Review

The lysosome and neurodegenerative diseases

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It has long been believed that the lysosome is an important digestive organelle. There is increasing evidence that the lysosome is also involved in pathogenesis of a variety of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. Abnormal protein degradation and deposition induced by lysosomal dysfunction may be the primary contributor to age-related neurodegeneration. In this review, the possible relationship between lysosome and various neurodegenerative diseases is described.

Introduction

Lysosomes are acidic, membrane-bound organelles in which >50 acid hydrolases are stored and perform the catabolism of the cells at an optimum pH in the range of 4.6–5.0 [1]. Lysosomes are responsible for the degradation of macromolecules derived from the extracellular space through endocytosis or phagocytosis, as well as from the cytoplasm through autophagy. Lysosomal storage disorders (LSDs) are a group of genetic disorders that result from a disorder of lysosomal catabolism, due to defects in specific hydrolytic enzyme, activator protein or cofactor, transport protein or enzyme required for the correct processing of other lysosomal proteins, such as mucopolysaccharidoses, sphingolipidoses, mucolipidoses, lipidoses, glycoproteinoses, glycogenosis, lipofuscinoses and mucopolysaccharidoses.

Neurodegenerative diseases are characterized by progressive dysfunction and death of cells that frequently affect specific neural systems, including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis, spinal cerebellar ataxias, and spinal muscular atrophy [2]. The aim of the present review is to describe the relationship between lysosome and neurodegenerative diseases.

Structure and Function of Lysosomes

Lysosomes and cathepsins

According to its physiological function at different stages, lysosome can be divided into the primary lysosome, the secondary lysosome, and the residual body. Primary lysosomes are membrane-bound intracellular organelles that contain a variety of hydrolytic enzymes, including acid phosphatase, glucuronidase, sulfatase, ribonuclease, and collagenase. These enzymes are synthesized in the rough endoplasmic reticulum and then packaged into vesicles in the Golgi apparatus. Primary lysosomes fuse with membrane-bound vacuoles that contain material to be digested, forming secondary lysosomes. Residual bodies contain only indigestible or slowly digestible materials and within which enzymatic activities have become virtually exhausted.

The main class of lysosomal proteases is represented by the cathepsin which is derived from the Greek term meaning 'to digest' [3]. Cathepsins are subdivided into three subgroups according to the amino acids of their active sites that confer catalytic activity: cysteine (cathepsins B, C, F, H, K, L, N, O, S, T, U, W, and X), aspartyl (cathepsins D and E), and serine cathepsins (cathepsins A and G).

Cathepsins are synthesized in membrane-bound ribosomes as N-glycosylated precursors and are transferred into the endoplasmic reticulum and later into the Golgi complex. During transport to the Golgi complex, procathepsins acquire modification of their carbohydrate

moieties, which includes the formation of the mannose 6-phosphate (M6P) residues. After binding to M6P-specific receptors, the enzyme–receptor complexes exit the trans-Golgi network in clathrin-coated vesicles and transport to the late endosomes [4]. Upon fusion with the late endosomes, the dissociation of ligands occurs. When the receptors are recycled back to the Golgi apparatus, the major parts of enzymes reach lysosomes through this targeting pathway. Subsequently, the active cathepsin can be produced after proteolytic removal of the propeptide in the acidic environments of late endosomes or lysosomes. The last step is accompanied by the actions of several proteases, such as pepsin, neutrophil elastase, and various cysteine proteases [5]. The cathepsin activity is regulated by several mechanisms including regulation of synthesis, zymogen processing, endogenous inhibitors (e.g. stefins and cystatins for cysteine cathepsins), and pH stability [6,7]. The cathepsins play important roles in many physiological processes such as protein degradation, antigen presentation, bone resorption, and hormone processing [6]. Felbor et al. [8] revealed that cathepsin $B^{-/-}/L^{-/-}$ mice showed a degree of brain atrophy not previously seen in mice. These results demonstrated that cathepsins B and L were essential for maturation and integrity of the postnatal central nervous system (CNS) and that the two proteases compensated for each other in vivo [8].

Lysosomes and apoptosis

Apoptosis is the most common form of physiological cell death in multicellular organisms. Apoptosis signaling is classically composed of two principle pathways. One is a direct pathway from death receptor (CD95, TNF-R1, and TRAIL-R1/TRAIL-R2 [9]) ligation to caspase cascade activation and cell death. Death receptor ligation triggers recruitment of the precursor form of caspase-8 to a death-inducing complex, through the adaptor protein FADD, which leads to caspase-8 activation. The other pathway triggered by stimuli such as drugs, radiation, infectious agents, and reactive oxygen species is initiated in mitochondria. After cytochrome c is released into the cytosol from the mitochondria, it binds to Apaf1 and ATP, which then activate caspase-9. Under either physiological or pathological conditions, apoptosis is mostly driven by interactions among several families of proteins, i.e. caspases, Bcl-2 family proteins, and inhibitor of apoptosis proteins [10]. Besides the caspases, lysosomal proteases such as cathepsins D, B, and L have been shown to act as mediators of apoptosis in a number of cell systems [11–14]. Increased expression or

activity of cathepsin D has been observed in apoptotic cells after activation of Fas/APO-12 and after exposure to oxidative stress or adriamycin [15]. Results show that p53 has two binding sites located at the cathepsin D promoter gene and that cathepsin D participates in p53-dependent apoptosis. Cathepsin D showed augmented activity soon after it was released and that was accompanied by increased levels of p53 protein, a cathepsin D transcription factor [16]. Therefore, the mechanism responsible for increase in cathepsin D activity might be an effect of increased synthesis regulated by p53. Cathepsin B has also been implicated in the activation of the pro-inflammatory caspases-1 and -11, and the cleavage of Bcl-2 family member Bid which may lead to cytochrome c release from the mitochondria and subsequent caspase activation [17]. Ishisaka et al. [13] revealed the participation of cathepsin L in a direct activation of caspase-3 [18].

It is known that lysosome is involved not only in apoptosis but also in other types of cell death. The permeabilization of the lysosome has been shown to initiate a cell death pathway in specific circumstances. Lysosomal membrane permeabilization (LMP) causes the release of cathepsins and other hydrolases from the lysosomal lumen to the cytosol. LMP is a potentially lethal event because the ectopic presence of lysosomal proteases in the cytosol causes digestion of vital proteins and the activation of additional hydrolases including caspases. This latter process is usually mediated indirectly, through a cascade in which LMP causes the proteolytic activation of Bid (which is cleaved by the two lysosomal cathepsins B and D). The Bid activation then induces mitochondrial outer membrane permeabilization, resulting in cytochrome c release and apoptosome-dependent caspase activation [19]. However, massive LMP often results in cell death without caspase activation, which may adopt a subapoptotic or necrotic appearance. Moreover, the pro-apoptotic Bcl-2 family member Bax can translocate from the cytosol to lysosomal membranes and induce LMP [20].

Lysosomes and autophagy

The lysosomal system is responsible for the degradation of several classes of macromolecules and for the turnover of organelles by several mechanisms collectively known as autophagy.

Autophagy is a regulated process of degradation and recycling of cellular constituents, participating in organelle turnover and in the bioenergetic management of starvation. This term embraces several different

mechanisms: macroautophagy, microautophagy, chaperone-mediated autophagy (CMA), and crinophagy [21]. In macroautophagy, the cytoplasm is sequestered into double-membrane structures known as autophagosomes that fuse with endosomes and lysosomes. After fusion, the vacuolar materials are degraded and recycled. In microautophagy, small cytosolic portions are internalized via lysosomal invaginations, and proteins are continuously degraded in the lumen of this organelle even under resting conditions. In contrast with these bulk autophagy pathways, a third lysosomal degradation pathway is CMA. In CMA, specific cytosolic proteins are transported into lysosomes via a molecular chaperone/receptor complex. Different from the other lysosomal degradation pathways, vesicular traffic is not involved in CMA. Functionally, secretory lysosomes are unusual, in that they serve both as a degradative and as a secretory compartment [22].

Some studies have clearly demonstrated that autophagy has a greater variety of physiological and pathophysiological roles than expected, such as starvation adaptation, intracellular protein and organelle clearance, development, anti-aging, elimination of microorganisms, cell death, tumor suppression, and antigen presentation [23]. Autophagy may also be involved in neurodegenerative diseases, as recent studies reported increased autophagy in AD and PD.

Lysosome and Neurodegenerative Diseases

Lysosome and AD

AD is a progressive neurodegenerative disorder characterized by cognition and memory impairment. AD brains are characterized by two pathological hallmarks in the cerebral cortex and hippocampus: senile plaques (SPs), consisting of deposits of β-amyloid peptide (Aβ), and neurofibrillary tangles (NFTs), composed of an abnormally phosphorylated form of the cytoskeleton-associated protein Tau. The pathological accumulation of Aβ and hyperphosphorylation of Tau may develop concomitantly within synaptic terminals and then induce loss of synapses, which is considered to be closely correlated with the cognitive decline in AD [24].

Lysosomal dysfunction and Aβ.

The identification of Aβ as the major component of the SPs leads to the idea that deposition of Aβ may induce neuronal dysfunction and cell death, which is one of the primary causes of AD [25]. The two most common isoforms of Aβ are Aβ40 and Aβ42, which vary by the length of the C-terminals [26].

Aβ is derived from β-amyloid precursor protein (APP) by proteolytic cleavage with α-, β-, and γ-secretases. α-Secretase cuts in the middle of the part of APP which will become Aβ and therefore blocks Aβ production, whereas β- and γ-secretases cleave the amino and C-terminals of the Aβ sequence, respectively, promoting Aβ formation [27]. There are at least two cellular pathways (subcellular locations) proposed for Aβ production, namely the secretory pathway and the endosomal lysosomal pathway. β-Secretase (β-APP-cleaving enzyme) is a type-1 transmembrane aspartyl protease, mainly localized in endosomes and lysosomes [28], so it is mainly involved in endosomal–lysosomal pathway, but not the secretory pathway. The γ-secretase often resides in a high molecular weight multimeric protein complex composed of at least four core components, i.e. presenilin 1 or 2 (PS1 or PS2), nicastrin, anterior pharynx defective-1, and presenilin enhancer-2 [29]. Its activity has been demonstrated in both the autophagosome and the lysosome, so Aβ could be produced in these compartments as well. In addition, chronic source of soluble, exogenous Aβ peptides in the blood can even cross a defective blood–brain barrier and interact with neurons in the brain and then accumulate within these cells [30].

In 1990, many researches showed the close relationship between lysosomal dysfunction and morphology in AD. Lysosomal dysfunction may be the earliest histological change in AD [31]. Amyloid plaques are full of active lysosomal hydrolases, implying that plaques may originate from lysosomal rupture. Cathepsins D and E (intracellular aspartyl proteases) are considered to influence Aβ peptides generation within the endosomal–lysosomal pathway because they exhibit β- and γ-secretase like-activity [32]. For this reason, the endosomal–lysosomal pathway is a site for cleavage of the APP into smaller β-amyloid-containing peptides, which are then degraded by cathepsins. Inhibition of cathepsins activity causes a rapid and pronounced build-up of potentially amyloidogenic protein fragments [33]. On the other hand, a failure to degrade aggregated Aβ1–42 in late endosomes or secondary lysosomes was a mechanism that contributed to intracellular accumulation of Aβ in AD. The cysteine protease cathepsin B in lysosomes degrades Aβ peptides, especially the aggregation-prone species Aβ1–42. Cathepsin B deletion increases Aβ1–42 levels and worsens plaque deposition in mice

expressing familial AD mutant human APP [34], whereas virus-mediated overexpression of the enzyme has the opposite effect [35,36]. Moreover, Ditaranto *et al.* demonstrated that cultured primary neurons were able to internalize soluble $A\beta1-42$ from the culture medium and accumulate inside the endosomal–lysosomal system. The intracellular $A\beta1-42$ is resistant to protease degradation and stable for at least 48 h within the cultured neurons. Incubation of cultured neurons with a cytotoxic concentration of soluble $A\beta1-42$ invokes the rapid free radical generation within lysosomes and disruption of lysosomal membrane proton gradient that precedes cell death [36].

Lysosomal dysfunction and Tau.

Tau, a microtubule-associated phosphoprotein, plays an important role in maintaining neuronal morphology. Tau protein is normally localized in the neuronal axon, where it promotes microtubule assembly and stabilizes microtubules. However, under pathological conditions, such as AD, hyperphosphorylated Tau accumulates in neurons in the form of paired helical filaments (PHFs) [37], which subsequently form NFTs. PHF-bearing neurons are abundant in the areas in which neuronal loss is found in AD [38].

Experimentally induced lysosomal dysfunction triggers the development of characteristic features of the aged human brain. These include proliferation of endosomes–lysosomes, hyperphosphorylation of Tau, production of Tau protein fragments resembling those found in NFTs, and the accumulation of 16–30 kDa proteins that incorporate the amyloid sequence [39]. Bi *et al.* [40] found that the novel cathepsin D inhibitors block the formation of hyperphosphorylated Tau fragments in hippocampus of AD. Moreover, recent evidence showed that autophagic-lysosomal system also plays a role in the clearance of Tau, whereas dysfunction of this system results in the formation of Tau insoluble aggregates in lysosomes [41].

Indeed, Tau is present in phosphorylated and aggregated form not only in AD but also in other pathological situations. Frontotemporal dementia with PD linked to chromosome-17 (FTDP-17) is an autosomal-dominant disease with variable clinical and neuropathological features. Neuropathological changes include frontotemporal atrophy, sometimes with atrophy of the basal ganglion, substantia nigra, and amygdala. FTDP-17 is caused by mutations in the gene for Tau. To investigate how Tau alterations provoke neurodegeneration, Lim *et al.* [42]

generated transgenic mice expressing human Tau with four tubulin-binding repeats and three FTDP-17 mutations: G272V, P301L, and R406W. Ultrastructural analysis of mutant Tau-positive neurons revealed a pre-tangle appearance, with filaments of Tau and increased numbers of lysosomes displaying aberrant morphology similar to those found in AD. Tau modifications can provoke lysosomal aberrations and suggest that this may be a cause of neurodegeneration in tauopathies [36].

Lysosome and Huntington's disease

Huntington's disease (HD) is an autosomal-dominant neurological disease characterized by involuntary movement accompanied by cognitive impairment and emotional disturbance. The most striking pathological feature of HD is atrophy, neuronal loss, and astrogliosis in the neostriatum [43]. Although multiple populations of striatal neurons are affected in HD, the spiny projection neurons containing γ-aminobutyric acid and substance P or enkephalin are most vulnerable. Other less severely affected brain regions include cerebral cortex and thalamic nuclei.

Like other neurological diseases including AD and PD, HD is also a protein-misfolding disease. It is caused by a CAG trinucleotide repeat expansion in the huntingtin gene, which results in an expansion of the polyglutamine tract in the amino N-terminus of the huntingtin protein. Normal individuals have ≤35 CAG repeats, whereas HD is caused by ≥36 repeats. The increase in the length of polyglutamine tract alters biochemical and biophysical properties of proteins. As a result, these proteins are prone to form stable β-sheet structure and assemble into oligomers. The bio-hallmark of mutant huntingtin is the formation of intranuclear inclusions and cytoplasmic aggregates in neurons in vulnerable brain areas. Expression of mutant huntingtin in cultured cells also causes the formation of intranuclear inclusions and aggregates in the cytoplasm. The inclusions and aggregates are usually formed by small N-terminal huntingtin fragments and are co-localized with other cellular proteins involved in proteolysis, vesicle trafficking, and protein degradation [44]. The formation of huntingtin aggregates and intranuclear inclusions has been proposed to play a role in HD pathogenesis.

Huntingtin protein (htt) cleavage may be a crucial, causal event in the pathogenesis of HD, and the most obvious consequence of htt cleavage is the release of N-terminal fragments containing the polyglutamine tract [45]. Fragments containing polyglutamine tracts of normal size do not accumulate within cells. In contrast,

fragments containing expanded polyglutamine tracts may fold into a structure that resists threading into the proteasome core, resulting in delayed clearance and accumulation within the cytoplasmic or nuclear compartment of the cell [46]. Therefore, the production and accumulation of N-terminal huntingtin (N-htt) fragments may be critical in the pathogenic process.

Huntingtin processing occurs through proteasome and endosomal−lysosomal pathways. Caspase-3 and calpain are proteases that cleave htt to produce stable N-htt fragments [47,48]. N-terminal mutant huntingtin (N-mhtt) fragments cause cell death *in vitro*. Mutant N-htt fragments accumulate in HD neurons because they resist degradation by the proteasome [49−51]. In addition, a decline in proteasome function with age may contribute to mutant N-htt fragment accumulation [52]. Yet, mutant htt expression or proteasome inhibition *in vitro* can increase levels of lysosomal proteases [49,50,53].

Degradation of truncated huntingtin by an autophagic mechanism was reported [50,54]. It was found that inhibiting autophagy with 3-methyladenine increased accumulation of mutant huntingtin and huntingtin aggregates, whereas stimulating autophagy with rapamycin reduced both huntingtin accumulation and huntingtin aggregates. Our recent studies found that autophagy was involved in activation of cathepsins and caspase-3 induced by overexpression of huntingtin. Both cathepsin D and L levels increased upon expression of huntingtin. *In vitro* studies revealed that wilt-type huntingtin was efficiently degraded by cathepsin D, whereas mutant huntingtin was more resistant to cathepsin D [50]. Biochemical analysis of lysates from HD patient brain suggests that mutant htt is more resistant to degradation than wild-type htt [46]. Autophagy may stimulate huntingtin cleavage and degradation through activation of caspase-3 and cathepsin D. The autophagic mechanism may also contribute to the formation of huntingtin bodies [47]. Increases in cathepsin D and H activity have been found in affected areas in HD brain [48].

Lysosome and PD

PD is a neurodegenerative disorder characterized by resting tremor, rigidity, hypokinesia, and postural instability. It is caused by the degeneration of dopaminergic (DA) neurons in the substantia nigra. The pathogenic hallmark of PD is the accumulation and aggregation of α-synuclein (α-syn) in susceptible neurons. The brain regions that are affected in PD exhibit neuronal intracytoplasmic inclusions that are termed Lewy bodies (LBs) when they are present in cell bodies and Lewy neurites in neuron processes. These inclusion bodies are particularly rich in aggregated α-syn, but also contain numerous other proteins, including components of the ubiquitin−proteasome system, molecular chaperones, and lipids [55−57].

The syn family of peptides is a group of presynaptic proteins with three members: α-, β-, and γ-syn [58,59]. These pro-proteins are characterized by natively unfolded structures with highly conserved N termini and divergent C-terminal acidic regions [60]. Importantly, α-syn is distinct from other members of the syn family in that it possesses a highly hydrophobic central region that has been identified as a non-amyloid-β component (NAC) of AD amyloid [61]. α-Syn is normally enriched in nerve terminals involved in synaptic function. During normal aging and in PD, levels of natively folded α-syn increase in the cytoplasm of substantia nigra neurons [62]. α-Syn is likely to play a key role in the development of PD as well as other synucleinopathies. In animal models, overexpression of full-length or C-terminally truncated α-syn has been shown to produce PD pathology. *In vitro* experiments, using either recombinant or endogenous α-syn as substrates and purified cathepsin D or lysosomes, have demonstrated that cathepsin D degrades α-syn very efficiently and that limited proteolysis resulted in the generation of C-terminally truncated species. Knockdown of cathepsin D in cells overexpressing wild-type α-syn increased total α-syn levels by 28%. And pepstatin A (the inhibitor of cathepsin D) completely blocked the degradation of α-syn in purified lysosomes. Furthermore, lysosomes isolated from cathepsin D knockdown cells showed a marked reduction in α-syn degrading activity, indicating that cathepsin D is the main lysosomal enzyme involved in α-syn degradation [63]. Recently, the colleagues of our lab observed the nuclear translocation of cathepsin L in nigral DA neurons. Cathepsin L may contribute to cell cycle arrest and death of DA neurons through its nuclear translocation [64].

α-Syn and ubiquitin are among the major components of LBs [65,66], suggesting again an association with PD pathogenesis. Some studies indicate that two separate α-syn mutations, A53T and A30P, are responsible for certain rare familial forms of the disease. Wild-type α-syn was selectively translocated into lysosomes for degradation by the CMA pathway. The pathogenic A53T and A30P α-syn mutants bound to the receptor for this pathway on the lysosomal membrane, but appeared to act as uptake blockers, inhibiting both their own degradation and that of other substrates [67]. Stable PC12 cell

lines expressing mutant but not wild-type α-syn show disruption of the ubiquitin-dependent proteolytic system, marked accumulation of autophagic–vesicular structures, and impairment of lysosomal hydrolysis and proteasomal function [68].

In contrast to α-syn, β-syn may be neuroprotective, because this molecule has a natural deletion in the middle of the NAC-associated region. Supporting this notion, neuropathological features of α-syn transgenic (tg) mice, such as formation of LBs and motor function deficits [69], are significantly ameliorated in α- and β-syn bigenic mice compared with α-syn single tg mice [70,71]. Furthermore, β-syn directly inhibited aggregation and proto-fibrillar formation of α-syn under cell-free conditions [70,72,73]. Although γ-syn also inhibits α-syn aggregation [72], the role of this molecule in neuroprotection is not completely clear.

Lysosome and Niemann–Pick disease type C

The LSDs are caused by the defective activity of lysosomal proteins, which results in the intra-lysosomal accumulation of non-degraded metabolites. Today, over 30 kinds of diseases in LSDs have been found. LSDs can be grouped according to characterization of the defective enzyme or protein [74]. Niemann–Pick C (NPC) is a very important type of LSDs. NPC belongs to the Niemann–Pick disease group of lipidoses along with Niemann–Pick types A and B. NPC is different from type A or B. NPA represents a classical acute neuropathic form of the disease, whereas NPB is a chronic form without nervous system involvement. In types A and B, the main problem in the body is the complete or partial lack of an enzyme called sphingomyelinase. Although clinically similar to NPA and NPB, NPC's sphingomyelinase is functional [75].

NPC is a neurovisceral lysosomal lipid storage disorder of autosomal recessive inheritance characterized at the cellular level by accumulation of unesterified cholesterol and glycolipids in the endosomal–lysosomal system. The disease is often diagnosed in early childhood, with patients typically displaying cerebellar ataxia, difficulty in speaking and swallowing, and progressive dementia. In NPC, cholesterol and glycolipids have varied roles in the cell. Cholesterol is normally used to either build the cell or forms a complex molecule called an ester. In the case of an individual with NPC, there are large amounts of cholesterol that are not used as a building material and also do not form esters. This cholesterol begins to accumulate within the cells throughout the body, especially in the spleen, liver, bone marrow, and

brain. These unprocessed cholesterol as well as glycolipids stored in the brain cause progressive neurological damage.

Mutations in either of the two human NPC genes, NPC1 and NPC2, cause a fatal neurodegenerative disease associated with abnormal cholesterol accumulation in cells. Approximately 95% of the NPC cases are caused by genetic mutations in the NPC1 gene, referred to as type C1; 5% are caused by mutations in the NPC2 gene, referred to as type C2 [76]. The NPC1 gene produces a protein that is located in membranes inside the cell and is involved in the movement of cholesterol and lipids within cells [77]. A deficiency of this protein leads to the abnormal build-up of lipids and cholesterol within cell membranes. The NPC2 gene produces a protein that binds and transports cholesterol [78,79], although its exact function is not fully understood. The increased cholesterol in NPC late endosomes and lysosomes interferes with transport of proteins between these compartments [80]. The lysosomal hydrolase, cathepsin B, was upregulated in NPC cells. Both cathepsins B and D can function as β-secretase enzymes and are partially mislocalized to early endosomes in NPC [81,82].

In this review, we are most interested in the close relationship between NPC and AD. Although NPC differs in major respects from AD, intriguing parallels exist in the cellular pathology of these two diseases, including neurofibrillary tangle formation, prominent lysosome system dysfunction, and influences of apolipoprotein E4 genotype [83]. These findings suggest that lipids are playing important roles in the development of neurodegenerative diseases. So, it can demonstrate that the widely used cholesterol-lowering drugs simvastatin and lovastatin reduce intracellular and extracellular levels of Aβ1–42 peptides in primary cultures of hippocampal neurons and mixed cortical neurons [84]. Furthermore, it evidences that dysfunction of the lysosomal in brain plays an important role in protein deposition diseases.

Concluding Remarks

In general, alterations in the lysosme degradation have been described in normal brain aging and in age-related neurodegenerative diseases including AD, HD, PD, and NPC. Cathepsins are now recognized as having more complex functions than simply being garbage disposers, and their imbalance during aging and age-related diseases may provoke deleterious effects on CNS neurons (**Table 1**). Lysosomes may be 'bioreactor' sites for the unfolding and partial degradation of membrane proteins

Table 1 The pathogenesis and lysosomes in some of the neurodegenerative disease

Neurodegenerative disease	Pathogenesis	Protein	Effect of lysosomes degradation
Alzheimer's disease	Aggregation of neurofibrillary tangles, β-amyloid-containing neuritic plaques	Cathepsins B, D, E	Cleavage and degradation of aggregated proteins (Aβ, Tau)
Huntington's disease	Aggregation of mutant huntingtin	Cathepsins D, L	Reduction and degradation of aggregated proteins (htt)
Parkinson's disease	Aggregation of α-synuclein mutants (A53T, A30P)	Cathepsins D, L	Degradation of aggregated proteins (α-syn)
Niemann–Pick disease type C	Accumulation of cholesterol and glycolipids (NPC1, NPC2)	Cathepsins B, D	Degradation of cholesterol and lipids

or their precursors that subsequently become expelled from the cell, or are released from dead cells and accumulate as pathological entities. The growing understanding of consequences of their age-related changes in neurons could contribute to the development of therapeutic interventions in massive neurodegeneration associated with these age-related diseases.

Funding

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