Patient-Derived iPSC Models as a Platform to Unravel Autophagy Dysregulation in Parkinson's Disease

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder and the second most prevalent cause of age-related disability worldwide. While existing therapies alleviate symptoms, they do not modify disease progression. Dysfunction of the autophagy–lysosome pathway (ALP), a principal component of cellular proteostasis, is significantly recognized as a key PD pathogenesis hallmark. ALP dysfunction contributes to the accumulation of misfolded proteins such as α-synuclein, defective organelle clearance, and neuronal vulnerability, with genetic forms of PD such as GBA1, *SNCA*, *LRRK2*, PRKN, *PINK1*, *VPS35* converging on distinct yet overlapping disruptions of autophagic flux, lysosomal acidification, and mitophagy. Patient-derived induced pluripotent stem cells (iPSCs) have transformed PD research by enabling the generation of disease-modifying neural and glial lineages that retain the donor's genetic background. These models have identified genotype-specific ALP dysfunctions, such as vesicular trafficking disruption in *LRRK2* PD reduced glucocerebrosidase activity in *GBA1* PD, and saturated flux inhibition in *SNCA* triplication models. iPSC-based systems have also shaped the evaluation of therapeutic interventions, including LRRK2 kinase inhibitors, GCase chaperones, TFEB activators, and chaperone-mediated autophagy enhancers, some of which in vitro studies have shown to partially restore ALP function. This review synthesizes key findings from patient-derived iPSC studies on ALP dysfunction in PD, highlighting mechanistic insights, therapeutic potentials, and methodological challenges. Standardization of differentiation protocols, adoption of consistent ALP assays, and integration of multi-disciplinary approaches are necessary to advance the translational potential of iPSC platforms for autophagy-targeted PD therapies.
Keywords: Parkinson's disease, Dopaminergic neurons, autophagy–lysosome pathway, induced pluripotent stem cells, α-synuclein, mitophagy, glucocerebrosidase.

1. Introduction

1.1. Parkinson's Disease and the Unmet Clinical Need

Parkinson's disease (PD) affects more than ten million individuals globally and represents a major cause of disability in the aging population. Clinically, PD is defined by its symptomatic motor dysfunction such as resting tremor, bradykinesia, rigidity, and postural instability with a spectrum of non-motor symptoms such as depression, cognitive impairment, hyposmia, autonomic dysfunction, and sleep disturbances [1]. Neuropathologically, PD is characterized by progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the accumulation of widespread α-synuclein containing Lewy bodies in affected brain regions [2]. Although dopamine replacement therapy such as levodopa and deep brain stimulation (DBS) can significantly reduce PD symptoms, they do not halt the underlying neurodegenerative process and they do not slow the progression of the disease, especially in the elderly. This lack of disease-modifying treatments possesses the urgency of elucidating the molecular drivers of PD pathogenesis [3].

1.2. The Autophagy–Lysosome Pathway in Neuronal Health

The autophagy–lysosome pathway (ALP) is a critical degradative mechanism that maintains neuronal proteostasis by clearing misfolded proteins, degrades aggregated α-synuclein

accumulates, and damaged organelles [4]. Neurons that have permanently exited the cell cycle are particularly dependent on efficient autophagy [Figure 1], as they cannot degrade toxic accumulated organelles through cell division. Dopaminergic neurons DA in SNpc are port mitotic due to protein aggregates and oxidative stress and therefore, this leads to irreversible motor and non-motor symptoms in PD patients [5].
Macroautophagy involves the sequestration of cytoplasmic material within autophagosomes that subsequently binds with lysosomes for enzymatic degradation [6]. Other forms, microautophagy and chaperone-mediated autophagy (CMA), also contribute to protein quality control. Disruption at any stage of the ALP from autophagosome biogenesis to lysosomal acidification may result in mitochondrial dysfunction, proteostatic stress, and cell death[7].

1.3. Genetic Evidence Linking PD to ALP Dysfunction

Multiple PD-associated genes directly and indirectly affect the ALP in PD pathophysiology.
α-synuclein accumulation is caused by the SNCA gene. Multiplications and point mutations of the SNCA gene, increases α-synuclein burden and it inhibits the natural cellular α-synuclein clearance. This leads to further accumulation of α-synuclein which impairs autophagosome clearance and lysosomal function [9]. Mutation of the LRRK2 gene leading to G2019S, results in a disruption in the vesicle trafficking and autophagosome–lysosome fusion [10]. While the GBA1 gene produces glucocerebrosidase (GCase), its mutation reduces its enzymatic activity. Consequently, with lower GCase activity, lysosomal lipid accumulation occurs. This accumulation, disrupts normal lysosomal clearance function and it contributes to secondary α-synuclein aggregation and accumulation, further contributing to PD pathology [11]. Mitophagy is the process where cells identify and remove damaged mitochondria, and it is regulated simultaneously by PINK1 and PRKN gene expression. Loss of PINK1/PRKN gene expression, disrupts mitophagy clearance activity, and it further contributes to oxidative stress, toxicity, and DA neuronal deaths in PD pathogenesis [12]. VPS35 expression encodes retromer complex which controls endosomal lysosomal trafficking. Its mutation disrupts this trafficking system and when this function is impaired, this results in poor degradation of toxic protein aggregates. This contributes to lysosomal stress, and thus, further accumulation of α-synuclein, leading to PD [13].
These converging disruptions make the ALP a compelling therapeutic target for PD.

1.4. Patient-Derived iPSC Models in PD Research

The advent of induced pluripotent stem cell (iPSC) technology allows somatic cells from PD patients to be reprogrammed into pluripotent stem cells and differentiated into astrocytes, dopaminergic neurons, and three-dimensional brain organoids. These models facilitate pre-clinical drug screening in a human genetic context, allow real-time observation of autophagy and lysosomal function, enable genotype-specific mechanistic studies and preserve patient specific genetic and epigenetic backgrounds. Studies using patient-derived iPSCs have recapitulated key ALP abnormalities observed in post-mortem PD brain tissue, validating these systems as translationally relevant disease models [14].

1.5. Purpose of This Review

This review aims to analyze the literature on ALP dysfunction in patient-derived PD models of IPSC, and to highlight common mechanistic themes, genotype specific findings, and emerging therapeutic strategies. In this review, we also discuss several methodological considerations such as assay standardization, model reproducibility and outline future research directions to improve clinical translation of iPSC-based autophagy research.

2. Discussion

1. Genotype-Specific Autophagy–Lysosome Pathway (ALP) Dysregulation in PD iPSC Models

2.1.1. *GBA1* Mutations

Recent studies of GBA1 mutations on patient-derived iPSC have shown lysosomal lipid accumulation, reduced GCase activity dysfunctional autophagic flux [15]. These deficits lead to secondary α-synuclein aggregation, mirroring pathology present in *GBA1*-associated PD brains [16]. Ambroxol, a mucolytic medication, can partially restore GCase activity, normalize lysosomal pH and reduce Sequestosome 1 (p62 autophagy adaptor protein) accumulation. Nevertheless, its effects on α-synuclein clearance remain to be elucidated.

Therapeutically, ambroxol — a small molecule chaperone — partially restores GCase activity, normalizes lysosomal pH, and reduces p62 accumulation, though effects on α-synuclein clearance remain variable [17]. Studies have shown that activating TFEB and, its substrate reducing strategies result in additive improvements, indicating multi-targeted treatment strategies for PD [18].

2.1.2. *LRRK2* G2019S Mutation

Leucine Rich Repeat Kinase – 2 (LRRK2) G2019S iPSC-derived neurons show defective retrograde vesicular trafficking and reduced autophagosome–lysosome fusion, due to the dysregulation of hyperactive kinase-driven Rab GTPase. These changes result in an impaired lysosomal degradation and increased vulnerability towards mitochondrial stress [19].

Studies have shown that LRRK2 kinase inhibitors such as MLi-2, GSK2578215A demonstrate efficacy in restoring vesicle dynamics, with combined TFEB activation yielding synergistic benefits in flux recovery [20].

2.1.3. *SNCA* Multiplications

One major contributor for α-synuclein overproduction and accumulation is the duplicate – expression of the SNCA gene, which saturates degradative pathways. iPSC-derived neurons from these patients exhibit severely dysfunctional autophagic flux, impaired lysosomal acidification, and diminished protease activity [21].

Therapeutic strategies targeting α-synuclein levels such as antisense oligonucleotides or CMA enhancers can partially restore lysosomal function. However, this does not fully reverse ALP dysfunction, suggesting downstream damage may persist even after aggregate reduction [22].

2.1.4. *PINK1*, *PRKN*, and *VPS35*

These mutations primarily impair the initiation of mitophagy and mitochondrial trafficking, with less pronounced basal lysosomal dysfunction. iPSC models have shown reduced mitochondrial clearance activity. However, this can be restored by PINK1 overexpression [23]. *VPS35* mutations further impairs endosomal–lysosomal trafficking, and it indirectly affects autophagy [24] .

2.2. Cross-Genotype Mechanistic Themes

Despite genetic heterogeneity, several common patterns emerge.

2.2.1. Autophagic flux impairment

Across multiple PD mutations such as SNCA and GBA1, elevated autophagosome accumulates such as LC3-II and proteins such as p62 increased levels, studies show that autophagy is activated but not fully completed [25].

2.2.2. Lysosomal acidification defects

Lysosomal acidification defects are prominent in SNCA and GBA1 PD models. Mutations in the GBA1 gene and SNCA duplications disrupt lysosomal pH regulation. This prevents efficacious enzymatic protein degradation [26].

2.2.3. Trafficking and fusion deficits

Mutations in LRRK2, VPS35 and the SNCA gene, disrupt vesicular trafficking and thus, impair their fusion with lysosomes and block their degradative effect [27].

2.2.4. Mitophagy vulnerability

Mutations in the PINK1/ AND PRKN gene, directly blocks neuronal mitophagy ability. This has also been observed in other genotypes that show vulnerability when cells are stressed [28].

These findings show that the ALP functions as a central hub in the pathogenesis of PD, where diverse genotype specific defects converge to

produce a shared downstream failure in cellular degradation.

2.3. Therapeutic Strategies in iPSC Models – Genotype Specific Approaches

2.3.1. GCase enhancement

Ambroxol, small-molecule chaperones, can increase misfolded GCase stability to lysosomes. Substrate reduction therapy, lowers glucosylceramide load. When combined, they can enhance lysosomal function and therefore, reduce α-synuclein stress in GBA1 PD models [29].

2.3.2. LRRK2 kinase inhibition

Reduces vesicle trafficking defects and restores fusion capacity [10].

2.3.3. α-Synuclein–targeted therapies

Antisense oligonucleotides (ASOs), can lower SNCA transcript and reduce pathology and improving neuronal function [30].

2.4. Methodological Challenges Limiting Comparability

iPSC models have transformed the study of Parkinson's disease (PD) pathogenesis. However, their use in probing autophagy–lysosome pathway (ALP) dysfunction is limited by several methodological limitations. These challenges complicate the comparison of results across studies and hinder the development of reproducible conclusions.

2.4.1. Variability in Differentiation Protocols:

Neuronal differentiation methods are a major source of inconsistency. Protocols vary in maturation stage, efficiency, and subtype specification, and they influence the baseline ALP function. For example, DA derived by midbrain patterning cues can show different autophagic activity, in comparison with cortical neuron protocols. This variability, imposes limitations for ALP cross-study interpretations and increases concerns on true disease mechanisms for the observed phenotypes [31].

2.4.2. Assay Inconsistency

Multiple studies continue to depend on LC3-II level static measurements as surrogate markers of autophagy activities. Nevertheless, such measurements show limitations when they are showing differences between an increased autophagosome formation and impaired clearance. Without dynamic "flux" confirmation using lysosomal inhibitors such as bafilomycin A1 or chloroquine, interpretations of autophagic defects may be inaccurate and misleading. This lack of standardized assays, limits mechanistic resolution and reproducibility across iPSC studies [32].

2.4.3. Control Selection

One of the major challenges limiting comparability is selecting the right control. Multiple investigations compare patient-derived iPSCs with unrelated healthy donor. This causes findings to be vulnerable to confounding by different genetic backgrounds. Isogenic controls, which were generated by pathogenic mutations of CRISPR-based correction, have been widely recognized as essential when analyzing observed phenotypes that are particularly specific to PD associated genotypes instead of donor variability [33].

2.4.4. Small Sample Sizes

Majority of iPSC-based PD studies are limited by small donor samples, and they often analyze only one to three patient lines per mutation type. Such sample sizes reduce statistical credibility and limit the ability to further analyze findings. Moreover, clinical phenotypes, heterogeneity in patient demographics, and disease duration add complexity. This makes replication across multiple lines important for establishing reliable conclusions [34].

Collectively, these limitations contribute to the urgency of standardizing differentiation protocols, adoption of isogenic controls, and implementing flux-based assays. Addressing these methodological challenges are necessary for building a cohort and reproducible variety of evidence for ALP dysfunction in IPSC models of PD.

3. Future Directions

3.1. Standardization of ALP Assays in iPSC Models

One barrier facing cross-study comparability is different approaches used when measuring ALP. Most studies only measure for static markers such as p62 or LC3-II levels, which fail to compare increased autophagic activity against impaired degradation [35].

Future work should compare enzymatic activity and lysosomal pH alongside autophagosome markers, incorporate flux assays such as chloroquine treatment or bafilomycin A1 treatment and adopt uniform data normalization methods for imaging, enzymatic assays, and Western blots [35].

3.2.Use of Isogenic Controls

Inter-donor genetic variability can obscure genotype-specific effects. Generating CRISPR/Cas9-corrected isogenic controls for each patient line will strengthen casual inference between phenotypes and mutation, facilitate multi-lab reproducibility when shared through biorepositories, and minimize background noise [36].

3.3. Integration of Multi-Omics Approaches

Combining lipidomics, proteomics, transcriptomics, and metabolomics can demonstrate how ALP defects interact with other cellular pathways. It can enable computational modelling of phenotype and genotype relationships and identify early biomarkers of dysfunction before overt pathology appears. It can also detect responses that may show potential as being therapeutic targets [37] .

3.4. Translation to Clinical Biomarkers

Linking in vitro ALP phenotypes to measurable patient biomarkers is essential to bridge pre-clinical discoveries with clinical applications. This can be obtained via cerebrospinal fluid (CSF) and plasma assays that quantify autophagy related proteins such as p62, LC3, and LAMP2, as well as through molecular imaging techniques like PET tracers to monitor lysosomal function in vivo. Moreover, longitudinal patient studies are required to validate these biomarkers as reliable indicators of therapeutic engagement and disease progression [38].

3.5. Combination of Therapeutic Strategies

Given the multifactorial nature of ALP dysfunction, combination approaches may demonstrate more efficacy compared to single-target therapies. This can be obtained by pairing genotype-specific interventions such as LRRK2 kinase inhibitors for LRRK2, and ambroxol for *GBA1* with genotype agonistic lysosomal enhancers such as TFEB activators [39].

4. Conclusion

Autophagy–lysosome pathway (ALP) dysfunction is a central mechanism in PD, spanning both familial and sporadic cases. Patient-derived iPSC models have illuminated lysosomal defects, impaired autophagic flux, and mitophagy deficits across SNCA, PRKN, LRRK2, *GBA1, PINK1,* and *VPS35* mutations, closely mirroring patient pathology. These models have advanced preclinical testing of genotype-specific therapies, including GCase chaperones and LRRK2 inhibitors, as well as broader lysosomal enhancers. Despite progress, effective therapeutic solutions remain incomplete, highlighting the need for multidisciplinary strategies. Standardization, isogenic controls, and biomarker alignment are essential to harness iPSC platforms for developing disease-modifying PD therapies.

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6. Appendix

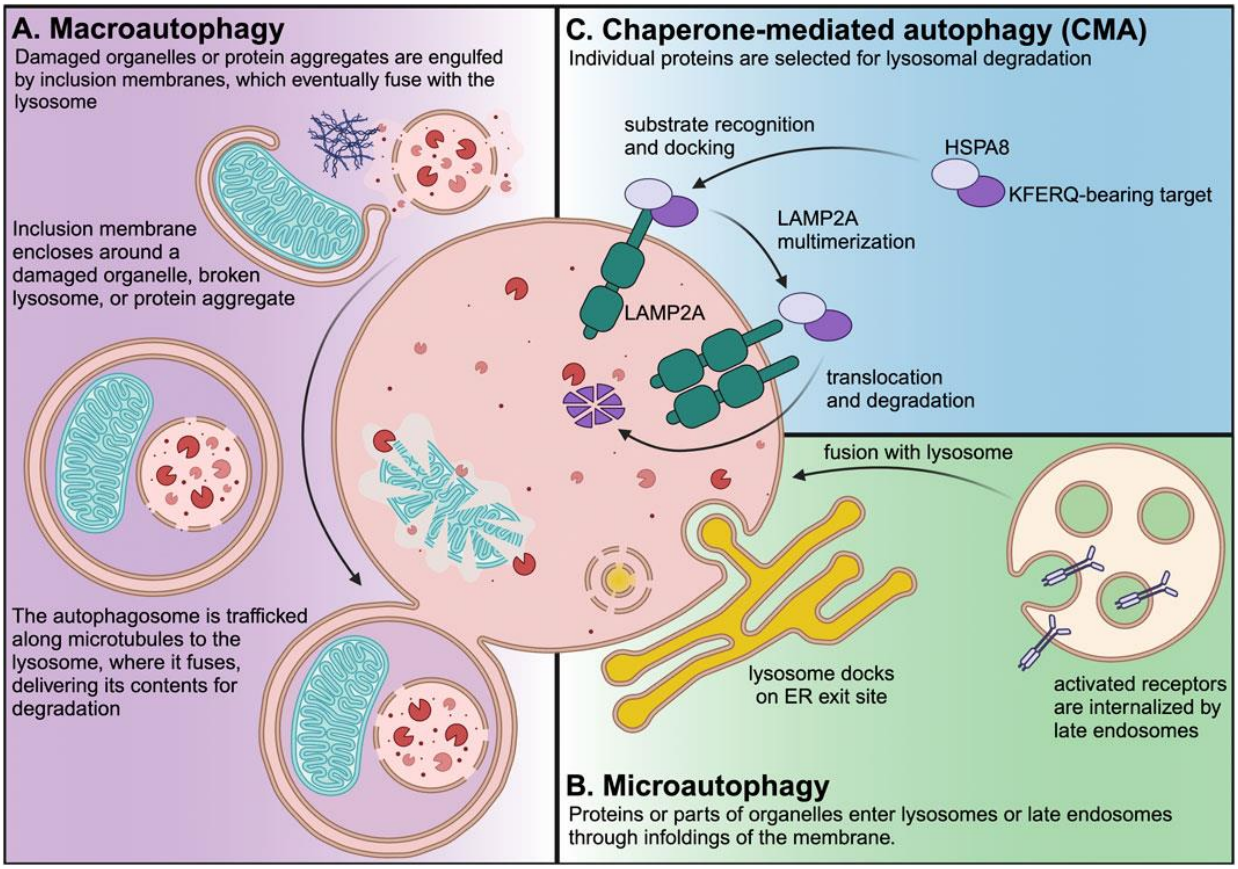

Figure 1: Overview of macroautophagy, microautophagy, and chaperone-mediated autophagy [8].