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Molecular Mechanisms of Autophagy-Lysosome Dysfunction in the Pathogenesis and Progression of Parkinson's Disease

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Abstract. Autophagy-lysosome dysfunction is a major molecular feature of Parkinson's disease because it connects impaired α-synuclein clearance, mitochondrial damage, lysosomal enzyme insufficiency, vesicular trafficking defects, and neuroinflammatory activation. Dopaminergic neurons are particularly dependent on effective autophagic flux and lysosomal degradation owing to their post-mitotic state, high metabolic load, extensive axonal architecture, and vulnerability to oxidative stress. Work from the last several years has refined the understanding of Parkinson's disease from a protein aggregation disorder into a network disease involving macroautophagy, chaperone-mediated autophagy, mitophagy, lysosomal acidification, hydrolase activity, lipid metabolism, and stress-responsive transcriptional control. Genetic and mechanistic evidence involving SNCA, GBA1, LRRK2, PINK1, PRKN, VPS35, LAMP2A, cathepsins, and TFEB further supports this integrated view. This review summarizes recent advances in the molecular basis of the autophagy-lysosome system, the mechanisms through which its dysfunction promotes α-synuclein pathology and neuronal injury, and the therapeutic strategies aimed at restoring degradative capacity in Parkinson's disease. Emphasis is placed on the GBA1/GCase axis, LRRK2-dependent lysosomal stress responses, PINK1/Parkin-mediated mitophagy, TFEB-regulated lysosomal biogenesis, and emerging aggregate-targeted clearance approaches.

Keywords: Parkinson's disease, autophagy, lysosome, α-synuclein, mitophagy

1. Introduction

Parkinson's disease is defined clinically by bradykinesia, resting tremor, rigidity, and postural instability, but its molecular pathology extends beyond motor circuitry. Loss of dopaminergic neurons in the substantia nigra pars compacta is accompanied by α-synuclein aggregation, mitochondrial injury, neuroinflammatory activation, impaired proteostasis, and progressive dysfunction of neuronal organelles. Autophagy-lysosome dysfunction connects many of these lesions because long-lived neurons depend on efficient clearance of misfolded proteins, damaged mitochondria, and oxidized macromolecular complexes. The autophagy-lysosome system does not operate as an isolated degradation pathway. It integrates nutrient sensing, vesicle trafficking, membrane repair, endolysosomal maturation, mitochondrial quality control, lipid metabolism, and innate immune signaling. In Parkinson's disease, defects in these processes converge on several

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genetically and pathologically validated nodes, including SNCA, GBA1, LRRK2, VPS35, PINK1, PRKN, ATP13A2, and lysosomal cathepsins [1, 2].

This article summarizes molecular evidence linking autophagy-lysosome impairment to the onset and progression of Parkinson's disease. The discussion follows three connected levels of organization. The first level concerns the normal biology of macroautophagy, chaperone-mediated autophagy, mitophagy, and lysosomal degradation in neurons. The second level addresses disease mechanisms through which α-synuclein accumulation, defective mitochondrial turnover, lysosomal acidification failure, hydrolase insufficiency, and vesicular trafficking defects injure dopaminergic cells. The third level considers PD-associated regulatory axes and therapeutic approaches, with emphasis on GBA1/GCase biology, LRRK2-dependent lysosomal stress responses, PINK1/Parkin-mediated mitophagy, TFEB-dependent lysosomal biogenesis, and emerging protein clearance technologies.

2. Molecular basis of the autophagy-lysosome system and neuronal homeostasis

2.1. Types of autophagy and their molecular regulation

Autophagy comprises several mechanistically distinct routes that deliver intracellular material to lysosomes. Macroautophagy begins with nucleation of a phagophore, expansion into a double-membrane autophagosome, cargo recognition through ubiquitin-binding receptors, and fusion with late endosomes or lysosomes to form degradative autolysosomes. The ULK1 complex, class III phosphatidylinositol 3-kinase complex, ATG conjugation systems, LC3 lipidation, and SNARE-dependent fusion machinery coordinate these stages. mTORC1 and AMPK couple autophagic flux to nutrient and energy state, whereas transcription factors of the MiT/TFE family regulate lysosomal and autophagy gene expression. Neurons impose specific demands on this machinery because axonal length, synaptic turnover, and polarized vesicle transport separate sites of cargo formation from the soma-enriched lysosomal compartment. Defective autophagosome maturation produces local axonal stress before cell-body degeneration becomes apparent [1, 2].

Chaperone-mediated autophagy and microautophagy add selectivity to neuronal quality control. Chaperone-mediated autophagy recognizes soluble proteins containing KFERQ-like motifs through HSC70 and transports them across the lysosomal membrane via LAMP2A. This pathway is directly relevant to α-synuclein because normal monomeric α-synuclein can be degraded by chaperone-mediated autophagy, whereas mutant or modified species can bind the receptor without efficient translocation, thereby impeding the degradation of other substrates. Microautophagy involves lysosomal or endosomal membrane invagination and contributes to basal protein turnover. Interactions among these pathways create compensatory capacity, but compensation has limits. When one route becomes chronically impaired, increased load on other pathways may accelerate lysosomal crowding, hydrolase stress, and vesicular traffic congestion [3, 4].

2.2. Maintenance of lysosomal homeostasis and degradative function

Lysosomal competence depends on acidification, hydrolase maturation, ion balance, lipid handling, membrane integrity, and fusion with incoming vesicles. The vacuolar H+-ATPase maintains an acidic lumen required for cathepsins and glycosidases. Mannose-6-phosphate receptor trafficking, endosomal maturation, and lysosomal exocytosis regulate the supply and distribution of degradative enzymes. LAMP proteins stabilize the lysosomal membrane, participate in substrate transport, and influence autophagosome-lysosome fusion. Failure at any of these points changes lysosomes from

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terminal degradative organelles into stress amplifiers, since incompletely digested proteins and lipids can disturb calcium signaling, reactive oxygen species production, and inflammatory responses [5].

Lysosomes also act as signaling platforms. mTORC1, TFEB, TFE3, and lysosomal calcium channels couple luminal state to cellular adaptation. Under lysosomal stress, TFEB translocates to the nucleus and induces genes involved in lysosomal biogenesis, autophagosome formation, and waste clearance. In neurons, this response must be balanced because excessive or poorly coordinated autophagy can deplete essential synaptic and mitochondrial components. Recent work on LRRK2 and the V-ATPase-ATG16L1 axis further indicates that damaged lysosomes recruit PD-associated kinases and autophagy proteins during lysosomal stress responses [6]. Lysosomes consequently function upstream as well as downstream of PD-associated proteostatic failure.

2.3. Autophagy-lysosome system in neuronal homeostasis

Neurons are highly sensitive to autophagy-lysosome impairment because they are post-mitotic, metabolically active, and structurally polarized. Proteins that escape efficient turnover may persist for years, while defective organelles cannot be diluted through cell division. Dopaminergic neurons of the substantia nigra are exposed to additional stress from autonomous pacemaking activity, high oxidative burden, dopamine metabolism, and extensive axonal arborization. Autophagy-lysosome activity supports neuronal survival by clearing misfolded α-synuclein, remodeling synaptic proteins, recycling membranes, and degrading mitochondria that have lost membrane potential. Perturbation of this system affects neuronal excitability, axonal transport, vesicle recycling, and inflammatory communication with glial cells [7].

Experimental and clinical observations link lysosomal dysfunction to PD heterogeneity with growing consistency. Genetic variants in lysosomal genes modify age at onset, progression rate, cognitive impairment, and Lewy body burden. Patient-derived neurons and brain tissues show altered lysosomal enzyme activity, impaired autophagic flux, and changes in mitochondrial quality control proteins [8]. These changes do not define a single linear pathway. Instead, they form a degradative network in which lysosomal stress reduces α-synuclein clearance, accumulated α-synuclein further disrupts vesicle trafficking and lysosomal function, and damaged mitochondria generate oxidative and inflammatory signals that return to the autophagy machinery [9].

Spatial organization adds another layer to this vulnerability. Autophagosomes often form distally within axons and then move retrogradely toward somatic lysosomes, acquiring degradative competence during transport. Any disturbance in microtubule-dependent trafficking, endosomal identity, or lysosomal distribution can separate cargo capture from cargo degradation. Synapses are affected early because local protein turnover and mitochondrial supply shape vesicle release, calcium buffering, and presynaptic energy state. A neuron can show impaired network function before overt cell death, and the same defect may later support Lewy pathology, neurite degeneration, and glial activation. This sequence places autophagy-lysosome stress within both prodromal and progressive stages of disease.

The neuronal autophagy-lysosome network integrates distal cargo capture, retrograde transport, endosomal maturation, and somatic degradation, as summarized in Figure 1.

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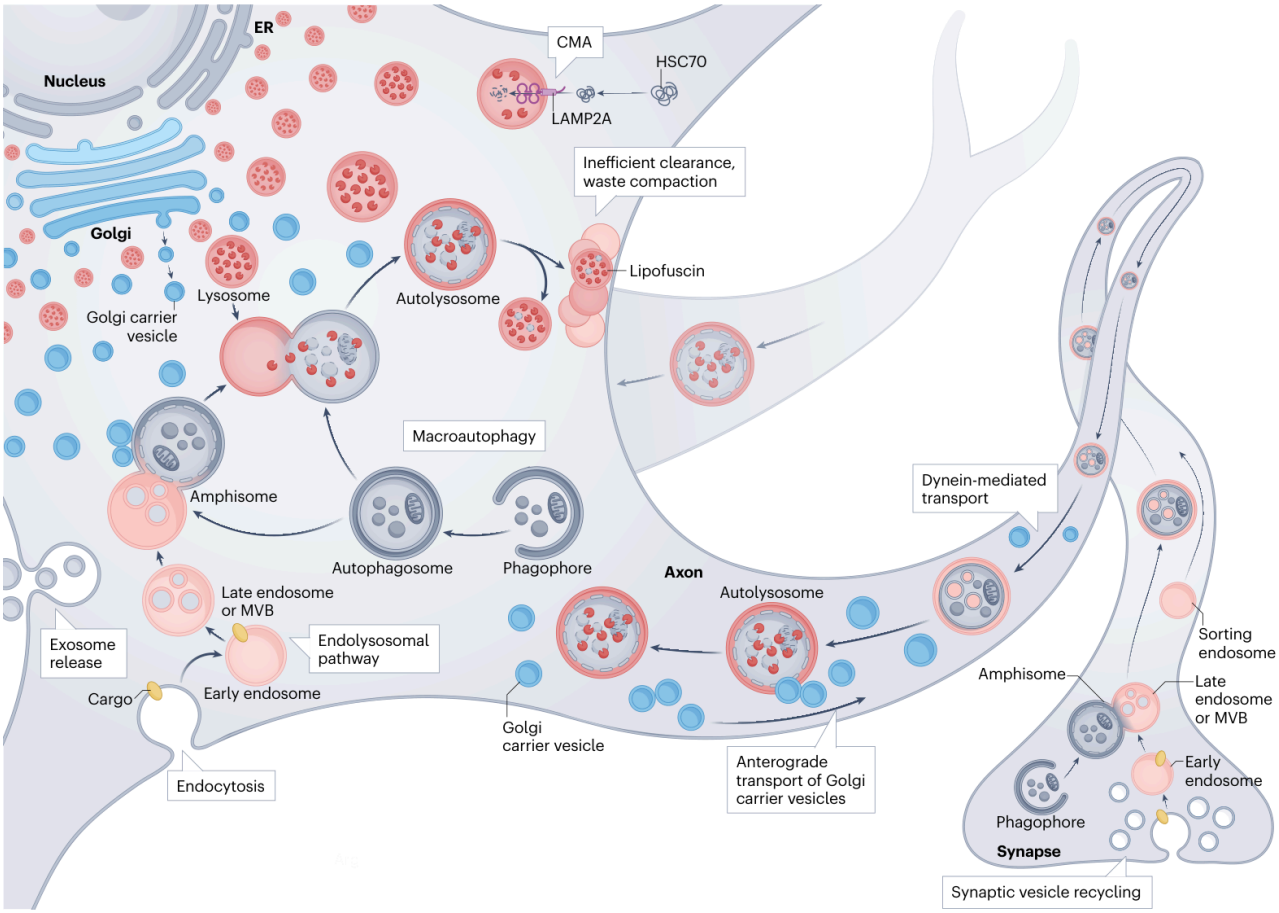


Figure 1. Spatial organization of neuronal autophagy-lysosomal pathways [1]

3. Molecular mechanisms by which autophagy-lysosome dysfunction mediates Parkinson's disease pathogenesis and progression

3.1. α-Synuclein aggregation and defective autophagic clearance

α-Synuclein is a presynaptic protein involved in vesicle dynamics, yet oligomeric and fibrillar species adopt conformations that resist normal proteolysis and seed further aggregation. Macroautophagy, chaperone-mediated autophagy, endosomal sorting, and lysosomal proteases participate in α-synuclein turnover. When autophagic flux is reduced, soluble and insoluble α-synuclein species accumulate, impair vesicular trafficking, and interfere with lysosomal fusion. Modified α-synuclein species can obstruct chaperone-mediated autophagy at the LAMP2A translocation step, while fibrillar species rely more heavily on macroautophagy and lysosomal cathepsins. Recent experimental and review literature describes lysosomal dysfunction as both a cause and a consequence of α-synuclein pathology [10, 11].

The feed-forward relationship between α-synuclein and lysosomal impairment has been modeled in human dopaminergic neurons exposed sequentially to α-synuclein fibrils and inflammatory cytokines. This paradigm recapitulates protein aggregation, neuronal vulnerability, and inflammatory sensitization, providing a human cellular context for studying how proteostatic and immune stress combine in PD [12]. Additional work has identified PLK2 as a modifier of SNCA pathology through disruption of autophagic flux, indicating that kinase-dependent regulation of

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autophagy can alter aggregate burden. Strategies designed to enhance aggregate delivery to lysosomes have also advanced. AUTOTAC-mediated degradation of α-synuclein aggregates links targeted cargo recognition to autophagic clearance, while recombinant pro-cathepsin D improves α-synuclein degradation in α-synucleinopathy models [13]. Lysosomal delivery and intralysosomal proteolysis should be treated as separable therapeutic variables.

The PLK2-DCTN1 model provides a defined route through which impaired autophagosome-lysosome fusion reduces pathological α-synuclein clearance, as illustrated in Figure 2.

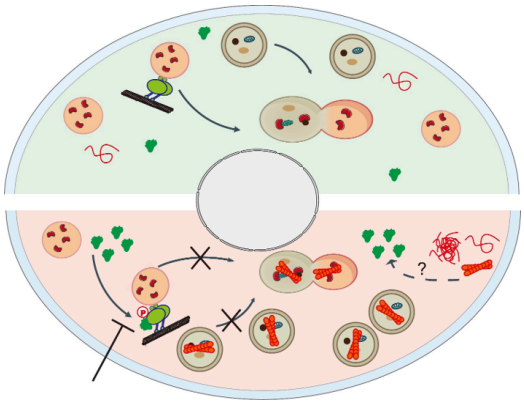


Figure 2. PLK2-mediated blockade of autophagosome-lysosome fusion and α-synuclein clearance [14]

The prion-like spread of α-synuclein places additional pressure on lysosomal pathways. Extracellular fibrils enter neurons through endocytic routes and must pass through endosomal and lysosomal compartments before degradation or escape into the cytosol. When endolysosomal maturation is incomplete, internalized seeds may persist long enough to recruit endogenous α-synuclein and amplify pathology. Microglia and astrocytes also internalize extracellular α-synuclein, and their degradative capacity influences the inflammatory environment surrounding vulnerable neuronal populations. In this setting, lysosomal dysfunction affects not only intracellular clearance within dopaminergic neurons but also intercellular handling of pathogenic protein species across neural and glial compartments.

3.2. Mitophagy defects and oxidative stress injury

Mitochondrial dysfunction is tightly connected to autophagy-lysosome failure in PD. Damaged mitochondria produce reactive oxygen species, release mitochondrial DNA and other danger signals, disturb calcium handling, and compromise ATP-dependent processes needed for vesicle trafficking and lysosomal acidification. PINK1/Parkin-mediated mitophagy marks depolarized mitochondria for selective autophagic removal through ubiquitin phosphorylation, Parkin recruitment, outer mitochondrial membrane ubiquitination, and engagement of autophagy receptors. Defects in this pathway allow damaged mitochondria to persist, which increases oxidative stress and sensitizes neurons to metabolic failure [15].

Translation from cell culture to brain tissue is complex because PINK1/Parkin mitophagy is robust in some in vitro systems but more difficult to capture in vivo. Recent analyses distinguish acute chemically induced mitophagy from slower endogenous mitochondrial quality control processes in neurons [16]. PD neurons also exhibit altered levels of mitochondrial quality control proteins, suggesting that mitochondrial surveillance is remodeled rather than uniformly absent [8]. Mitochondrial stress can alter lysosomal function by changing calcium signaling, redox state, and

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lipid handling. Conversely, lysosomal defects impair mitophagic completion because autophagosomes carrying damaged mitochondria must ultimately fuse with acidic, enzyme-competent lysosomes. This interdependence helps explain why mitochondrial injury and lysosomal impairment are frequently detected together in PD models and patient-derived cells [17].

3.3. Lysosomal imbalance and neuronal injury mechanisms

Lysosomal imbalance in PD includes impaired acidification, reduced hydrolase activity, altered membrane repair, lipid storage, trafficking defects, and defective autophagosome-lysosome fusion. These abnormalities reduce degradation of α-synuclein and other long-lived proteins, but their consequences are broader than substrate accumulation. Enlarged or poorly acidified lysosomes can disrupt axonal transport and synaptic vesicle recycling. Defective cathepsin activity may permit partially degraded proteins to form aggregation-prone intermediates. Impaired lipid catabolism can alter membrane curvature, endosomal sorting, and mitochondrial function. The resulting cellular state favors proteostatic stress, oxidative damage, and inflammatory signaling [7].

Cathepsin biology illustrates the relevance of intralysosomal proteolysis to dopaminergic vulnerability. Cathepsin D has been linked to α-synuclein degradation, and recombinant pro-CTSD enhances SNCA clearance in models of α-synucleinopathy. Cathepsin B has also been identified as a PD risk gene that promotes fibrillar α-synuclein clearance, lysosomal function, and glucocerebrosidase activity in dopaminergic neurons [18]. Lysosomal enzymes are not interchangeable terminal degraders. Their substrate preferences, maturation requirements, and interactions with lipid metabolism may determine whether accumulated α-synuclein is resolved or converted into persistent pathology.

Lysosomal damage can also initiate inflammatory signaling. Rupture or permeabilization of lysosomal membranes releases cathepsins and incompletely degraded material into the cytosol, where they may activate inflammasome-related pathways and stress kinase signaling. Mitochondrial DNA and oxidized lipids generated during defective mitophagy provide further danger signals. GCase insufficiency and lysosomal lipid storage have been connected to innate immune activation in Gaucher and Parkinson's disease models [19]. Neuronal injury and microglial activation can emerge from the same degradative defect, which helps explain why protein aggregation, organelle damage, and neuroinflammation often advance together in affected regions.

4. Parkinson's disease-related molecular regulatory mechanisms and targeted intervention progress

4.1. GBA1 and GCase axis-mediated lysosomal dysfunction

GBA1 variants represent one of the strongest genetic risk factors for PD and provide direct evidence connecting lysosomal lipid metabolism to α-synuclein pathology. GBA1 encodes glucocerebrosidase, a lysosomal enzyme that hydrolyzes glucosylceramide and glucosylsphingosine. Reduced GCase activity leads to lipid substrate accumulation, altered lysosomal membrane properties, impaired autophagic flux, and increased α-synuclein aggregation. A reciprocal loop has been proposed in which α-synuclein accumulation interferes with GCase trafficking and lysosomal delivery, further decreasing GCase activity. This loop may contribute to earlier onset, faster progression, and higher risk of cognitive impairment in GBA1-associated PD [20].

Mechanistic and translational studies have expanded the GBA1/GCase model beyond simple enzyme deficiency. GCase insufficiency can affect mitochondrial function, innate immune

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activation, and lysosomal stress responses. Ambroxol and related pharmacological chaperone strategies are being investigated because they can enhance GCase folding, trafficking, or activity in selected contexts [21]. The interaction between lysosomal GCase and mitochondrial homeostasis has gained attention because lipid imbalance may compromise mitochondrial membranes and mitophagic turnover [22]. Therapeutic concepts now combine enzyme stabilization, substrate reduction, lysosomal biogenesis, and anti-inflammatory modulation, while genotype, residual enzyme activity, and brain exposure shape the feasibility of clinical development.

4.2. LRRK2 and PINK1/Parkin pathway-mediated autophagy regulation

LRRK2 regulates vesicle trafficking, endolysosomal dynamics, autophagy, and lysosomal stress responses through kinase-dependent phosphorylation of Rab GTPases. Pathogenic LRRK2 variants can alter Rab8A and Rab10 signaling, lysosomal positioning, autophagosome formation, and membrane tubulation. In experimental systems, LRRK2 phosphorylation status and kinase activity regulate macroautophagy in a Rab8A/Rab10-dependent manner [23]. LRRK2 also participates in lysosomal sorting and tubulation, processes that may influence enzyme distribution, membrane repair, and cargo recycling. The recruitment of LRRK2 through a V-ATPase-ATG16L1 axis under lysosomal stress links lysosomal damage sensing to PD-associated kinase signaling.

A phosphorylation-dependent model further links increased LRRK2 kinase activity to Rab8A and Rab10 phosphorylation and reduced autophagic flux, as shown in Figure 3.

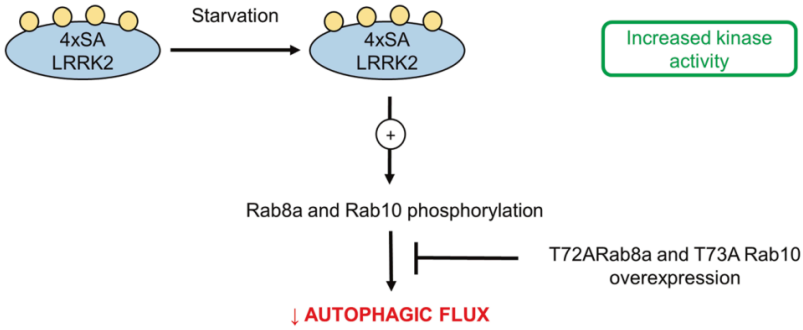


Figure 3. LRRK2 kinase activity and Rab8A/Rab10 phosphorylation in autophagic flux regulation [23]

PINK1 and Parkin regulate a different but complementary arm of autophagy by directing mitophagic clearance of damaged mitochondria. Loss of PINK1/Parkin activity can preserve dysfunctional mitochondria, increase oxidative burden, and disturb neuronal energy balance. The LRRK2 and PINK1/Parkin pathways may intersect through shared effects on mitochondrial quality control, vesicle trafficking, and lysosomal capacity. Rodent models and cell systems that combine LRRK2 and GBA1 biology indicate that lysosomal pathogenesis cannot be assigned to a single gene product [24]. Therapeutic modeling should consider whether a candidate intervention restores only autophagosome formation, only kinase signaling, or the full sequence of cargo recognition, vesicle maturation, lysosomal fusion, and degradation.

The relationship between LRRK2 and mitophagy is also relevant to disease stratification. Increased LRRK2 kinase activity can alter vesicular transport and lysosomal responses, whereas impaired PINK1/Parkin signaling reduces mitochondrial disposal. These defects may converge on a shared endpoint in which mitochondria remain damaged and lysosomes remain overloaded. Because

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LRRK2 inhibitors, GCase enhancers, and mitophagy-directed interventions act at different levels of the pathway, combined biomarker readouts will be needed to determine whether they correct a common cellular phenotype or only normalize a proximal molecular signal.

4.3. Therapeutic strategies targeting the autophagy-lysosome system

Therapeutic strategies directed at the autophagy-lysosome system differ according to their primary point of action, although the biological effects often overlap. mTOR inhibition and AMPK activation promote macroautophagy initiation, but increased autophagosome formation is insufficient when lysosomal degradation remains defective. TFEB activation aims to expand lysosomal biogenesis and degradative capacity. A GSK-3β inhibitor has been reported to amplify autophagy-lysosomal pathways through TFEB regulation in PD models, supporting the feasibility of targeting transcriptional lysosomal programs [25]. Small-molecule autophagy modulators can engage broad proteostatic stress responses, but dose, cell-type selectivity, chronic safety, and disease stage determine whether enhanced autophagy is protective or maladaptive.

Other approaches seek greater specificity. Pharmacological chaperones and enzyme-enhancing strategies target GCase defects in GBA1-associated PD [21]. LRRK2 kinase inhibitors and antisense strategies aim to normalize excessive kinase activity and Rab phosphorylation, although the physiological roles of LRRK2 in peripheral tissues require monitoring. Protein-targeting technologies such as AUTOTAC attempt to route pathogenic aggregates into lysosomal degradation pathways. Cathepsin augmentation strategies address intralysosomal proteolytic capacity rather than upstream autophagosome formation. These strategies may be most effective when paired with biomarkers that report lysosomal enzyme activity, autophagic flux, α-synuclein burden, mitochondrial injury, and inflammatory state in defined patient subgroups.

Clinical translation faces two measurement problems. First, peripheral enzyme activity or vesicular markers may not fully represent the state of dopaminergic neurons in the brain. Second, static accumulation of LC3, p62, α-synuclein, or lysosomal proteins can reflect either increased formation or blocked degradation. Longitudinal assays that combine genetic background, cerebrospinal fluid biomarkers, imaging markers, patient-derived neuronal models, and pharmacodynamic measures of target engagement will be required for rational trial design. Disease stage is equally important. Early intervention may aim to preserve lysosomal resilience and mitochondrial turnover, whereas later intervention may need to reduce established α-synuclein aggregates and dampen secondary inflammation.

5. Conclusions and perspectives

Autophagy-lysosome dysfunction links α-synuclein aggregation, mitochondrial injury, lysosomal enzyme insufficiency, vesicle trafficking defects, and inflammatory activation within a single degradative network. Work published in the last several years indicates that PD-related autophagy defects cannot be reduced to impaired autophagosome initiation. Many pathogenic changes occur at later stages, including cargo recognition, vesicle transport, fusion, lysosomal acidification, hydrolase activity, and lipid handling. Therapeutic design must account for this distribution of defects, since increasing autophagosome formation without restoring lysosomal competence may increase cellular burden rather than improve clearance.

Future translational progress requires biomarkers and models that measure pathway flux instead of isolated static markers. Patient-derived dopaminergic neurons, organoids, induced aggregate models, genetic models, and in vivo imaging of lysosomal and mitochondrial function can clarify

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which defects dominate in specific molecular subtypes. GBA1-associated PD, LRRK2-associated PD, and sporadic PD with prominent α-synuclein pathology may require different intervention points within the same network. Restoration of balanced proteostatic flow from pathogenic cargo recognition to lysosomal degradation offers a rational direction for disease-modifying therapy. Combining lysosomal enzyme restoration, kinase pathway modulation, mitophagy correction, and inflammation control can refine that direction further.

A refined therapeutic framework also requires separation between pathway correction and clinical modification. Normalization of Rab phosphorylation, GCase activity, TFEB nuclear localization, or mitophagy markers can demonstrate target engagement, but symptomatic stability and slowed neurodegeneration require durable correction across vulnerable neuronal populations. Trial enrichment by genotype, lysosomal biomarker profile, α-synuclein burden, and inflammatory state may increase the probability of detecting treatment effects. Autophagy-lysosome biology has the greatest translational value when it guides patient stratification, timing of intervention, and selection of clinically meaningful pharmacodynamic endpoints together.

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