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Endo-lysosomal dysfunction: a converging mechanism in neurodegenerative diseases

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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).

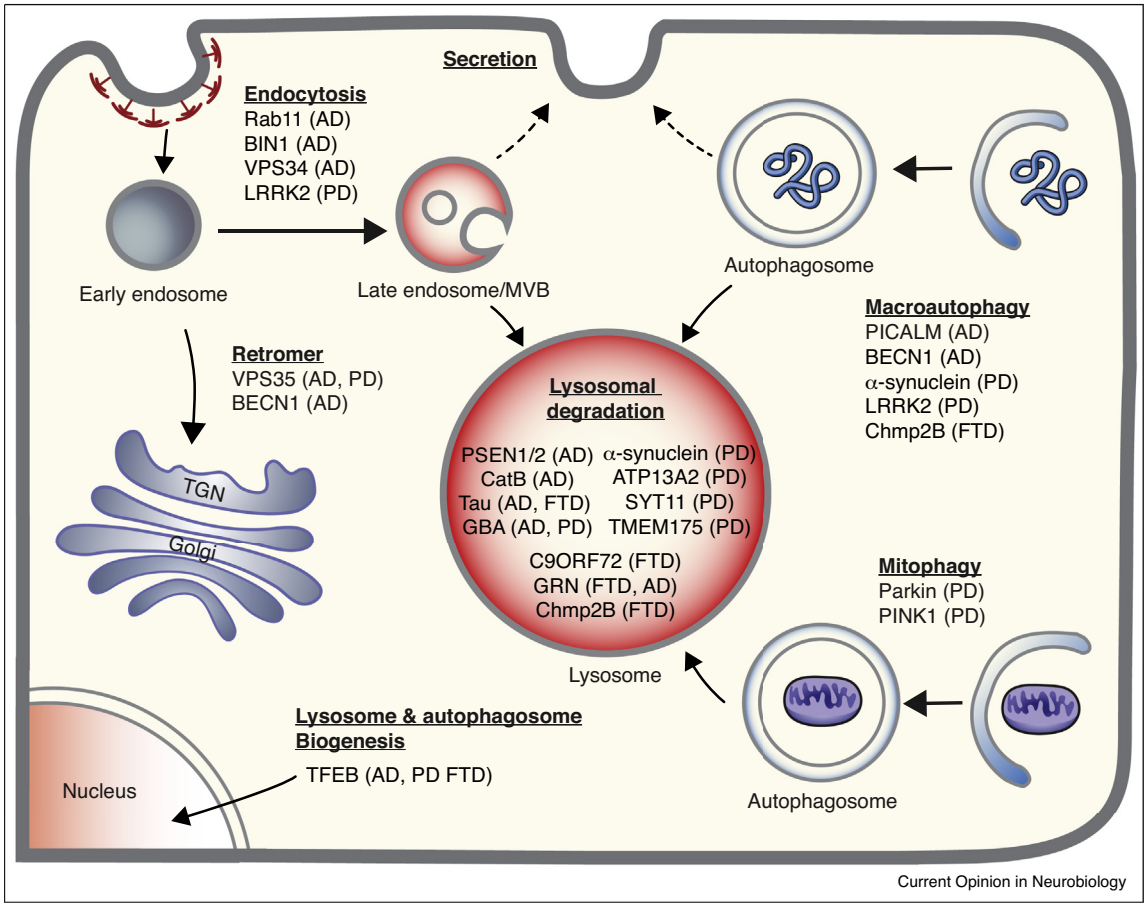
Alzheimer's disease

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