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REVIEW

Lysosomal dysfunction in α-synuclein pathology: molecular mechanisms and therapeutic strategies

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Abstract

In orchestrating cell signaling, facilitating plasma membrane repair, supervising protein secretion, managing waste elimination, and regulating energy consumption, lysosomes are indispensable guardians that play a crucial role in preserving intracellular homeostasis. Neurons are terminally differentiated post-mitotic cells. Neuronal function and waste elimination depend on normal lysosomal function. Converging data suggest that lysosomal dysfunction is a critical event in the etiology of Parkinson's disease (PD). Mutations in Glucosylceramidase Beta 1 (GBA1) and leucine-rich repeat kinase 2 (LRRK2) confer an increased risk for the development of parkinsonism. Furthermore, lysosomal dysfunction has been observed in the affected neurons of sporadic PD (sPD) patients. Given that lysosomal hydrolases actively contribute to the breakdown of impaired organelles and misfolded proteins, any compromise in lysosomal integrity could incite abnormal accumulation of proteins, including α-synuclein, the major component of Lewy bodies in PD. Clinical observations have shown that lysosomal protein levels in cerebrospinal fluid may serve as potential biomarkers for PD diagnosis and as signs of lysosomal dysfunction. In this review, we summarize the current evidence regarding lysosomal dysfunction in PD and discuss the intimate relationship between lysosomal dysfunction and pathological α-synuclein. In addition, we discuss therapeutic strategies that target lysosomes to treat PD.

Keywords Chaperone-mediated autophagy · GBA1 · TMEM175 · Therapeutic strategies · Biomarkers

Introduction

Parkinson's disease (PD) is a neurodegenerative disease characterized by the death of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the formation of axonal and intracytoplasmic inclusions [1]. The intracytoplasmic inclusions are known as Lewy neurites (LNs) and Lewy bodies (LBs), which mainly consist of abnormally aggregated α-synuclein (α-syn) [1]. The etiology of PD has not been fully elucidated but is thought to be multifactorial. Both environmental and genetic factors contribute to the onset and progression of PD [1]. Recent evidence has shown that lysosomal dysfunction plays a central role in PD pathogenesis [2–4].

Lysosomes, vesicular structures integral to cellular metabolism, play pivotal roles in the degradation and recycling of diverse organelles and intricate molecules [5]. Additionally, they actively contribute to various cellular processes, including cytomembrane repair and the maintenance of cholesterol homeostasis [5]. Neurons, postmitotic cells that cannot divide, heavily depend on the ability of lysosomes to prevent the accumulation of aberrant proteins and impaired organelles within their cellular milieu [6]. Lysosomal dysfunction leads to massive accumulations of proteins, lipids and damaged organelles [6]. The functions of the lysosome are regulated by multiple factors, including luminal pH and proteolytic enzyme activity [5]. Lysosomal dysfunction is implicated in the

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pathogenesis of neurodegenerative diseases such as PD, frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). The nuances and shared characteristics of lysosomal dysfunction in PD and other neurodegenerative disorders have been meticulously described in prior reviews [4, 6]. Moreover, lysosomal enzymes and proteins can be detected in cerebrospinal fluid (CSF), and they may reflect the disease state and hold promise as diagnostic biomarkers for PD [7]. Within this review, we present substantiated evidence delineating lysosomal dysfunction in PD and delve into its correlation with α-syn pathology. We also discuss the possibility of using lysosomal proteins as diagnostic biomarkers for PD. Furthermore, we summarize potential lysosomal-targeting compounds as therapeutic strategies for PD.

The physiological function of the lysosomal system

The physiological functions and intricate composition of lysosomes have been comprehensively summarized in several recent reviews [8, 9]. Lysosomes are membrane-bound organelles that contain a variety of hydrolytic enzymes responsible for the degradation and recycling of macromolecules, including proteins, lipids, carbohydrates, and nucleic acids [8]. They play a pivotal role in (1) intracellular digestion: lysosomes breakdown endocytosed materials, cellular debris, and damaged organelles, ensuring the efficient turnover of cellular components; (2) autophagy; (3) maintenance of cellular homeostasis by regulating the turnover of biomolecules, lysosomes contribute to maintaining cellular homeostasis and energy balance; (4) regulation of cellular signaling: lysosomal enzymes and their activity influence various cellular signaling pathways, including those involved in growth, stress responses, and apoptosis; and (5) metal ion homeostasis: lysosomes help regulate the intracellular concentration of metal ions such as iron and copper, which is crucial for numerous enzymatic and structural functions within the cell [8]. Lysosomes, recognized as the ultimate terminals for the degradation of both intracellular and exogenous cargo, receive substrates through two principal pathways. Extracellular elements enter lysosomes via endocytosis, a process initiated at the plasma membrane, culminating in the formation of endocytic vesicles laden with cargo molecules [8]. Moreover, intracellular substances enter lysosomes through various autophagic pathways. These pathways, comprising macroautophagy, chaperone-mediated autophagy (CMA), and microautophagy, delineate distinct mechanisms orchestrating the targeted delivery of cellular constituents to the lysosomal degradative machinery [2, 10]. In the realm of microautophagy, lysosomes engulf cytosolic proteins by invaginating either endosomal or lysosomal membranes. Chaperone-mediated autophagy (CMA) is a precision-driven process that selectively targets cytoplasmic proteins bearing a distinctive recognition motif. This motif is duly acknowledged and bound by the cytoplasmic companion protein heat shock cognate protein 70 (Hsc70) and serves as the gateway for the trafficking of these proteins to lysosomes. Facilitated by interactions with the membrane protein LAMP2A, these complexes undergo transport to the lysosomal realm. In stark contrast, macroautophagy, the most prevalent form of autophagy, involves the biogenesis of autophagic vesicles (AVs) and is characterized by the presence of double membrane-bound organelles known as autophagosomes [10, 11]. This paper focuses primarily on therapeutic targets and lysosomal dysfunction in PD. For an in-depth discussion of the physiological functions of lysosomes, readers are directed to previous reviews [8, 9].

Converging evidence for a role of lysosome dysfunction in PD

Evidence of lysosomal dysfunction in PD has been extensively documented, encompassing several key aspects: (1) structural abnormalities of lysosomes, (2) alterations in lysosomal hydrolase activity, (3) genetic factors, and (4) the accumulation of α-syn [4, 12–14]. Autopsy studies of patients with sporadic PD have revealed significant structural abnormalities within lysosomes, including changes in their size, shape, and number in dopaminergic neurons [15]. Immunoreactivity for lysosome-associated membrane protein 1 (LAMP1), cathepsin D (CTSD), and heat shock protein 73 (HSP73) is significantly lower in the nigral neurons of PD patients than in those of age-matched controls [15]. Electron microscopy has revealed swollen and fragmented lysosomes, indicative of impaired lysosomal function [16]. We provide a detailed description of genetic factors, alterations in lysosomal activity, and α-syn accumulation during lysosomal dysfunction.

Genetic evidence

Mutations in lysosome-related genes play pivotal roles in the onset of PD. A summary of the gene mutations associated with PD is provided in Table 1. A comprehensive review systematically examined and detailed the intricate relationships between lysosomal genes and PD [12].

GBA1

Glucosylceramidase beta 1 (GBA1) is the most common gene associated with familial PD. Patients with Gaucher disease (GC) or carriers of GBA1 mutations are more likely to develop PD, multiple system atrophy (MSA), or dementia with Lewy bodies (DLB) [17]. Current evidence indicates that GBA1-associated PD involves multiple dysfunctions, including mitochondrial dysfunction, ER stress, aberrant

Table 1 Pathogenic mutations in lysosomal genes involved in PD

Gene	Protein	Function	Proposed mechanism	Findings in PD model
GBA1	Glucocerebrosidase	Hydrolysis of GlcCer	Loss-of-function (enzymatic deficiency)	Mitochondrial dysfunction [156] ER stress [157] Calcium homeostasis dysregulation [11, 18] GlcCer accumulation and α-syn aggregation[26, 28, 78, 158]
LRRK2	Leucine rich repeat kinase 2	Recruitment to lysosome and phosphorylation of Rab proteins	Gain-of-function (increased kinase activity)	Alterations in the regulation of macroautophagy [159] Impaired lysosomal function with abnormal lysosomal morphology and increased alkalinization [160] Impaired CMA by enhanced binding to LAMP2A and blockage of degradation of other CMA substrates including α-syn [161] α-syn accumulation and oligomerization[162]
TMEM175	Transmembrane protein 175	Lysosomal K^+ channel	Loss-of-function	α-syn aggregates accumulation [44] Reduced activity of GCase [47]
ATP13A2	ATPase cation transporting 13A2	Exporter of polyamines such as spermine	Loss-of-function	Impaired lysosomal acidification [55] Decreased lysosomal-mediated clearance of autophagosomes Deficiency of lysosomal enzymes Lysosomal substrates accumulation
ATP10B	ATPase phospholipid transporting 10B	Flippase of GlcCer/PC	Loss-of-function	Impaired ATPase activity, GluCer and PC translocation activity and lysosomal function [13, 163]
VPS35	Vacuolar protein sorting-associated protein 35	Role in endosome–Golgi complex trafficking	Loss-of-function	Increased Aβ, elevated β-secretase activity, synaptic dysfunctions, and memory deficits [66] α-syn accumulation, degeneration of dopaminergic neurons, locomotor behavior impairment, alteration of lysosomal morphology [65]

processing of abnormal or misfolded proteins, disruption of the autophagy−lysosome system, and dysregulation of calcium homeostasis [11, 18]. GBA1-associated PD is characterized by a more severe clinical course, earlier onset, greater incidence of nonmotor and cognitive symptoms, and earlier age of death than sPD [19, 20]. Interestingly, the pattern of dopaminergic neuronal loss in PD patients is similar to that in sPD patients [21]. Intriguingly, both pathogenic (e.g., N370S, D496H, L444P) and benign (e.g., T369M, E326K) variants of the GBA1 gene have been identified within the spectrum of PD, adding a layer of complexity to the genetic landscape associated with this neurodegenerative disorder [22].

The GBA1 gene encodes lysosomal acid β-glucocerebrosidase (GCase), which hydrolyzes lysosomal glucosylceramide (GlcCer) [23]. After translation on ribosomes, GCase undergoes four N-linked glycosylations (Asn309, Asp 185, Asn98, and Asn58) at the endoplasmic reticulum (ER). Glycosylation is conducive to chaperone-mediated folding of GCases in the ER [19]. After accurate folding, GCase is transported into the Golgi network (TGN), where it can undergo N-glycan modification. Mature GCase

is subsequently transported to lysosomes. In lysosomes, saposin C determines the activity of GCase.

GBA1 mutations are also closely associated with α-syn aggregation [18, 20, 22, 24]. α-Syn is primarily localized to presynaptic nerve terminals. It accumulates abnormally and aggregates under pathological conditions. Studies indicate the accumulation of α-syn within GBA1-related PD patients [19]. Intriguingly, this accumulation impedes the trafficking of GCase from the endoplasmic reticulum (ER) to lysosomes [25]. Furthermore, mutant forms of GCase exacerbate the aggregation of α-syn, contributing to the intricate interplay between lysosomal dysfunction and α-syn pathology in the context of GBA1-related PD [26]. An increase in α-syn levels is observed in Mesencephalic MES23.5 cells overexpressing mutant GCase [27]. Mutant GCase also increases the half-life of α-syn in vivo and in vitro [27]. Furthermore, chaperone-mediated autophagy is impaired in the presence of mutant GCase [11, 18]. The increased half-life of α-syn and impaired autophagy cause α-syn accumulation. Furthermore, a GCase inhibitor induces GlcCer accumulation and α-syn aggregation and accumulation [26, 28].

LRRK2

Leucine-rich repeat kinase 2 (LRRK2) is a 2527-amino acid protein with two enzymatic domains, namely, a serine/threonine kinase domain and a Ras-of-complex (ROC) C-terminal of the Roc domain (COR) (ROC-COR) GTPase domain [29]. The most frequent autosomal dominant monogenic PD is caused by mutations in LRRK2. LRRK2 variants are involved in both familial PD and sPD [30–32]. However, the pathogenesis of LRRK2 is unclear. The most common pathogenic mutations are R1441G/C/H and Y1669C in the ROC-COR GTPase domain and I2020T and G2019S in the kinase domain. Foremost among these variants is G2019S, which is the most prevalent variant, constituting 4% of familial PD cases and 1% of sPD cases on a global scale [29]. These pathogenic mutations all result in elevated kinase activity.

LRRK2 is involved in numerous cellular processes, including various types of autophagy, such as macroautophagy and mitophagy; endocytosis; intracellular transport involving the trans-Golgi network (TGN) and other organelles; the regulation of microtubules; interactions with bacterial pathogens; and the maintenance of lysosomal homeostasis, among other functions [33]. Interestingly, LRRK2 is recruited to impair lysosomes, a process that is exacerbated by PD-related LRRK2 mutations [32]. However, the mechanism and results of LRRK2 recruitment to lysosomes are unclear [34]. Important evidence for the physiological role of LRRK2 in regulating autophagy comes from knockout animal studies. Specifically, in LRRK2 knockout kidneys, there is an accumulation of lipofuscin granules, aggregated α-synuclein, and increased levels of the autophagosomal marker LC3-II [35]. These effects are age dependent, showing biphasic alterations in autophagy: an initial increase in p62 and LC3-II at 7 months, followed by a decrease at 20 months. However, no changes in LC3-II were observed in an independent study of the kidneys of 14-month-old LRRK2 knockout mice [36]. Under conditions that stimulate autophagy but inhibit lysosomal fusion, LRRK2 knockdown results in a reduced accumulation of autophagosomes [37]. Furthermore, inhibition of LRRK2 kinase activity has been demonstrated to increase the levels of the lipidated autophagosome marker LC3-II and the adaptor protein p62 [38]. Recent studies have shown that this kinase-dependent regulation of LC3 lipidation operates through Beclin-1 signaling and is independent of mTOR/ULK1 signaling, indicating a non-canonical pathway for autophagy regulation [39]. Moreover, elevated levels of lysosomal markers and the lysosomal protease cathepsin D have been observed in the kidneys of LRRK2 knockout mice compared with their wild-type counterparts, regardless of age [40]. These findings demonstrate a close relationship between LRRK2 and lysosomal function. Studies have shown that LRRK2 is involved in the transport and formation of endosomes [41, 42]. Early endosomes are the primary step in the endolysosomal pathway. Rab GTPases bind to membranes and utilize their guanine nucleotide-binding status to form specific functional domains on their corresponding organelle membranes, thus earning the title of master regulators of intracellular vesicular trafficking [33]. LRRK2 appears to regulate lysosomal function through its kinase activity on a subset of Rab GTPases, which have been confirmed as bona fide substrates of LRRK2 [43]. Upon lysosomal stress, LRRK2 is recruited from the cytoplasm to enlarged lysosomes by Rab7L1 (also known as Rab29) [43]. Moreover, Rab8a and Rab10 accumulate in LRRK2-positive enlarged lysosomes in an LRRK2 kinase-dependent manner [43]. This sequential recruitment of Rab7L1, LRRK2, phosphorylated Rab8a, and Rab10 to lysosomes under stress conditions suppresses lysosomal enlargement and promotes the release of lysosomal contents, highlighting the role of the Rab7L1−LRRK2 pathway in maintaining lysosome homeostasis [43]. Disruption of early endosome maturation or transport to late endosomes may affect overall lysosomal function. Swollen Rab5-positive early endosomes accumulate in SN dopaminergic neurons during disease progression [42]. Interestingly, LRRK2 colocalizes with early endosome antigen 1 (EEA1)-positive early endosomes [31]. Blockade of LRRK2 activity with PF-360 inhibited the accumulation of Rab5-positive early endosomes in a mouse model of PD [32]. Moreover, Rab5b, but not Rab5a, is viewed as a potential substrate for LRRK2 in overexpression studies. These observations indicate that

the increase in LRRK2 kinase activity may be responsible for the accumulation of Rab5-positive endosomes [30]. In the endolysosomal pathway, newly internalized cargo from the cytomembrane is rapidly targeted to Rab5-positive early endosomes, after which the early endosome eventually matures into a Rab7-positive late endosome where the luminal pH of the endosome is gradually reduced. Given that degrading or recycling endosomes are regulated by various Rab GTPases and that a series of these Rab GTPases are substrates of LRRK2, LRRK2 is thought to regulate the endolysosomal pathway. Elevated LRRK2 kinase activity results in the accumulation of Rab5-positive early endosomes and ultimately causes fewer Rab7-positive late endosomes. Endolysosomal dysfunction in turn exacerbates LRRK2 activity, creating a vicious cycle.

TMEM175

As a lysosomal potassium channel, transmembrane protein 175 (TMEM175) participates in the regulation of lysosomal pH and autophagy [44]. Multiple genome-wide association studies (GWASs) of PD have identified both risk and protective variants of TMEM175 [45, 46]. The TMEM175 p.M393T (rs34311866) variant is the most significant risk factor for PD, whereas the TMEM175 p.Q65P (rs34884217) variant is a protective factor [46]. The risk variant p.M393T likely destabilizes the hydrophobic core of one TM domain, therefore damaging its folding and activity in the lysosome [44]. The protective variant p.Q65P potentially elevates K^+ conductance, thus potentially promoting lysosomal function [47]. TMEM175 has been identified as a K^+ channel that mediates potassium conductance across lysosomal and endosomal membranes, thereby regulating both lysosomal membrane potential and pH [48]. In the p.Q65P variant, a mutation occurs at the first codon of the fourth exon, which stabilizes the ion-selective portion of the structural domain. This modification enhances the permeability of the TMEM175 channel to potassium ions, thereby exerting a protective effect [47]. Moreover, lysosomes lacking TMEM175 exhibit decreased luminal pH stability and potassium conductance [49]. A reduction in TMEM175 leads to increased accumulation of hyperphosphorylated α-syn aggregates induced by α-syn preformed fibrils (α-syn PFFs), whereas TMEM175 overexpression reduces α-syn PFF-induced inclusions[44]. Primary hippocampal neurons were treated with AAV-TMEM175 and then incubated with α-syn PFFs for 14 days. The results showed that TMEM175 overexpression reduced α-syn PFF-induced inclusions. Furthermore, genetic removal of TMEM175 also results in reduced activity of GCase in cellular models due to altered lysosomal pH [47]. Moreover, decreased GCase activity may result in increased α-syn cell-to-cell transmission, as well as reduced chaperone-mediated autophagy, all of which potentially contribute to PD pathogenesis. The roles of TMEM175 and PD have been summarized in a previous review [50].

ATP13A2

Studies have shown that ATPase cation transporting 13A2 (ATP13A2) mRNA levels are highest in the substantia nigra and lowest in the cerebellum [51, 52]. Moreover, compared with those in postmortem healthy brains, ATP13A2 levels are significantly elevated in human SN dopaminergic neurons from postmortem idiopathic PD brains. Moreover, ATP13A2 colocalizes with α-syn in the LBs of sPD patients [53]. This evidence highlights the important role of ATP13A2 in dopamine neurons. The intricate association between ATP13A2 and PD was meticulously explored and described in previous reviews [51, 54].

To date, multiple ATP13A2 mutations (c.1597G > A, c.35C > T, c.2236G > A, c.3040G > A, c.844A > T, c.746C > T, c.1346G > A, and c.2939G > A) have been found to be involved in early-onset PD (onset < 40 years). These missense mutations in the ATP13A2 gene result in ATP13A2 dysfunction and impaired targeting of ATP13A2 to lysosomes [55]. Mutant ATP13A2 causes several lysosomal alterations, including diminished proteolytic processing of lysosomal enzymes, impaired lysosomal acidification, decreased lysosomal-mediated clearance of autophagosomes (APs), and reduced degradation of lysosomal substrates. Analogously, lysosomal dysfunction was observed in ATP13A2-knockdown dopaminergic cell lines. Supplementation of ATP13A2 in ATP13A2-mutant or ATP13A2-depleted cells can alleviate cell death and rescue lysosomal function [16].

The transport function of ATP13A2 in lysosomes is unclear. The polyamine spermidine (PA) is viewed as a potential substrate [56]. As physiologically vital polycations, PAs are tightly regulated by a complex interplay of export, import, degradation and synthesis. Extracellular PAs can bind to heparan sulfate proteoglycans in the plasma membrane and enter the cell via endocytosis before being transported into the cytosol by ATP13A2 [56]. Defective ATP13A2 results in decrease in cellular polyamine levels, which may intensify the disease phenotype because polyamines are scavengers of reactive oxygen species and heavy metals [58]. Moreover, ATP13A2 dysfunction inhibits late endolysosomal polyamine export and sensitizes cells to lysosomal disruption caused by exogenous polyamines [58]. Polyamine levels decrease in an age-dependent manner, whereas supplementation with polyamines increases lifespan in several model organisms [16, 57–61].

VPS35

Vacuolar protein sorting-associated protein 35 (VSP35) is involved in endosomal–lysosomal trafficking associated with autophagy [62]. The intricate nexus between VPS and PD has been diligently scrutinized in previous reviews [62–64]. VPS35 is a subunit of the retromer complex. The retromer complex includes two assembling subcomplexes: a sorting nexin (SNX) dimer and the cargo recognition VPS26–VPS29–VPS35 trimer. The retromer complex binds to the cytosolic portion of endosomes and mediates the reverse transport of transmembrane cargo from endosomes to the TGN. After sorting on the TGN, proteins are targeted to different destinations. It is involved in a series of vital physiological processes, including the classification of acid hydrolases into lysosomes, apoptotic cell clearance, Wnt secretion, biological development, and other cellular activities [65].

Mutations in VPS35 lead to a rare form of autosomal dominant PD [66]. The p.D620N (c.1858G > A) mutation has been recognized as a novel case of familial PD [66]. Among patients with the VPS35 p.D620N mutation, the incidences of rigidity, bradykinesia, postural instability, and tremor were at least 80%, 91.4%, 60%, and 77.1%, respectively. Almost all patients respond well to levodopa treatment. VPS35 mutations result in inactivity of the retromer complex, which impairs the classification of acid hydrolases into lysosomes and Wnt secretion. Removal of the VPS35 gene in flies and mice causes increased Aβ levels, elevated β-secretase activity, synaptic dysfunctions, and memory deficits [66]. These pathological changes have also been observed in VPS35-deficient mice [67]. VPS35 is mislocated in the brains of PD patients and is found in LBs [64]. Interestingly, VPS35 levels are decreased in dopaminergic neurons in the SNpc in sPD patient brains. Many studies have shown that VPS35 is involved in α-syn clearance by mediating autophagy [65, 68]. VPS35 deficiency causes widespread accumulation of α-syn aggregates in the SNpc, accompanied by degeneration of dopaminergic neurons, a decrease in DA levels, locomotor behavior impairment, and alterations in lysosomal morphology in vivo [65]. In contrast, the overexpression of VPS35 alleviates the formation of α-syn aggregates, the loss of DA neurons, and astrocyte proliferation in a mouse model of PD [65]. Consistent with these findings, genetic ablation of VPS35 in Drosophila causes α-syn accumulation and aggregation [68]. These results indicate that endosomal dysfunction caused by VPS35 deficiency interferes with the ability of neurons to address the abnormal accumulation and aggregation of α-syn, thus intensifying the spread of PD pathology and α-syn pathology.

The cation-independent 6 mannose phosphate receptor (CI-MPR) and sortilin are recognized as VPS35 cargo proteins. They act as lysosomal hydrolase receptors to regulate the sorting of acid hydrolases, such as cathepsins, from the TGN to lysosomes [69]. The VPS35 p.D620N mutation cannot be used to sort CI-MPRs [62]. Therefore, VPS35 is involved in lysosomal function by sorting receptors for lysosomal hydrolases. By regulating the recruitment of the WASH complex and the trafficking of the ATG9a protein, VPS35 participates in macroautophagy. The WASH complex regulates the autophagic process of autophagosome development and endosome-to-cell surface recycling. The VPS35 p.D620N mutant induces defects in autophagosome formation by impairing WASH complex recruitment to endosomes [66]. ATG9a participates in the autophagic pathway and controls the interaction of LC3-positive compartments with autophagosomes. Moreover, VPS35 is essential for retrieving the receptor LAMP2A [65].

VPS35 has also been implicated in the sorting of retromer complex-mediated DMT1 (divalent metal transporter 1) [70]. DMT1 is an endogenous transporter of ferrous iron that carries endosomal iron to the cytoplasm and imports extracellular iron [70]. Increasing evidence shows that iron is related to the pathology of PD. Iron accumulation has been detected in the SNpc of PD patients and mouse models [71]. Interestingly, DMT1 is upregulated in the same region [72]. Decrease of VPS35 by RNA interference causes misorting of DMT1 to lysosomal membrane-associated protein 2 (LAMP2)-positive structures, where it might act as an iron transporter [73]. These results indicate the vital role of VPS35 in PD pathogenesis via retromer-mediated endosomal recycling of the iron transporter DMT1.

In summary, pathogenic mutations in PD-related genes are involved in endosomal trafficking, indicating that

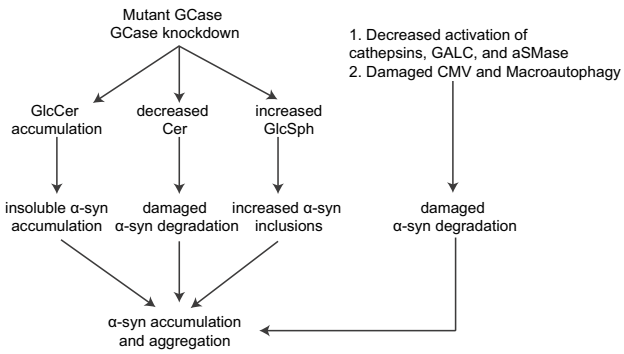

Fig. 1 Lysosomal dysfunction in α-syn pathology. Mutant GCase or GCase knockdown leads to α-syn accumulation by three ways: (1) GlcCer directly promotes the transformation of physiological α-synuclein into insoluble forms; (2) GlcSph enhances α-syn inclusion formation; (3) decreased Cer impairs α-syn degradation. Moreover, decreased activation of cathepsins, GALC, and aSMase result in damage of α-syn degradation. Damaged CMV and macroautophagy also impair α-syn degradation. These damaged pathways eventually cause α-syn accumulation and aggregation

dopaminergic neurons in the SN are specifically susceptible to endosomal dysfunctions.

Lysosomal dysfunction may contribute to α-syn pathology

Cathepsins and α-syn pathology

Cathepsins have been reported to directly participate in the degradation of monomeric and aggregated α-syn (Fig. 1) [74]. The cathepsin family comprises a total of 15 proteases systematically classified into three distinct groups on the basis of their catalytic mechanisms: serine cathepsins (A and G), cysteine cathepsins (B, C, F, H, K, L, O, S, V, W, and X), and aspartic cathepsins (D and E) [74]. CTSD, CTSL, and CTSB are notably prevalent in the central nervous system (CNS) and are implicated in pivotal neuronal functions, including synaptic plasticity [74]. CTSD activity degrades membrane-bound α-syn monomers and fibrils, whereas CTSL and CTSB degrade free α-syn monomers and fibrils [75, 76]. Importantly, CTSB activity is negatively correlated with α-syn high-molecular-weight (hMW) species [77]. Interestingly, the incomplete degradation of α-syn monomers and fibrils by CTSB and CTSL results in the formation of truncated aggregation-prone C-termini [75, 76].

GCase and α-syn pathology

GCase is not directly involved in α-syn degradation, but reduced GCase availability and activity exacerbates accumulation and aggregation of α-syn by compromising its protein degradation capacity [24, 78, 79]. Furthermore, GCase knockdown enhances the formation of insoluble and soluble α-syn high molecular weight (hMW) species in Drosophila [80]. Moreover, the glucosylceramide (GlcCer, the GCase substrate) and glucosylceramide/ceramide (GlcCer/Cer, where Cer is the GCase product) ratios in red blood cells are positively correlated with the α-syn dimer/monomer ratio [81]. GlcCer directly promotes the transformation of physiological α-synuclein into insoluble forms in iPSCs derived from individuals with PD [72]. Intriguingly, this phenomenon was reversed by reducing the level of GlcCer [72]. Glucosylsphingosine (GlcSph) causes hippocampal dysfunction and a reduction in excitatory synaptic proteins [83]. Moreover, GlcSph enhances α-syn inclusion formation in the hippocampus [83]. As a consequence of GCase failure, the levels of Cer in the lysosomal and endosomal compartments decrease [82]. Considering that Cer binds to CTSD and drives its cleavage into a catalytically active form, reduced Cer may also reduce the capacity of the lysosome to degrade α-syn [77, 84]. Compared with those in controls, decreased Cer in plasma samples and in the anterior cingulate cortex of PD patients have been reported [85–87]. Carmofur enhances Cer by inhibiting acid ceramidase activity and reducing α-syn accumulation in GBA1-PD-derived dopaminergic neurons [88]. GCase activity can also modulate the aggregation propensity of α-syn through its effect on lipid membrane composition [89].

GALC, aSMase, and α-syn pathology

The other two enzymes, galactosylceramidase (GALC) and acid sphingomyelinase (aSMase), catalyze the production of Cer within the lysosome and are known to be susceptibility factors for PD and other α-synucleinopathies [90–92]. Catalyzing the decomposition of sphingomyelin into Cer and phosphorylcholine decreases the occurrence of aSMase in the blood 3.5–5.8 years earlier than in the absence of PD [93]. GALC can catalyze the hydrolysis of galactosylceramide and galactosylsphingosine. Compared with that in age-matched controls, the level of galactosylsphingosine in the cortex was elevated in PD patients [94]. Moreover, galactosylsphingosine intensifies α-syn aggregation in a dose-dependent manner [95].

ALP dysfunction and α-syn pathology

In addition to decrease in hydrolase activity, autophagic−lysosomal pathway (ALP) dysfunction has also been shown to promote exocytosis and intercellular proliferation of α-syn aggregates. Blocking the ALP with bafilomycin A1 results in the accumulation of α-syn aggregates in primary cortical neurons and nonneuronal cells [96, 97]. Similarly, macroautophagy inhibition by 3-methyladenine results in increased α-syn in PC12 cells [98]. Rapamycin, an inhibitor of mTOR, can reduce α-syn accumulation [99]. These studies suggest that impaired autophagy plays an important role in the aggregation and dissemination of α-syn. Therefore, regulating lysosomal function may be an important strategy for alleviating PD.

Chaperone-mediated autophagy in α-syn pathology

α-Syn is closely linked to chaperone-mediated autophagy (CMA), a lysosomal degradation process in which substrates are delivered by a chaperone protein [100]. In CMA, substrates must possess a conserved recognition motif, such as KFERQ, or other structurally analogous sequences [100]. Interestingly, α-syn harbors the sequence 95VKKDQ99, which is specifically recognized by HSP70 and facilitates its translocation to the lysosomal surface, where it associates with LAMP2 for subsequent degradation. In neuronal cell lines and primary neurons, wild-type α-syn is subject to degradation via CMA. However, this process

is markedly impaired in mutant forms of α-syn that lack the 95VKKDQ99 sequence [101]. Furthermore, the levels of CMA-associated HSP70 and LAMP2 are markedly decreased in the SNpc and amygdala of PD patients, suggesting that disruptions in CMA play a role in disease pathogenesis [15]. Additionally, the A53T mutant form of α-syn has a robust affinity for LAMP2, accompanied by the inhibition of CMA and compromised lysosomal degradation. In the early stages of PD, the decrease in LAMP2A levels is influenced by elevated α-syn levels, which occur even prior to the accumulation of α-syn itself [102]. These findings indicate that CMA dysfunction represents an early event in PD. CMA is also integral to the turnover of essential factors critical for cell survival. Myocyte enhancer factor 2D (MEF2D), a pivotal protein for neuronal longevity, is known to be degraded via CMA. Both wild-type and mutant forms of α-syn can impede the degradation of MEF2D, leading to aberrant MEF2D activity and subsequent neuronal apoptosis [103]. Furthermore, elevated levels of MEF2D have been observed in α-syn transgenic mice as well as in PD patients, indicating that the pathological accumulation of MEF2D, due to CMA impairment, may constitute a significant mechanism underlying PD pathogenesis [104]. Nitration and oxidation of α-syn moderately compromise CMA, whereas phosphorylation of α-syn and dopamine-mediated modifications entirely inhibit CMA-mediated degradation of α-syn [105]. In summary, excessive aggregation of α-syn is closely tied to autophagy; however, under certain conditions, α-syn can also impede autophagic processes. This paradoxical relationship is crucial in the progression of PD. Therefore, elucidating the molecular mechanisms by which α-syn modulates autophagy is essential for the development of small molecule compounds aimed at restoring autophagic function.

Lysosome-mediated lipid destabilization in α-syn pathology

The major mammalian subclasses of lipids encompass five categories: sphingolipids, fatty acyls, glycerolipids, sterol lipids, and glycerophospholipids. Lipids have a wide range of functions. They can act as nutrients, hormone precursors, essential components of membranes, and necessary signaling molecules. Gene mutation, oxidative stress, aging and excess nutrients all pose challenges to lipid homeostasis [106–109]. Hence, cells need a precise system to contend with toxic, oxidized, and excess lipids, ensuring the maintenance of lipid homeostasis. Lipid droplets derived from the ER serve as eukaryotic organelles dedicated to lipid storage. Compared with the hydrophobic core, which houses neutral lipids and an encompassing phospholipid monolayer, lipid droplets feature an outer layer equipped with membrane proteins facilitating contact with other organelles to facilitate lipid transfer [110]. The predominant membrane proteins are perilipins, adipophilin, and a tail-interacting protein of 47 kDa.

In addition to cytosolic lipolysis, lipid droplets can also selectively target the autophagy pathway and are degraded by lysosomal acid lipases to produce glycerol and free fatty acids [2]. This process of selective autophagy is called the lipophagy [110]. Its dysfunction or overload can cause disease. Perilipins take part in regulating lipophagy initiation and lipase access to the core of lipid droplets. Primarily, protein kinase A phosphorylates perilipins, after which the phosphorylated perilipins are degraded via the proteasome [110]. Alternatively, perilipins are degraded through the chaperone-mediated autophagy (CMA)-dependent pathway, in which perilipin is identified by the heat shock cognate protein HSPA8/Hsc70 and is subsequently transported to the lysosome with the help of cochaperones upon attachment to the lysosomal membrane receptor LAMP2a. The surface of patatin-like phospholipase domain containing 2 (PNPLA2) is subsequently exposed. Known as an adipocyte triglyceride lipase, PNPLA2 binds to LC3b through its LC3-interacting motif and attaches lipids droplet to the autophagosomal membrane, thereby initiating macroautophagy [110]. Thus, lysosomes play a crucial role in inhibiting lipidosis by degrading lipids through lipophagy.

Lipid accumulation occurs in cases of lysosomal dysfunction. LBs may be composed of multitudinous lipid droplets and dystrophic organelles [111]. This finding has caused considerable debate in this field, that is, whether PD is a proteinopathy or should be regarded as a lipidopathy [106]. Galactosylceramidase inactivation results in the accumulation of cytotoxic lipid psychosine [94], which has been demonstrated to promote the aggregation of α-syn in vitro [112]. Moreover, after exposure to polyunsaturated fatty acids such as linoleic acid and arachidonic acid, α-syn abnormally and rapidly aggregates [113]. These studies suggest that lipid dysregulation caused by lysosomal dysfunction promotes α-syn aggregation.

Perspective on the diagnostic and therapeutic value of lysosomal dysfunction in PD

Lysosomal proteins assist in the diagnosis of PD

sPD accounts for the vast majority of PD cases and is the common result of aging and detrimental environmental factors plus a susceptible genetic background [12]. Mounting evidence indicates a diminishing trend in lysosomal activity as a corollary of the aging process [2]. Importantly, the activities of several lysosomal enzymes are significantly altered in PD patien ts compared with controls (summarized in

Table 2 CSF lysosomal enzymes as diagnostic biomarkers for PD

Enzymes	Changes in CSF of PD patients	Ref
α-mannosidase	Reduced	[164]
β-mannosidase	Reduced	[164]
GCase	Reduced	[164]
β-galactosidase	Increased	[165]
β-hexosaminidase	Increased	[118, 165]
cathepsin E	Increased	[165]
α-fucosidas	Reduced	[165]
β-glucocerebrosidase	Reduced	[118, 155]
cathepsin D	Reduced	[118]

Table 2). The activities of GCase, α-galactosidase A (α-Gal A), and cathepsin-D (CTSD) are decreased in the CSF of sPD patients [75, 77, 84, 114–116]. Compared with that in controls and patients with Alzheimer's disease (AD) or frontotemporal dementia, GCase activity is decreased in the CSF of Lewy-body dementia patients [117]. Reduced activity of GCase has been observed not only in CSF but also in dried blood spots [24, 78, 118, 119]. The activity and level of GCase in the SNpc and other brain regions of sPD and DLB patients are significantly decreased [24]. Furthermore, brain regions with decreased GCase activity also show increased α-syn accumulation [24, 26, 28, 79, 80, 120]. Compared with those in age-matched healthy controls, CTSD, LAMP1, and heat shock protein 73 are decreased in the dopaminergic neurons of PD patients. Significantly decreased CTSD and α-Gal A activities have been reported in the brains of PD patients in the early stage of disease [77]. CTSD has also been found to be involved in AD and Huntington's disease [121]. Compared with those in controls, HSC70 and LAMP2A are downregulated in the SNpc and amygdala of sPD patients [15, 122]. Furthermore, lower LAMP2A levels are directly correlated with increased α-syn. In summary, lysosomal enzymes can be supplemented with other diagnostic tests to improve the accuracy of PD diagnosis.

Potential lysosomal therapeutic targets for PD

Therapeutic strategies targeting GBA1

Genetic and biochemical studies have shown that PD-related pathogenic GBA1 mutations result in loss-of-function of GCase activity. There are two main therapeutic strategies for mitigating the effects of reduced GCase activity: (1) small-molecule chaperones to promote GCase activity and (2) therapies to inhibit the accumulation of GlcCer by GCase inhibition (summarized in Table 3).

Small-molecule chaperones that promote GCase activity

Ambroxol was identified as a GCase chaperone. Ambroxol treatment exhibited remarkable therapeutic efficacy in preclinical trials: it promoted GCase activity by increasing mRNA and protein levels [123], increasing LIMP-2 and saposin C levels [124], decreasing α-syn and phosphorylated α-syn levels [125], and reducing lysosomal substrate storage [126]. In clinical trials, ambroxol has shown good safety and tolerability profiles and good blood−brain barrier permeability. In addition, reduced levels of oxidative stress markers have been observed in patients treated with ambroxol [127]. Furthermore, in an open-label clinical trial involving 17 patients with PD (ClinicalTrials.gov ID: NCT02941822), ambroxol administration induced an increase in CSF GCase and improved motor function [128]. A phase 3a, multicenter, randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov ID: NCT05778617) revealed that ambroxol treatment alleviated symptoms. Two trials of ambroxol have also been conducted in DLB patients (ClinicalTrials.gov ID: NCT04405596; NCT04588285). Other compounds targeting GCase include NCGC00188758, which has been shown to promote the clearance of pathological α-syn in iPSCs derived from PD [129], and NCGC607, which has been shown to restore GCase activity and protein levels and reduce glycolipid storage in iPSC-derived macrophages and dopaminergic neurons [126].

Therapies to inhibit the accumulation of GlcCer via GCase inhibition

GlcCer accumulation has been suggested to be a pathogenic mechanism of PD in GBA1 mutation carriers. Strategies for reducing GlcCer via GCase inhibition have also been reported. The brain-penetrating GCS inhibitor GZ667161 was proven to slow the accumulation of hippocampal aggregates of α-syn, ubiquitin, and tau and improve the associated memory deficits in synucleinopathy models [130]. Studies have shown that benzoxazole 1 rescues lysosomal deficits, α-syn pathology and neuronal toxicity [131]. These promising findings promoted the implementation of a phase 2, multicenter, randomized, double-blinded, placebo-controlled trial testing the effect of venglustat (GZ/SAR402671) in PD patients carrying GBA1 variants (ClinicalTrials.gov ID: NCT02906020). Administration of venglustat dose-dependently reduced CSF GlcCer levels. However, an initial worsening of motor function was observed [132, 133]. Subsequent advancements in the development of venglustat for GBA1-related PD have been halted. Other GCase chaperones, including miglustat, eliglustat, and lucerastat,

Table 3 Therapeutic strategies targeting GBA1

Agent	Tarkets	Stage	Primary outcome	NCT No	Ref
Ambroxol	Increaseing GCase activity	Preclinical	Increased LIMP-2 and saposin C levels	NA	[124]
		Preclinical	Decreased α-syn and phosphorylated α-syn levels	NA	[125]
		Preclinical	Reduced lysosomal substrate storage and α-syn levels in cell	NA	[126]
		Phase I	Increased GCase activity and reduced markers of oxidative stress	NA	[127]
		Phase IIa	Ambroxol detected in CSF Increased CSF GCase protein levels Increased CSF α-syn levels in patients Improvement of motor function	NCT02941822	[128]
		Phase II	Changes in ADAS-cog and the CGIC	NCT02914366	NA
		Phase II	Changes in MOCA score and cognitive status	NCT05287503	NA
		Phase III	Slowed progression	NCT05778617	NA
		Observational	NA (ongoing)	NCT04388969	NA
		Phase I/II	NA (ongoing)	NCT04405596	NA
		Phase IIa	NA (ongoing)	NCT04588285	NA
NCGC607	Restoring GCase activity	Preclinical	Restored GCase activity and protein levels Reduced glycolipid storage	NA	[126]
Isofagomine (AT2101)	Enhancing GCase activity	Preclinical	Improved motor and nonmotor function Reduced neuroinflammation and α-synuclein aggregates,	NA	[166]
		Phase I	Safety, tolerability	NCT00875160	NA
		Phase II	Safety, tolerability	NCT00813865	NA
		Phase II	Safety, tolerability	NCT00446550	NA
		Phase II	Safety, tolerability	NCT00433147	NA
NCGC00188758	Enhancing GCase activity	Preclinical	Promoted clearance of pathological α-syn	NA	[129]
LTI-291	Enhancing GCase activity	Phase I	Safety, tolerability	NA	[167]
PR001 (LY3884961)/Prevail Therapeutics	Restoring GCase activity	Phase I/II	Safety, tolerability, immunogenicity	NCT04127578	NA
				NCT04411654	NA
				NCT05487599	NA
GZ667161	GCS inhibition	Preclinical	Slowed the accumulation of hippocampal aggregates of α-syn, ubiquitin, and tau Improved the associated memory deficits	NA	[130]
Benzoxazole 1	GCS inhibition	Preclinical	Rescued lysosomal deficits, α-syn pathology and neuron toxicity	NA	[131]
Venglustat (GZ/SAR402671)	GCS inhibitor	Phase II	Reduction in CSF GlcCer Safety, tolerability	NCT02843035	[168]
		Phase II	Safety, tolerability Resulting in an early deterioration in motor function	NCT02906020	[132, 133]
Miglustat	GCS inhibition	Marketed	Safety, tolerability	NA	[134, 169]
Eliglustat	GCS inhibition	Phase I	Safety, tolerability	NCT01659944	[134, 135]
Lucerastat	GCS inhibition	Preclinical	Improved neurological performance	NA	[136, 137]
Genz-682452	Enhancing GCase activity	Preclinical	Reduced the GluCer and hexosylsphingosine substrates Enhanced the clearance of pathological α-syn	NA	[170]
		Phase I	Safety, tolerability	NCT01710826	NA
		Phase I	Safety, tolerability	NCT01674036	NA

ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale, *CGIC* ADCS-Clinician's Global Impression of Change, *CSF* cerebrospinal fluid, *GCase* glucocerebrosidase, *MDS-UPDRS* MDS-Unified Parkinson's Disease Rating Scale, *MOCA* Montreal Cognitive Assessment, *NA* not available

Table 4 Therapeutic strategies targeting LRRK2

Agent	Stage	Primary outcome	NCT No	Ref
GZD-824	Preclinical	NA	NA	[171]
EB-42168	Preclinical	NA	NA	[172]
MLi-2	Preclinical	Chronic in-diet dosing with MLi-2 does not attenuate the behavioral phenotype in in MitoPark mice	NA	[139, 140]
	Preclinical	No change in motor phenotypes, pathological α-synuclein accumulation or neuron loss	NA	[173]
PF-06447475	Preclinical	Protecting against nigral dopamine cell loss in MPTP mouse modle	NA	[141]
PF-06685360	Preclinical	Increasing α-syn overlap with glutamatergic, cortico-striatal terminals, and dopaminergic nigral-striatal presynaptic terminals	NA	[142]
LRRK2-in-1	Preclinical	An activation of the autophagic pathway	NA	[174]
DNL201 (GNE-0877)	Phase I	well tolerated without serious adverse events	NCT04551534	[143]
	Phase I	Patients with mild to moderate PD	NCT03710707	[143]
DNL151 (BIIB122)	Phase III	Early-stage PD participants with specific LRRK2 genetic variants	NCT05418673	[143]
	Phase I	PD patients	NCT04056689	NA
	Phase I	Healthy volunteers	NCT04557800	NA
	Phase I	Healthy volunteers	NCT05005338	NA
	Phase IIb	Early-stage PD patients	NCT05348785	NA
	Phase I	Healthy volunteers	NCT05119790	NA
BIIB094 (ASO)	Phase I	evaluate the safety and tolerability	NCT03976349	[175]
WXWH0226	Phase I	Healthy volunteers	CXHL2000520	NA
NEU-723	Phase I	Healthy volunteers	NCT05633745	NA

have also been found to improve neurological performance [134–137].

Therapeutic strategies targeting LRRK2

Genetic and biochemical evidence underscores that pathogenic mutations associated with PD, notably the G2019S mutation and its variants in LRRK2, lead to a detrimental gain-of-function increase in LRRK2 kinase activity. In light of this pathogenic elevation in kinase function, ongoing therapeutic strategies for LRRK2-related PD are predominantly centered around the development and utilization of LRRK2 kinase inhibitors (summarized in Table 4).

Small-molecule inhibitors targeting LRRK2 kinase activity are under investigation. A druggable compound should have commendable oral bioavailability, the capacity to permeate the blood−brain barrier, and selectivity toward the kinase [138]. Cis-2,6-dimethyl-4-(6-(5-(1-methylcyclopropoxy)-1H-indazol-3-yl) pyrimidin-4-yl) morpholine (MLi-2) is a selective LRRK2 kinase inhibitor. However, MLi-2 reportedly does not attenuate the behavioral phenotype in MitoPark mice or pathological α-syn accumulation or neuron loss [139, 140]. PF-06447475 protected against nigral dopaminergic neuronal loss in an MPTP mouse model [141]. Moreover, PF-06685360 was found to increase the overlap of α-syn with glutamatergic and corticostriatal terminals and with dopaminergic nigral–striatal presynaptic terminals [142]. However, additional preclinical and clinical trials are needed to demonstrate the effectiveness of these small molecule compounds in the treatment of PD.

Four LRRK2 kinase inhibitors (DNL201, WXWH0226, NEU-723, and BIIB122) and one antisense oligonucleotide (ASO) (BIIB-094) are undergoing clinical trials (summarized in Table 4). DNL201 (GNE-0877) was assessed in a phase Ia study involving 122 healthy volunteers, during which favorable outcomes were demonstrated. Notably, an investigation revealed that DNL201 was well tolerated and not associated with serious adverse events [143]. A randomized, placebo-controlled phase 1b clinical trial in patients with mild to moderate PD with and without LRRK2 mutations is ongoing to assess its safety (ClinicalTrials.gov ID NCT03710707). RNA therapeutics are also under evaluation. Most studies have focused on RNA interference (RNAi) and antisense oligonucleotide (ASO) approaches. ASOs can inhibit RNA translation or regulate pre-mRNA maturation by splicing correction and reduce protein levels by targeting specific transcripts. Studies have shown that ASOs targeting LRRK2 can ameliorate α-syn aggregate formation in primary neurons and in mice treated with α-syn-preformed fibrils (PFFs) [144]. Moreover, LRRK2-ASO has been shown to ameliorate ER stress, promote neurite outgrowth, and decrease LRRK2 levels [145]. Strikingly, because of their good safety, efficacy and pharmacokinetics, ASOs

Table 5 Therapeutic strategies targeting others lysosomal components

Agent	Target	Stage	Primary outcome	Ref
Trehalose	Activity of TFEB	Preclinical	Decreased aggregation and accumulation of α-syn Alleviated motor impairment Reduced loss of dopaminergic neurons	[99]
			Reduced striatal dopaminergic deficits	[146]
			Reversed α-syn aggregation Enhanced autophagy	[147]
Rapamycin and Rp analogs (CCI-779, RAD001 and AP23573)	Inhibitors of mTOR C1	Preclinical	Decreased phospho-Ser129 α-syn levels	[151]
			Reduced cell death	[176]
			Improved motor function Reduced synaptic injury	[177]
			Reduced mitochondrial dysfunction	[178]
Nilotinib	Tyrosine kinase inhibitor	Preclinical	Reduced α-syn levels, Suppressed DA neuronal loss Improved motor deficits in mice	[152]
		Phase II	The efficacy data trending in the negative direction indicate that nilotinib should not be further tested in PD	[179]
Metformin	AMPK	Preclinical	Decreased cell death	[180]
			Reduced phospho-Ser129 α-syn levels	[181]
AICAR	AMPK	Preclinical	Decreased cell death	[180]
Resveratrol	AMPK	Preclinical	Promoted α-syn clearance	[182]
KYP-2047	Beclin-1	Preclinical	Decreased oligomeric α-syn Increased striatal DA levels	[183]
Isorhynchophylline	Beclin-1	Preclinical	Promoted α-syn clearance	[184]
			Reduced α-syn accumulation	[185]
Acidic Nanoparticles	Lysosome	Preclinical	Restoration of lysosomal function Reduced DA cell loss	[186]

provide a potential strategy for PD treatment without causing peripheral adverse effects.

Therapeutic strategies targeting other lysosomal components

Given the pivotal role of lysosomes and autophagy in the pathogenesis of PD, a variety of compounds targeting lysosomes are under investigation in animal models and clinical trials (summarized in Table 5). Trehalose is a disaccharide that regulates the activity of TFEB and activates autophagy processes. It has been proven to have therapeutic effects in vivo and in vitro [99, 146–150]. Trehalose inhibits lysosomal enlargement and the formation of massive aggregates in primary neurons. Moreover, the oral administration of trehalose decreases the aggregation and accumulation of α-syn in the SNpc, alleviates motor impairment, and reduces the loss of dopaminergic neurons in rats o overexpressressing A53T α-syn and in mice injected with MPTP [99]. However, the safety and effectiveness of trehalose in PD patients need further verification. As a key regulator of lysosomal biogenesis, TFEB is another vital therapeutic target for PD [149]. It has been reported that the activation and overexpression of TFEB alleviate the formation of α-syn inclusions and the loss of TH-positive neurons. Rapamycin and Rp analogs (CCI-779, RAD001 and AP23573) have been identified as inhibitors of mTORC1. Studies have reported that rapamycin and Rp analogs can improve motor function and reduce cell death by decreasing phospho-Ser129 α-syn levels and mitochondrial dysfunction [151]. Nilotinib, an inhibitor of Abelson tyrosine kinase (c-Abl), has been used to test the effect of Beclin-1-mediated autophagic α-syn clearance [152]. Nilotinib can reverse the loss of dopamine neurons and improve motor behavior via the autophagic degradation of a-synuclein in Parkinson's disease models [152]. The results showed that nilotinib is potentially effective at mitigating motor and nonmotor symptoms in PD and DLB patients [153, 154].

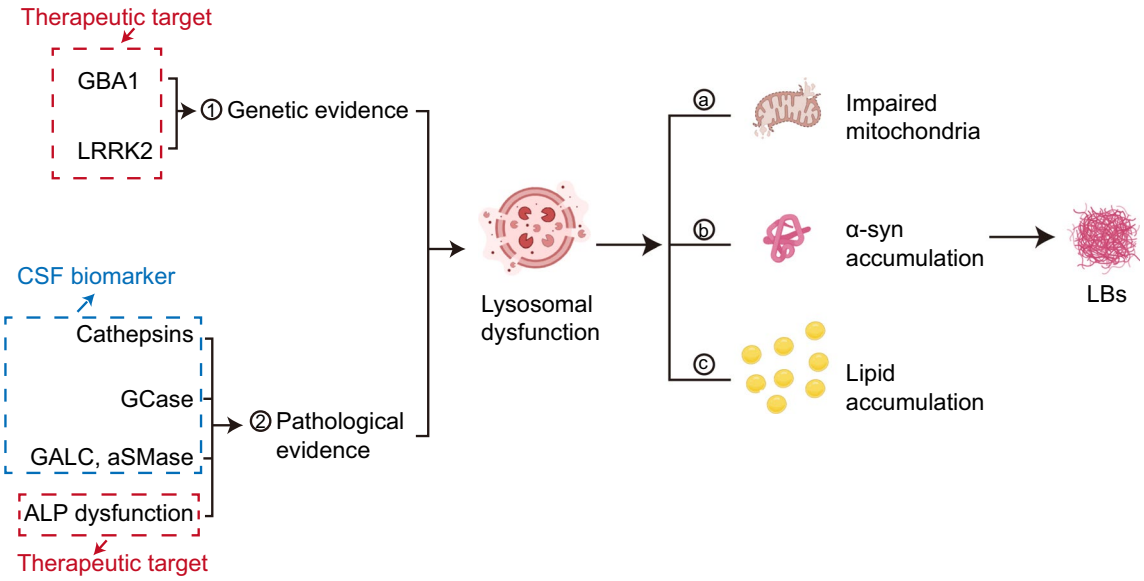

Fig. 2 Lysosomal dysfunction contributes to the pathogenesis of PD. Genetic mutations, notably in pivotal genes such as GBA1 and LRRK2, in conjunction with diminished activity of lysosomal enzymes such as glucocerebrosidase (GCase), cathepsins, and galactosylceramidase (GALC), synergistically contribute to a state of lysosomal dysfunction. Lysosomal dysregulation prompts the accumulation of impaired mitochondria and lipids within the cellular cytoplasm. α-Syn, which is primarily subjected to degradation within the lysosomal milieu, faces compromised degradation due to lysosomal dysfunction. Consequently, α-syn accumulation and aggregation ensue. Furthermore, the byproducts of lysosomal damage precipitate the increase in α-syn levels, fostering its aggregation. Ultimately, insoluble aggregates form within the cytoplasm, precipitating neurodegeneration. The image was created with BioRender.com, with permission

Conclusions and future perspectives

Here we summarize the evidence demonstrating the relationship between lysosomal dysfunction and PD pathogenesis. Given that lysosomes play a central role in waste elimination and signal transduction, their dysfunction may lead to devastating consequences. The dysregulation of lysosomal function attributable to the aging process may constitute a fundamental etiological factor in sPD (Fig. 2). Gene mutations related to lysosomes, including GBA1, LRRK2, and VPS35, play a pathogenic role in both familial and sPD. However, the causal link between these mutations and α-syn aggregation is still unclear. Moreover, altered levels of lysosomal proteins, such as GCase and CTSD, in CSF and plasma have emerged as promising biomarkers for PD. GCase activity was 0.51 mU/ml in the CSF of PD patients and 0.78 mU/ml in the control group [155]. Moreover, CTSD-specific activity was lower in PD patients than in controls (−21%) [118]. However, lysosomal enzyme activity alone cannot discriminate between PD patients and patients with other degenerative diseases. A range of biomarkers, including a conformational and/or post-translated form of α-syn, mitochondrial dysfunction, inflammation, and other pathological proteins in PD, are needed to achieve the unique ability, sensitivity, and specificity to meet diagnostic criteria.

Lysosomal damage plays a critical role in the pathogenesis of PD. Generalized lysosomal impairment is intimately associated with the failure to degrade α-syn aggregates. Nonetheless, the question of whether specific factors arising from lysosomal dysfunction can elucidate the selective aggregation of α-syn in PD remains unresolved. More research is needed to focus on this area in the future.

Moreover, elucidation of the correlation between lysosomal dysfunction and PD has yielded fresh perspectives on the pathogenic mechanisms that underlie PD, paving the way for innovative therapeutic strategies. A diverse array of small-molecule compounds has been formulated to modulate lysosomal function. Caution is paramount when investigating lysosomal activation or inhibition owing to the variability in lysosomal activity across different organs or tissues. Moreover, lysosomal activity can be irregularly heightened or diminished within specific organs or tissues, as well as within individual lysosomes of the same cell. Therefore, biodistribution studies conducted in vivo are imperative to prevent the undue accumulation of pharmaceutical agents in healthy tissues or organs. Ensuring safety is of utmost importance, particularly concerning the use of drugs intended as lysosome modulators for specific lysosomal disorders, to guard against inadvertently exacerbating susceptibility to other diseases. Further investigations are

warranted to ascertain the safety, efficacy, and potential therapeutic applications of these compounds.

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Declarations

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