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Role of autophagy in the pathogenesis of Alzheimer disease

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Abstract: Alzheimer disease (AD) is the most common progressive neurodegenerative disorder causing increased morbidity and mortality. It is characterized by accumulation of amyloid-β in neurons. As there is no known definitive treatment of this disorder, studies trying to determine its exact pathogenetic pathways and target therapies for these specific pathways are being rapidly conducted. Autophagy is one of the areas of interest in studies on the pathogenesis of AD. It is a process of self-digestion that is thought to be a response to stressors and allows cells to adapt to environmental changes. There is accumulating evidence showing an association between autophagy and some disorders like cancer, infectious disease, and, in particular, neurodegenerative disorders. Growing attention has been focused on impaired autophagy in neurodegenerative disorders including AD, resulting in buildup of toxic molecules because of inappropriate activation of proteases or defective proteolysis. The question of whether autophagic response may be precisely modulated to prevent or treat neurodegenerative disorders like AD is still unanswered. In the future, it is thought that the autophagic process may be the one of the cornerstones of the treatment of AD. In this review, we summarize the knowledge of autophagy in the pathogenesis of AD in light of the current literature.

Key words: Autophagy, Alzheimer disease, neurodegenerative disorders

1. Introduction

Alzheimer disease (AD) is mainly characterized by progressive degeneration of the brain cells and leads to irreversible decline in cognitive abilities. The major pathological factor of this disorder is accumulation of amyloid-β (Aβ) protein in the cortex and hippocampal area, resulting in cognitive impairment and memory loss. Researches on therapeutic strategies for AD have mainly focused on anti-Aβ strategies, but most recently, studies examining the effect of monoclonal antibodies against Aβ protein such as solanezumab and bapineuzumab have resulted in disappointment due to high toxicity or ineffectiveness (1,2).

Autophagy is thought to be one of the cleaving systems clearing toxic Aβ proteins from neurons. This pathway sustains cell life by protecting cells against deprivation and other threatening stressors (3). Another hallmark pathological process in AD is accumulation of hyperphosphorylated tau protein in the brain, resulting in neurofibrillary tangles. Autophagy is an inhibitor of the mammalian target of rapamycin (mTOR) induction pathway, which has been shown to be a promoter of hyperphosphorylation and accumulation of tau proteins (4).

There is growing clinical and preclinical evidence about association of autophagy and AD in the literature, but none of these studies have succeeded in showing a link between autophagy and modulation of the disease progression yet (5). In this review, the importance of autophagy in AD pathogenesis will be discussed in light of the current knowledge in the literature.

2. Definition and mechanisms of autophagy

Autophagy is a process of self-digestion. It is thought to be a response to stressors and it allows cells to adapt to environmental changes (6). Deprivations in cell conditions may cause induction of autophagy to provide energy for the synthesis of essential substrates that are important for survival of organelles and cells (7). Since de Duve first described autophagy in 1963, our knowledge about this issue has continued to grow, especially in the last decade (6). Today it is thought that there is an association between autophagy and some disorders like cancer, infectious disease, and neurodegenerative disorders (8).

Sequestration in the autophagy process first begins with the formation of a phagophore (Figure) (9). It then expands into a double-membrane autophagosome and surrounds a portion of the cytoplasm (6). Endosome, the product of endocytosis, fuses with the autophagosome, and this new product is called an amphisome (6). The autophagosome or amphisome fuses with a lysosome

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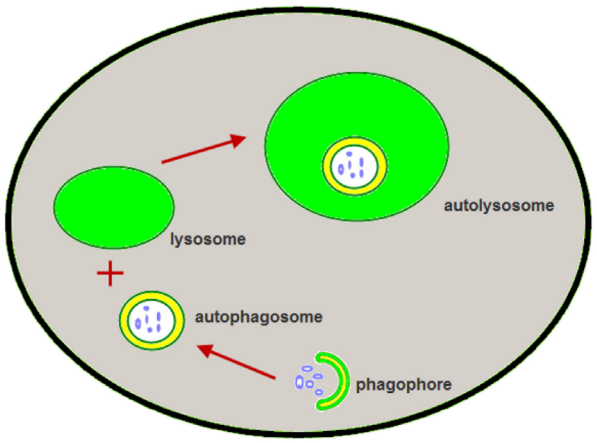

Figure. Summary of the autophagic pathway. A double-membrane phagophore sequesters the assembly of lipids and proteins from the cytosol as cargo. This autophagosome encounters and fuses with a lysosome, and finally luminal hydrolases degrade the cargo. In the autolysosome, macromolecules are digested and the products are used in the cell through recycling in the cytosol.

(which supplies acid hydrolases), resulting in an autolysosome (6). In the autolysosome, macromolecules are digested and the products are used in the cell through recycling in the cytosol (6,9).

There are three types of autophagic pathways: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA) (10).

Macroautophagy is the classical and main autophagic pathway in mammalian cells. Autophagic gene (Atg) proteins play a major role here. A double-membrane phagophore sequesters the assembly of lipids and proteins from the cytosol as cargo (10). This autophagosome encounters and fuses with a lysosome, and finally luminal hydrolases degrade the cargo (10–12). If the cargo is assembled in a particular area of the cell, this autophagy is accordingly called mitophagy (in mitochondria), lipophagy (in lipid droplets), ribophagy (in ribosomes), etc. (10).

Microautophagy is generally seen in yeasts. Cargo sequestration plays an important role here, too, but the difference from macroautophagy is that vesicles come from invagination of the limiting membrane of the vacuole in yeast and late endosomes in endosomal microautophagy (10). Autophagosomes occur after these vesicles fuse with lysosomes (10,13,14).

In CMA, selective cytosolic proteins, chaperones, bind the client proteins in cytosol and carry these proteins to the lysosomes (10). For example, if a protein is bound to the lysosomal membrane protein (LAMP), this protein reaches the lysosomal lumen through this chaperon complex (10,15). The first step of CMA is the recognition of substrate proteins by hsc70/co-chaperones (10). After that, a substrate–chaperon complex binds to LAMP-2A, and then the substrate unfolds and translocates into lysosomes (10,15). Subsequent degradation occurs and finally LAMP-2A disassembles into the lysosomal membrane (15).

These three autophagic pathways are regulated by some hormonal and enzymatic mechanisms. The regulation of autophagy is extremely complex and not very well known yet. Nevertheless, some inhibiting and stimulating factors have been shown in the regulation of autophagic process.

The first described regulator of autophagy is the target of rapamycin (TOR). Inhibition of TOR with rapamycin is shown to induce autophagy (16,17). The major inhibitors of autophagy are 3-methyladenine (3-MA) and wortmannin (Wm) (16,18). They inhibit phosphatidylinositol-3-kinases (PI3K), which are needed for autophagy process (16). Beclin-1, Atg4, c-Jun N-terminal kinase (JNK), and reactive oxygen species also have some roles in regulation of autophagy (16,19). BECN1 is expressed to promote the synthesis of beclin-1, which has a key role in autophagy in neurons and glia in human and mouse brains (20). It regulates the autophagic activity and is essential for the development of autophagosomes (20). Deficiency of beclin-1 may promote neurodegeneration and accelerate Aβ accumulation. The proteins and enzymes associated with autophagy are regulated by autophagy-related genes. There are more than 30 types of identified autophagy-related genes in the literature (21).

3. Role of autophagy in the pathogenesis of neurodegenerative disorders

Growing attention has been focused on impaired autophagy in neurodegenerative disorders causing buildup of toxic molecules in neurons due to inappropriate activation of proteases or defective proteolysis. Although it is clear that the autophagy pathway might be involved in the pathogenesis of neurodegenerative diseases, it is not certain yet whether it has a causative role or a protective role, or if it a consequence of the disease process (22).

Cytoplasmic, extracellular, and nuclear inclusions and aggregation of proteins are the cornerstones of pathogenesis of neurodegenerative disorders including not only AD but also Parkinson disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington disease (HD). These aggregates cause neuronal damage and synaptic dysfunction. The main therapeutic approach in the treatment of these disorders is thought to be related to clearance of these proteins from the cell. One of the cleaving systems of these particles from the cell is autophagy. An impairment of macroautophagy, which inhibits the turnover of free radicals of oxidized membranes and proteins and of damaged mitochondria, is likely to speed up neuronal degeneration (23).

There are some signaling and modulating factors of autophagy shown to have an impact in the pathogenesis of neurodegenerative disorders. The major signaling factors of autophagy are beclin-1, mTOR, LC3 (light chain 3), p62/sequestosome 1, dynein, parkin, and PINK1 (24). The main modulating factors are rapamycin, glucose transporter, small molecular enhancers, lithium, sodium valproate, clonidine, and carbamazepine (24).

Beclin-1 is shown to participate in the formation of autophagosomes. In the postmortem analysis of brain cells of patients with AD, reduced beclin-1 expression is detected (20). Transgenic AD mice with beclin-1 deficiency are prone to develop early Aβ accumulation, which seems to be closely related with reduced autophagy (20). PINK1, a serine threonine kinase, is a signaling factor for mitophagy and loss of PINK1 function is shown to be related with autosomal recessive PD (25). Conversion of LC3-I to LC3-II is important for the development of autophagosome formation, and in symptomatic amyotrophic lateral sclerosis mice models, it was found that there was an increased level of LC3-II (26). Mutation of dynein, which has a role in fusion of autophagosomes and lysosomes, is shown to participate in familial ALS pathogenesis (27). Numerous studies also suggested that mTOR-dependent autophagy can provide neuroprotection in HD (24).

Synuclein, a major constituent of Lewy bodies, is found to play a role in PD pathogenesis. Macroautophagy and CMA degrade synuclein and this relationship is evidence that autophagy has a critical role in PD progression (24,28).

One of the well-known pathogenic mechanisms in PD is mitochondrial dysfunction (29). Impaired mitochondrial content of toxic reactive oxygen species may cause damage to neurons and it has been shown that mitophagy eliminates these defective mitochondria and protects the neurons from their negative effects (30). Parkin and PINK1 mutation are shown to be related to the development of autosomal recessive PD due to mitophagy dysfunction and consequent mitochondrial damage (31).

The major pathogenic event in HD is accumulation of some oligomeric and monomeric aggregates in the neurons. The triggering factor for this aggregation is mutation in Htt (32). Studies indicate that sequestration of mTOR leads to elimination of these aggregates from neurons, and some modifiers of autophagy have also been shown to improve neuron survival in various animal models (24,33). This evidence shows the benefit of autophagy process in HD pathogenesis.

ALS causes respiratory failure and mortality as a result of neuronal degeneration and motor neuron loss. In ALS patients, some abnormalities in autophagy have been shown (34). Defective autophagy leads to accumulation of proteins in neurons. The main pathological factor causing defective autophagy in ALS is increased clearance of mutant superoxide dismutase 1 (SOD1) from the neurons by heat shock protein (HSPB8), which is a strong promoter of autophagy (26,35).

4. Role of autophagy in the pathogenesis of AD

AD is the most common neurodegenerative disorder in the elderly and is characterized by accumulation of Aβ proteins in the neurons. Normally, there is no accumulation of Aβ proteins in the human central nervous system, because the rate of clearance is higher than the production rate, at 8.3% per hour and 7.6% per hour, respectively (36).

There are two pathognomonic findings in the pathological examination of the brain in AD. The first is neurofibrillary tangle, which is present in the affected neurons, and the second is senile plaque, which is especially seen in the extracellular compartment of the brain (37). The cleavage of Aβ proteins from amyloid precursor proteins (APPs) is provided by secretases (24). There are three proteolytic enzymes known as α-, β-, and γ-secretases in the cleaving of APPs in neurons. The β- and γ-secretases are thought to be related to accumulation of Aβ proteins in neuronal cells (24).

The major pathological process related to autophagic pathways in AD is maturation defect of autophagosomes, which ends with massive accumulations of autophagosomes in neurons (24,37). Because of impaired clearance of autophagosomes which contain APPs, accumulation gives rise to damage to neurons (38). Normally, during autophagy, autophagosomes fuse with lysosomes and Aβ protein-containing vacuoles are degraded within lysosomes by hydrolysis. In AD, however, impairment of this pathway causes an accumulation of Aβ proteins, which become the major intracellular toxic peptides in the neurons (24).

In the AD process, generally autophagy is stimulated to clear the increased Aβ load, but the last step of autophagy, which is the fusion of autophagosomes with lysosomes, is defective, leading to massive accumulation of autophagic vacuoles in the cytoplasm (39).

5. Animal models and studies on the relationship between autophagy and AD

The number of studies searching for evidence about the relationship between autophagy and AD is increasing rapidly. A study conducted by Pickford et al. was designed to show the effect of autophagy and deficiency of beclin-1 on the pathogenesis of AD in an animal model, and they analyzed cortical beclin-1 protein levels of the brain in two different lines of very old APP transgenic mice (20). They found that beclin-1 levels were reduced early in AD in the affected mid-frontal cortex and beclin-1 deficiency, which disrupts neuronal autophagy, induces APP metabolism, and causes neurodegeneration, is associated with reduced

autophagy. This reduction is demonstrated by a decrease in the relative levels of LC3-II compared with LC3-I. The authors suggested that increasing beclin-1 levels might have therapeutic potential in AD (20).

In an effort to demonstrate whether oligodendroglial precursor cells called NG2 cells can clear β-amyloid peptides through endocytosis and autophagy in AD, Li et al. found that there were recruited and clustered NG2 cells around the amyloid plaques in APPswe/PS1dE9 mice and the NG2 cell line (40).

A recent study by Fant et al. investigated the potential therapeutic application of leucettines, pharmacological inhibitors of tyrosine phosphorylation regulated kinases, in the treatment of AD, and it was found that leucettines may trigger autophagy in immortalized mouse hippocampal HT22 cells in this preclinical study (41). They concluded that leucettines might activate the autophagic mTOR/PI3K pathway and give an advantage in the treatment of AD (41).

François et al. tried to show the link between autophagy and inflammation in AD. They examined the inflammatory reaction and autophagy in murine tricultures of neurons, astrocytes, and microglia under 48-h application of various inflammatory stresses like lipopolysaccharide and amyloid peptide (Aβ42) (42). They found a strong relationship between inflammation and autophagy and IL-1β played a particularly major role in the induction of the microglial autophagy, and they emphasized that new therapeutic strategies in AD could target inflammation and autophagy in microglia (42).

Zhu et al. investigated and aimed to show the therapeutic effects of arctigenin, a natural product from *Arctium lappa*, and found that arctigenin reduces Aβ production by inhibiting the amyloid cleaving enzyme system and induces Aβ clearance by activating the autophagic pathway via AKT/mTOR inhibition in APP/PS1 transgenic AD model mice (43). They also concluded that treatment with arctigenin might decrease Aβ and senile plaque formation and might improve memory impairment (43).

One of the major proteins in the pathogenesis of AD is tau protein. In the animal models designed by Caccamo et al., it was found that increased mTOR activity elevated endogenous hyperphosphorylated tau proteins (44). They also showed that pharmacologically reduction of mTOR signaling with rapamycin could cause reduction in these proteins in a mouse model (44). They concluded that reducing the mTOR with therapeutic agents may be a good way to treat taupathies including AD by increasing autophagy activity in neuronal cells (44).

To show the effect of beclin-1 on autophagy, Xue et al. examined cell viability by incubation of a medium that contained neuron-specific enolase in PC12 cells with elevated concentrations of Aβ for 3, 6, 12, 24, 48, and 72 h (45). They found that viability was negatively correlated with neuron-specific enolase levels, and beclin-1 levels decreased from 3 to 72 h (45). It was found that cell viability was increased by rapamycin (an activator of autophagy) but decreased by 3-methyladenine (an inhibitor of autophagy), and they suggested that activation of beclin-1-dependent autophagy before Aβ-induced cell damage may prevent neuronal death (45).

In some studies, it was claimed that latrepirdine, an antihistaminic agent, may affect regulation of Aβ metabolism (46). One of these studies showed that latrepirdine could stimulate mTOR and Atg5-dependent autophagy, leading to reduction of Aβ protein (46). It was also found that the biomarkers (TgCRND8) thought to be correlated with autophagy levels increased after using chronic latrepirdine in the mouse model (46).

Biopsy specimens of the neocortex from 7 patients with AD and 3 non-AD control brains were analyzed using immunoelectron microscopy in a study designed by Nixon et al. to identify characterization of autophagosomes and related autophagic vacuoles and to differentiate them from other lysosome-related compartments in AD brains and investigate the possible involvement of autophagy in AD (47). It was found that there were accumulated multivesicular and multilamellar bodies, autophagosomes, and cathepsin-containing autophagolysosomes in large numbers and they were different from lysosomes, which were previously shown to be accumulated in dystrophic neurites. It was concluded that impaired macroautophagy could have a role in the pathogenesis of AD (47).

6. Conclusion

Growing concern about the knowledge of pathophysiological effects of autophagy in the AD process can be seen in the literature, but studies showing the exact relationship between AD and autophagy are still not sufficient. The present evidence shows impaired autophagy causing accumulation of some pathological proteins, which lead to degeneration of neurons resulting in neurodegenerative disorders like AD. Complex genetic and enzymatic relationships in these mechanisms may provide new therapeutic approaches to the treatment of AD. It is not certain whether AD would become a curable disease via targeting therapies in the future, but the therapies concerning autophagic pathways are promising. Future studies are needed in this area to improve the clinical outcomes of AD and other neurodegenerative disorders.

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