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The role of autophagy in Parkinson's disease☆

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Abstract

Although Parkinson's disease is the most common neurodegenerative movement disorder, the mechanisms of pathogenesis remain poorly understood. Recent findings have shown that deregulation of the autophagy-lysosome pathway is involved in the pathogenesis of Parkinson's disease. This review summarizes the most recent findings and discusses the unique role of the autophagy-lysosome pathway in Parkinson's disease to highlight the possibility of Parkinson's disease treatment strategies that incorporate autophagy-lysosome pathway modulation.

Key Words: autophagy-lysosome pathway; Parkinson's disease; pathogenesis; review

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INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disorder, with a prevalence of 410 and 529 per 100 000 in elderly populations aged > 55 and 65 years, respectively[1]. On a cellular level, neuronal loss is accompanied by the presence of cytoplasmic inclusions known as Lewy bodies, which are a pathological hallmark of this disorder[2].

Despite significant advances in the identification of genetic mutations and signaling pathways associated with PD[3], the precise mechanisms remain poorly understood. Recently, growing evidence has suggested that dysfunctional degradation of cellular proteins is involved in the pathogenesis of PD[2].

A normal balance between synthesis and degradation of cellular proteins is required for cell survival. The pathways by which most cytosolic and misfolded proteins are degraded and removed require the ubiquitin-proteasome system and autophagy-lysosome pathway (ALP). Impairment of either of these systems correlates with the pathogenesis of PD and the accumulation and aggregation of proteins, subsequently resulting in cellular toxicity and eventual neurodegeneration observed in PD[2]. Because the ubiquitin-proteasome system has been already extensively reviewed[4], the present review will focus on ALP and its unique role in PD.

AUTOPHAGIC PATHWAY

Autophagy was first described by De Duve[5] in 1963 as a process of self-degradation of cellular components. In contrast to the ubiquitin-proteasome system, which is mainly responsible for breakdown of short-lived proteins, autophagy is likely the primary mechanism involved in degradation of long-lived proteins, protein aggregates, and cytoplasmic organelles. Autophagy plays an essential role in removal of toxic/aggregated proteins and damaged organelles, such as mitochondria, which would otherwise damage cells during stress. In mammals, according to the mode of delivery of substrates to lysosomes for degradation, three types of autophagy have been described: macroautophagy (generally referred to as autophagy), microautophagy, and chaperone-mediated autophagy (CMA). The autophagy process is traditionally regarded as a cellular response to stress, such as nutrient deprivation, toxin exposure, pathogen infection, growth factor deprivation, or oxidative stress. It can be induced within short periods of nutrient deprivation, and CMA can be induced after prolonged nutrient deprivation, but microautophagy is not activated by nutritional deprivation or stress.

Macroautophagy is the best characterized form of autophagy to date. It is a multi-step process, the first of which is the formation of double membrane structures known as autophagosomes. The autophagosome fuses with the lysosomal membrane to form autophagolysosomes. The autophagosome and autophagolysosome are collectively referred to as autophagic vacuoles and are considered the characteristic components of autophagy. 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 needed by the cells[6].

Microautophagy is responsible for the removal of selective organelles and continuous turnover of intracellular constituents; it is active during the resting state. In microautophagy, cytosolic material is brought into the lysosome *via* direct invagination of the lysosomal membrane and subsequent budding of vesicles into the lysosomal lumen.

Unlike macroautophagy or microautophagy, CMA does not involve membrane vacuoles. CMA is predominantly involved in degradation of soluble proteins and is activated by starvation, as well as other stressors, which result in protein damage. In CMA, the CMA-targeting motif (KFERQ-like) in the substrate protein is recognized by cytosolic hsc70, which is delivered to the lysosome surface where it binds to lysosomes-associated membrane protein 2A. This results in substrate translocation across the lysosomal membrane. Once in the lumen, the substrate is rapidly degraded[7].

AUTOPHAGY AND PD

In recent years, growing evidence obtained from PD patients and PD models has demonstrated that autophagy plays a pivotal role in PD pathogenesis[8].

Autophagy and PD patients

As early as 1997, the accumulation of autophagic vacuoules was observed in post mortem brain tissues of PD patients[9]. Since then, significant activation of the autophagy response has been identified in peripheral blood mononuclear cells from PD patients[10]. Mice lacking Atg5 or Atg7 expression, the genes essential for autophagy, have been shown to rapidly develop neurodegenerative phenotypes in selected neuronal populations accompanied by accumulation of cytoplasmic inclusion bodies in neurons or massive neuronal loss in cerebral and cerebellar cortices[11-12]. These results suggested that autophagy provides protection against neurodegeneration.

Autophagy and PD gene mutation models

Mutations in the α-synuclein gene are recognized as the primary inducer of a Mendelian form of PD. The α-synuclein protein is normally unfolded, but the mutant gene product is misfolded and resists proteasomal degradation, which clinically presents as autosomal dominant PD. In addition, α-synuclein has been shown to be degraded by autophagy[13-15]. Inhibition of CMA induces the formation of high-molecular weight and detergent-insoluble species of α-synuclein[14], suggesting that α-synuclein clearance *via* CMA is crucial for limiting α-synuclein oligomerization. In contrast, overexpression of wildtype α-synuclein is toxic and impairs macroautophagy in mammalian cells and transgenic mice[16].

In addition, mutant α-synuclein has been shown to interfere with normal functions of macroautophagy and CMA. In PC12 cells, expression of mutant α-synuclein increases accumulation of autophagic-vesicular structures[17]. In brains from transgenic mice overexpressing mutant α-synuclein, microtubule associated protein 1 light chain 3-II (LC3-II) and beclin 1, indicators of autophagy, were significantly increased[18]. Moreover, activation of macroautophagy in primary cortical neurons that overexpress mutant A53T α-synuclein leads to massive mitochondrial destruction and loss, which is associated with a bioenergetic deficit and neuronal degeneration. The inhibition of targeting mitochondria to autophagosomes was partially protective against mutant A53T α-synuclein-induced neuronal cell death[19]. In contrast, A53T and A30P mutants of α-synuclein inhibit CMA processes *via* a greater binding affinity for the lysosomal marker lysosomes-associated membrane protein 2A, which mediates the autophagy pathway, compared with wild-type α-synuclein. These appear to function as uptake blockers, inhibiting their own degradation and other substrates[20]. Those accumulated substrates further perturb cellular homoeostasis and contribute to neuronal toxicity. Therefore, CMA dysfunction mediates aberrant α-synuclein toxicity[21].

It has been suggested that a modified version of α-synuclein also impairs CMA degradation. A fraction of α-synuclein purified from Lewy bodies is monoubiquitinated, and autophagy inhibition promotes accumulation of monoubiquitinated α-synuclein and formation of cytosolic inclusions[22].

Because autophagy has been shown to function as an important clearance route for mutant α-synuclein, methods to enhance cellular autophagy for removing accumulating toxic synuclein oligomers have been suggested as potential therapies for PD. Trehalose-induced autophagy enhances clearance of autophagy substrates, such as A30P and A53T mutants of α-synuclein. By inducing autophagy, trehalose protects cells against subsequent pro-apoptotic insults *via* the mitochondrial pathway[23]. Co-expression of beclin 1 also activates autophagy due to α-synuclein overexpresssion, and also reduces α-synuclein accumulation and ameliorates associated neuritic alterations. In the brains of α-synuclein transgenic mice, beclin 1 injections ameliorate synaptic and dendritic pathology and reduce accumulation of α-synuclein in the limbic system[24].

Mutations in the parkin gene result in early-onset PD, which is the most common of the known recessive forms. To date, more than 100 parkin mutations have been identified in PD cases worldwide. Parkin has also been shown to be involved in the autophagy process. Parkin-mediated K63-linked polyubiquitination of misfolded DJ-1 promotes sequestration into aggresomes and subsequent clearance by autophagy. Furthermore, fibroblasts lacking parkin display deficits in targeting misfolded DJ-1 to aggresomes[25]. Parkin is selectively re-localized to functionally impaired and depolarized

mitochondria, which are subsequently eliminated by macroautophagy, a process known as mitophagy. Parkin promotes autophagy of damaged mitochondria as a mechanism of mitochondrial quality control and implicates a failure to eliminate dysfunctional mitochondria in the pathogenesis of PD[26-27]. Pathogenic parkin mutations interfere with these distinct steps of mitochondrial translocation, ubiquitylation, and/or final clearance *via* mitophagy[28].

The ubiquitin C-terminal hydrolase L1 gene encodes the protein ubiquitin carboxy-terminal hydrolase L1 and is regarded as a candidate in PD pathogenesis. I193M missense mutation in ubiquitin C-terminal hydrolase L1 was shown to interrupt the CMA process by binding to key players in the CMA pathway, such as lysosomes-associated membrane protein 2A and hsc70, with abnormally high affinity, thereby inducing a CMA inhibition-associated increase in α-synuclein[29].

In previous studies, PTEN-induced kinase 1 (PINK1) mutations have accounted for percentages ranging from 1% to 8% of sporadic cases with early-onset PD[30]. Stable PINK1 knockdown induces mitochondrial fragmentation and autophagy. In a chronic model, autophagy plays a protective role, and RNA interference inhibition of autophagy exacerbates cell death. PINK1 overexpression suppresses toxin-induced autophagy/mitophagy. In addition, parkin overexpression, which facilitates autophagic degradation of depolarized mitochondria, provides protection to PINK1-deficient cells[26, 31]. Autophagy induction rescues PINK1 mutant phenotypes, and autophagy is regarded as a compensatory cellular response to mitochondrial dysfunction caused by PINK1 inactivation[32].

Loss of DJ-1, another PD gene, leads to the loss of mitochondrial polarization, mitochondrial fragmentation, and accumulation of autophagy markers around mitochondria in human dopaminergic cells[33].

In several populations, G2019S is the most frequent among the established disease-causing LRRK2 mutations. G2019S LRRK2-transfected cells exhibit striking increases in autophagic vacuoles in neuritic and somatic compartments. RNA interference knockdown of LC3 or Atg7, two essential components of the conserved autophagy machinery, reverses the effects of G2019S LRRK2 expression on neuronal process length, whereas rapamycin potentiates these effects, indicating a link between mutant LRRK2-induced neurite degeneration and autophagy[34]. Expression of the R1441C mutation in LRRK2 induces an impaired autophagic balance. Conversely, LRRK2 siRNA knockdown increases autophagic activity and prevents cell death caused by inhibition of autophagy in starvation conditions, indicating that LRRK2 functions as a direct regulator of autophagy[35].

Autophagy and neurotoxin-induced PD models

Some neurotoxins have been used to induce an animal model of PD, and results suggest that many of these neurotoxins also influence the autophagy pathway.

The mitochondrial complex I inhibitor rotenone induces cellular inclusions, such as Lewy body, as well as cell death and autophagy[36], which might serve as a protective mechanism. Rotenone-induced α-synuclein aggregates are cleared following rapamycin stimulation of autophagy[18].

In SH-SY5Y cells, 6-hydroxydopamine induces autophagy[37]. *In vivo*, accumulated autophagic vacuoles and activation of lysosomes are observed in 6-hydroxydopamine-injured rat nigral neurons. In addition, LC3 is enriched in dopamine neurons following 6-hydroxydopamine treatment, indicating that autophagy contributes to dopamine neuronal death induced by 6-hydroxydopamine[38]. Furthermore, CMA is activated in animal models of PD, which are established by a unilateral lesion of the nigrostriatal pathway induced by 6-hydroxydopamine[39].

The parkinsonian neurotoxin 1-methyl-4-phenylpyridinium elicits increased autophagy in SH-SY5Y cells, and RNA interference, which targets core Atg proteins, reduces autophagic vacuole content and cell death[40]. The substantia nigra of mice treated chronically with N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) exhibits autophagic cell death[41], and further treatment with rapamycin rescues dopaminergic neurons and ameliorates cell loss following MPTP treatment[42].

Paraquat induces accumulation of autophagic vacuoles in cytoplasm of SH-SY5Y cells, leading to cell death with hallmarks of apoptosis. When autophagy is inhibited, paraquat-induced apoptotic cell death is accelerated, indicating a relationship between autophagy and apoptotic cell death[43].

Proteasomal inhibitors have been used to establish *in vivo* and *in vitro* PD models. Chronic low-level proteasome inhibition causes increased macroautophagic activity in clonal SH-SY5Y cells[44]. In NB69 cells, the proteasomal inhibitor epoxomicin increase levels of α-synuclein, which correlates with an enhanced rate of cell death. Autophagy stimulation completely prevents cellular necrosis induced by epoxomicin and reverts protein accumulation, as well as α-synuclein intracellular aggregates[45]. Genetic deletion of 26S proteasomes in the mouse brain results in neurodegeneration and Lewy-like inclusions in midbrain dopaminergic neurons, which is accompanied by the formation of double-membraned autophagolysomes[46].

CONCLUSION

Given the lack of effective treatment to slow disease progression in PD, advancements in the development of novel therapeutic strategy would benefit from a better understanding of the pathogenic mechanisms of PD. In recent years, there has been a rapid growth of evidence for the role of ALP in PD pathogenesis. However, to date, the physiological pathway of ALP and the neuroprotective role of ALP in PD remain controversial.

Therefore, time and length of modulation will be a great challenge in future designs of therapeutic strategies. Hopefully, with the development of novel experimental approaches, progress in this field will provide valuable knowledge regarding ALP and the treatment of PD.

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