REVIEW

Mitophagy links oxidative stress conditions and neurodegenerative diseases

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Funding: *This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT and Future Planning, No. 2018R1C1B5029745 (to HJC), 2011-0030072 (to YH), 2018R1D1A1B07040282 (to JJ), and 2018R1A2B6001123 (to NYJ).*

Abstract

Mitophagy is activated by a number of stimuli, including hypoxia, energy stress, and increased oxidative phosphorylation activity. Mitophagy is associated with oxidative stress conditions and central neurodegenerative diseases. Proper regulation of mitophagy is crucial for maintaining homeostasis; conversely, inadequate removal of mitochondria through mitophagy leads to the generation of oxidative species, including reactive oxygen species and reactive nitrogen species, resulting in various neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. These diseases are most prevalent in older adults whose bodies fail to maintain proper mitophagic functions to combat oxidative species. As mitophagy is essential for normal body function, by targeting mitophagic pathways we can improve these disease conditions. The search for effective remedies to treat these disease conditions is an ongoing process, which is why more studies are needed. Additionally, more relevant studies could help establish therapeutic conditions, which are currently in high demand. In this review, we discuss how mitophagy plays a significant role in homeostasis and how its dysregulation causes neurodegeneration. We also discuss how combating oxidative species and targeting mitophagy can help treat these neurodegenerative diseases.

Key Words: *nerve regeneration; mitophagy; central nervous system; Alzheimer's disease; Parkinson's disease; Huntington's disease; amyotrophic lateral sclerosis; oxidative species; reactive oxygen species; reactive nitrogen species*

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doi: *10.4103/1673-5374.249218*

Received: *June 19, 2018*
Accepted: *October 20, 2018*

Introduction

Mitophagy is a term that was introduced by Le Masters in 2005 to describe the selective removal of mitochondria by autophagy (Lemasters, 2005). The degradation of mitochondria by mitophagy is especially important in cellular metabolism in which mitochondria play an essential role. The removal of dysfunctional and elderly mitochondria is essential for cell survival (Wallace, 2005). Additionally, neuronal cells are dependent on mitochondrial function, whereas its dysfunction is associated with neurodegenerative diseases. Disturbed mitochondrial function makes neurons especially sensitive to a wide variety of insults such as oxidative stress and bioenergetic defects. Thus, mitochondrial defects can greatly affect neuronal fate (Palomo and Manfredi, 2015).

Mitochondria are considered the main intracellular source of reactive oxygen species (ROS), which they produce during oxidative phosphorylation within all mammalian cells (Dai et al., 2014). ROS and reactive nitrogen species (RNS) play crucial roles in maintaining normal cellular behavior when regulated properly (Finkel and Holbrook, 2000). When ROS and RNS levels are excessive in terms of normal cellular requirements, it causes molecular damage and cellular debilitation. Higher levels of ROS may oxidize cellular constituents such as lipids, proteins and deoxyribonucleic acid (DNA), which interferes with cellular integrity (Finkel and Holbrook, 2000).

A previous study that used a mouse model of Purkinje cell degeneration demonstrated that altered mitophagy can cause excessive neuronal cell death, which was observed in the cerebellum. These results suggested that both uncontrollable mitophagy and inadequate mitophagy produce harmful effects (Kamat et al., 2014). Reduced autophagic function is believed to be responsible for many neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). Therefore, mitochondria were recently considered a potential therapeutic drug target (Kamat et al., 2014).

In this review, we briefly discuss mitophagy and its involvement in the central nervous system (CNS) (*i.e.*, AD, PD, HD, and ALS) and how these disease conditions occur when normal mitophagic function is compromised. By proper regulation of mitophagic pathways, the body can avoid harmful oxidative species, such as ROS and RNS, and harmful neurodegenerative diseases. Thus, by targeting these pathways, we can gain more knowledge about the therapeutic options to mitigate neurodegenerative disease conditions. Database search strategy is shown in **Additional file 1**.

Mitophagy

Mitophagy is induced by oxidative stress. Direct production of mitochondrial ROS by using a mitochondrial-targeted photosensitizer can also induce mitophagy (Wang et al., 2012). The induction of autophagy results in the recruitment of autophagy-related genes (Atgs) to a particular subcellular location, termed the phagophore assembly site, and nucleation of an isolation membrane that forms a cup-shaped structure, termed a phagophore (**Figure 1**). Eventual elongation of the curved isolation membrane results in expansion of the phagophore into a sphere around a portion of the cytosol. The isolation membrane subsequently seals into a double-membraned vesicle termed the autophagosome (**Figure 1**), trapping the engulfed cytosolic material as autophagic cargo (Dikic and Elazar, 2018). Previous studies that utilized the autophagosome indicator green fluorescent-protein-light chain 3 (GFP-LC3) *in vitro* and *in vivo* demonstrated that autophagy is eminently maintained in neurons (Mizushima and Kuma, 2008). More recent studies have also revealed the distinctions of basal autophagy between non-neuronal and neuronal cells (Tsvetkov et al., 2009). For example, GFP-LC3-positive autophagosomes were rarely observed in normal neurons, as huge aggregations of autophagic vacuoles were observed under disease conditions (Lee, 2009).

After clearance of most Atgs and delivery along microtubules to the lysosome, the outer membrane of the autophagosome fuses with the lysosomal membrane to form an autophagolysosome (**Figure 1**). This fusion results in the release of a single-membrane autophagic body into the lysosomal lumen, followed by degradation of the autophagic body together with its cargo by the autolysosomal hydrolytic milieu (Abada and Elazar, 2014). Another study using mutant mice, in which Atg5 or Atg7 gene, specifically in the brain was deleted, showed the importance of basal autophagy in neurons (Komatsu et al., 2007). In the mutant mice, neurons lacked Atg5 or Atg7, and animals experienced continuous neurodegeneration (Koike et al., 2008). According to another experiment, rapamycin, which is involved in autophagy induction, conferred protection in animal models of neurodegenerative diseases (Sarkar et al., 2008).

Additionally, NIX, which is also known as beclin-2 (BCL2)/adenovirus E1B 19 kDa protein-interacting protein 3-like (BNIP3L), is transcriptionally upregulated in the period of reticulocyte maturation to erythrocytes. NIX/BNIP3L interacts directly with LC3B or Golgi-associated ATPase Enhancer of 16 kDa (GATE-16) *via* an LC3-interacting region (LIR), hence mediating the sequestration of NIX-expressing mitochondria *via* the growing phagophore (Novak et al., 2010). Interestingly, hypoxia also mediates the expression of NIX/BNIP3L and a related BH3 protein, BHIP3, demonstrating similar receptor-induced mitophagy mechanisms in injury-mediated mitophagy. Post-translational modifications also play a major role in mitophagy, permitting a more rapid response to hypoxic stress, as observed for the mitophagy receptor Fun14 domain-containing protein 1 (FUNDC1) (Lv et al., 2017).

Mitophagy is a selective form of autophagy that removes dysfunctional mitochondria and their harmful byproducts and oxidative species to help maintain homeostasis.

PINK1/PARKIN Pathway in the Regulation of Mitophagy

There are several pathways through which mitochondria are targeted for degeneration at the autophagosome; however, PTEN-induced putative kinase protein 1 (PINK1)/cytosolic E3 ubiquitin ligase PARKIN (PINK1/PARKIN-induced mitophagy is the most well-understood pathway regarding the maintenance of mitochondrial homeostasis in degenerative diseases (Kitagishi et al., 2017). PINK1 is a mitochondrial-targeted serine/threonine kinase that plays a protective role against mitochondrial dysfunction and apoptosis with mitochondrial quality control by activating PINK1/PARKIN-induced mitophagy (**Figure 2**) (Fivenson et al., 2017). The significance of PINK1 in the mitochondria is needed in cell-protective characteristics for combating oxidative stress (Eiyama and Okamoto, 2015). The role of PINK1 has been well-documented in neurodegenerative and aging-related diseases (Li and Hu, 2015).

The cytosolic E3 ubiquitin ligase PARKIN and mitochondrial PINK1 have been implicated in the abnormal expression of genes associated with a recessive form of Parkinsonism (Schiavi and Ventura, 2014). However, the engagement of these proteins in the pathogenesis of PD remains unclear. Previous studies in *Drosophila melanogaster* have demonstrated that PINK1 and PARKIN function in the same genetic pathway to maintain mitochondrial network integrity (Greene et al., 2012). In healthy mitochondria, PINK1 is imported *via* the translocase complexes of the outer and inner mitochondrial membranes. PINK1 is then degraded by various proteases, such as mitochondria-processing protease (MPP^+), the inner membrane presenilin-related rhomboid-like protease (Meissner et al., 2011). Following mitochondrial depolarization, PINK1 is translocated to the inner mitochondrial membrane, degraded, and sustained on the mitochondrial membrane (Lazarou et al., 2012). The aggregation of PINK on the mitochondrial surface induces mitophagy by volunteering PARKIN to degrade mitochondria *via* a mechanism that is not completely understood. Hence, PINK1 likely acts as a sensor for degraded mitochondria. Translocation of PARKIN to damaged mitochondria has been shown to weaken PINK1 function (Geisler et al., 2010).

As a consequence of its translocation, PARKIN ubiquitylates outer mitochondrial membrane proteins. Another adaptor molecule, such as p62, is then engaged to mitochondria to induce mitophagy. The mitochondrial fusion proteins mitofusion 1 (Mfn1) and mitofusion 2 (Mfn2) have been recognized as substrates of PARKIN (Rakovic et al., 2011), as illustrated in **Figure 2**. PARKIN hinders mitochondrial fusion *via* the degeneration of mitofusions, thus isolating damaged mitochondria from the healthy mitochondrial membrane proteins, such as the voltage-dependent anion channel (VADC), the mitochondrial RhoGTase (MIRO) 1 (**Figure 2**) and constituents of the mitochondrial translocase complex (TOM70, TOM40 and TOM20) (Yoshii et al.,

2011). It is important to note that mitochondrial mobility is strongly maintained by the mitochondrial MIROs. MIRO1 and MIRO2 are both GTPases. MIRO function is essential for neuronal health: knockout of Miro1 in mice is lethal in the early postnatal period (Devine and Kittler, 2018).

Recessive mutations in PINK1 and PARKIN can cause PD and lead to a failure of mitophagy, causing mitochondrial damage (Kahle et al., 2009) and contributing to disease pathogenesis. Mitochondrial fission is also important for the function of neurons: dominant-negative dynamin-associated protein 1 (Drp1) mutation can cause a lethal infantile neurodegenerative phenotype. Drp1 knockout mice revealed embryonic lethality characterized by aberrant development of the brain and failure of synapse formation (Dagda et al., 2009).

Mitophagy and Neurodegeneration Diseases

The maintenance of mitochondrial physiology is essential for the nervous system because a disorder causes oxidative damage and many neurodegeneration diseases.

Alzheimer's disease

AD is a chronic neurodegenerative disease characterized by the extracellular accumulation of β-amyloid (Aβ) (Wang et al., 2018). As the current therapies have limited effectiviness against AD, there is an urgent need for more research efforts concentrated at developing new agents for preventing the disease process (Aso and Ferrer, 2014).

ROS-mediated injury is observed in AD brains, and higher levels of malondialdehyde (MA) and 4-hydroxy nonenal (4-HNE) are observed in the brain (**Figure 3**) and cerebrospinal fluid of AD patients compared to controls (Butterfield and Lauderback, 2002). Transactive response DNA-binding protein of 43 kDa (TDP-43) pathology may be present as a comorbidity in approximately 20–50% of sporadic AD cases (Di et al., 2018). A recent study showed that resveratrol weakened $A\beta_{1-42}$-induced cell death and significantly increased mitophagy (*i.e.*, increased the acidic vesicular organelle number, LC3-II/LC3-I ratio, Parkin and Beclin-1 (Bcl-1) expression and LC3 and TOMM20 co-localization in $A\beta_{1-42}$-treated PC12 cells) (Wang et al., 2018).

Ultrastructural analysis revealed extensive dystrophy of virtually all neurites in the vicinity of and within β-amyloid deposits. There is also marked aggregation of vacuoles (mostly autophagic vacuoles [AVs] and smaller numbers of condensed mitochondria). The numbers of AVs in neuritic processes of AD brains have exceeded the incidence of AVs in cell bodies, although the AV numbers in neuronal Perikarya were also remarkably increased in AD (Nixon et al., 2005). On the other hand, AD may cause improper clearance of autophagosomes that contain both amyloid precursor protein (APP) and its processing enzymes, thus increasing the propensity to produce toxic Aβ peptides (**Figure 3**) (Butler et al., 2006). Aβ is transported to mitochondria where it interacts with mitochondrial proteins, causing an increase in ROS production, excess accumulation of mitochondrial Ca^{2+} and mitochondrial fragmentation, a decrease in the number of functionally active mitochondria and, ultimately, neuronal damage (Duchen, 2012). In an APP transgenic mouse model, the down- or up-regulation of Bcl-1 enhanced or decreased, respectively, extracellular Aβ aggregation and neurodegeneration, highlighting the importance of mitophagy in AD-associated pathology. Furthermore, a correlation between flavin adenine dinucleotide (FAD) and autophagy was currently noted, reporting that autophagy needs functional presenilin (PS-1) for lysosomal maturation, which is altered by Alzheimer-related presenilin 1 (PS-1) mutations (Lee et al., 2010). Hence, PS-1 alterations may indirectly affect mitochondrial function by impairing its recycling by mitophagy (García-Escudero et al., 2013).

An increasing number of studies have investigated the defensive aspect of mitophagy in various harmful situations, such as coenzyme Q10 (CoQ10) inadequacy, hypoxia (Zhang et al., 2008), and exposure to rotenone, thereby making mitophagy an appropriate target for therapeutic mediation. Similarly, injection of lentivirus-infected Bcl-1 in a mouse model of spinocerebellar ataxia type 3 (Machado-Joseph disease) elevated motor function and subsequently decreased protein accumulation (Hetz et al., 2013). Consistent with these results, haploinsufficiency of Bcl-1 promoted the advancement of experimental AD *in vivo* (Pickford et al., 2008). These phenomena were accompanied by the aggregation of p62, diminished levels of LC3-II and a modified equality between monomeric and oligomeric components of mutant superoxide dismutase 1 (SOD1) in the spinal cord (Nassif et al., 2014).

Using transgenic *Drosophila* expressing human tau, Iijima-Ando et al. (2012) demonstrated that RNAi-mediated *Drosophila* Miro (dMiro) knockdown enhanced human tau phosphorylation at the AD-related site Ser262 (phopgo-tau), resulting in enhanced levels of active PAR-1 and increased tau-mediated neurodegeneration. Moreover, knockdown of Miro generated late-onset neurodegeneration in the fly brain, an effect that was suppressed by knockdown of *Drosophila* tau or PAR-1 (Kay et al., 2018). Surprisingly, the heterozygous Miro mutation (miro[Sd32]) has been connected to mitochondrial mislocalization and the amyloid-β 42 ($A\beta_{42}$)-mediated onset of AD symptoms in an attenuated fly model (Kay et al., 2018).

AD is most prevalent in the elderly. It is defined by the accumulation of Aβ plaques and occurs when the normal mitophagic functions of the body are decreased; conversely, it produces ROS, which acts as an initiator of AD.

Parkinson's disease

PD is the second most common progressive disorder of the CNS and is caused by a continuous loss of dopaminergic neurons (Tian et al., 2012). In dopaminergic neurons of the substantia nigra (SN), PD proteins such as Parkin, PINK1, DJ-1, and leucine-rich repeat serine/threonine-protein kinase 2 (LARRK2) as well as α-synucelin, play important roles in preventing cell death by maintaining normal mitochondrial function, protecting against oxidative stress, mediating mitophagy, and preventing apoptosis (Mukherjee et al., 2015). In addition to defective mitochondrial clearance,

knockdown of PINK1 (**Figure 3**) also causes mitochondrial fragmentation followed by the activation of mitophagy (Dagda et al., 2009). A previous study also showed that oxidative stress is one of the most common causes of PD (Gaki and Papavassiliou, 2014).

Damaged mitochondria can also hinder movement *via* the PINK1-PARKIN-mediated degradation of MIRO1. MIRO1 turnover on degraded mitochondria is altered in fibroblasts from individuals with PD-related E3 ubiquitin protein ligase PARKIN (PARK2) mutations (Pickrell and Youle, 2015). The PD-related protein named Leucine-rich repeat kinase 2 (LRRK2) was recently shown to bind to MIRO1, inducing its degradation. A pathogenic mutation in LRRK2 impairs such binding, delaying the arrest and eventual removal of degraded mitochondria (Hsieh et al., 2016).

In a *Drosophila* PD model with loss of PINK1 function, weakened dMiro function improved the degenerative phenotype (as demonstrated in PINK1-mutant DA neurons). This result indicates a role for mitochondrial transport and Miro in PINK1-related PD pathogenesis (Pickrell and Youle, 2015), an idea further supported by the profound effects observed in altered PINK1 function or the transportation of axonal mitochondria in *Drosophila* larval motor neurons or mammalian hippocampal neurons (Kay et al., 2018).

Lee et al. (2018) reported that transgenic *Drosophila melanogaster* expressing fluorescent mitophagy affected PINK1/PARKIN mutations on basal mitophagy under physiological conditions. The author also showed that PINK1 and PARKIN are not essential for bulk basal mitophagy in *Drosophila*. More importantly, this is the first work to visualize mitophagy in fly models. The degree of/extent to which PINK1-triggered mitophagy is essential for mitochondrial quality control in the mammalian brain and the extent to which its deviated regulation is responsible for PD pathogenesis remain unclear (Chu, 2018). By contrast, a complementary study demonstrated the effect of PINK1 on the mito-QC reporter system in PINK1 knockout mice (McWilliams et al., 2018). The same study also showed that basal mitophagy is unaffected by the loss of PINK1 in most tissues (Lee et al., 2018).

Cardiolipin in mitochondria is redistributed to the surface of degraded mitochondria, where it engages LC3 to assist in the generation of autophagosomes centered on mitochondria termed mitosomes (Chu et al., 2013). In cardiolipin-mediated mitophagy, a cargo-targeting mechanism does not require PINK1 aggregation or PARKIN association with the mitochondria (Chu et al., 2013). Another study revealed that the Atg32 system in yeast cells, the association of LIR proteins such as BNIP3, BNIP3L/NIX, sequestosome 1 (SQSTM1), or FUNDC1, and the PINK1-PARKIN2/PARKIN pathway, which is defined by two proteins, are genetically linked to PD (Chu et al., 2014). However, according to another study, PINK1 along with PARKIN is not needed for receptor-induced mitophagy. A concurrent study reported that NIX compensated for the dysfunction of PINK1 or PARKIN in fibroblasts from PD patients (Koentjoro et al., 2017).

In general, defects in the formation of autophagosomes cause impaired mitophagy, which causes PARKIN mutations that further result in neurodegenerative disorders, such as PD (**Figure 3**). Moreover, AVs were recently observed in an experimental neurodegenerative model and in dying striatal neurons in PD; however, information on the extent to which autophagy is associated with neurodegeneration and its pathogenic significance is limited (Nixon et al., 2005).

In PD, the accumulation of α-synucelin in the SN, which results in excessive ROS, eventually impairs the normal mitophagic pathways to regulate the redox balance and homeostasis (Gaki and Papavassiliou, 2014).

Huntington's disease

Motor deficits in HD patients are related to abnormal dopamine neurotransmission in the striatum (Vidoni et al., 2017). In HD, mitochondrial ROS production and oxidation of mitochondrial lipids play important roles in mitophagy (Johri et al., 2013).

In addition, it has been delineated that nitric oxide increases mitochondrial fission in neurons, initiating neuronal loss in a mouse model of stroke (Barsoum et al., 2006). In contrast, exhibition of Mfn or a dominant-negative Drp1 mutant in cultured neurons is defensive against oxidative insults. Apart from these, mechanistic target of rapamycin sequestration causes the aggregation of Huntington protein (Htt), which results in the upregulation of autophagy or polymorphisms in the autophagy-related gene Atg7 that further causes HD (Barsoum et al., 2006; Jahani-Asl et al., 2007) (**Figure 3**). Oxidative damage is found in the plasma of HD patients, HD postmortem brain tissue, lymphoblasts and cerebrospinal fluid (Khalil et al., 2015). In HD, degradation by autophagy is poorly understood, but the alterations in mitochondrial fission/fusion are likely to interfere with mitophagy, leading to the aggregation of degraded mitochondria in the cytoplasm. Martinez-Vicerte et al. (2010) showed that autophagosomes had a defect in cargo recognition that affects organelle sequestration by inducing autophagy, which may explain improper mitochondrial aggregation in HD cells. It was recently demonstrated that Htt is immensely associated with mitophagy by serving as a frame for both sequestosome 1 (SQSTM1/p62) and the autophagy-inducing kinase, UNC-51-like kinase-1 (ULK1), supporting the involvement of mutant Htt in these processes (Rui et al., 2015). In another study, dopamine-induced oxidative stress triggered apoptotic cell death in dopaminergic neuroblastoma SH-SY5Y cells that hyper-express mutant PolyQ Htt (PolyQ-Htt) protein. Dopamine toxicity was accompanied by impaired autophagy clearance of PolyQ-Htt aggregates. Dopamine also affected the stability and function of ATG4, a redox-sensitive cysteine protein associated with the process of LC3, a main step in autophagosome formation. Resveratrol, a dietary polyphenol with anti-oxidant and pro-autophagic characteristics, has demonstrated neuroprotective potential in HD (Vidoni et al., 2018).

Mitochondrial ROS plays an important role in the generation of HD, and abnormal ROS production imparts mitophagic dysregulation and fails to maintain the normal redox

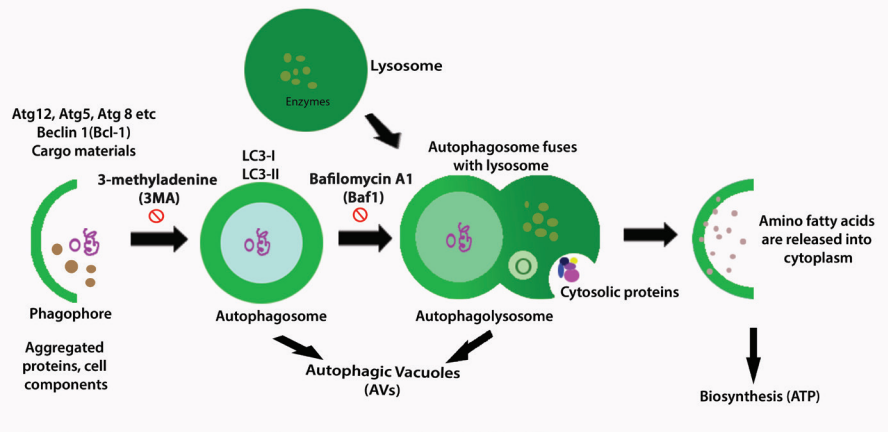

Figure 1 General process of autophagy.
At the begining of this process, cup-shaped phagophore is formed around the folded or aggregated proteins and with other cellular components, this is called nucleation. In the first step, the autophagic proteins (Atgs) such as Atg12, Atg 5, Atg 8, Beclin-1 (Bcl-1) and cargo materials are brought about through the ubiquitin-like conjugation systems Atg12-Atg5-Atg16L and Atg8 (LC3)-phosphatidylethanolamine (PE). In the second step, the expansion and maturation of the cup-shaped structure become rounded one and form autophagolysosomes which are double membraned vesicles with presence of LC3-I, LC3-II where the 3-methyladenine (3-MA) plays an inhibitatory role. In the third step, with an inhibitiory effect of bafilomycin A1 (Baf1), autophagosome is fused with lysosome and form single membraned autophagolysosome and this step is called fusion and autophagic vacuoles (AVs) and cytosolic proteins are seen. In the last step, the degradation of the autophagolysosome, with hyrolytic enzymes contributes to degradation of sequestered material, release of amino or fatty acids, and maintaineance of biogenesis.

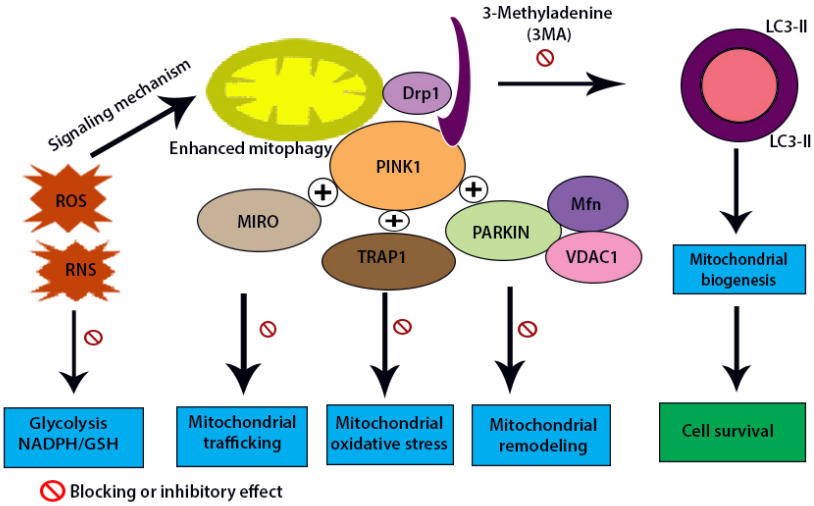

Figure 2 Protective roles of mitophagy.
Reactive oxygen species such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) acts as a signaling mechanism to induce autophagy or mitophagy which has a role in bioenergetic pathway and protective roles in cell survival. On the other hand, an increase in mitochondrial fusion protects mitochondria through mitophagy. The PTEN-induced putative kinase protein 1 (PINK1) of mitochondria is destabilized by presenilin rhomboid like (PARL) and cytosolic E3 ubiquitin ligase PARKIN (PARKIN) ubiquitinates mitofusion (Mfn), voltage dependent protein channel 1 (VDAC1) *etc.* that results in elevated mitophagy. PINK1 with different proteins such as mitochondrial RhoGTase (MIRO), tumor necrosis factor receptor associated protein 1 (TRAP1), PARKIN combined with Mfn and voltage dependent anion channel 1 (VDAC1) has different inhibitory roles such as mitochondrial trafficking and mitochondrial remodeling. Clearance of damaged mitochondria by mitophagy enhances mitochondrial biogenesis and increases the rate of cell survival.

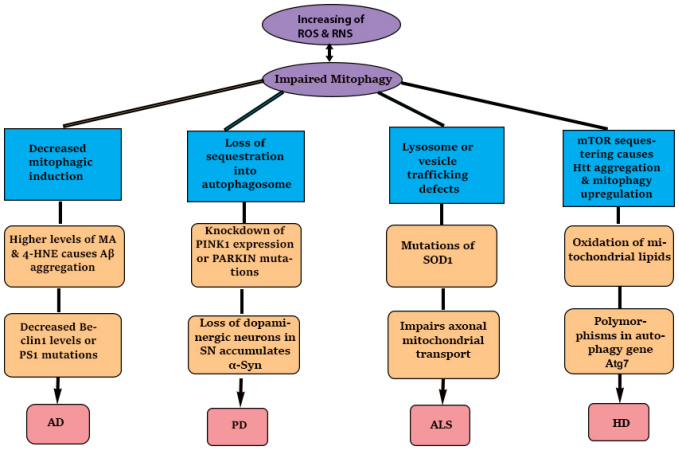

Figure 3 Correlation of mitophagy and neurodegenerative diseases.
Upregulation or downregulation of autophagic and mitophagic function has a role in the development of many neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Hungtington's disease (HD), and amyotrophic lateral sclerosis (ALS). AD is caused by decreased mitophagic induction which causes higher levels of malondehyde (MA), 4-hydroxynonela (4-HNE), and Beclin-1 (Bcl-1), and increases amyloid beta (Aβ) aggregation and presenilin (PS1) mutations. PD is caused by loss of sequestration into autophagosome which causes loss of dopaminergic neurons in substantia nigra (SN) as well as knockdown of PINK1 expression or PARKIN mutations. ALS is caused by decreased lysosome or vesicle trafficking defects that result in formation of SOD1 formation and inpair axonal mitochondrial transport. HD is caused by mechanistic target of rapamycin (mTOR) sequestering into huntingtin protein (Htt) aggregates and oxidation of mitochondrial lipids which inhibits signaling that results in upregulation of mitophagy and polymorphism of autophagy related protein 7 (Atg7). It is shown that the dysfunction of mitochondria is responsible for generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) to cause malfunction in mitophagy which is *vice versa*.

balance, resulting in impaired homeostasis.

Amyotrophic lateral sclerosis

ALS is a neurodegenerative disease affecting the spinal cord and brain motor neurons that ultimately leads to paralysis and early death (Mancuso and Navarro, 2017). Motor neuron death is caused by the dysfunction of mitochondria by directing them toward calcium-mediated excitotoxicity, by stimulating ROS generation and initiating the intrinsic apoptotic pathway (Julien, 2007). The particular mechanism of ALS is still under investigation because it is associated with cells other than neuronal cells. However, many lines of evidence suggest that huge amounts of autophagosomes and increased amounts of autophagic proteins and their activation are harmful for the survival of motor neurons. An increase in the LC3II macroautophagy marker protein and a decreased amount of phosphorylated mechanistic target of rapamycin-positive motor neurons revealed impaired mitophagy related to the loss of motor neurons in ALS (Okamoto et al., 2010). Various studies have reported dysfunctional Miro in ALS patients or animal models of the disease, including a report of significantly lower levels of Miro1 present in spinal cord samples of ALS patients (Zhang et al., 2015).

Mitochondrial fission and fusion hamper mitophagic clearance, which may also be affected by mutant SOD1 (**Figure 3**) (Albers and Beal, 2000). Glutathione (GSH) is a free radical scavenger tripeptide and acts as a main regulator of the intracellular redox state. GSH levels were lower in the motor cortex of ALS patients than those in the control volunteers (Weiduschat et al., 2014), and decreased levels of GSH result in neurological deficits and promoted the progression of mitochondrial pathology in the mutant SOD1 ALS mouse model (Vargas et al., 2011). Mutant SOD1 has been reported to impart Parkin-dependent degradation of MIRO1, which may explain the mitochondrial trafficking defect (Devine and Kittler, 2018). The same study also described Miro1-knockout mice, which exhibited upper motor neuron degeneration (Nguyen et al., 2014).

The expression of mutant TDP-43 in a motor neuron-like cell line induced oxidative species, mitochondrial disorder, and the accumulation of nuclear factor protein 2 (Nrf2), a modulator of oxidative species in a yeast model. TDP-43-expressing cells displayed increased markers of oxidative stress (Guareschi et al., 2012). Additionally, mitochondrial disorder was noticed, together with oxidative damage, as well as the induction of mitophagy in the mouse motor neuron-like cell line (NSC34) expressing wild-type or mutant TDP-43, representing a pathology resembling ALS. Moreover, motor neurons from these mice displayed cytoplasmic TDP-43-positive inclusions (Hong et al., 2012). In conclusion, lysosome or vesicle trafficking defects result in mutations in dynactin, which result in impaired mitophagy and ALS (**Figure 3**).

In a mouse model of motor neuron disease, full-length TDP-43 increased the involvement of mitochondria and blocked the TDP-43/mitochondria interaction, ameliorating mitochondrial TDP-43-interacting partners including VDAC1 and prohibitin 2 (PHB2), a vital mitophagy receptor (Davis et al., 2018). Mutant SOD1 impairs mitochondrial retrograde axonal transport (Magrané et al., 2013) along with mitochondrial network fragmentation, indicating the induction of mitophagy (Carrì et al., 2017).

Based on this review, we conclude that the loss of motor neurons and breakdown of the redox balance cause ALS in which ROS are an important component.

Conclusion and Future Perspectives

Mitophagy can prevent damaged mitochondrial aggregation and induce protective actions against cell demise. Clearing of degraded and aged mitochondria is an essential process for neuron survival. Focal mitophagy eradicates degraded mitochondria and decreases ROS-induced neuronal death (Kubli and Gustafsson, 2012). Li et al. (2014) demonstrated that rapamycin enhanced mitophagy, as evidenced by the increase in LC3-II and Bcl-1 expression in the mitochondria as well as p62 translocation to the mitochondria. Rapamycin decreased infarct volume, thus improving neurological outcomes, and decreased mitochondrial dysfunction compared with control animals. However, the mechanism by which rapamycin increases mitophagy should be further investigated (Li et al., 2014). In addition to 3-MA, other phosphoinositide 3-kinase (PI3K) inhibitors, such as bafilomycin and chloroquine, alter vascular and lysosomal pH and inhibit autophagosomal-lysosomal fusion, and E64 and pepstatin A prevent lysosomal protease activities. The prevention of autophagy usually leads to increased cell death; however, in some cases, autophagy leads to cytotoxicity. Investigating compounds that modulate autophagy and mitophagy will aid in the treatment of various diseases caused by oxidative protein modification aggregation within the cells (Zhang, 2013). It has been demonstrated in the abovementioned studies that mitophagy plays an important role in the course of neurodegenerative diseases by combating ROS in diseases such as AD, PD, HD, and ALS. We believe that by investigating different molecules that induce or inhibit mitophagy *in vivo* and *in vitro*, we can develop neuroprotective drugs.

Author contributions: *Conception and design of the manuscript: US, JJ, and YH; defining intellectual contents: US, IOS, NYJ, DK, HJC, JJ and YH; manuscript writing: US, JJ and YH; fundraising: JJ, NYJ, HJC and YH. All authors approved the final version of this paper.*
Conflicts of interest: *The authors reported no potential conflict of interests.*
Financial support: *This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT and Future Planning, No. 2018R1C1B5029745 (to HJC), 2011-0030072 (to YH), 2018R1D-1A1B07040282 (to JJ), and 2018R1A2B6001123 (to NYJ).*
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Data sharing statement: *Datasets analyzed during the current study are available from the corresponding author on reasonable request.*
Plagiarism check: *Checked twice by iThenticate.*
Peer review: *Externally peer reviewed.*

Open peer reviewer: *Ivan Fernandez-Vega, Hospital Universitario Central de Asturias, Spain.*

Additional files:

Additional file 1: *Database search strategy.*

Additional file 2: *Open peer review report 1.*

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P-Reviewer: Fernandez-Vega I; C-Editor: Zhao M; S-Editor: Li CH; L-Editor: Song LP; T-Editor: Liu XL

Database search strategy- Mitophagy links oxidative stress conditions and neurodegenerative diseases

Serial No.	Article title	Eligibility criteria	Keywords/ Key terms	Publication date/Year	Database	Publishing language
1.	Getting ready for building: signaling and autophagosome biogenesis	A review that discusses recent progress in our understanding of autophagosome biogenesis	Atgs, autophagosome, biogenesis, autophagy, MTOR signaling	July 15, 2014	Google scholar	English
2.	Mitochondrial dysfunction and oxidative stress in aging and neurodegenerative disease	A report that discusses age-dependent onset and progressive course of these neurodegenerative diseases	Neurodegenerative diseases, Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD) and progressive supranuclear palsy (PSP), oxidative damage, superoxide dismutase (SOD1)	2000	Google scholar	English
3.	Cannabinoids for treatment of Alzheimer's disease: Moving toward the clinic	A review that discusses the polyvalent properties of cannabinoid compounds for the treatment of AD, which together encourage progress toward a clinical trial.	Alzheimer's disease (AD), cannabinoid, β-amyloid peptide, oxidative stress	March 5, 2014	Google scholar	English
4.	Nitric oxide‐induced mitochondrial fission is regulated by dynamin‐related GTPases in neurons	An article that discusses persistent mitochondrial fission may play a causal role in NO-mediated neurotoxicity	Mitochondria, nitric oxide (NO), autophagy, Dynamin related protein 1, mitochondrial fission	July 27, 2006	Google scholar	English
5.	Potential compensatory responses through autophagic/lysosomal pathways in neurodegenerative diseases	An article that discusses positive modulation of protein degradation processes represents a strategy to promote clearance of toxic accumulations and to slow the synaptopathogenesis	Protein degradation, protein accumulation, age-related neurodegenerative disorders, synaptopathogenesis	March 22, 2006	Google scholar	English
6.	Lipid peroxidation and protein oxidation in Alzheimer's disease brain: potential causes and consequences involving amyloid β-peptide-associated free radical oxidative	A review summarizes current knowledge on phospholipid peroxidation and protein oxidation in AD brain, one potential cause of this oxidative stress, and consequences of Aβ-induced lipid peroxidation and protein oxidation in AD brain.	Amyloid β-peptide (Aβ), Alzheimer's disease (AD), free radical oxidative stress, phospholipid peroxidation, oxidation, lipid peroxidation	June 1, 2002	Google scholar	English

	stress 1, 2					
7.	Pathways to mitochondrial dysfunction in ALS pathogenesis	An article that describes the genetic and mechanistic evidence that make dysfunction of mitochondria a candidate major player in this process.	Mitochondria , Amyotrophic Lateral Sclerosis, upper and lower motor neurons, neurodegenerative disease	February 19, 2017	Google scholar	English
8.	Multiple pathways for mitophagy: a neurodegenerative conundrum for Parkinson's disease	An review that discusses role of mitophagy in modulating neuronal vulnerability in Parkinson's spectrum (PD/PDD/DLB) and other neurodegenerative diseases.	Mitochondria, autophagy, neurodegeneration, mitophagy, Parkinson's disease, dementia, dementia with Lewy bodies, Parkinson's disease	2018	Google scholar	English
9.	LC3 binds externalized cardiolipin on injured mitochondria to signal mitophagy in neurons: implications for Parkinson disease	An article that discusses fine-tune the mitochondrial recycling response	Mitophagy, Parkinson, cardiolipin, rotenone, MAP1-LC3, neurons, 6-hydroxydopamine, cargo recognition, autophagy, neurodegenerative diseases	November 26, 2013	Google scholar	English
10.	Cardiolipin externalization to the outer mitochondrial membrane acts as an elimination signal for mitophagy in neuronal cells	This article discusses redistribution of cardiolipin serves as an 'eat-me' signal for the elimination of damaged mitochondria from neuronal cells.	Mitochondria, macroautophagy, cardiolipin, mitophagy, neuronal cells	September 15,2013	Google scholar	English
11.	Beclin 1-independent pathway of damage-induced mitophagy and autophagic stress: implications for neuro-degeneration and cell death	Discusses about Beclin 1 may serve to prevent harmful overactivation of autophagy	Macroautophagy, neuronal cell death, neurodegeneration, autophagy, autophagy proteins, Lewy body diseases, autophagic stress	November 1, 2007	Google scholar	English
12.	Loss of PINK1 function promotes mitophagy through effects on oxidative stress and mitochondrial fission	Discusses about PINK1 and Parkin may cooperate through different mechanisms to maintain mitochondrial homeostasis	Mitochondrial dysregulation, Parkinson's disease, PTEN-induced kinase 1 (PINK1), familial parkinsonism, neuropsychiatric disorders, mitochondrial fragmentation, RNAi knockdown	March 10, 2009	Google scholar	English
13.	Mitochondrial oxidative stress in aging and healthspan	A review that focuses on mitochondrial protective drugs, such as the mitochondrial antioxidants MitoQ, SkQ1, and the mitochondrial protective peptide SS-31	Mitochondria, oxidative stress, aging, healthspan	May 1, 2014	Google scholar	English
14.	TDP-43 interacts with mitochondrial proteins critical for	Discusses TDP-43 processing may contribute to metabolism and mitochondrial function	TDP-43, APP/PS1, PHB2, mitophagy, MFN2 mitochondria, PMPCA	June 21, 2018	Google scholar	English

	mitophagy and mitochondrial dynamics.					
15.	Mitochondria at the neuronal presynapse in health and disease	Importance of presynaptic mitochondria in maintaining neuronal homeostasis and how dysfunctional presynaptic mitochondria might contribute to the development of disease.	Synapses, mitochondria, neuronal homeostasis	January 19, 2018	Google scholar	English
16.	AMBRA1-mediated mitophagy counteracts oxidative stress and apoptosis induced by neurotoxicity in human neuroblastoma SH-SY5Y cells.	Important role in limiting ROS-induced dopaminergic cell death, and the utmost potential to prevent PD or other neurodegenerative diseases associated with mitochondrial oxidative stress	Parkinson's disease (PD) , Oxidative stress, autophagy of mitochondria, cell homeostasis, neurodegenerative diseases	April 18, 2018	Google scholar	English
17.	Mechanism and medical implications of mammalian autophagy.	Discusses about deregulation of autophagy in the context of various human pathologies, including cancer and neurodegeneration, and its modulation has considerable potential as a therapeutic approach.	Autophagy, cellular stress, catabolic process, cytoprotective functions, cancer, neurodegeneration	April 4, 2018	Google scholar	English
18.	Mitochondria, calcium-dependent neuronal death and neurodegenerative disease	Possible roles of cell type-specific calcium signaling mechanisms in defining the pathological phenotype of each of these major diseases and review central mechanisms of calcium-dependent mitochondrial-mediated cell death.	Mitochondria, intracellular calcium, neurodegenerative disease, glutamate excitotoxicity	May 22, 2012	Google scholar	English
19.	PINK1/Parkin-mediated mitophagy in mammalian cells	Discusses about how PINK1 activates Parkin in response to mitochondrial malfunction, how Parkin localizes specifically to impaired mitochondria, and how ubiquitination and deubiquitination regulate PINK1/Parkin-mediated mitophagy.	Mitophagy, parkin, PINK1, ubiquitination, deubiquitination, mitochondria	April, 2015	Google scholar	English
20.	Oxidants, oxidative stress and the biology of ageing	Describes that the appropriate and inappropriate production of oxidants, together with the ability of organisms to respond to oxidative stress, is intricately connected to ageing and life span.	Reactive oxygen species, oxidative stress, ageing and life span, metabolites	November 9, 2000	Google scholar	English
21.	Mitophagy in neurodegeneration and aging	Overview of mitophagy pathways and discuss the role of reduced mitophagy in neurodegeneration	Mitochondrial dysfunction, Parkinson's disease, Alzheimer's disease, proteolysis, mitophagy, autophagy, homeostasis	October, 2017	Google scholar	English
22.	Oxidative stress-induced signaling pathways implicated in the pathogenesis of Parkinson's disease	This article discusses the mechanisms and effects of oxidative stress, the emerging concept of the impact of environmental toxins, and a possible neuroprotective role of the antioxidant astaxanthin in various neurodegenerative disorders with particular emphasis in Parkinson's	Parkinson's disease, oxidative stress, signaling pathways, PINK1, MPTP, Astaxanthin	February 13, 2014	Google scholar	English

		disease				
23.	Deconstructing mitochondrial dysfunction in Alzheimer disease	This article summarizes the novel protocols for the generation of neurons by reprogramming or direct transdifferentiation, which offer useful tools to achieve this result	mitochondrial damage, Alzheimer's disease, mitochondrial-targeted antioxidant	2013	Google scholar	English
24.	The PINK1/Parkin-mediated mitophagy is compromised by PD-associated mutations	Importance of compromised PINK1 kinase activity, reduced binding of PINK1 to Parkin leads to failure in Parkin mitochondrial translocation, resulting in the accumulation of damaged mitochondria, which may contribute to disease pathogenesis	Mitochondrial dysfunction, neurodegenerative diseases, mitophagy, macroautophagy, damaged mitochondria	October 1, 2010	Google scholar	English
25.	Mitochondrial processing peptidase regulates PINK1 processing, import and Parkin recruitment	Highlights a new role for MPP in PINK1 import and mitochondrial quality control via the PINK1–Parkin pathway	Mitochondria, mitophagy, Parkinson's disease, PINK1, proteases	February 21, 2012	Google scholar	English
26.	An over-oxidized form of superoxide dismutase found in sporadic amyotrophic lateral sclerosis with bulbar onset shares a toxic mechanism with mutant SOD1	Demonstrates the existence of an iper-oxidized SOD1 with toxic properties in patient-derived cells and identifies a common SOD1-dependent toxicity between mutant SOD1-linked familial ALS and a subset of sporadic ALS, providing an opportunity to develop biomarkers to subclassify ALS and devise SOD1-based therapies that go beyond the small group of patients with mutant SOD1.	Superoxide dismutase, amyotrophic lateral sclerosis, posttranslational modifications, mitochondria	March 27, 2012	Google scholar	English
27.	Targeting the unfolded protein response in disease.	Discusses recent advances in the design of novel compounds and therapeutic strategies to manipulate levels of ER stress in disease.	Unfolded proteins, endoplasmic reticulum (ER), cellular adaptation, apoptosis, neurodegenerative disorders	August 30, 2013	Google scholar	English
28.	Full-length TDP-43 and its C-terminal fragments activate mitophagy in NSC34 cell line	Discusses about human TDP-43 and its C-terminal fragments may cause mitochondrial dysfunction and enhance mitophagy.	Amyotrophic lateral sclerosis, TDP-43, Mitochondrial dysfunction, Mitophagy	November 21, 2012	Google scholar	English
29.	Functional impairment in Miro degradation and mitophagy is a shared feature in familial and sporadic Parkinson's disease	Reveals that prolonged retention of Miro, and the downstream consequences that ensue, may constitute a central component of PD pathogenesis.	Homeostasis, oxidative stress, outer mitochondrial membrane, induced pluripotent stem cell, mitophagy, Parkinson's disease	December 1, 2016	Google scholar	English
30.	Loss of axonal mitochondria promotes tau-mediat-ed neurodegeneration	Loss of axonal mitochondria may play an important role in tau phosphorylation and toxicity in the pathogenesis of AD	Alzheimer's disease (AD), Tau phosphorylation, neurodegeneration ,	August 30, 2012	Google scholar	English

	and Alzheimer's disease–related tau phosphorylation via PAR-1		axonal mitochondria			
31.	Mitofusin 2 protects cerebellar granule neurons against injury-induced cell death	Highlights a signaling role for Mfn2 in the regulation of apoptosis that extends beyond its role in mitochondrial fusion	Mitofusin 2 (Mfn2), nervous system, neuronal injury, oxidative stress, apoptosis, mitochondrial fusion	May 30, 2007	Google scholar	English
32.	PGC-1α, mitochondrial dysfunction, and Huntington's disease	Discusses the role of PGC-1α in mitochondrial dysfunction in HD and its potential as a therapeutic target to cure HD.	Mitochondria, energy metabolism, calcium buffering, reactive oxygen species, neurodegeneration, mitochondrial biogenesis	September, 2013	Google scholar	English
33.	ALS: astrocytes move in as deadly neighbors	Discusses non-neuronal cells contribute to ALS pathogenesis	Amyotrophic lateral sclerosis, motor neurons, astrocytes, superoxide dismutase, motor neuron death	May 1, 2007	Google scholar	English
34.	DJ-1 and prevention of oxidative stress in Parkinson's disease and other age-related disorders	Augmenting DJ-1 activity might provide novel approaches to treating chronic neurodegenerative illnesses such as Parkinson's disease and acute damage such as stroke	DJ-1 redox signaling neurodegeneration Parkinson's disease free radicals	November 15, 2009	Google scholar	English
35.	Autophagy of mitochondria: a promising therapeutic target for neurodegenerative disease	Explores new approaches that can prevent mitochondrial dysfunction, improve neurodegenerative etiology, and also offer possible cures to the aforementioned neurodegenerative diseases.	Autophagy, mitophagy, neurodegeneration, oxidative stress	May 8, 2014	Google scholar	English
36.	Understanding miro GTPases: implications in the treatment of neurodegenerative disorders.	Potential human Miros hold as novel therapeutic targets for the treatment of such disease.	Miro GTPase, atypical GTPase, neurodegenerative diseases, amyotropic lateral sclerosis	February 6, 2018	Google scholar	English
37.	PINK1-induced mitophagy promotes neuroprotection in Huntington's disease	Mitophagy is altered in the presence of mHtt and that increasing PINK1/Parkin mitochondrial quality control pathway may improve mitochondrial integrity and neuroprotection in HD	Huntington's disease (HD), huntingtin gene, mitochondria, PTEN-induced putative kinase 1 (PINK1), neuroprotection	January 22, 2015	Google scholar	English
38.	PINK1 signaling in mitochondrial homeostasis and in aging	Cellular protection could be critical for developing treatments to prevent and control excessive progression of neurodegenerative disorders.	Mitochondrial dysfunction, Parkinson's disease, oxidative stress, neurodegenerative disorders, mitophagy	December 12, 2016	Google scholar	English
39.	Nix restores mitophagy and mito-chondrial function to protect against	Demonstrate that Nix can serve as an alternative mediator of mitophagy to maintain mitochondrial turnover, identifying Nix as a promising target for	Parkinson's disease (PD), mitophagy, dysfunctional mitochondria, Nip3-like protein X (Nix)	March 10, 2017	Google scholar	English

	PINK1/Parkin-related Parkinson's disease	neuroprotective treatment in PINK1/Parkin-related PD.				
40.	Inhibition of autophagy prevents hippocampal pyramidal neuron death after hypoxic-ischemic injury	Autophagy plays an essential role in triggering neuronal death execution after hypoxia/ischemia injury and Atg7 represents an attractive therapeutic target for minimizing the neurological deficits associated with H/I brain injury	Brain injury, cognitive and motor dysfunction, gene essential, autophagy, caspase-3	February, 2008	Google scholar	English
41.	Homeostatic levels of p62 control cytoplasmic inclusion body formation in autophagy-deficient mice	Highlight the unexpected role of homeostatic level of p62, which is regulated by autophagy, in controlling intracellular inclusion body formation, and indicate that the pathologic process associated with autophagic deficiency is cell-type specific.	Autophagy, cytoplasmic protein, neurodegeneration, protein aggregates, genetic ablation, inclusion body	December 14, 2007	Google scholar	English
42.	Mitochondria and mitophagy: The yin and yang of cell death control	The importance of mitochondria and mitophagy in cardiovascular health and disease and provide a review of our current understanding of how these processes are regulated.	Apoptosis, autophagy, mitochondria, p53, Parkin, phosphatase and tensin homolog–induced putative kinase 1	2012	PubMed	English
43.	Role of PINK1 binding to the TOM complex and alternate intracellular membranes in recruitment and activation of the E3 ligase Parkin	The association of PINK1 with the TOM complex allows rapid reimport of PINK1 to rescue repolarized mitochondria from mitophagy, and discount mitochondrial-specific factors for Parkin translocation and activation.	Mitochondria, mitophagy, peroxisomes, ubiquitin ligase, translocase of the outer membrane (TOM)	February 14, 2012	Google scholar	English
44.	Lysosomal proteolysis and autophagy require presenilin 1 and are disrupted by Alzheimer-related PS1 mutations	Defective lysosomal proteolysis represents a basis for pathogenic protein accumulations and neuronal cell death in AD and suggests previously unidentified therapeutic targets.	Macroautophagy, Alzheimer's disease, presenilin-1, proteolysis, autophagosome, autolysosome acidification, cathepsin	June 25, 2010	Google scholar	English
45.	Autophagy in neurodegeneration: Two sides of the same coin	The two sides of autophagy will be discussed in the context of several neurodegenerative diseases.	Autophagy; cell death; cell survival; neurodegeneration	June 30, 2009	Google scholar	English
46.	Basal mitophagy is widespread in Drosophila but minimally affected by loss of Pink1 or parkin	Pink1 and parkin are not essential for bulk basal mitophagy in Drosophila	Parkinson's disease, stress-induced mitophagy, basal mitophagy, dopaminergic neurons	March 2, 2018	Google scholar	English
47.	Selective mitochondrial autophagy, or mitophagy, as a targeted defense against oxidative stress, mitochondrial	Mitophagy may play a key role in retarding accumulation of somatic mutations of mtDNA with aging.	Autophagy, autophagosomes, mitochondria, outer membrane protein	March 29, 2005	Google scholar	English

	dysfunction, and aging					
48.	Pink1 protects cortical neurons from thapsigargin-induced oxidative stress and neuronal apoptosis	Neuronal protective role of Pink1 against oxidative stress and afford rationale for developing new strategy to the therapy of neurodegenerative diseases.	Apoptosis, neurogenesis, neurodegeneration, oxidative stress, endoplasmic reticulum, antioxidant gene	February 1, 2015	Google scholar	English
49.	Rapamycin attenuates mitochondrial dysfunction via activation of mitophagy in experimental ischemic stroke	Rapamycin treatment attenuates mitochondrial dysfunction following cerebral ischemia, which is linked to enhanced mitophagy.	Brain ischemia, mitochondria function, mitophagy, rapamycin	February 7, 2014	Google Scholar	English
50.	Structural insights into the recognition of phosphorylated FUNDC1 by LC3B in mitophagy	Reversible phosphorylation modification of mitophagy receptors may be a switch for selective mitophagy	Microtubule-associated protein light chain 3 beta, Fun14 domain-containing protein 1, mitophagy, phosphorylation	October 18, 2016	Google scholar	English
51.	Abnormal mitochon-drial transport and morphology are common pathological denominators in SOD1 and TDP43 ALS mouse models	Manifestation of mitochondrial abnormalities between the two mouse models of familial ALS imply that different molecular mechanisms may be involved.	Amyotrophic lateral sclerosis, mitochondrial transport, mitochondria, sciatic nerve	October 23, 2013	Google scholar	English
52.	Sigma-1 receptor in motoneuron disease. In: Sigma receptors: their role in disease and as therapeutic targets	The multi-functional nature of the Sigma-1R represents an attractive target for treating aspects of ALS and other motoneuron diseases	Sigma-1 receptor, motorneuron disease, amyotropic lateral sclerosis, etipathology	March 18, 2017	Google Scholar	English
53.	Cargo recognition failure is responsible for inefficient autophagy in Huntington's disease	Inefficient engulfment of cytosolic components by autophagosomes is responsible for their slower turnover, functional decay and accumulation inside HD cells.	Autophagy, cellular homeostasis, macroautophagy, autophagosomes, cytosolic components	April 11, 2010	Google scholar	English
54.	Basal mitophagy occurs independently of PINK1 in mouse tissues of high metabolic demand	Orchestrating mammalian mitochondrial integrity in a context-dependent fashion, and this has profound implications for our molecular understanding of vertebrate mitophagy	Mitophagy, Parkinson's disease, dopaminergic neurons, mammalian mitophagy	February 6, 2018	Google scholar	English
55.	The mitochondrial intramembrane protease PARL cleaves human Pink1 to regulate Pink1 trafficking	Two Parkinson's disease-causing mutations decrease the processing of Pink1 by PARL, with attendant implications for pathogenesis.	Intramembrane proteolysis, Parkinson's disease, mitophagy, mitochondrial integrity	March 23, 2011	Google scholar	English
56.	Autophagosomes in GFP-LC3 transgenic mice	GFP-LC3 transgenic mice and describe here how we determine the occurrence of autophagy in vivo using this mouse model.	Autophagsome, GFP, green fluorescent protein, LC3, Atg8	2008	Google scholar	English
57.	Parkinson's disease proteins: novel	The role of these PD proteins in the heart and explore their potential as novel	Coronary heart disease, Parkinson's disease,	December, 2015	Google scholar	English

	mitochondrial targets for cardioprotection	mitochondrial targets for cardioprotection	myocardial ischaemia-reperfusion injury, mitochondria ischaemic preconditioning			
58.	Pathogenic role of BECN1/Beclin 1 in the development of amyotrophic lateral sclerosis	Dual role of BECN1 in ALS and depict a complex scenario in terms of predicting the effects of manipulating autophagy in a disease context	ALS, autophagy, Beclin 1, neurodegenerative disease, SOD1	May 12, 2014	Google scholar	English
59.	Loss of Miro1-directed mitochondrial movement results in a novel murine model for neuron disease	Defects in mitochondrial motility and distribution are sufficient to cause neurological disease	Calcium-binding mitochondrial Rho, mitochondrial respiration, Miro GTPase	August 18, 2014	Google scholar	English
60.	Extensive involvement of autophagy in Alzheimer disease: an immuno-electron microscopy study	Neuroprotecive functions of autophagy	Lysosomes, neurodegeneration, amyloid, apoptosis, necrosis	February 1, 2005	Google scholar	English
61.	Nix is a selective autophagy receptor for mitochondrial clearance	Nix functions as an autophagy receptor, which mediates mitochondrial clearance after mitochondrial damage and during erythrocyte differentiation	GABARAP, LC3, mitophagy, Nix, selective autophagy	December 11, 2009	Google Scholar	English
62.	Pathology of protein synthesis and degradation systems in ALS	The main morphological abnormalities detected in the anterior horn cells of ALS patients	Protein synthesis, pathomechanisms, autophagic systems, ubiquitin-proteasomal	March 21, 2010	Google scholar	English
63.	Exploring new pathways of neurode-generation in ALS: the role of mitochondria quality control	Since ALS motor neurons progressively accumulate damaged mitochondria, it is plausible that the MQC is ineffective or overwhelmed by excessive workload imposed by the chronic and extensive mitochondrial damage.	ALS, mitochondria, mitophagy, SOD1, Parkin, p62	May 14, 2015	Google scholar	English
64.	The autophagy-re-lated protein beclin 1 shows reduced expression in early Alzheimer disease and regulates amyloid β accumulation in mice	Beclin 1 deficiency disrupts neuronal autophagy, modulates APP metabolism, and promotes neurodegeneration in mice and that increasing beclin 1 levels may have therapeutic potential in AD.	Autophagy, neurodegeneration, AD, amyloid-β, APP metabolism	May 22, 2008	Google scholar	English
65.	The roles of PINK1, Parkin, and mitochondrial fidelity in Parkinson's disease	PINK1 and Parkin play within cells, their molecular mechanisms of action, and the pathophysiological consequences of their loss.	Parkinson's disease, parkinsonism , Parkin, mitochondria, E3 ubiquitin ligase, membrane proteins	January 21, 2015	Google scholar	English
66.	Mutations in PINK1 and Parkin impair ubiquitination of Mitofusins in human	UPS is involved in mitofusin degradation.	Parkinson's disease (PD), Mitofusins, mitochondrial stress, Mitofusin degradation	March 8, 2011	Google scholar	English

	fibroblasts					
67.	HTT/Huntingtin in selective autophagy and Huntington disease: A foe or a friend within?	Role of HTT/Huntingtin in selective autophagy	aggrephagy, cargo recognition, Huntingtin, Huntington disease, lipophagy, mitophagy, MTORC1, nonselective autophagy, selective autophagy, SQSTM1/p62, ULK1	May 18, 2015	Google scholar	English
68.	A rational mechanism for combination treatment of Huntington's disease using lithium and rapamycin	Rational combination treatment approach in vivo by showing greater protection against neurodegeneration in an HD fly model with TOR inhibition and lithium, or in HD flies treated with rapamycin and lithium, compared with either pathway alone	Huntington's disease, mammalian target of rapamycin, glycogen synthase kinase-3b	October 6, 2007	Google scholar	English
69.	The interplay between mitochondria and autophagy and its role in the aging process	Mitochondrial function and autophagy with particular focus on their crosstalk and its possible implication in the aging process	Aging, autophagy, *C. elegans*, diseases, mitochondria, mitophagy, hormesis	August, 2014	Google scholar	English
70.	Neuroimmune crosstalk in the central nervous system and its significance for neurological diseases	The immune function of both glial cells and neurons, and the roles they play in regulating inflammatory processes and maintaining homeostasis of the CNS.	Microglia, astrocyte, neuron, neuroinflammation, innate immunity, adaptive immunity	July 2, 2012	Google scholar	English
71.	Protein turnover differences between neurons and other cells	Revealed some surprising differences in the ways that neurons regulate protein turnover compared with non-neuronal cells, which we discuss further in this article.	Huntington disease, autophagy, neurodegeneration, rapamycin, everolimus, LC3	October, 2009	Google scholar	English
72.	Decreased glutathione accelerates neurological deficit and mitochondrial pathology in familial ALS-linked hSOD1 G93A mice model	The potential difference in the molecular pathways by which different hSOD1 mutants generate disease	Amyotrophic lateral sclerosis, Glutathione, GCLM, Mitochondria	September, 2011	Google scholar	English
73.	Resveratrol protects neuronal-like cells expressing mutant Huntingtin from dopamine toxicity by rescuing ATG4-mediated autophagosome formation	Mechanistic explanation of the neuroprotective activity of Resveratrol and support its inclusion in a therapeutic regimen to slow down HD progression.	Huntington, Parkinson, dopaminergic neurons, autophagy, anti-oxidant neurodegeneration	July, 2018	Google scholar	English
74.	Mitochondria and cancer: Warburg addressed	The increased ROS mutagenizes nuclear proto-oncogenes (initiation) and drives nuclear replication (promotion), resulting	Oxidative phosphorylation, reactive oxygen	2005	Google scholar	English

		in cancer. Therefore, hexokinase II and mitochondrial ROS may be useful alternate targets for cancer therapeutics.	species, glycolytic metabolism			
75.	Resveratrol attenuates oxidative damage through activating mitophagy in an in vitro model of Alzheimer's disease	Mitophagy pathway may become a new targeted therapy to attenuate neuronal damage induced by AD.	Autophagy, oxidative stress, apoptosis, 3-MA, Aβ1-42	January 5, 2018	Google Scholar	English
76.	ROS-induced mitochondrial depolarization initiates PARK2/PARKIN-dependent mitochondrial degradation by autophagy.	ROS-induced mitochondrial damage may be an important upstream activator of mitophagy.	neurodegenerative disorders, mitophagy, mitochondrial morphology, KillerRed, live-cell imaging, reactive oxygen species, SOD2, PARK2/PARKIN, PINK1	August 14, 2012	Google scholar	English
77.	Motor cortex glutathione deficit in ALS measured in vivo with the J-editing technique.	Discrepancy is attributed to small but opposite changes in NAA and tCr in ALS that, as a ratio, resulted in a statistically significant group difference, further suggesting caution in using tCr as an internal reference under pathological conditions.	Magnetic resonance spectroscopy, amyotrophic lateral sclerosis, glutathione, oxidative stress, neurodegeneration, biomarker	June 6, 2014	Google scholar	English
78.	Parkin mediates proteasome-dependent protein degradation and rupture of the outer mitochondrial membrane	Parkin regulates degradation of outer and inner mitochondrial membrane proteins differently through proteasome- and mitophagy-dependent pathways.	Autophagy, Electron microscopy (EM), Parkinson's disease, proteasome, mitophagy, parkin	March 18, 2011	Google scholar	English
79.	Miro1 deficiency in amyotrophic lateral sclerosis	Miro1 deficiency in ALS patients and ALS animal models and suggest glutamate excitotoxicity as a likely cause of Miro1 deficiency.	Amyotrophic lateral sclerosis, Miro1, spinal cord, lutamate excitotoxicity	May 26, 2015	Google scholar	English
80.	Mitochondrial autophagy is an HIF-1-dependent adaptive metabolic response to hypoxia	Mitochondrial autophagy is an adaptive metabolic response which is necessary to prevent increased levels of reactive oxygen species and cell death.	Autophagy, cytoplasmic organelles, Beclin-1, reactive oxygen species	February 15, 2008	Google scholar	English
81.	Autophagy and mitophagy in cellular damage control.	Mitophagy are described in the context of bioenergetic dysfunction.	Neurodegeneration, alpha-synuclein, lysosomes, fission, fusion, reactive species, cellular bioenergetics pharmacological agents	2013	Google scholar	English