβ-independent manner [53]. Increasing evidence shows the existence of a strong relationship between mitophagy failure and neuron degeneration. Studies by Fang et al. showed that mitophagy is reduced in APP/PS1 mouse model, Aβ-based *C. elegans* model, and even in the hippocampus of AD patients’ brains [54]. Another study also showed mitochondria fragmentation and dysfunction in Aβ expression of *Drosophila melanogaster*, suggesting that mitophagy failure may be a hallmark of AD [55]. Considering that mitochondria regulate energy generation in neurons, dysfunctional mitochondria will badly influence the signal delivery from one neuron to another. In addition, hyper-phosphorylated Tau, as another hallmark protein in AD, seemingly aggregates in AD patients and the loss of Tau is neuroprotective [56]. Numerous findings suggest that Tau expression leads to impairment in mitophagy [57][58][59]. This indicates that protein aggregate degradation is a potential strategy to reduce their impairment to CNS and protect neurons.

On the other hand, mitochondria are highly dynamic organelles; their shape and size, distributive situation, and physiological functions are regulated by their fission and fusion [60]. These processes include Drp1-mediated fission and OPA1-mediated fusion of mitochondria. Recent studies have reported that both levels of Drp1 and OPA1 are remarkably decreased in AD [61][62]. This indicates that the imbalance between fission and fusion affects the normal structure and function of mitochondria, promoting AD pathology. Mitophagy and mitochondrial dynamics interact with each other to maintain a healthy mitochondrial recycling balance [63]. Based on accumulating evidence, abnormal structures, functional defects, and variations in mitochondrial dynamics, and decline in the level of mitophagy are observed in neurons of AD patients [64][65]. Moreover, as terminally differentiated cells, neuronal cells are susceptive to various types of mitochondrial dysfunctions and irreversible damage, eventually leading to neuron death once compromising mitophagy cannot recycle damaged or redundant mitochondria properly.

Recent research has reported compounds including beta-Asarone and UMI-77 that help improve the learning and memory of AD mice as well as ameliorate disease pathologies by promoting mitophagy [66][67]. Another two compounds (nicotinamide riboside and urolithin A) are also reported to induce mitophagy. Nicotinamide riboside is a precursor of $NAD^+$ and can be metabolized to produce $NAD^+$ in cells and reduces Aβ levels in APP/PS1 mice [68][69][70]. This suggests that enhancement of $NAD^+$ may be beneficial for AD treatment. Urolithin A (UA) is a natural compound that ameliorates cognitive decline in the APP/PS1 mouse model via mitophagy activation [15][54][71]. A recent study showed that rapamycin, an mTOR inhibitor that can induce autophagy, also induces mitophagy and alleviates cognition in a mouse model of Alzheimer's disease [72]. This suggests that mitochondrial dysfunction is the most prominent feature of AD, whereas induction of mitophagy appears as a potential strategy for AD treatment.

## 4. Huntington's Disease

Huntington's disease (HD) is a rare autosomal dominant disorder caused by an expansion of cytosine-adenine-guanine (CAG) repeats within the huntingtin (Htt) gene. This results in polyglutamine (polyQ) expansion in the encoded huntingtin protein. Since the clinical syndrome of HD displays apparent neuropathic traits including motor dysfunction, cognitive decline, and psychiatric disturbances, it can also be classified into neurodegenerative diseases. The prevalence of Huntington's disease is estimated at 4–10 per 100,000 in the Western world and the onset time and severity of HD is positively related to the length of CAG repeats [73]. Although the pathogenesis of HD remains unclear and lacks effective therapeutic methods, increasing evidence reveals that mitochondria regulate the HD pathology process.

Aberrant mitochondrial morphology, fragmentation, and decreased mitochondrial mass are observed in HD patients. Besides, the mutant huntingtin severely impairs mitochondrial respiration and ATP production, suggesting that energy metabolism in HD may fall into disorder [74]. As for the fragmented mitochondria in HD pathology, scientists believe that excessive mitochondrial fission is potentially caused by increasing levels of Drp1 and decreasing levels of OPA1 and mitofusin 1 (Mfn1) [32][75][76]. These findings show that mutant huntingtin impairs mitochondria by disturbing mitochondrial dynamics, further influencing its function. This indicates that functional mitochondria restoration might be an effective treatment for HD. In line with the findings by Khalil's [77] group, PINK1 overexpression, which regulates Parkin-mediated mitophagy, partially restored mitophagy and promoted neuroprotection in Huntington's disease. Nonetheless, Guo et al. [33] suggested that accumulation of valosin-containing protein (VCP), an mtHtt-binding protein on the mitochondria, induces superabundant mitophagy, causing the death of neurons. Moreover, Rhes, a type of GTPase, was reported to upregulate mitophagy via the NIX receptor. This led to striatal cell death and striatal lesions, speculating that exaggerated mitophagy might be a contributing factor of HD [34][78]. Overall, abnormal mitochondrial size and morphology have been confirmed in HD, but the role of mitophagy (i.e., eliminating dysfunctional and unwanted mitochondria) remains controversial.

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