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Endo-lysosomal dysfunction: a converging mechanism in neurodegenerative diseases

Chao Wang[1,2], Maria A Telpoukhovskaia[1,2], Ben A Bahr[3], Xu Chen[1,2] and Li Gan[1,2]

Endo-lysosomal pathways are essential in maintaining protein homeostasis in the cell. Numerous genes in the endo-lysosomal pathways have been found to associate with neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and frontotemporal dementia (FTD). Mutations of these genes lead to dysfunction in multiple steps of the endo-lysosomal network: autophagy, endocytic trafficking and lysosomal degradation, resulting in accumulation of pathogenic proteins. Although the exact pathogenic mechanism varies for different disease-associated genes, dysfunction of the endo-lysosomal pathways represents a converging mechanism shared by these diseases. Therefore, strategies that correct or compensate for endo-lysosomal dysfunction may be promising therapeutic approaches to treat neurodegenerative diseases.

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Introduction

Neurodegenerative diseases are often characterized by intracellular protein inclusions or extracellular protein aggregates. Failure of proper trafficking and degradation of these proteins could underlie neuronal and network dysfunction in these diseases. The lysosome system is one of the major cellular mechanisms for protein degradation, especially in long-lived, post-mitotic cells, such as neurons. Lysosomes serve as the hub for proteostasis (Figure 1). Protein substrates of extracellular and intracellular origin are delivered to lysosome through endocytic trafficking and autophagic pathways, respectively. Complex cross talk between these trafficking systems ensures proper sorting and degradation of the substrates. Dysfunction of various steps in this network can lead to insufficient clearance of pathogenic proteins, impaired membrane trafficking and signaling, and damage to the cell. Numerous studies in human genetics and model organisms support critical roles of lysosomal dysfunction in neurodegeneration. In this review, we focus on the role of endo-lysosomal dysfunction in three of the most common and devastating neurodegenerative diseases: Alzheimer's disease (AD), Parkinson's disease (PD) and frontotemporal dementia (FTD).

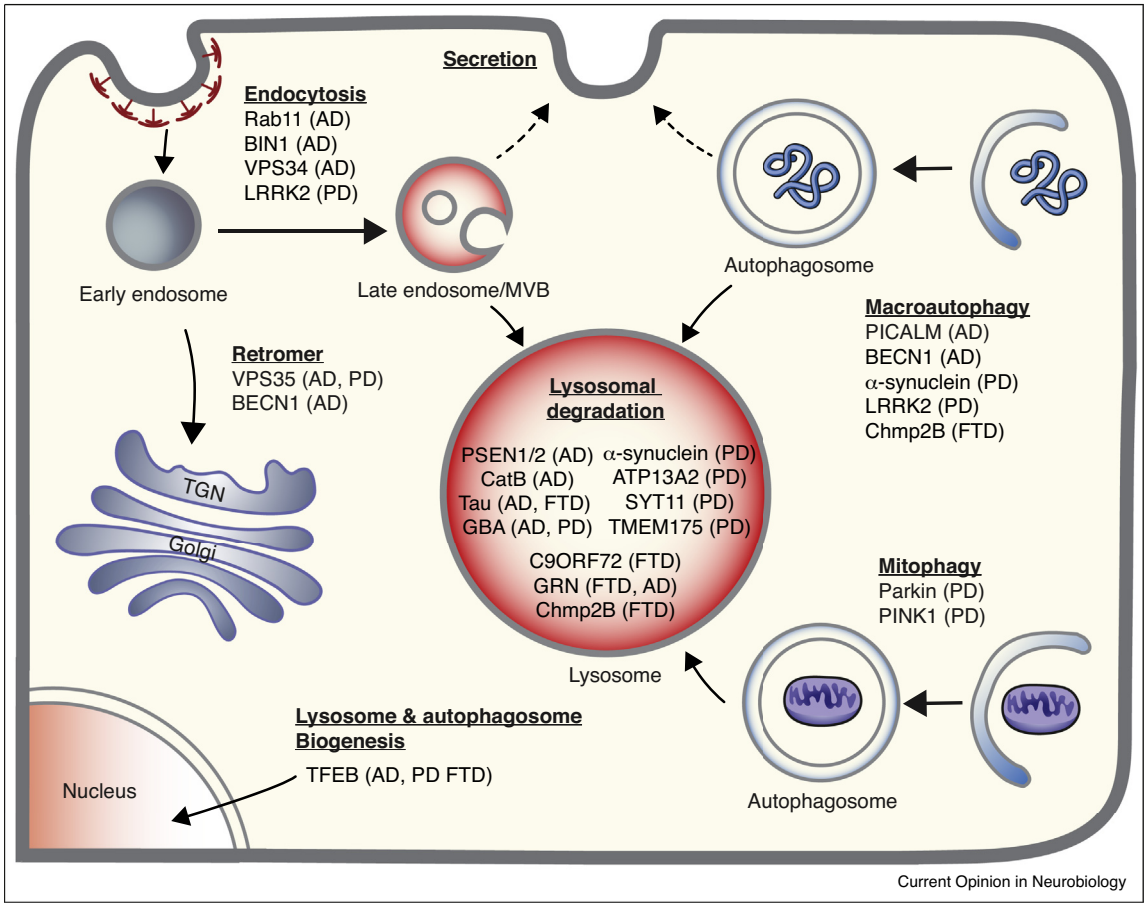
Alzheimer's disease

AD, the most common dementia, is characterized by extracellular amyloid-β (Aβ) plaques and neurofibrillary tangles (NFT), consisting of hyperphosphorylated tau. The endo-lysosomal and autophagic networks are critical to maintain the homeostasis of Aβ and tau. Dysfunctions of this network are common in AD and result in abnormal lysosomal enzymatic activity and accumulation of autophagosomes and autolysosomes in the dystrophic neurites in AD brains [1]. More importantly, both familial mutations and polymorphisms associated with late onset sporadic AD are linked with autophagic and endo-lysosomal dysfunctions (Figure 1).

Mutations in presenilins 1 and 2 (PS1, 2), the proteases of the γ-secretase complex, cause rare early-onset familial cases of AD (FAD). Most FAD-linked mutations of PS1 and PS2 increase the production of Aβ42, supporting amyloid hypothesis. However, PS1 also appears to regulate autophagic-lysosomal function, resulting in alterations in the hydrolysis of amyloid precursor protein (APP). *PS1* mutations or knockout (KO) cause v-ATPase V0a1 subunit deficiency and disruption of lysosomal acidification, leading to abnormal Ca^{2+} homeostasis and defective autophagy [2•]. PS2 localizes to late endosomes/lysosomes and produces a distinct intracellular pool of Aβ [3•]. FAD mutations in *PS2* increase Aβ production, and some *PS1* mutations phenocopy the late endosome/lysosome location of PS2 [3•].

Recent genome-wide association studies (GWAS) further highlighted the importance of autophagic-lysosomal function in AD pathogenesis [4]. The risk factors include

Figure 1



Overview of the endo-lysosomal system involved in pathogenesis of AD, PD and FTD. Lysosomes receive inputs from both the endocytic pathway and autophagic pathway, delivering protein substrates from extracellular environment and intracellular compartment, respectively. Proteins undergoing clathrin-mediated endocytosis are enclosed by early endosomes, where they are sorted to trans-Golgi network (TGN) by retromers, or to the late endosomes/multivesicular body (MVB), which fuses with lysosome for degradation. Cytosolic protein substrates are engulfed by double-membrane phagophore, which becomes an autophagosome, and delivered to lysosome. Autophagy is also responsible for degradation of damaged organelles, such as mitochondria (mitophagy). TFEB, a master regulator of the biogenesis of lysosomes and autophagosomes, is translocated from the cytosol to nucleus in response to mTORC inactivation (e.g. nutrient starvation), leading to increased transcription of autophagic and lysosomal genes. Vesicles in the endo-lysosomal system could fuse with plasma membrane and release the undegraded substrates, leading to secretion of the pathogenic proteins (dash arrow). Causative genes and risk factors in AD, PD and FTD that are involved in the endo-lysosomal dysfunction are indicated.

genes related to autophagic initiation and early autophagosome formation, such as phosphatidylinositol-binding clathrin assembly protein (*PICALM*), a key component of clathrin-mediated endocytosis machinery. Altered PICALM protein levels were observed in late-onset AD brains and are closely related to tau pathology [5,6]. mRNA and protein levels of beclin 1 (*BECN1*), a key component of autophagy biogenesis, are reduced in AD brains [7]. BECN1 was also reduced in microglia from AD patients, which are associated with reduced retromer trafficking, suggesting deficits in receptor-mediated Aβ phagocytosis [8]. Besides Aβ degradation, autophagy might also be involved secretion of Aβ to the extracellular space and may contribute to plaque formation [9].

AD-associated genetic variations also contribute to abnormal sorting and trafficking in endo-lysosomal networks. Deletion of bridging integrator 1 (*BIN1*), a genetic risk factor of late-onset AD, increases cellular β-secretase (BACE1) levels by impairing its lysosomal degradation, leading to increased Aβ production [10]. Rab11, a component that regulates membrane trafficking, controls BACE1 recycling to the plasma membrane and is a genetic factor involved in late-onset AD [11]. Endosomal trafficking is largely controlled by phosphatidylinositol-3-phosphate (PI3P), and deficiency of PI3P (caused by VPS34 reduction) reduces sorting of APP to intraluminal vehicles and contributes to AD [12]. The optimal pH of early endosome for BACE1 makes the endosome the

predominant location for beta cleavage of APP, whereas APP delivered to lysosome is rapidly degraded. Deletion of components of endosomal sorting complexes required for transport (ESCRT) inhibited delivery of APP to lysosome and increased Aβ accumulation [13]. On the other hand, enhancing lysosome biogenesis through targeting transcription factor EB (TFEB), a master regulator of lysosome biogenesis and a substrate of mTOR, reduced steady state APP levels and amyloid deposits in APP/PS1 mice [14], and ameliorated neurofibrillary tangle pathology in rTg4510 tauopathy model [15].

AD brains have altered lysosomal protein levels and enzymatic activity, some of which are directly involved in Aβ degradation. Increased lysosomal activities of β-hexosaminidase and β-galactosidase were found in the cortex of the TgCRND8 mouse model as the disease progresses and were associated with synapses loss [16]. The protein level and enzymatic activity of lysosomal enzyme glucocerebrosidase (GBA) are significantly reduced in sporadic AD [17]. Overexpression of GBA promotes Aβ42 degradation and protects against Aβ42 induced toxicity [17]. Cathepsin B (CatB), a lysosomal cysteine protease, degrades Aβ42 [18–20]. CatB activity has also been linked to the clearance of tau species [21]. A progressive, age-dependent reduction of CatB activity was observed in an APP/PS1 AD mouse model [22]. Loss of CatB in culture cell results in accumulation of BACE1, βCTF and Aβ, together with cholesterol and other lysosomal proteins [23]. Genetic deletion of the endogenous inhibitors of lysosomal cysteine proteases leads to cathepsin-dependent amelioration of amyloid pathologies [19,24,25]. Moreover, increasing CatB expression through AAV reduces Aβ and rescues AD-associated memory deficits [26]. Interestingly, exercise elevates CatB levels in monkeys and humans, and those levels correlated with improvements in the type of memory encoding lost in AD [27].

Parkinson's disease

PD is the second most common late-onset neurodegenerative disease and is characterized by an accumulation of α-synuclein and mitochondrial dysfunction. Increasing evidence from genetics and model systems indicates that intracellular trafficking and endo-lysosomal/autophagic dysfunction is the primary cause in PD [28].

PTEN-induced putative kinase 1 (PINK1) and parkin, two key components for mitophagy, are associated with autosomal recessive parkinsonism, providing compelling evidence that autophagy dysfunction has a key role in PD [29]. α-Synuclein is not only a substrate of autophagy, but also a regulator of autophagic network. Overexpressing α-synuclein causes mislocalization of the autophagosome formation protein Atg9 and impairs macroautophagy [30]. Mutations in the leucine-rich repeat kinase 2 (*LRRK2*) are one of the most common causes of autosomal dominant PD. Although its exact effect is controversial, LRRK2 regulates autophagy. This regulation involves vesicle sorting, lysosome positioning and clustering, and interaction with Rab proteins, including Rab7, Rab5 and Rab32 [31–33]. PD-causing mutations in LRRK2 (G2019S and R1441C) inhibit autophagy and accelerate age-related autophagy dysfunction, whereas wildtype LRRK2 improved autophagy [34]. Mutations of late endosomal/lysosomal ATPase ATP13A2 (Park9) are associated with early-onset of PD [35,36]. ATP13A2 regulates autophagy by regulating another PD-associated gene synaptotagmin 11 (SYT11) [37•]. In addition, altered autophagosome trafficking could lead to increased secretion of α-synuclein [38], suggesting a role of the autophagic-lysosomal system in the unconventional secretion of their protein substrates.

Lysosomal dysfunction has a prominent role in PD pathogenesis (Figure 1). α-Synuclein oligomeric intermediates are degraded by lysosomes [39]. Several lysosomal genes were identified as genetic risk factors for PD. Heterozygous mutations of glucocerebrosidase (GBA) are one of the most common risk factors for PD. About 10% PD patients carry *GBA* mutations (PD-GBA). Reduced GBA activity and impaired autophagic flux, together with accumulation of α-synuclein in lysosome, were found in neurons derived from induced pluripotent stem cells (iPSCs) carrying *GBA* mutations [40]. Consistently, activation of GBA by a small-molecule modulator or chaperone reduced α-synuclein levels and restored lysosomal function in iPSC-derived dopaminergic neurons, implicating that lysosomal enzyme is a viable target for PD treatment [41,42]. Human transmembrane protein 175 (TMEM175) gene, encoding a K^+ channel located in late endosomes and lysosomes, was identified as a risk factor by a PD GWAS meta-analysis [43]. Deficiency of TMEM175 resulted in unstable lysosomal pH, decreased GBA activity and mitochondrial respiration, impaired autophagosome clearance and increased phosphorylated α-synuclein aggregates [44•]. Deficiency or loss-of-function mutations of ATP13A2 result in impaired lysosomal acidification and degradation capacity, leading to accumulation of α-synuclein [45]. However, in an ATP13A2 KO mouse model, lysosomal and protein trafficking deficiency occurred without any α-synuclein abnormalities, suggesting the presence of α-synuclein-independent neurotoxicity induced by endo-lysosomal dysfunction in PD [46].

Dysfunction of endo-lysosomal sorting and trafficking also contributes to PD pathogenesis. α-Synuclein disrupts hydrolase trafficking and reduces lysosomal function, which can be rescued by expression of small GTPase Rab1a [47••]. VPS35 is a component of retromer complex involved in endosome-lysosome sorting and trafficking. An autosomal-dominant PD-causing mutation in VPS35 implicated retromer dysfunction in familial PD [48]. Moreover, cells expressing mutated VPS35 (D620N) show Atg9 mislocalization and impaired macroautophagy

[49], suggesting that VPS35 links retromer complex to other trafficking machinery.

Frontotemporal dementia

FTD is the second most common cause of dementia in people under 65 years old. Pathologically, major FTD variants include inclusions of microtubule-associated protein tau or the TAR DNA-binding protein (TDP)-43, named FTLD-tau and FTLD-TDP, accordingly. FTD mutations of tau lead to increased tau accumulation and aggregation, where autophagic dysfunction plays an important role. Blocking autophagy increases tau accumulation [50], while enhancing autophagy lowers the levels of total and phosphorylated tau [51–53]. Phosphorylated tau linked to Aβ42 treatment was also found to be reduced through enhancement of the autophagy-lysosomal pathway [54], from a study that implicates lysosomal cross talk with the proteasomal protein clearance system. Besides tau degradation, it is speculated that autophagy could be involved in release of tau through a process called unconventional secretion [55], although exact mechanism is unknown. TDP-43 inclusions are found in about 45–60% of all FTLD cases. Stimulation of the autophagy pathway enhances the TDP-43 clearance, and therefore, the survival of mouse neurons [56]. Thus, autophagy might play a role in the degradation of aggregated TDP-43.

Up to 50% of FTD cases are genetic, associated with causative mutations (e.g. C9orf72, GRN) or risk factors (e.g. TMEM106B), many of which are genes involved in endo-lysosomal system. Other rare mutations in FTLD-causing genes, namely valosin-containing protein (VCP)/p97, charged multivesicular body protein 2B (CHMP2B), optineurin (OPTN), TANK binding protein 1 (TBK1), SQSTM1/p62 and ubiquilin 2 (UBQLN2) affect proteins that are directly involved in protein degradation, especially in autophagy-lysosome pathways.

C-Terminal truncations in CHMP2B are a rare genetic cause of FTD, identified in two European families. CHMP2B is part of ESCRT-III, a multiprotein complex involved in the endo-lysosome pathway. Patients with this mutation show ubiquitin and p62 inclusions in the dentate gyrus, and enlarged vacuoles in cortical neurons resembling late endosomes [57], pointing to defects in the endo-lysosomal pathway. CHMP2B dysfunction is also linked to impaired autophagosome formation and accumulation of protein aggregates [58]. Mice expressing $CHMP2B_{Intron5}$ developed large and dense autofluorescent aggregates in several brain regions (90% of microglia and over 50% of neurons) by 18 months of age [59]. Likewise, FTD patients have a significant amount of autofluorescent deposits in brain [59]. Moreover, iPSC-derived neurons from patients with CHMP2B mutation have enlarged endosomes that can be reverted in the CRISPR/Cas9-edited isogenic control [60•], demonstrating a causative role of CHMP2B mutation in FTD.

C9orf72 mutations with GGGGCC repeat expansion in the non-coding region account for more than 20% of familial FTD. Pathogenic mechanisms of these mutations include a toxic gain of function and lysosomal dysfunction. C9orf72 localizes to the lysosomes under starvation conditions in HEK cells [61], implicating its involvement in autophagy. C9orf72 KO leads to lysosomes enlargement and redistribution in Hela cell [61], and accumulation of vesicles in mouse bone marrow-derived macrophages and microglia [62••]. The mechanism underlying the lysosomal dysfunction in C9orf72 deficiency has been connected to TFEB, the master regulator of lysosome biogenesis. Under starvation conditions, C9orf72 KO MEFs show increased TFEB expression in response to mTOR inactivation [63]. Likewise, brain homogenates from C9orf72 KO mice had increased numbers of TFEB and the lysosomal markers, Lamp1 and Lamp2 [63]. Fibroblasts from patients with C9orf72 mutation had fewer endosomes and a different expression pattern of mannose 6-phosphate receptor (M6PR), hinting at disruption of endo-lysosomal pathway [64].

Another major cause of familial FTLD-TDP is mutations on progranulin (*GRN*, PGRN), which lead to nonsense-mediated decay and PGRN halpoinsufficiency. Interestingly, a homozygous GRN loss-of-function mutation causes adult-onset neuronal ceroid lipofuscinosis, but results in FTLD-TDP when in a heterozygous state. Further supporting critical role of PGRN in lysosomal function, PGRN knockout mice exhibit striking lipofuscinosis and intracellular PGRN is highly enriched in the lysosomes. Expressed by microglia and neurons, PGRN is involved in the lysosomal and inflammatory pathways in the brain. PRGN KO leads to upregulation of lysosomal and innate immunity genes, increased complement production, and enhanced synaptic pruning in microglia [65•]. While lysosome biogenesis and microglial activation were evident, lysosomal degradation was compromised in glia and neurons [66]. A recent study showed that FTD patients with PGRN haploinsufficiency exhibit lysosomal dysfunction and a mild form of NCL [67••]. Lysosomal protease is impaired in FTD patient-derived fibroblasts [67••], and retinal scanning revealed preclinical retinal lipofuscinosis in heterozygous GRN mutation carriers [67••]. These findings provide evidence that lysosomal dysfunction induced by PGRN haploinsufficiency could underlie the pathogenesis of FTLD-TDP [67••].

Conclusion

Accumulating genetic evidence from GWAS has pointed to a critical role for the endo-lysosomal network in neurodegenerative diseases. Dysfunction of these genes and their pathways converges on impaired lysosomal

degradation, leading to accumulation of pathogenic proteins. Besides, accumulation of intermediate vesicles containing undegraded proteins might lead to increased secretion and propagation of the pathogenic proteins, although the molecular mechanism remains elusive. Therapeutically, those disease-associated genes and their interacting components in the endo-lysosomal pathway could be targets for interventions. Several studies have shown therapeutic potentials from various aspects in the endo-lysosomal system, through increasing autophagic/lysosomal biogenesis (e.g. TFEB), promoting vesicular trafficking (e.g. Rab11, Chmp2B), and enhancing lysosomal degradation (e.g. GBA, CatB). On the other hand, deficits in components of endo-lysosomal and autophagic networks can serve as biomarkers for disease diagnosis. As we gain a more complete understanding of the molecular mechanisms underlying these pathways, more therapeutic targets and strategies will be revealed for treating these disorders.

Conflict of interest statement

Dr. Bahr is co-inventor on U.S. Patent 8,163,953 (Compounds for lysosomal modulation and methods of use) and on pending patents on compounds for treating Alzheimer's disease, mild cognitive impairment, and α-synucleinopathies.

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