The role of autophagy-lysosome pathway in neurodegeneration associated with Parkinson’s disease

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The ubiquitin-proteasome system (UPS) and autophagy-lysosome pathway (ALP) are the two most important mechanisms that normally repair or remove abnormal proteins. Alterations in the function of these systems to degrade misfolded and aggregated proteins are being increasingly recognized as playing a pivotal role in the pathogenesis of many neurodegenerative disorders such as Parkinson’s disease. Dysfunction of the UPS has been already strongly implicated in the pathogenesis of this disease and, more recently, growing interest has been shown in identifying the role of ALP in neurodegeneration. Mutations of α-synuclein and the increase of intracellular concentrations of non-mutant α-synuclein have been associated with Parkinson’s disease phenotype. The demonstration that α-synuclein is degraded by both proteasome and autophagy indicates a possible linkage between the dysfunction of the UPS or ALP and the occurrence of this disorder. The fact that mutant α-synucleins inhibit ALP functioning by tightly binding to the receptor on the lysosomal membrane for autophagy pathway further supports the assumption that impairment of the ALP may be related to the development of Parkinson’s disease. In this review, we summarize the recent findings related to this topic and discuss the unique role of the ALP in this neurodegenerative disorder and the putative therapeutic potential through ALP enhancement.

Keywords: autophagy-lysosome pathway; neurodegenerative disease; neuroprotection; Parkinson’s disease; ubiquitin-proteasome system

Abbreviations: ALP = autophagy-lysosome pathway; Ambral = activating molecule in beclin1-regulated autophagy; BaFaI = bafilomycin A1; CMA = chaperone-mediated autophagy; HDAC6 = histone deacetylase 6; IMPase = inositol monophosphatase; mTOR = mammalian target of rapamycin; PI3K = phosphatidylinositol 3-kinase; PTEN = phosphatase and tensin homologue; 3-MA = 3-methyladenine; UPS = ubiquitin-proteasome system.

Introduction

Normal balance between the formation and degradation of cellular proteins is required for cell survival. The pathways by which most cytosolic and misfolded proteins are degraded are carried out by ubiquitin-proteasome system (UPS) and autophagy-lysosome pathway (ALP) (Ciechanover, 2005; Rubinsztein, 2006). Impairment of either of these systems may lead to the accumulation and aggregation of proteins resulting in cellular toxicity and eventual neurodegeneration as seen in Parkinson’s disease, Alzheimer’s disease, Huntington’s disease, amyotrophic lateral sclerosis and other related protein conformation disorders.

Recently, there has been a growing interest in identifying the role of the ALP in neurodegeneration (Martinez-Vicente and Cuervo, 2007). Defects in this pathway have been linked to neurodegenerative diseases (Ravikumar et al., 2002, 2004), cancer (Kondo and Kondo, 2006) and cardiomyopathy (Nakai et al., 2007). Since the UPS has been already extensively reviewed (Olanow and McNaught, 2006;
Rubinsztein, 2006), in this article we will focus on the ALP and its unique role in Parkinson’s disease. We will also discuss the putative therapeutic potential of autophagy upregulation. Parkinson’s disease is one of the most common neurodegenerative diseases in the elderly. Lewy bodies, cytoplasmic inclusions that contain aggregated proteins and degeneration of substantia nigra dopamine neurons represent the pathological hallmarks of the disorder (Taylor et al., 2000; Braak et al., 2003; Lansbury and Lashuel, 2006; McNaught and Olanow, 2006). Increasing numbers of proteins, such as $\alpha$-synuclein, have been identified in Lewy bodies, but their role in the pathogenesis of both sporadic and familial Parkinson’s disease is not well understood (Zarranz et al., 2004; Chua and Tang, 2006; Mizuta et al., 2006). Mutations of $\alpha$-synuclein, such as A53T, A30P and E46K (Polymeropoulos et al., 1997; Krüger et al., 1998; Zarranz et al., 2004), and the increase of intracellular concentrations of non-mutant $\alpha$-synuclein, such as triplication of the $\alpha$-synuclein gene, have been implicated in the cause of the disorder (Singleton et al., 2003).

Beside excessive accumulation of misfolded proteins, several lines of evidence have converged to suggest that environmental neurotoxins, including herbicides, such as paraquat, and other mitochondrial poisons, such as rotenone, (Betarbet et al., 2000; Sherer et al., 2003), mutant proteins such as DJ-1 (Bonifati et al., 2003), PINK1 (Valente et al., 2004) and LRRK2 (West et al., 2005), may contribute to mitochondrial dysfunction and increase cellular oxidative stress, all of which have been implicated in the aetiopathogenesis of Parkinson’s disease. Increased oxidative stress, associated with depletion of ATP, is considered to contribute to the reduction of proteasome activity and aggregation of abnormal proteins (Norris and Giasson, 2005; Abou-Sleiman et al., 2006; Lin and Beal, 2006; Schapira, 2006). Moreover, mutations of parkin (Foroud et al., 2003; Kay et al., 2007) and UCH-L1 (Maraganore et al., 2004; Das et al., 2006), components of the UPS and mutations of ATP13A2 that codes for a lysosomal ATPase (Ramirez et al., 2006; Di Fonzo et al., 2007) have also been shown to result in impaired protein degradation. Thus, a failure of protein degradation caused by various factors may lead to neuronal cell death related to Parkinson’s disease and other neurodegenerative disorders (Webb et al., 2003) (Fig. 1).

**Protein clearance systems in Parkinson’s disease**

**UPS**

The UPS is responsible for a highly selective degradation of short-lived intracellular and plasma membrane proteins under basal metabolic conditions, as well as misfolded or damaged proteins in the cytosol, nucleus or endoplasmic reticulum. The system involves the targeting of susceptible proteins by ubiquitin and only the unfolded ubiquitinated proteins can pass through the narrow pore of the proteasome barrel. Dysfunction of the UPS and the
resultant accumulation of misfolded proteins have been strongly implicated in the pathogenesis of Parkinson’s disease (Larsen and Sulzer, 2002; McNaught et al., 2003; Olanow and McNaught, 2006; Rubinsztein, 2006), which is supported by molecular genetic studies of Parkinson’s disease-causing genes, including \( \alpha \)-synuclein, parkin and \( \text{UCH-L1} \) (Foroud et al., 2003; Maraganore et al., 2004; Das et al., 2006; Kay et al., 2007). Parkin mutations in autosomal recessive juvenile parkinsonism showed a decrease in ubiquitin-ligase enzymatic activity in the substantia nigra (Shimura et al., 2000, 2001), which also support the hypothesis that failure of the UPS leads to the neurodegeneration underlying Parkinson’s disease.

**ALP**

**General function**

The ALP can be divided into three distinct pathways based on the ways substrates reach the lysosomal lumen: macroautophagy (generally referred to as autophagy), microautophagy and chaperone-mediated autophagy (CMA) (Cuervo et al., 2004; Levine and Klionsky, 2004) (Fig. 2). Autophagy can be induced within short periods of nutrient deprivation, and CMA can be induced after prolonged nutrient deprivation, while microautophagy is not activated by nutritional deprivation or stress. In contrast to the UPS, the major inducible pathway autophagy is likely to be the primary mechanism involved in the degradation of long-lived, stable proteins and is the only mechanism by which entire organelles such as mitochondria are recycled. Large membrane proteins and protein complexes (including oligomers and aggregates) that fail to pass through the narrow proteasome barrel can be degraded by autophagy (Klionsky and Emr, 2000; Cuervo et al., 2004; Levine and Klionsky, 2004; Hideshima et al., 2005).

Autophagy is a multi-step process, involving the formation of double membrane structures known as autophagosomes. Later, the autophagosome fuses with lysosomes, where their contents are then degraded by hydrolytic enzymes. The autophagosomes and autophagolysosomes are collectively referred to as autophagic vacuoles, which are considered to be the characteristic components of autophagy (Takeuchi et al., 2005). Finally, the inner membrane structure within the autophagolysosome disintegrates while its contents are digested, and the vacuolar contents are recycled to provide amino acids and energy as needed by the cells (Fig. 2). Microautophagy is responsible for the gradual, continuous turnover of cytosolic proteins, pinched off from the lysosome membrane even under resting conditions. CMA is a secondary response that temporally follows autophagy. In CMA, a specific cytosolic protein–molecular chaperone (heat-shock cognate protein of 70 kDa, hsc70) complex binds to the lysosomal membrane receptor, lamp2a, and is then transported into lysosomes for degradation by hydrolases (Crotzer and Blum, 2005).

There are many steps at which the dysfunction of the ALP may occur, including the failure of autophagosome formation or autophagosome fusion with lysosomes, deficiency of enzymes in lysosomes and the dysfunction of the molecular chaperone or lysosomal membrane receptor, any of which may consequently cause the aggregation of unwanted proteins leading to the death of cells.

Autophagy is an important process in a variety of human diseases caused by toxic, aggregate-prone, intracytosolic
proteins, which become inaccessible to the proteasome when they form oligomers (Ravikumar et al., 2002, 2004; Webb et al., 2003; Rubinsztain et al., 2007). It has been reported that suppression of the basal autophagy gene Atg5 (autophagy-related gene 5) or Atg7 (autophagy-related gene 7) in the CNS leads to accumulation of polyubiquitinated proteins with neurodegeneration in mice (Kuma et al., 2004; Hara et al., 2006; Komatsu et al., 2006; Massey et al., 2006) and increases the susceptibility to certain types of apoptosis (Larsen and Sulzer, 2002; Boya et al., 2005; Ravikumar et al., 2006), further providing the evidence that there is a relationship between autophagy deficiency and the development of neurodegenerative diseases. One of the examples for neurodegeneration caused by deficiency of enzymes in lysosomes is lysosome storage disorder, which is an inherited metabolic disease, characterized by an abnormal build-up of various toxic materials in the cells as a result of the lysosomal enzyme deficiencies (Fukuda et al., 2006; Kiselyov et al., 2007) (Table 1).

**Involvement of ALP in Parkinson’s disease**

Mutations of α-synuclein and the increase of intracellular concentrations of non-mutant α-synuclein have been implicated in the pathogenesis of Parkinson’s disease (Polymeropoulos et al., 1997; Krüger et al., 1998; Singleton et al., 2003; Zarranz et al., 2004). In addition to the UPS, α-synuclein is also cleared by autophagy (Webb et al., 2003; Cuervo et al., 2004; Lee et al., 2004; Bandhyopadhyay and Cuervo, 2007), which supports the hypothesis that impaired autophagic degradation of α-synuclein is an important mechanism of neurodegeneration in Parkinson’s disease (Cuervo et al., 2004).

Furthermore, it has been shown that wild-type α-synuclein, but not the mutant α-synuclein, is selectively translocated into lysosomes for degradation by the CMA pathway (Cuervo et al., 2004). The failure of CMA to clear mutant α-synucleins may be explained by their exceptionally high affinities for the lysosomal membrane receptors that mediate the autophagy pathway as compared with the wild-type α-synucleins (Cuervo et al., 2004). The binding of mutant α-synucleins to the receptors probably blocks the lysosomal uptake and inhibits the degradation of not only mutant α-synucleins, but also other CMA substrates. Although the blockage of CMA could potentially result in a compensatory activation of other degradation pathways, these auto-activated pathways may not be able to sustain efficient rates of protein degradation. Thus, the accumulated mutant α-synucleins and other substrates further perturb cellular homoeostasis and contribute to neuronal toxicity.

The findings that lysosomal malfunction accompanies α-synuclein aggregation in a progressive mouse model (Meredith et al., 2002), and that mutations in ATP13A2, a lysosomal ATPase, lead to a failure of autophagy execution and aggregation of α-synuclein in Parkinson’s disease (Ramirez et al., 2006; Di Fonzo et al., 2007) further support the hypothesis that ALP dysfunction is an important mechanism of neurodegeneration.

In addition to the primary causes of ALP dysfunction already discussed, aging may be another important factor related to the dysfunction of protein control systems since it has been found that the activities of both the UPS and ALP are decreased in almost all old organisms (Keller et al., 1997; Cuervo et al., 2005; Martinez-Vicente et al., 2005; Kiffin et al., 2007). Since age is one of the chief risk factors for Parkinson’s disease (Dauer and Przedborski, 2003; Jankovic, 2005; Nagatsu and Sawada, 2006), it is reasonable to postulate that the aging brain is particularly vulnerable to dysfunction of the ALP.

**Auto-regulation of autophagy in Parkinson’s disease**

Alterations of the UPS have been implicated in the pathogenesis of Parkinson’s disease. Along with ubiquitinated protein aggregates, affected neurons often contain structures related to autophagy. For example, an increased number of autophagic vacuoles and related structures of autophagy have been found in Parkinson’s disease patients (Anglade et al., 1997), animal models of Parkinson’s disease (Öztap and Topal, 2003) and in other disorders, including Huntington’s disease (Sapp et al., 1997; Kegel et al., 2000; Petersen et al., 2001) and Alzheimer’s disease (Nixon et al.,

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**Table 1** The pathogenesis and autophagy in some of the PCDs and LSDs

<table>
<thead>
<tr>
<th>Neurodegenerative disease</th>
<th>Pathogenesis</th>
<th>Protein degradation</th>
<th>Number of AV</th>
<th>Effect of autophagy enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s disease</td>
<td>Aggregation of α-synuclein mutants (A53T, A30P, E46K)</td>
<td>UPS and ALP</td>
<td>Increased in dopamine neurons</td>
<td>Degradation of aggregated proteins</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>Aggregation of mutant huntingtin</td>
<td>UPS and ALP</td>
<td>Increased in HD neurons</td>
<td>Degradation of aggregated proteins</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>Aggregation of neurofibrillary tangles, β-amyloid-containing neuritic plaques</td>
<td>UPS and ALP</td>
<td>Increased</td>
<td>Enhance degradation of aggregated proteins</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis (ALS)</td>
<td>Aggregation of mutant SODI</td>
<td>UPS and ALP</td>
<td>?</td>
<td>Reduces the toxicity of mutant SODI proteins</td>
</tr>
<tr>
<td>Lysosomal storage diseases (LSDs)</td>
<td>Accumulation of substrates targeted by lysosomal enzymes that are genetic defect</td>
<td>ALP</td>
<td>unchanged</td>
<td>Compensate for the defects in lysosome function caused by deficiency of lysosomal enzymes</td>
</tr>
</tbody>
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PCD = protein conformation disorder; ? = not clear/not known.

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Fig. 3 Autophagy compensates for impaired UPS function. Proteasome inhibition-induced dysfunction of UPS leads to neurodegeneration. When UPS is impaired, autophagy can be compensatively induced to help remove the excessive unwanted proteins caused by UPS dysfunction and rescues neurodegeneration. The activity of HDAC6, a microtubule-associated deacetylase that interacts with poly-ubiquitinated proteins, is essential for autophagy to compensate for impaired UPS function. HDAC6 rescues neurodegeneration associated with UPS dysfunction in an autophagy-dependent manner (Pandey et al., 2007).

This increase in autophagic markers raises the argument whether autophagy is a cause or a protective factor of neuron death. It has been suggested that the increased number of autophagic vacuoles is responsible for the neuronal cell death, but an alternative view is emerging that autophagy is induced to protect neurons by enhancing degradation of abnormal proteins that might trigger injury or apoptosis in the early stages of cell death (Butler et al., 2006; Bandhyopadhyay and Cuervo, 2007).

Several lines of evidence suggest that once the UPS is inhibited, autophagy is upregulated and the remaining aggregated proteins are degraded (Iwata et al., 2005; Massey et al., 2006). Thus, this is considered to be a default pathway when an aggregate-prone substrate cannot efficiently be cleared by the proteasome (Rideout et al., 2004; Olanow and McNaught, 2006). The auto-regulative mechanism that accelerates the degradation of misfolded proteins as a defence or protection may be one of the explanations of the increased number of autophagic vacuoles in the brains of Parkinson’s disease patients (Anglade et al., 1997), possibly in response to dysfunction of the UPS (Fig. 3). However, with pathogenic deterioration, this compensatory auto-regulative mechanism is ultimately unable to maintain the cellular balance and eventually results in neuronal death (Trojanowski and Lee, 2000). This auto-regulative concept to explain the increased number of autophagic vacuoles is also supported by the finding that autophagic structures occur in the early stage of the MPTP-injected mouse model of Parkinson’s disease (Öztap and Topal, 2003) and in a progressive mouse model of Parkinson’s disease with lysosomal malfunction accompanied by α-synuclein aggregation (Meredith et al., 2002).

A recent report has shown that histone deacetylase 6 (HDAC6) is an essential mechanistic link in this compensatory induction of autophagy when the UPS is impaired in Drosophila melanogaster (Pandey et al., 2007).

The mitochondrial toxin paraquat (1, 1′-dimethyl-4, 4′-bipyridinium dichloride), a widely used herbicide, is thought to be a putative aetiological factor in the development of Parkinson’s disease. The facts that paraquat induces the accumulation of autophagic vacuoles and increases the degradation of long-lived proteins in the cytoplasm of human neuroblastoma SH-SY5Y cells (Gonzalez-Polo et al., 2007a) indicate that enhanced oxidative stress possibly activates autophagy during the early stage of mitochondrial dysfunction and helps to resist the enhanced oxidative stress (Gonzalez-Polo et al., 2007b). It seems that autophagy is induced in the early stage and impaired in the later period of the neurodegenerative process (Boland and Nixon, 2006; Bandhyopadhyay and Cuervo, 2007).

Although cells can activate different compensatory mechanisms in response to various insults in order to prevent or minimize damage, this is often not enough to completely avoid injury to cells. Strategies focusing not only on ameliorating the symptoms of Parkinson’s disease, but also on neuroprotection, or neurorescue that can favourably modify the natural course of the disease will be the most important aspect of therapeutic development (Jankovic, 2006). Thus far, there are no effective therapies to slow or prevent neuronal degeneration in this disorder. Since the formation of inclusion bodies that contain the misfolded and aggregated proteins is one of the pathological features, development towards the effective and safe targeting of aggregate-prone proteins will be an important aim for therapies in Parkinson’s disease (Eriksen et al., 2005).

Although dysfunction of the UPS has been implicated in Parkinson’s disease, it is undesirable to upregulate proteasome activity as a therapeutic strategy since proteasomes degrade not only toxic proteins but also key short-lived intracellular regulators (for example, the tumour suppressor p53), whose steady-state levels are dependent on their degradation rates. Enhancing the degradation of such proteins may have deleterious consequences, such as cancer in the case of p53. On the other hand, upregulating autophagy may be beneficial, since in contrast to many UPS substrates, autophagy substrates are typically long-lived proteins and are not believed to be selectively degraded.

Autophagy has been largely recognized as an inducible process because its activity can be regulated by nutrient or growth factor-deprivation, stress or pathogenic invasion (Levine, 2005; Kiffin et al., 2006). The autophagic activity is maintained at low levels in the brain even with nutrient starvation, a condition that usually induces autophagy in most other organs (Mizushima et al., 2004); however, neural cells have the ability to induce autophagy in response to factors other than nutrient limitation. Thus, autophagy enhancement might be a novel strategy for the treatment of neurodegenerative disease (Menzies
et al., 2006). Utilizing different signalling pathways (Fig. 4), autophagy may participate in cell growth, proliferation, cell survival and death.

**Enhancement of autophagy through the mTOR-dependent pathway**

Although various manipulations can be used in vitro to upregulate autophagy, most of these strategies are not suitable for clinical application. One pharmacological strategy for upregulating autophagy in mammals, however, is to use rapamycin or its analogues through the inhibition of mammalian target of rapamycin (mTOR), thereby inhibiting autophagy. Phosphatase and tensin homologue (PTEN) enhance the autophagy through the inhibition of class I PI3K. Class III PI3K is an activator of autophagy and plays a crucial role at an early step of autophagosome formation. The beclin 1/PI3K-III complex is involved in the formation of autophagosomes and initiation of autophagy. Ambra 1 (activating molecule in beclin1-regulated autophagy), is a positive regulator of the beclinl-dependent programme of autophagy (Fimia et al., 2007). Autophagy is regulated through energy metabolism. During the nutrient starvation or ATP deficiency due to mitochondrial complex I inhibition, autophagy is enhanced through the mTOR pathway. At the sequestration step, 3-MA interferes with the activity of class III PI3K to interrupt autophagy (Blommaart et al., 1997; Petiot et al., 2000). Wortmannin, LY294002 inhibit class III PI3K to reduce autophagy. Furthermore, neither wortmannin nor LY294002 displays selectivity for different members of the class I PI3K. At higher concentrations, wortmannin inhibits PI3K-related enzymes, such as mTOR. Rapamycin inhibits mTOR to induce autophagy. Mood-stabilizing drugs, such as lithium, carbamazepine and VPA, induce autophagy through inhibition of inositol monophosphatase (IMPase), which is mTOR-independent pathway.

**Enhancement of autophagy through an mTOR-independent pathway**

Recent studies have identified novel small-molecule enhancers (SMER) of mammalian autophagy, which boost the clearance of autophagy substrates including mutant
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huntingtin and A53T α-synuclein. These agents seem to act either independently or downstream to the target of rapamycin (Sarkar et al., 2007b).

Lithium, one of the mood-stabilizing drugs, can increase the clearance of aggregate-prone proteins, including mutant huntingtin and the A30P and A53T mutants of α-synuclein through induction of autophagy by inhibiting inositol monophosphatase (IMPase) (Sarkar et al., 2005; Sarkar and Rubinsztein, 2006). The stimulation of autophagy by lithium is thought to involve a novel mTOR-independent pathway by decreasing free inositol (Sarkar et al., 2005; Sarkar and Rubinsztein, 2006). Since inositol depletion is a common mechanism for mood-stabilizing drugs, including lithium, carbamazepine and valproic acid, by enhancing autophagy, these may have an important therapeutic potential in the treatment of Parkinson’s disease.

In addition, trehalose, a disaccharide present in many non-mammalian species, has been reported to enhance the clearance of mutant huntingtin and the A30P and A53T mutants of α-synuclein and protect cells against various environmental stresses through autophagy induction in an mTOR-independent pathway (Sarkar et al., 2007a). Furthermore, the combination of trehalose and mTOR inhibition by rapamycin has been shown to exert an additive effect on the clearance of these aggregate-prone proteins because of increased autophagic activity (Sarkar et al., 2007a).

Deleterious effects of autophagy

The discovery of the molecular basis of autophagy has uncovered its importance during development, life extension and in pathological conditions, such as cancer, certain myopathies and neurodegenerative diseases. Besides, autophagy may play an important cytoprotective role by facilitating removal of protein aggregates before they become toxic (Kuma et al., 2004; Baehrecke, 2005). In addition, autophagy can function in cell death by execution of self-killing programme of irreversibly injured cells (Bursch, 2001; Dickson, 2007). In some extreme instances of programmed cell death, cells can be completely degraded through autophagic digestion. Accumulating evidence demonstrates that late-stage neuronal cell loss generally occurs via autophagy and it has been suggested that over activation of autophagy in neurons is the eventual cause of ‘physiological’ death (Takacs-Vellai et al., 2006).

Autophagy has been linked to disease processes by various morphological studies (Klionsky and Emr, 2000). Thus, whether autophagy protects against disease or causes it may depend on the specific situation and stage in the pathological process (Rubinsztein et al., 2005). Although many issues remain unclear, there is emerging evidence that abnormal regulation of autophagic pathways may lead to apoptosis and cell death (Degterev et al., 2005; Chu, 2006; Klionsky, 2006).

From a therapeutic viewpoint, it is not certain that prolonged upregulation of autophagy would be without risks because autophagy enhancement may cause a lower steady-state level of mitochondrial load and a decrease in oxidative phosphorylation (Ravikumar et al., 2006; Rubinsztein, 2006). However, the finding that the activities of some respiratory complexes can be reduced by 25–80% before respiration or ATP synthesis in brain mitochondria are affected (Murphy, 2001) indicates that upregulation of autophagy will not result in eventual total depletion of mitochondria. It is, therefore, possible to induce autophagy and reduce mitochondrial load to the levels that have substantial protective effects against proteinopathies but do not adversely affect cellular respiration. Hence, the ability to maintain proper autophagic activity, rather than massive upregulation of autophagy, should be the therapeutic goal in diseases associated with protein aggregation.

Conclusion

Knowledge of the ALP has advanced rapidly in the last few years and its dysfunction has emerged as a theme in neurodegenerative disorders. It is believed that activating autophagy, which may have beneficial effect on the clearance of misfolded and aggregated proteins and prevention of neurodegeneration, may become a new therapeutic target in neurodegenerative disorders, such as Parkinson’s disease. However, due to the dual role of autophagy in cell survival and death, it is imperative to keep in mind that the regulation of autophagy is a very delicate process. Inappropriate or prolonged activation of autophagy may lead to the complete demise of the cells involved. Thus, to determine when and for how long this activation should be maintained will be another major challenge in the future development of the therapeutic strategy.

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