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REVIEW ARTICLE

Role of Lysosomal Genes for Parkinson's Pathogenesis: Insights from Molecular Mechanism to Therapeutic Strategies

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Abstract: Current review aims to clarify the role of lysosomal genes in the pathogenesis of Parkinson’s Disease (PD), directing on the molecular mechanisms underlying lysosomal dysfunction and its involvement to α-synuclein accumulation. To deliberates PD-related genes including *GBA1, LRRK2, VPS35, PRKN, PINK1, TMEM175, ATP13A2, ATP10B,* and *DJ1*, highlighting their contribution in lysosomal damage. It investigates the disorder of lysosomal enzymes such as cathepsins, glucocerebrosidase, galactocerebrosidase, and acid sphingomyelinase, and the consequent impairment of the autophagic-lysosomal pathway, which helps pathological α-synuclein accumulation. Therapeutic approaches targeting lysosomal dysfunction and α-synuclein pathology are reviewed, including pharmacological chaperones, immunization strategies, enzyme replacement therapies, and small-molecule oligomer modulators. While recent clinical trials expose certain limitations, combinatorial treatment strategies show potential to improve therapeutic efficacy. Lysosomal pathways are critical contributors to PD pathogenesis and denote promising targets for intervention. Integrating mechanistic understandings with developing therapies underlines the importance of targeting lysosomal dysfunction to mitigate α-synuclein aggregation and advance PD treatment.

Keywords: Parkinson's disease, lysosomal dysfunction, α-synuclein, pharmacological chaperones, enzyme replacement therapies, active immunization, passive immunization.

1. INTRODUCTION

Parkinson’s Disease (PD) is a neurological disorder caused by irreversible impairment of dopaminergic neurons in the substantia nigra part of the brain. Early-Onset Parkinson’s Disease (EOPD) accounts for almost 10% of cases, taking place in younger people, while only about 1% of those over 60 years are affected [1, 2]. Monogenic forms, resulting from mutations in high-risk genes, account for 5-10% of cases, although 15-25% of patients report a family history. Pathological mutations in genes associated with the genetic form of PD have been identified in several genes, notably *GBA1, LRRK2, VPS35, PRKN, PINK1, TMEM175, ATP13A2, ATP10B*, and *DJ1* [3-5]. PD is a multifaceted condition resulting from a combination of genes, environment, and personal habits [6]. One of the key features of PD is the presence of Lewy bodies, which are composed of aggregated alpha-synuclein and a number of associated proteins. The presence of Lewy bodies in PD highlights the role of lysosomes and their dysfunction in the evolution of the disease [7, 8].

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Symptomatic management can be obtained through methods such as replacement therapy using dopamine. However, such methods do not have an impact on the progression of the condition. Approaches under investigation include pharmacological chaperones, enzyme replacement therapies targeting *GBA1*-related lysosomal enzyme dysfunction, immunotherapies to reduce pathological α-synuclein, small-molecule modulators to avert toxic protein aggregation, and gene therapy [9, 10].

Further cellular pathways implicated in lysosomal dysfunction in PD include dysregulation of the mTOR-AMPK-ULK1 axis, which influences autophagy, PERK-eIF2α-CHOP-mediated endoplasmic reticulum (ER) stress, dropping proteostasis [11], neuroinflammatory signaling *via* TLR4/NF-κB impairing α-synuclein aggregation, and mitochondrial-lysosomal crosstalk through the PINK1/Parkin pathway involving mitophagy failure to dopaminergic neuron loss [12]. Understanding these integrated pathways may reveal new biomarkers and therapeutic targets, thereby enhancing understanding of PD pathology. This review aims to bridge mechanistic insights into lysosomal dysfunction with the translational developing of these novel therapies.

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2. PHYSIOLOGICAL FUNCTION OF THE LYSOSOMAL SYSTEM IN PD

Lysosomes are very important organelles that play significant roles in critical cellular processes such as autophagy and endocytosis, by which pathogens and other toxic substrates and degradation products are cleared [13]. Their degradative capacity depends on more than 60 hydrolytic enzymes, including lipid-degrading enzymes, proteases, phosphatases, glycosidases, nucleases, and sulfatases, which require a tightly regulated acidic environment (pH ~4.6-5.0) for optimal activity. These enzymes are synthesized in the endoplasmic reticulum and are tagged with mannose-6-phosphate, facilitating their recognition and transport *via* the mannose-6-phosphate receptor [14, 15]. Among the proteins, lysosomal integral membrane protein 2 mediates the transport of glucocerebrosidase into the lysosome. Approximately 50 associated membrane proteins maintain lysosomal homeostasis by regulating lysosomal pH, metabolic signal transport, and hydrolysis product, substrate, and ion transport [16].

As illustrated in Fig. (**1**), besides catalyzing secondary lysosomal transport, functions such as maintaining lysosomal pH, supplying substrates, distributing metabolites *via* exocytosis, and interacting with the cell membrane all contribute to lysosomal function. The buildup of toxic substrates, cell debris, pathogens, and ruptured proteins disrupts cellular function and may contribute to cell death [15]. Chaperone-mediated autophagy is another cellular process that entails the transport and delivery of substrates to lysosomes [17]. The control of protein and signaling pathways involved in autophagosomes and autolysosomes is important in efficient autophagy [18-20].

Ineffective lysosomal protein degradation compromises the processing of neurodegeneration-related proteins like α-synuclein aggregates and other toxic substances [21]. As such, the episodic aggregate buildup could culminate in the induction of a pathogenic cascade that targets a molecule other than the defective enzyme. The pathogenic cascades include mitochondrial pathology, disrupted membrane integrity, impaired vesicle formation and transport, impaired autophagy, disrupted calcium balance, and accumulation of the RCS [22]. The complex lysosomal impairment has thus established its pivotal implication in the pathophysiology of the disease.

3. LYSOSOMAL SIGNALING PATHWAYS IN PD

The mTOR-AMPK signaling pathway modulates the initiation of autophagosomes and lysosome formation through transcription factors such as transcription factor EB

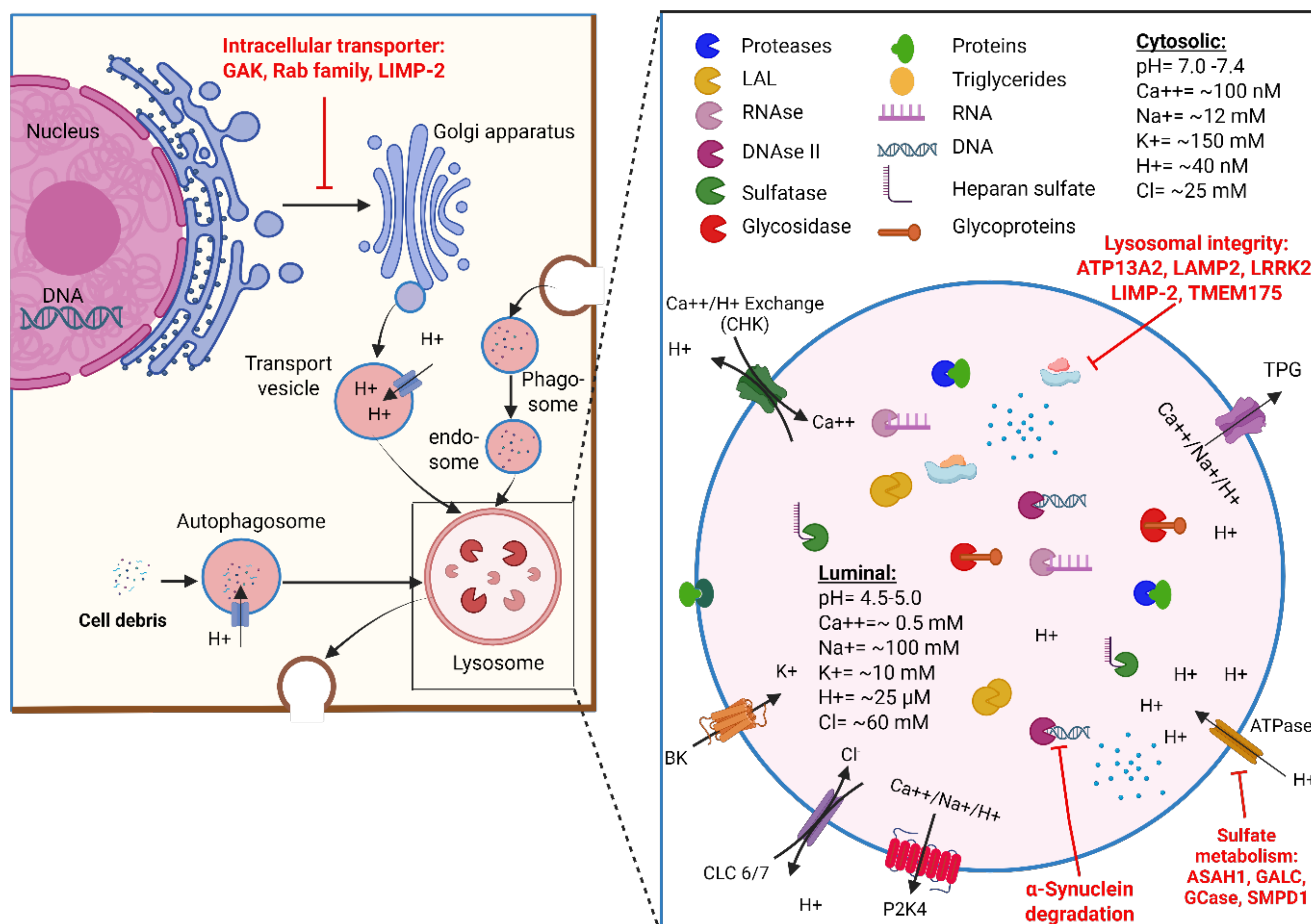

Fig. (1). Impression of lysosomal formation and function, highlighting corresponding PD-associated pathways and selected genetic variants. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. Molecular pathways linked to lysosomal dysfunction and PD pathogenesis.

Pathway	Key Components	Mechanistic Role in PD	References
mTOR/AMPK–TFEB signaling	mTORC1, AMPK, ULK1, TFEB	Controls autophagy initiation and lysosomal biogenesis; changed mTOR activity suppresses autophagic flux in PD	[23]
Mitochondrial lysosomal crosstalk	PINK1, PRKN, ATP13A2	Manages mitophagy and energy metabolism; defective crosstalk leads to mitochondrial ROS and dopaminergic neuron damage	[24]
ER-stress/Unfolded Protein Response	PERK, IRE1α, ATF6, CHOP	Misfolded protein accumulation triggers unfolded protein response; chronic ER stress contributes to α-synuclein aggregation.	[25]
Neuroinflammatory (NF-κB/TLR)	TLR4, MyD88, NF-κB, TNF-α, IL-1β	Microglial activation and cytokine release impair α-synuclein propagation and neuronal damage.	[26]
Oxidative stress and Nrf2	Nrf2, Keap1, HO-1, SOD2	Oxidative imbalance damages proteins and lipids; Nrf2 activation encourages antioxidant defense.	[27]

and transcription factor enhancer 3 [23]. Additionally, the activation of the mammalian Target Of Rapamycin Complex 1 (mTORC1) by the nutrient-deprived or oxidative-stressed state is negatively modulated through the activation of the protein kinase associated with the regulation of the mammalian target of rapamycin complex 1-activated protein kinase (AMP-activated protein kinase or AMPK), which promotes the nuclear translocation of the transcription factor EB protein. This is because the mammalian target of rapamycin complex 1 is positively modulated through the endogenous suppression of the transcriptional activity of the transcription factor EB protein [24]. The endoplasmic reticulum (ER) stress response pathways, specifically the "sensor" pathways of the IRE1α and Protein Kinase RNA-like ER Kinase (PERK), modulate the regulation of Ca^{2+} transport and autophagic removal (Table **1**) [25]. Moreover, aberrant regulation of nuclear factor kappa B (NF-κB) and pro-inflammatory gene pathways sustains the elevated activity of inflammatory processes that compromise lysosomal integrity. It creates a vicious inflammatory cycle that propagates α-synuclein-mediated neuronal toxicity [26]. Taken together, these interconnected metabolic and inflammatory pathways suggest that lysosomal dysfunction in PD results from a complex network of overlapping mechanisms rather than isolated defects [27].

4. LYSOSOMAL GENE MUTATIONS ASSOCIATED WITH PD

Genetic disruption of lysosomal function thus appears as a central pathogenic axis in PD. Mutations in lysosome-associated genes disrupt substrate degradation, vesicular trafficking, lipid homeostasis, and autophagic clearance, and converge on α-synuclein accumulation and neuronal vulnerability. Table (**2**) summarizes key lysosomal genes implicated in PD. Each gene is reviewed below in a uniform format covering physiological function, mutation-specific mechanisms, clinical relevance, and therapeutic implications [28-38].

4.1. *GBA1*

The gene *GBA1* encodes lysosomal acid β-glucocerebrosidase, an enzyme that hydrolyzes glucosylceramide into glucose and ceramide to maintain sphingolipid homeostasis in the lysosome [39]. Pathogenic mutations in GBA1 (*e.g*., *N370S*, *L444P*, *D496H*) and mild/benign mutations (*e.g*., *E326K, T369M*) impair the folding efficiency and intracellular targeting of glucocerebrosidase, thereby inducing the accumulation of glucosylceramide in cells [40, 41]. The lipid imbalance promotes the stabilization of soluble α-synuclein oligomers and hinders chaperone-mediated autophagy; in turn, it creates a pathogenic cycle between glucocerebrosidase activity reduction and α-synuclein aggregation [42, 43]. *GBA1*-associated PD is defined by an earlier age at onset, faster disease progression, the preponderance of non-motor symptoms, and a higher incidence of cognitive disability than idiopathic PD. Pharmaceutical chaperones to improve glucocerebrosidase protein folding and secretion, substrate reduction therapy targeting glucosylceramide production, and gene therapies to normalize enzyme levels are used in its management [44].

4.2. *LRRK2*

LRRK2 encodes a multidomain kinase that controls vesicular trafficking, endolysosomal dynamics, and autophagosome maturation. Gain-of-function mutations (*e.g*., *G2019S, R1441C/G/H*) increase kinase activity, disorderly lysosomal positioning, and Rab-mediated vesicle trafficking [45, 46]. These changes impair autophagic flux independently of canonical mTOR signaling, leading to ineffective α-synuclein clearance. *LRRK2*-associated PD often phenotypically resembles idiopathic PD but displays mutable penetrance and age at onset [47, 48]. Brain-penetrant LRRK2 kinase inhibitors and antisense oligonucleotides are under clinical development to normalize lysosomal aggregation and autophagic effectiveness [49, 50].

4.3. *TMEM175*

TMEM175 encodes a lysosomal potassium channel that is important for maintaining membrane potential, pH stability, and enzymatic activity. Risk variants such as *p.M393T* decrease potassium conductance, destabilize lysosomal pH, and, secondarily, diminish glucocerebrosidase activity [51]. This makes a tolerant environment for α-synuclein aggrega-

Table 2. Lysosomal gene mutation involved in PD.

Gene	Encoded Protein	Location	Proposed Mechanisms	References
GBA1	Glucosidase	Lysosomes	Lysosomal dysfunction, α-syn aggregation	[28, 29]
LRRK2	LRRK2	Cytoplasm, organelles	Hyperactive kinase disrupts trafficking, autophagy	[30]
VPS35	VPS35	Endosomes	Retromer dysfunction, mitochondrial stress	[31]
PRKN	Parkin	Cytoplasm/mitochondria	Impaired mitophagy, oxidative stress	[32]
PINK1	PINK1	Mitochondria	Mitophagy failure, mitochondrial dysfunction	[33]
TMEM175	TMEM175	Lysosomes	Lysosomal ion imbalance, α-syn accumulation	[34, 35]
ATP13A2	ATP13A2	Lysosomes	Impaired autophagy, lysosomal stress	[36]
ATP10B	ATP10B	Lysosomes	Lipid imbalance, α-synuclein toxicity	[37]
DJ1	DJ-1	Cytoplasm/mitochondria	Loss of oxidative stress defense	[38]

tion due to compromised proteolytic capacity [52]. *TMEM175* variants modulate PD susceptibility across diverse populations, highlighting lysosomal ion homeostasis as a disease modifier. Repair of lysosomal ionic balance through channel modulators represents an emerging therapeutic idea [53, 54].

4.4. *ATP13A2*

ATP13A2 encodes a lysosomal P5-type ATPase intricate in polyamine transport, metal ion homeostasis, and membrane integrity [55]. Loss-of-function mutations damage lysosomal acidification and polyamine export, promoting oxidative stress and imperfect autophagosome clearance [56]. *ATP13A2* mutations cause early-onset, fast progressive PD with prominent cognitive decline and severe lysosomal pathology. Potential strategies include restoring polyamine balance, enhancing lysosomal biogenesis, and gene replacement methods [57, 58].

4.5. *VPS35*

VPS35 is a main component of the retromer complex, mediating endosome-to-Golgi trafficking of lysosomal enzymes and autophagy-related proteins [59]. The *D620N* mutation disturbs retromer stability, leading to malfunctioning hydrolase recycling, reduced autophagosome formation, and increased α-synuclein burden. *VPS35*-associated PD typically presents as a late-onset disease with autosomal-dominant inheritance. Retromer-stabilizing pharmacological chaperones and gene therapy methods are being discovered to reestablish trafficking reliability [60].

4.6. *ATP10B*

ATP10B encodes a lysosomal phospholipid flippase accountable for translocating glucosylceramide and phosphatidylcholine across the lysosomal membrane [61]. *ATP10B* deficiency disrupts lipid asymmetry, impairs lysosomal acidification, and impairs autophagic degradation, indirectly enhancing α-synuclein aggregation [62]. Rare *ATP10B* variants contribute to PD susceptibility in both familial and sporadic cases. Interventions aimed at correcting lipid imbalance or dipping substrate load denote rational therapeutic methods [63].

4.7. *PRKN*

PRKN encodes Parkin, an E3 ubiquitin ligase critical for tagging injured mitochondria for mitophagic removal [64]. Damage to Parkin function impairs effective mitophagy, leading to the accumulation of dysfunctional mitochondria, amplified oxidative stress, and neuronal injury [65, 66]. *PRKN*-associated PD typically manifests in adolescence or early adulthood, progresses slowly, and often lacks Lewy body pathology. Methods focus on enhancing mitophagy, stabilizing mitochondrial function, and gene replacement strategies [67, 68].

4.8. *PINK1*

PINK1 encodes a mitochondrial kinase that senses membrane depolarization and triggers Parkin-dependent mitophagy [69, 70]. *PINK1* loss-of-function mutations prevent recruitment of autophagy receptors, damaging mitochondrial quality control and promoting oxidative damage [71, 72]. *PINK1*-associated PD is characterized by early onset and marked mitochondrial involvement. Mitophagy enhancers and mitochondrial bioenergetic stabilizers are under investigation [73].

4.9. *DJ-1*

DJ-1 is a redox-sensitive chaperone complex in oxidative stress sensing, protein stabilization, and mitochondrial defense [74]. Loss of *DJ-1* redox activity increases susceptibility to oxidative stress and, indirectly, disrupts autophagic degradation pathways [75, 76]. *DJ-1* mutations cause EOPD with heightened oxidative vulnerability. Antioxidant

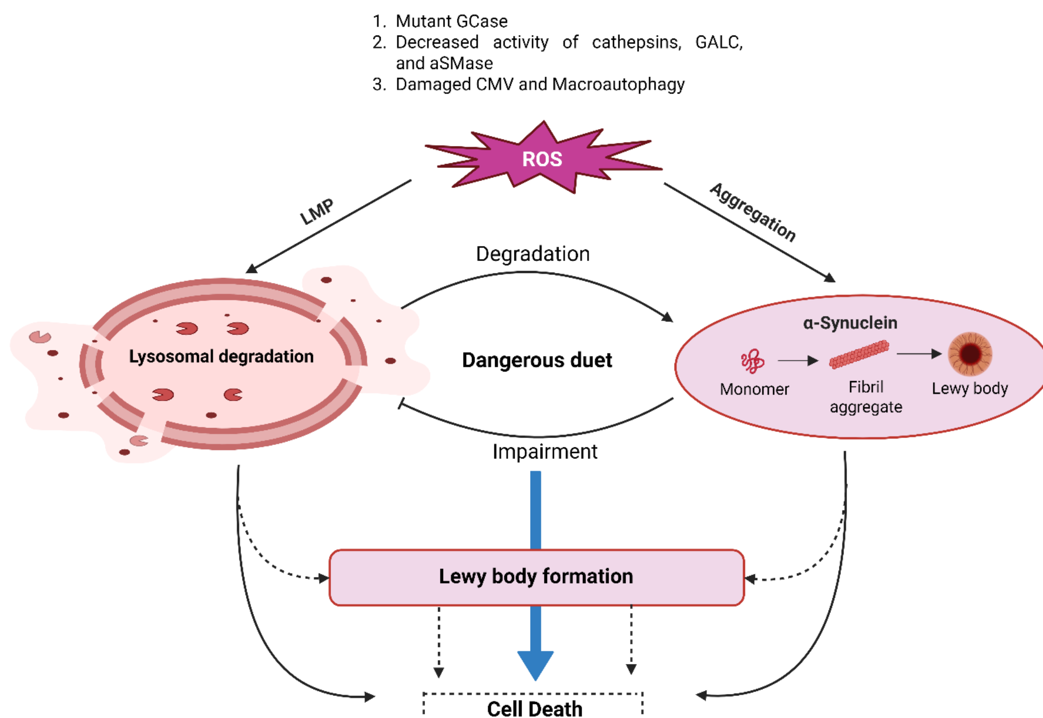

Fig. (2). Lysosomal dysfunction in α-synuclein pathology. Mutant GCase or GCase knockdown leads to α-synuclein accumulation. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

strategies, Nrf2 pathway activation, and gene therapy methods are being explored [77, 78].

5. THE PATHOPHYSIOLOGY OF A-SYNUCLEIN IS INFLUENCED BY LYSOSOMAL MUTAGENIC DYSFUNCTION

Lysosomal hydrolases (*e.g*., cathepsins [CTSD, CTSL, CTSB]) promote the accumulation of species prone to aggregation [79]. Deficiencies of other lysosomal hydrolases, including galactocerebrosidase and acid sphingomyelinase, increase ceramide excesses and thereby increase the toxicity of α -synuclein [80-82]. Together, these observations emphasize the role of α-synuclein pathology as a causative agent and the extent to which lysosomal dysfunction contributes to it, as shown in Fig. (**2**) [83].

5.1. The Pathology of α-synuclein and Glucocerebrosidase

Lower Cer levels may impair lysosomal degradation of α-synuclein because Cer binds to and activates cathepsin D. Decreased Cer levels have been observed in brain regions such as the anterior cingulate. Glucocerebrosidase activity influences the propensity of α-synuclein to aggregate by altering lipid membrane composition [84].

5.2. Galactocerebrosidase, Acid Sphingomyelinase, and α-synuclein Pathology

Besides acid sphingomyelinase and galactocerebrosidase, two lysosomal enzymes that generate Cer, dysregulation of these enzymes is implicated in PD and α-synucleinopathies. Acid sphingomyelinase catalyzes sphingomyelin breakdown into Cer and phosphorylcholine; its blood levels decline 3.5-5.8 years before PD onset. Galactosylceramidase hydrolyzes galactosylceramide and galactosylsphingosine, with elevated cortical galactosylsphingosine levels found in PD patients compared to controls. Moreover, galactosylsphingosine dose-dependently enhances α-synuclein aggregation [85, 86].

5.3. ALP Dysfunction and Pathology of α-synuclein

Inhibition of the ALP decreases hydrolase activity, smoothing α-synuclein aggregate accumulation and intercellular propagation. For example, bafilomycin A1-mediated ALP obstruction causes α-synuclein aggregates to accumulate in primary cortical neurons and non-neuronal cells [87].

6. THERAPEUTIC STRATEGIES TARGETING LYSOSOMAL DYSFUNCTION IN PD

Advances in the molecular understanding of lysosomal dysfunction in PD have allowed the development of therapeutic approaches aimed at restoring proteostasis, lipid balance, vesicular trafficking, and autophagic-mitochondrial crosstalk. Rather than targeting individual genes in isolation, most current methods converge on shared pathogenic mechanisms, including impaired lysosomal enzyme activity, malfunctioning autophagy, disrupted ion and lipid homeostasis, and secondary α-synuclein accumulation. It synthesizes therapeutic efforts by mechanistic class, highlighting translational progress and limitations (Table **3**).

6.1. Therapeutic Targeting of *GBA1*

The *GBA1* is a primary target for treating *GBA1*-associated PD and GD. Pharmacological chaperones

Table 3. Ongoing and completed therapeutic strategies targeting lysosomal dysfunction in PD disease.

Target / Strategy	Drugs	Clinical Phase	Mechanism of Actions	Outcome	References
GBA1	Ambroxol	Phase II (NCT02914366)	BBB-penetrant pharmacological chaperone enhancing glucocerebrosidase activity.	Increased enzyme activity observed in early clinical studies	[90]
	Isofagomine	Phase I (NCT01353585)	ER chaperone stabilizing glucocerebrosidase folding and trafficking	Improved enzyme stability and lysosomal delivery	[90]
	LTI-291	Phase I (NCT03939522)	Non-inhibitory activator of β-glucocerebrosidase	Currently under clinical evaluation	[91]
	S-181	Preclinical	Small-molecule non-inhibitory glucocerebrosidase activator	Demonstrated enzymatic activation in preclinical models	[91]
	Eliglustat	Approved for GD1 (NCT00358150)	Substrate reduction therapy; non-BBB permeable	Effective in systemic Gaucher disease; limited CNS benefit	[92]
	Miglustat	Approved for GD1 (NCT00074985)	Inhibits glucosylceramide synthesis	Reduces systemic substrate burden with minimal CNS efficacy	[93]
LRRK2	DNL151 (BIIB122)	Phase II (NCT04556630)	LRRK2 kinase inhibition reduces Rab phosphorylation	Favorable safety and efficacy signals in PD trials	[97]
	DNL201	Phase I (NCT03710707)	Brain-penetrant LRRK2 kinase inhibitor	Positive pharmacodynamic and safety outcomes	[97]
	MLi-2	Preclinical	Selective LRRK2 kinase inhibition	Neuroprotective effects in PD models	[98, 108]
	PF-06447475	Preclinical	LRRK2 kinase inhibition	Improved lysosomal and autophagic function	[99]
	GNE-7915	Preclinical	Reversible LRRK2 kinase inhibitor	Restoration of lysosomal homeostasis	[99]
ATP13A2	PBT2	Phase II (NCT00462701)	Metal chelation reduces oxidative stress	Neuroprotection observed in experimental models	[104]
	Clioquinol	Phase I/II (NCT01273141)	Chelation of zinc and manganese	Attenuation of oxidative neuronal damage	[104]
TFEB	Trehalose	Preclinical	TFEB activation promoting lysosomal biogenesis	Enhanced α-synuclein clearance in PD models	[105]
VPS35	R55	Preclinical	Retromer stabilization improving intracellular trafficking	Mitochondrial rescue in PD models	[107]
	R33	Preclinical	Pharmacological chaperone correcting VPS35 mutation effects	Improved retromer complex stability	[107]
PRKN	Nicotinamide Riboside	Phase II (NCT03432871)	Enhances mitochondrial biogenesis and mitophagy	Improved mitochondrial function	[113]
	Urolithin A	Phase I/II (NCT04160312)	Induction of mitophagy	Positive bioenergetic outcomes	[113]
	KH176	Phase II (NCT03562494)	Redox modulation supporting mitochondrial integrity	Promoted neuronal survival	[114]
	EPI-589	Phase II (NCT02462630)	Redox-balancing neuroprotective agent	Improved mitochondrial health	[114]
PINK1	Niclosamide	Phase I (NCT02521870)	PINK1-independent mitophagy activation	Enhanced mitochondrial clearance	[116]
DJ-1 pathway	Sulforaphane	Preclinical	Augments DJ-1-mediated antioxidant defenses	Reduced ROS-mediated neurotoxicity	[120]
	Dimethyl fumarate	Phase II (NCT04200911)	Nrf2 activation compensating for DJ-1 dysfunction	Enhanced antioxidant gene expression	[122]

enhance correct folding and lysosomal trafficking of mutant enzymes, thereby increasing residual enzymatic activity [88, 89]. For example, a brain-penetrant chaperone, Ambroxol, has demonstrated increased glucocerebrosidase activity and reduced α-synuclein burden in patient-derived cells and early clinical studies [90]. Non-inhibitory chaperones such as LTI-291 and S-181 aim to avoid competitive substrate interference and are undergoing clinical evaluation [91].

Substrate reduction therapies (SRTs) prevent the synthesis of glucosylceramide, thereby reducing the lysosomal lipid burden. While eliglustat and miglustat are effective in systemic Gaucher disease, their limited blood-brain barrier (BBB) penetration limits their utility in PD [92, 93]. CNS-penetrant SRTs remain an active area of examination, particularly for conditions involving *ATP10B*- and *GBA1*-related lipid dysregulation [94].

6.2. Therapeutic Targeting of *LRRK2*

Therapeutic methods targeting *LRRK2*, particularly for pathogenic mutations such as *G2019S*, which increase kinase activity and disrupt cellular homeostasis, are the main focus in PD treatment [95]. Numerous small-molecule inhibitors, kinase blockers, and antisense oligonucleotides have been developed to control their activity [96]. Denali Therapeutics and Biogen developed brain-penetrant inhibitors DNL201 and DNL151 (BIIB122), which control lysosomal and mitochondrial dysfunction by reducing LRRK2 kinase activity and phosphorylation of Rab proteins. Phase I and II studies have shown positive safety and pharmacodynamics [97]. MLi-2 is another selective inhibitor that determines strong *LRRK2* inhibition and neuroprotection in preclinical trials [98]. Pfizer's PF-06447 and Genentech's GNE-7915 also suppress *LRRK2* selectively and reversibly, dipping the phosphorylation of *LRRK2* substrates and enhancing lysosomal function [99].

6.3. Therapeutic Targeting of *TMEM175*

TMEM175, a lysosomal potassium channel linked to PD and lysosomal function, is progressively related to neurodegenerative research. It preserves the lysosomal membrane potential, pH stability, and degradative capacity [100]. Direct pharmacological modulators are in the primary stages of research, with no approved drugs or advanced inhibitors. Structure-based drug design and high-throughput screening have identified small compounds that modulate *TMEM175*, encouraging ongoing efforts to develop channel agonists or potentiators to reestablish function of PD [101].

6.4. Therapeutic Targeting of *ATP13A2*

ATP13A2, also known as PARK9, is a protein that, when disturbed, contributes to the pathogenesis of PD and Kufor-Rakeb Syndrome. *ATP13A2* plays important roles in lysosomal homeostasis, metal ion transport, and autophagic clearance [102]. Current therapeutic strategies aim to re-establish *ATP13A2* activity. To date, direct modulation of *ATP13A2* has been minimally studied [103]. Metal ion chelation therapy with PBT2 or clioquinol decreases the accumulation of intracellular metals, reduces oxidative stress, and provides some neuroprotective effects in models derived from *ATP13A2*-deficient mice [104]. Trehalose, 2-Hydroxypropyl-β-cyclodextrin, and rapamycin are TFEB activators that upregulate the expression of lysosomal genes and increase lysosomal clearance [105].

6.5. Therapeutic Targeting of *VPS35*

VPS35 (*Vacuolar Protein Sorting 35*), an important retromer complex component, is involved in PD, with the *D620N* mutation disrupting lysosomal trafficking, mitochondrial dynamics, and endosomal sorting. This mutation decreases autophagy and causes mitochondrial fragmentation and α-synuclein accumulation, contributing to neurodegeneration [106]. Pharmacological chaperones R55 and R33 stabilize the retromer, develop cargo recognition, adapt trafficking, mitigate α-synuclein pathology, and enhance mitochondrial function in models [107]. *LRRK2* inhibitors, such as DNL151 and MLi-2, which lower Rab protein phosphorylation and normalize lysosomal and mitochondrial function, are under clinical study for *LRRK2* and *VPS35*-linked PD [108].

6.6. Therapeutic Targeting of *ATP10B*

Variants in *ATP10B*, a lysosomal P4-type ATPase responsible for lipid movement, that impair function increase the risk for developing PD [109]. No drugs are currently approved that directly affect *ATP10B*, but therapies are being developed with the intent to correct lipid metabolic balance, reduce the substrate burden, or remedy the loss of the protein (*ATP10B*) itself [110]. Other potential therapies that promote the use of lysosomal contents *via* autophagy and enhance lysosomal gene expression and increase α-synuclein clearance in the absence of ATP10B deficiency include rapamycin, trehalose, and transfected expression vectors [111].

6.7. Therapeutic Targeting of *PRKN*

PRKN (Parkin) plays a crucial role in mitochondrial housekeeping and the autophagic clearance of damaged mitochondria, a process known as mitophagy [112]. No approved drugs directly reestablish Parkin function. Indirect methods include mitophagy activators such as nicotinamide riboside (NR), urolithin A, and actinonin, which improve mitochondrial biogenesis and autophagy, mitigate stress, and recover existence in models [113]. Redox modulators KH176, Sonlicromanol, and EPI-589 aim to decrease oxidative stress and restore cellular redox balance, contributing to neuroprotection. Gene therapy using AAV vectors to deliver functional *PRKN* and mRNA-based treatments for transient Parkin expression is under development [114].

6.8. Therapeutic Targeting of *PINK1*

PINK1, a mitochondrial kinase that controls mitophagy, accumulates on injured mitochondria to recruit Parkin, initiating clearance. *PINK1* mutations disrupt this pathway, leading to mitochondrial damage and neurodegeneration [115]. No FDA-approved *PINK1* targeted drugs exist. Therapeutic directions include mitophagy activators bypassing *PINK1*, such as niclosamide, CCCP, and urolithin

A, and NAD+ boosters like nicotinamide riboside to improve mitochondrial biogenesis [116]. Kinase modulators that stabilise or enhance *PINK1* activity are in development. Redox modulators EPI-589 and KH176 are explored for falling oxidative stress in *PINK1*-mutant neurons [117].

6.9. Therapeutic Targeting of *DJ-1*

DJ-1 (*PARK7*), involved in oxidative stress response, mitochondrial function, and neuroprotection, is related to early-onset PD [118]. Recently, no approved *DJ-1*-targeted drugs have existed [119]. Small molecular compounds, including isatin and sulforaphane, activate or stabilise *DJ-1*, enhancing antioxidant protective barricades [120]. AAV vectors carrying the wild-type *DJ-1* gene have been demonstrated to restore function and protect neurons from damage in models of neurodegeneration. mRNA-based approaches that target the *DJ-1* protein are also under investigation [121]. Moreover, pharmacologic activation of the Nrf2 pathway with dimethyl fumarate or bardoxolone methyl (a synthetic triterpenoid) has been shown to improve outcomes in patients with *DJ-1* deficiency [122].

6.10. Blood-Brain Barrier (BBB) Delivery Challenges

Discuss the significant obstacle posed by the BBB in delivering AAV vectors and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) components well to the central nervous system. Highlight current strategies to overcome this, such as engineering AAV capsids for improved BBB penetration, intrathecal or intracerebroventricular administration routes, and the limitations these approaches present in terms of efficiency, safety, and scalability [123].

6.11. Translational Limitations

Emphasise the gap between preclinical success and clinical application, including differences in disease models, immune responses to viral vectors, off-target effects of gene editing, and long-term safety concerns. Address the challenges of scaling doses from animal models to humans, as well as the regulatory hurdles gene therapies must overcome.

6.12. Realistic Interpretation of Gene Therapy and CRISPR Approaches

Deliver a balanced view on the current stage of these technologies, acknowledging that while AAV-mediated wild-type *VPS35* gene therapy and CRISPR-based editing targeting the *D620N* mutation are hopeful, they remain experimental. Discourse potential risks such as immunogenicity, insertional mutagenesis, and incomplete editing efficacy. Stress the need for rigorous clinical trials to establish efficacy and safety before these therapies can be considered practical treatment options [123].

7. INTEGRATION OF FAMILIAL AND SPORADIC PD MECHANISMS: LYSOSOMAL DYSFUNCTION AND MITOPHAGY

Idiopathic PD arises from various genetic and environmental factors. Familial PD is linked to mutations in genes such as *GBA1, LRRK2, ATP13A2, PRKN,* and *PINK1,* which disrupt lysosomal or mitochondrial homeostasis. *GBA1* mutations decrease glucocerebrosides activity, causing accumulation of glucocerebrosides and α-synuclein aggregates, while hyperactivation of glucocerebrosidase alters vesicle trafficking within the endo-lysosomal system, damaging autophagy [124]. Mutations in *PINK1* and *PRKN* damage mitophagy and the clearance of damaged mitochondria. Sporadic PD shares these mechanisms, compounded by aging, oxidative stress, and toxic exposures, leading to similar lysosomal and mitophagy dysfunctions [125]. Both forms exhibit overlapping transcriptional and translational profiles, including common regulation of autophagy mediators (LAMP2, TFEB) and mitochondrial genes (*DJ-1, PINK1*). Contempt genetic differences, lysosomal dysfunction, and mitophagy failure are common drivers of dopaminergic neurodegeneration [126].

CONCLUSIONS AND FUTURE PERSPECTIVES

Lysosomal dysfunction plays an essential and multifaceted role in the pathogenesis of PD, influencing key pathological features, including α-synuclein aggregation, impaired autophagy, disrupted lipid homeostasis, and mitochondrial dysfunction. Genetic mutations in lysosomal genes, including *GBA1, LRRK2, TMEM175, ATP13A2, VPS35, ATP10B, PRKN, PINK1*, and *DJ-1*, highlight the close interaction between lysosomal pathways and neurodegeneration. Therapeutic approaches targeting these pathways, ranging from pharmacological chaperones and substrate-reduction therapies that manage symptoms. Still, significant translational challenges remain, particularly regarding BBB delivery, safety, and long-term efficacy of advanced therapies such as AAV-mediated gene delivery and CRISPR-based editing. Continued research to improve these mechanistic understandings and overcome translational challenges is important for developing effective, disease-modifying treatments for PD.

STUDY LIMITATIONS

This review assesses the effects of lysosomal dysfunction and genetic mutations in PD, allowing for various limitations. It points out possible discrimination by only including confident studies and using preclinical models and small clinical studies, which makes it less useful in reality. The review also examines the difficulties of PD, which is caused by a number of genetic and environmental factors. This type is difficult to understand, as lysosomal dysfunction is involved. Furthermore, some of the therapeutic strategies studied are still in early clinical stages and lack sufficient long-term safety and efficacy data.

AUTHORS' CONTRIBUTIONS

The authors confirm contribution to the paper as follows: study conception and design: VCB., AKG: data collection: MKS. analysis and interpretation of results: AK., SKT. AKP. draft manuscript: VCB. SK. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

AAV	=	Adeno-Associated Virus
ALP	=	Alkaline Phosphatase
AMPK	=	AMP-activated Protein Kinase
BBB	=	Blood-Brain Barrier
CM	=	Chaperone-mediated Autophagy
CRISPR	=	Clustered Regularly Interspaced Short Palindromic Repeats
EOPD	=	Early-Onset Parkinson's Disease
ER	=	Endoplasmic Reticulum
mTORC1	=	Mammalian Target of Rapamycin Complex 1
NF-κB	=	Nuclear Factor Kappa B
NR	=	Nicotinamide Riboside
PD	=	Parkinson's Disease
PERK	=	Protein Kinase RNA-like ER Kinase
RCS	=	Reactive Carbonyl Species
SRTs	=	Substrate Reduction Therapies

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Naeini SM, Lopez MD, Fraser PE, Tandon A. Parkinson's disease beyond the brain: Implications for treatments. Front Aging Neurosci 2025; 17: 1600782. http://dx.doi.org/10.3389/fnagi.2025.1600782 PMID: 41143245

[2] Bala VC, Sultan T, Kumar D, Tiwari SK, Kumar A, Kumar S. Neuroprotective Activity of Amaranthus tricolor Leaves Extract for Haloperidol Induce Catalepsy by Behavior Method. Adv Pharmacol Pharm 2025; 13(2): 253-9. http://dx.doi.org/10.13189/app.2025.130209

[3] Kolicheski A, Turcano P, Tamvaka N, *et al.* Early-Onset Parkinson's disease: Creating the right environment for a genetic disorder. J Parkinsons Dis 2022; 12(8): 2353-67. http://dx.doi.org/10.3233/JPD-223380 PMID: 36502340

[4] Koros C, Bougea A, Alefanti I, *et al.* A global perspective of *GBA1*-related Parkinson's disease: A narrative review. Genes 2024; 15(12): 1605. http://dx.doi.org/10.3390/genes15121605 PMID: 39766872

[5] Mächtel R, Boros FA, Dobert JP, Arnold P, Zunke F. From lysosomal storage Disorders to Parkinson's Disease – challenges and opportunities. J Mol Biol 2023; 435(12): 167932. http://dx.doi.org/10.1016/j.jmb.2022.167932 PMID: 36572237

[6] Kung PJ, Elsayed I, Reyes-Pérez P, Bandres-Ciga S. Immunogenetic determinants of Parkinson's disease etiology. J Parkinsons Dis 2022; 12(s1): S13-27. http://dx.doi.org/10.3233/JPD-223176 PMID: 35367971

[7] Ye H, Robak LA, Yu M, Cykowski M, Shulman JM. Genetics and pathogenesis of Parkinson's syndrome. Annu Rev Pathol 2023; 18(1): 95-121. http://dx.doi.org/10.1146/annurev-pathmechdis-031521-034145 PMID: 36100231

[8] Bonam SR, Wang F, Muller S. Lysosomes as a therapeutic target. Nat Rev Drug Discov 2019; 18(12): 923-48. http://dx.doi.org/10.1038/s41573-019-0036-1 PMID: 31477883

[9] Isidoro C. Pathophysiology of lysosomes in a nutshell. Int J Mol Sci 2023; 24(13): 10688. http://dx.doi.org/10.3390/ijms241310688 PMID: 37445864

[10] Henriquez G, Narayan M. Targeting alpha-synuclein aggregation with immunotherapy: A promising therapeutic approach for Parkinson's disease. Explor Neuroprot Ther 2023; 3(4): 207-34. http://dx.doi.org/10.37349/ent.2023.00048

[11] Zhi Y, Zhang T, Lu D, *et al.* Lysosomal and mTORC1 signaling dysregulation underpin the pathology of spastic paraplegia type 80. Nat Commun 2025; 16(1): 9833. http://dx.doi.org/10.1038/s41467-025-64800-5 PMID: 41203601

[12] Dai L, Liu M, Ke W, Chen L, Fang X, Zhang Z. Lysosomal dysfunction in α-synuclein pathology: Molecular mechanisms and therapeutic strategies. Cell Mol Life Sci 2024; 81(1): 382. http://dx.doi.org/10.1007/s00018-024-05419-5 PMID: 39223418

[13] Darios F, Stevanin G. Impairment of lysosome function and autophagy in rare neurodegenerative diseases. J Mol Biol 2020; 432(8): 2714-34. http://dx.doi.org/10.1016/j.jmb.2020.02.033 PMID: 32145221

[14] Zhang Z, Yue P, Lu T, Wang Y, Wei Y, Wei X. Role of lysosomes in physiological activities, diseases, and therapy. J Hematol Oncol 2021; 14(1): 79. http://dx.doi.org/10.1186/s13045-021-01087-1 PMID: 33990205

[15] Blumenreich S, Barav OB, Jenkins BJ, Futerman AH. Lysosomal storage disorders shed light on lysosomal dysfunction in Parkinson's disease. Int J Mol Sci 2020; 21(14): 4966. http://dx.doi.org/10.3390/ijms21144966 PMID: 32674335

[16] Skrahin A, Horowitz M, Istaiti M, *et al. GBA1*-associated Parkinson's disease is a distinct entity. Int J Mol Sci 2024; 25(13): 7102. http://dx.doi.org/10.3390/ijms25137102 PMID: 39000225

[17] Xu J, Gu J, Pei W, Zhang Y, Wang L, Gao J. The role of lysosomal membrane proteins in autophagy and related diseases. FEBS J 2024; 291(17): 3762-85. http://dx.doi.org/10.1111/febs.16820 PMID: 37221945

[18] Hou X, Watzlawik JO, Fiesel FC, Springer W. Autophagy in Parkinson's Disease. J Mol Biol 2020; 432(8): 2651-72. http://dx.doi.org/10.1016/j.jmb.2020.01.037 PMID: 32061929

[19] Jiao F, Zhou B, Meng L. The regulatory mechanism and therapeutic potential of transcription factor EB in neurodegenerative diseases. CNS Neurosci Ther 2023; 29(1): 37-59. http://dx.doi.org/10.1111/cns.13985 PMID: 36184826

[20] Gao AYL, Montagna DR, Hirst WD, Temkin PA. RIT2 regulates autophagy lysosomal pathway induction and protects against α-synuclein pathology in a cellular model of Parkinson's disease. Neurobiol Dis 2024; 199: 106568. http://dx.doi.org/10.1016/j.nbd.2024.106568 PMID: 38885848

[21] Jiang Y, Rex DAB, Schuster D, *et al.* Comprehensive overview of Bottom-Up proteomics using mass spectrometry. ACS Meas Sci Au 2024; 4(4): 338-417. http://dx.doi.org/10.1021/acsmeasuresciau.3c00068 PMID: 39193565

[22] Parenti G, Medina DL, Ballabio A. The rapidly evolving view of lysosomal storage diseases. EMBO Mol Med 2021; 13(2): 12836. http://dx.doi.org/10.15252/emmm.202012836 PMID: 33459519

[23] Paquette M, El-Houjeiri L, C Zirden L, *et al.* AMPK-dependent phosphorylation is required for transcriptional activation of TFEB and TFE3. Autophagy 2021; 17(12): 3957-75. http://dx.doi.org/10.1080/15548627.2021.1898748 PMID: 33734022

[24] Du X, Chen M, Fang Z, *et al.* Evaluation of hepatic AMPK, mTORC1, and autophagy-lysosomal pathway in cows with mild or moderate fatty liver. J Dairy Sci 2024; 107(5): 3269-79. http://dx.doi.org/10.3168/jds.2023-24000 PMID: 37977448

[25] Liu S, Yao S, Yang H, Liu S, Wang Y. Autophagy: Regulator of cell death. Cell Death Dis 2023; 14(10): 648. http://dx.doi.org/10.1038/s41419-023-06154-8 PMID: 37794028

[26] Kumar S, Sánchez-Álvarez M, Lolo FN, Trionfetti F, Strippoli R, Cordani M. Autophagy and the lysosomal system in cancer. Cells 2021; 10(10): 2752. http://dx.doi.org/10.3390/cells10102752 PMID: 34685734

[27] Moradi N, Sanfrancesco VC, Champsi S, Hood DA. Regulation of lysosomes in skeletal muscle during exercise, disuse and aging. Free Radic Biol Med 2024; 225: 323-32. http://dx.doi.org/10.1016/j.freeradbiomed.2024.09.028 PMID: 39332541

[28] Zhang X, Wu H, Tang B, Guo J. Clinical, mechanistic, biomarker, and therapeutic advances in GBA1-associated Parkinson's disease. Transl Neurodegener 2024; 13(1): 48. http://dx.doi.org/10.1186/s40035-024-00437-6 PMID: 39267121

[29] Menozzi E, Toffoli M, Schapira AHV. Targeting the GBA1 pathway to slow Parkinson disease: Insights into clinical aspects, pathogenic mechanisms and new therapeutic avenues. Pharmacol Ther 2023; 246: 108419. http://dx.doi.org/10.1016/j.pharmthera.2023.108419 PMID: 37080432

[30] Rui Q, Ni H, Li D, Gao R, Chen G. The role of LRRK2 in neurodegeneration of Parkinson disease. Curr Neuropharmacol 2018; 16(9): 1348-57. http://dx.doi.org/10.2174/1570159X16666180222165418 PMID: 29473513

[31] Rowlands J, Moore DJ. VPS35 and retromer dysfunction in Parkinson's disease. Philos Trans R Soc Lond B Biol Sci 2024; 379(1899): 20220384. http://dx.doi.org/10.1098/rstb.2022.0384 PMID: 38368930

[32] Clausen L, Okarmus J, Voutsinos V, Meyer M, Lindorff-Larsen K, Hartmann-Petersen R. PRKN-linked familial Parkinson's disease: Cellular and molecular mechanisms of disease-linked variants. Cell Mol Life Sci 2024; 81(1): 223. http://dx.doi.org/10.1007/s00018-024-05262-8 PMID: 38767677

[33] Eldeeb MA, Ragheb MA. N-degron-mediated degradation and regulation of mitochondrial PINK1 kinase. Curr Genet 2020; 66(4): 693-701. http://dx.doi.org/10.1007/s00294-020-01062-2 PMID: 32157382

[34] Feng T, Zheng H, Zhang Z, Fan P, Yang X. Mechanism and therapeutic targets of the involvement of a novel lysosomal proton channel TMEM175 in Parkinson's disease. Ageing Res Rev 2024; 100: 102373. http://dx.doi.org/10.1016/j.arr.2024.102373 PMID: 38960046

[35] Schulze T, Rauh O, Thiel G, Fertig N, Bazzone A, Grimm C. Unraveling pH regulation of TMEM175, an endolysosomal cation channel with a role in Parkinson's Disease. J Cell Physiol 2025; 240(2): 70008. http://dx.doi.org/10.1002/jcp.70008 PMID: 39902728

[36] Kong SMY, Chan BKK, Park JS, *et al.* Parkinson's disease-linked human PARK9/ATP13A2 maintains zinc homeostasis and promotes α-Synuclein externalization *via* exosomes. Hum Mol Genet 2014; 23(11): 2816-33. http://dx.doi.org/10.1093/hmg/ddu099 PMID: 24603074

[37] Martin S, Smolders S, Van den Haute C, *et al.* Mutated ATP10B increases Parkinson's disease risk by compromising lysosomal glucosylceramide export. Acta Neuropathol 2020; 139(6): 1001-24. http://dx.doi.org/10.1007/s00401-020-02145-7 PMID: 32172343

[38] Dolgacheva LP, Berezhnov AV, Fedotova EI, Zinchenko VP, Abramov AY. Role of DJ-1 in the mechanism of pathogenesis of Parkinson's disease. J Bioenerg Biomembr 2019; 51(3): 175-88. http://dx.doi.org/10.1007/s10863-019-09798-4 PMID: 31054074

[39] Moors TE, Paciotti S, Ingrassia A, *et al.* Characterization of brain lysosomal activities in GBA-related and sporadic Parkinson's Disease and dementia with lewy bodies. Mol Neurobiol 2019; 56(2): 1344-55. http://dx.doi.org/10.1007/s12035-018-1090-0 PMID: 29948939

[40] Gan-Or Z, Liong C, Alcalay RN. GBA-associated Parkinson's disease and other synucleinopathies. Curr Neurol Neurosci Rep 2018; 18(8): 44. http://dx.doi.org/10.1007/s11910-018-0860-4 PMID: 29884970

[41] Somerville EN, Krohn L, Senkevich K, *et al.* Genome-wide association study of glucocerebrosidase activity modifiers. Mol Neurobiol 2025; 62(9): 11560-71. http://dx.doi.org/10.1007/s12035-025-04996-1 PMID: 40299299

[42] Omer N, Giladi N, Gurevich T, *et al.* Glucocerebrosidase activity is not associated with Parkinson's disease risk or severity. Mov Disord 2022; 37(1): 190-5. http://dx.doi.org/10.1002/mds.28792 PMID: 34550621

[43] Rocha EM, Smith GA, Park E. Glucocerebrosidase gene therapy prevents alpha-synucleinopathy of midbrain dopamine neurons. Neurobiol Dis 2015; 82: 495-503. http://dx.doi.org/10.1016/j.nbd.2015.09.009 PMID: 26392287

[44] Murphy KE, Gysbers AM, Abbott SK, *et al.* Reduced glucocerebrosidase is associated with increased α-synuclein in sporadic Parkinson's disease. Brain 2014; 137(3): 834-48. http://dx.doi.org/10.1093/brain/awt367 PMID: 24477431

[45] Tolosa E, Vila M, Klein C, Rascol O. LRRK2 in Parkinson disease: Challenges of clinical trials. Nat Rev Neurol 2020; 16(2): 97-107. http://dx.doi.org/10.1038/s41582-019-0301-2 PMID: 31980808

[46] Bonet-Ponce L, Beilina A, Williamson CD, *et al.* LRRK2 mediates tubulation and vesicle sorting from lysosomes. Sci Adv 2020; 6(46): eabb2454. http://dx.doi.org/10.1126/sciadv.abb2454 PMID: 33177079

[47] Komori T, Kuwahara T. An update on the interplay between LRRK2, Rab GTPases and Parkinson's Disease. Biomolecules 2023; 13(11): 1645. http://dx.doi.org/10.3390/biom13111645 PMID: 38002327

[48] Pang SYY, Lo RCN, Ho PWL, *et al.* LRRK2, GBA and their interaction in the regulation of autophagy: Implications on therapeutics in Parkinson's disease. Transl Neurodegener 2022; 11(1): 5. http://dx.doi.org/10.1186/s40035-022-00281-6 PMID: 35101134

[49] Piccoli G, Volta M. LRRK2 along the Golgi and lysosome connection: A jamming situation. Biochem Soc Trans 2021; 49(5): 2063-72. http://dx.doi.org/10.1042/BST20201146 PMID: 34495322

[50] Rocha EM, Miranda B, Castro S. LRRK2 inhibition prevents endolysosomal deficits seen in human Parkinson's disease. Neurobiol Dis 2020; 134: 104626. http://dx.doi.org/10.1016/j.nbd.2019.104626 PMID: 31618685

[51] Jinn S, Blauwendraat C, Toolan D, *et al.* Functionalization of the TMEM175 p.M393T variant as a risk factor for Parkinson disease. Hum Mol Genet 2019; 28(19): 3244-54. http://dx.doi.org/10.1093/hmg/ddz136 PMID: 31261387

[52] Krohn L, Öztürk TN, Vanderperre B, *et al.* Genetic, structural, and functional evidence link TMEM175 to synucleinopathies. Ann Neurol 2020; 87(1): 139-53. http://dx.doi.org/10.1002/ana.25629 PMID: 31658403

[53] Wu L, Lin Y, Song J, *et al.* TMEM175: A lysosomal ion channel associated with neurological diseases. Neurobiol Dis 2023; 185: 106244. http://dx.doi.org/10.1016/j.nbd.2023.106244 PMID: 37524211

[54] Tang T, Jian B, Liu Z. Transmembrane protein 175, a lysosomal ion channel related to Parkinson's disease. Biomolecules 2023; 13(5): 802. http://dx.doi.org/10.3390/biom13050802 PMID: 37238672

[55] Tillinghast J, Drury S, Bowser D, Benn A, Lee KPK. Structural mechanisms for gating and ion selectivity of the human polyamine transporter ATP13A2. Mol Cell 2021; 81(22): 4650-4662.e4. http://dx.doi.org/10.1016/j.molcel.2021.10.002 PMID: 34715014

[56] Gao H, Sun H, Yan N, *et al.* ATP13A2 declines Zinc-induced accumulation of α-synuclein in a Parkinson's disease model. Int J Mol Sci 2022; 23(14): 8035. http://dx.doi.org/10.3390/ijms23148035 PMID: 35887392

[57] van Veen S, Martin S, Van den Haute C, *et al.* ATP13A2 deficiency disrupts lysosomal polyamine export. Nature 2020; 578(7795): 419-24. http://dx.doi.org/10.1038/s41586-020-1968-7 PMID: 31996848

[58] Cutillo G, Simon DK, Eleuteri S. VPS35 and the mitochondria: Connecting the dots in Parkinson's disease pathophysiology. Neurobiol Dis 2020; 145: 105056. http://dx.doi.org/10.1016/j.nbd.2020.105056 PMID: 32853677

[59] Eleuteri S, Albanese A. VPS35-based approach: A potential innovative treatment in Parkinson's Disease. Front Neurol 2019; 10: 1272. http://dx.doi.org/10.3389/fneur.2019.01272 PMID: 31920908

[60] Wu A, Lee D, Xiong WC. VPS35 or retromer as a potential target for neurodegenerative disorders: Barriers to progress. Expert Opin Ther Targets 2024; 28(8): 701-12. http://dx.doi.org/10.1080/14728222.2024.2392700 PMID: 39175128

[61] Zhang F, Wu Z, Long F, *et al.* The roles of ATP13A2 gene mutations leading to abnormal aggregation of α-synuclein in Parkinson's disease. Front Cell Neurosci 2022; 16: 927682. http://dx.doi.org/10.3389/fncel.2022.927682 PMID: 35875356

[62] Dang T, Cao WJ, Zhao R, Lu M, Hu G, Qiao C. ATP13A2 protects dopaminergic neurons in Parkinson's disease: From biology to pathology. J Biomed Res 2022; 36(2): 98-108. http://dx.doi.org/10.7555/JBR.36.20220001 PMID: 35387901

[63] Miceli C, Leri M, Stefani M, Bucciantini M. Autophagy-related proteins: Potential diagnostic and prognostic biomarkers of aging-related diseases. Ageing Res Rev 2023; 89: 101967. http://dx.doi.org/10.1016/j.arr.2023.101967 PMID: 37270146

[64] Yi W, MacDougall EJ, Tang MY, *et al.* The landscape of Parkin variants reveals pathogenic mechanisms and therapeutic targets in Parkinson's disease. Hum Mol Genet 2019; 28(17): 2811-25. http://dx.doi.org/10.1093/hmg/ddz080 PMID: 30994895

[65] Wang XL, Feng ST, Wang ZZ, Yuan YH, Chen NH, Zhang Y. Parkin, an E3 ubiquitin ligase, plays an essential role in mitochondrial quality control in Parkinson's disease. Cell Mol Neurobiol 2021; 41(7): 1395-411. http://dx.doi.org/10.1007/s10571-020-00914-2 PMID: 32623547

[66] Menon PJ, Sambin S, Criniere-Boizet B, *et al.* Genotype–phenotype correlation in PRKN-associated Parkinson's disease. NPJ Parkinsons Dis 2024; 10(1): 72. http://dx.doi.org/10.1038/s41531-024-00677-3 PMID: 38553467

[67] Wasner K, Grünewald A, Klein C. Parkin-linked Parkinson's disease: From clinical insights to pathogenic mechanisms and novel therapeutic approaches. Neurosci Res 2020; 159: 34-9. http://dx.doi.org/10.1016/j.neures.2020.09.001 PMID: 32949666

[68] Agarwal S, Muqit MMK. PTEN-induced kinase 1 (PINK1) and Parkin: Unlocking a mitochondrial quality control pathway linked to Parkinson's disease. Curr Opin Neurobiol 2022; 72: 111-9. http://dx.doi.org/10.1016/j.conb.2021.09.005 PMID: 34717133

[69] Gonçalves FB, Morais VA. PINK1: A Bridge between Mitochondria and Parkinson's Disease. Life 2021; 11(5): 371. http://dx.doi.org/10.3390/life11050371 PMID: 33919398

[70] Chen W, Zhao H, Li Y. Mitochondrial dynamics in health and disease: Mechanisms and potential targets. Signal Transduct Target Ther 2023; 8(1): 333. http://dx.doi.org/10.1038/s41392-023-01547-9 PMID: 37669960

[71] Wang S, Long H, Hou L, *et al.* The mitophagy pathway and its implications in human diseases. Signal Transduct Target Ther 2023; 8(1): 304. http://dx.doi.org/10.1038/s41392-023-01503-7 PMID: 37582956

[72] Meng K, Jia H, Hou X, *et al.* Mitochondrial dysfunction in neurodegenerative diseases: Mechanisms and corresponding therapeutic strategies. Biomedicines 2025; 13(2): 327. http://dx.doi.org/10.3390/biomedicines13020327 PMID: 40002740

[73] Kung HC, Lin KJ, Kung CT, Lin TK. Oxidative stress, mitochondrial dysfunction, and neuroprotection of polyphenols with respect to resveratrol in Parkinson's disease. Biomedicines 2021; 9(8): 918. http://dx.doi.org/10.3390/biomedicines9080918 PMID: 34440122

[74] Zondler L, Miller-Fleming L, Repici M, *et al.* DJ-1 interactions with α-synuclein attenuate aggregation and cellular toxicity in models of Parkinson's disease. Cell Death Dis 2014; 5(7): 1350. http://dx.doi.org/10.1038/cddis.2014.307 PMID: 25058424

[75] Xu CY, Kang WY, Chen YM, *et al.* DJ-1 inhibits α-synuclein aggregation by regulating chaperone-mediated autophagy. Front Aging Neurosci 2017; 9: 308. http://dx.doi.org/10.3389/fnagi.2017.00308 PMID: 29021755

[76] Cuervo AM, Wong E. Chaperone-mediated autophagy: Roles in disease and aging. Cell Res 2014; 24(1): 92-104. http://dx.doi.org/10.1038/cr.2013.153 PMID: 24281265

[77] Huh YE, Usnich T, Scherzer CR, Klein C, Chung SJ. GBA1 variants and Parkinson's disease: Paving the way for targeted therapy. J Mov Disord 2023; 16(3): 261-78. http://dx.doi.org/10.14802/jmd.23023 PMID: 37302978

[78] Huang M, Chen S. DJ-1 in neurodegenerative diseases: Pathogenesis and clinical application. Prog Neurobiol 2021; 204: 102114. http://dx.doi.org/10.1016/j.pneurobio.2021.102114 PMID: 34174373

[79] Drobny A, Huarcaya SP, Dobert J, *et al.* The role of lysosomal cathepsins in neurodegeneration: Mechanistic insights, diagnostic potential and therapeutic approaches. Biochim Biophys Acta Mol Cell Res 2022; 1869(7): 119243. http://dx.doi.org/10.1016/j.bbamcr.2022.119243 PMID: 35217144

[80] Shin DW. Lipophagy: Molecular mechanisms and implications in metabolic disorders. Mol Cells 2020; 43(8): 686-93. http://dx.doi.org/10.14348/molcells.2020.0046 PMID: 32624503

[81] Shahmoradian SH, Lewis AJ, Genoud C, *et al.* Lewy pathology in Parkinson's disease consists of crowded organelles and lipid membranes. Nat Neurosci 2019; 22(7): 1099-109. http://dx.doi.org/10.1038/s41593-019-0423-2 PMID: 31235907

[82] Fiebelkorn IC. There is more evidence of rhythmic attention than can be found in behavioral studies: Perspective on brookshire. J Cogn Neurosci 2022; 35(1): 128-34. http://dx.doi.org/10.1162/jocn_a_01936 PMID: 36306250

[83] Suzuki M, Fujikake N, Takeuchi T, *et al.* Glucocerebrosidase deficiency accelerates the accumulation of proteinase K-resistant α-synuclein and aggravates neurodegeneration in a Drosophila model of Parkinson's disease. Hum Mol Genet 2015; 24(23): 6675-86. http://dx.doi.org/10.1093/hmg/ddv372 PMID: 26362253

[84] Zunke F, Moise AC, Belur NR, *et al.* Reversible conformational conversion of α-synuclein into toxic assemblies by glucosylceramide. Neuron 2018; 97(1): 92-107.e10. http://dx.doi.org/10.1016/j.neuron.2017.12.012 PMID: 29290548

[85] Mahoney-Crane CL, Viswanathan M, Russell D, *et al.* Neuronopathic GBA1L444P mutation accelerates glucosylsphingosine levels and formation of hippocampal alpha-synuclein inclusions. J Neurosci 2023; 43(3): 501-21. http://dx.doi.org/10.1523/JNEUROSCI.0680-22.2022 PMID: 36639889

[86] Galvagnion C, Marlet FR, Cerri S, Schapira AHV, Blandini F, Di Monte DA. Sphingolipid changes in Parkinson L444P GBA mutation fibroblasts promote α-synuclein aggregation. Brain 2022; 145(3): 1038-51. http://dx.doi.org/10.1093/brain/awab371 PMID: 35362022

[87] Chang D, Nalls MA, Hallgrímsdóttir IB, *et al.* A meta-analysis of genome-wide association studies identifies 17 new Parkinson's disease risk loci. Nat Genet 2017; 49(10): 1511-6. http://dx.doi.org/10.1038/ng.3955 PMID: 28892059

[88] Ali A, Holman AP, Rodriguez A, Osborne L, Kurouski D. Elucidating the mechanisms of α-synuclein-lipid interactions using site-directed mutagenesis. Neurobiol Dis 2024; 198: 106553. http://dx.doi.org/10.1016/j.nbd.2024.106553 PMID: 38839022

[89] Azeggagh S, Berwick DC. The development of inhibitors of leucine-rich repeat kinase 2 (LRRK2) as a therapeutic strategy for Parkinson's disease: The current state of play. Br J Pharmacol 2022; 179(8): 1478-95. http://dx.doi.org/10.1111/bph.15575 PMID: 34050929

[90] Grasso D, Galderisi S, Santucci A, Bernini A. Pharmacological chaperones and protein conformational diseases: Approaches of computational structural biology. Int J Mol Sci 2023; 24(6): 5819. http://dx.doi.org/10.3390/ijms24065819 PMID: 36982893

[91] Chen Y, Sam R, Sharma P, Chen L, Do J, Sidransky E. Glucocerebrosidase as a therapeutic target for Parkinson's disease. Expert Opin Ther Targets 2020; 24(4): 287-94. http://dx.doi.org/10.1080/14728222.2020.1733970 PMID: 32106725

[92] Clark EH, Vázquez de la Torre A, Hoshikawa T, Briston T. Targeting mitophagy in Parkinson's disease. J Biol Chem 2021; 296: 100209. http://dx.doi.org/10.1074/jbc.REV120.014294 PMID: 33372898

[93] Huq TS, Luo J, Fakih R, Sauvé V, Gehring K. Naturally occurring hyperactive variants of human Parkin. Commun Biol 2024; 7(1): 961. http://dx.doi.org/10.1038/s42003-024-06656-x PMID: 39117722

[94] Cores Á, Piquero M, Villacampa M, León R, Menéndez JC. NRF2 regulation processes as a source of potential drug targets against neurodegenerative diseases. Biomolecules 2020; 10(6): 904. http://dx.doi.org/10.3390/biom10060904 PMID: 32545924

[95] Daci R, Flotte TR. Delivery of adeno-associated virus vectors to the central nervous system for correction of single gene disorders. Int J Mol Sci 2024; 25(2): 1050.

http://dx.doi.org/10.3390/ijms25021050 PMID: 38256124

[96] Sharma N, Rao SP, Kalivendi SV. The deglycase activity of DJ-1 mitigates α-synuclein glycation and aggregation in dopaminergic cells: Role of oxidative stress mediated downregulation of DJ-1 in Parkinson's disease. Free Radic Biol Med 2019; 135: 28-37. http://dx.doi.org/10.1016/j.freeradbiomed.2019.02.014 PMID: 30796974

[97] Chen X, Tsika E, Levine N, Moore DJ. VPS35 and α-synuclein fail to interact to modulate neurodegeneration in rodent models of Parkinson's disease. Mol Neurodegener 2023; 18(1): 51. http://dx.doi.org/10.1186/s13024-023-00641-4 PMID: 37542299

[98] Filippone A, Praticò D. Endosome dysregulation in down syndrome: A potential contributor to Alzheimer disease pathology. Ann Neurol 2021; 90(1): 4-14. http://dx.doi.org/10.1002/ana.26042 PMID: 33547827

[99] Grabowski GA, Golembo M, Shaaltiel Y. Taliglucerase alfa: An enzyme replacement therapy using plant cell expression technology. Mol Genet Metab 2014; 112(1): 1-8. http://dx.doi.org/10.1016/j.ymgme.2014.02.011 PMID: 24630271

[100] Hernandez-Diaz S, Soukup SF. The role of lipids in autophagy and its implication in neurodegeneration. Cell Stress 2020; 4(7): 167-86. http://dx.doi.org/10.15698/cst2020.07.225 PMID: 32656499

[101] Oh S, Lee J, Choi HJ, *et al.* Discovery of selective inhibitors for the lysosomal Parkinson's disease channel TMEM175. J Am Chem Soc 2024; 146(33): 23230-9. http://dx.doi.org/10.1021/jacs.4c05623 PMID: 39116214

[102] Pereira SL, Grossmann D, Delcambre S, Hermann A, Grünewald A. Novel insights into Parkin-mediated mitochondrial dysfunction and neuroinflammation in Parkinson's disease. Curr Opin Neurobiol 2023; 80: 102720. http://dx.doi.org/10.1016/j.conb.2023.102720 PMID: 37023495

[103] Rusmini P, Cortese K, Crippa V, *et al.* Trehalose induces autophagy *via* lysosomal-mediated TFEB activation in models of motoneuron degeneration. Autophagy 2019; 15(4): 631-51. http://dx.doi.org/10.1080/15548627.2018.1535292 PMID: 30335591

[104] Rahman AA, Morrison BE. Contributions of VPS35 mutations to Parkinson's disease. Neuroscience 2019; 401: 1-10. http://dx.doi.org/10.1016/j.neuroscience.2019.01.006 PMID: 30660673

[105] Sánchez-Fernández EM, García Fernández JM, Mellet CO. Glycomimetic-based pharmacological chaperones for lysosomal storage disorders: Lessons from Gaucher, G_{M1} -gangliosidosis and Fabry diseases. Chem Commun 2016; 52(32): 5497-515. http://dx.doi.org/10.1039/C6CC01564F PMID: 27043200

[106] Schulze MSED, Scholz D, Jnoff E, *et al.* Identification of ß-glucocerebrosidase activators for glucosylceramide hydrolysis. ChemMedChem 2024; 19(7): 202300548. http://dx.doi.org/10.1002/cmdc.202300548 PMID: 38381042

[107] Skou LD, Johansen SK, Okarmus J, Meyer M. Pathogenesis of DJ-1/PARK7-mediated parkinson's disease. Cells 2024; 13(4): 296. http://dx.doi.org/10.3390/cells13040296 PMID: 38391909

[108] Tang FL, Liu W, Hu JX, *et al.* VPS35 deficiency or mutation causes dopaminergic neuronal loss by impairing mitochondrial fusion and function. Cell Rep 2015; 12(10): 1631-43. http://dx.doi.org/10.1016/j.celrep.2015.08.001 PMID: 26321632

[109] Wie J, Liu Z, Song H, *et al.* A growth-factor-activated lysosomal K^+ channel regulates Parkinson's pathology. Nature 2021; 591(7850): 431-7. http://dx.doi.org/10.1038/s41586-021-03185-z PMID: 33505021

[110] Tarozzi A, Angeloni C, Malaguti M, Morroni F, Hrelia S, Hrelia P. Sulforaphane as a potential protective phytochemical against neurodegenerative diseases. Oxid Med Cell Longev 2013; 2013: 1-10. http://dx.doi.org/10.1155/2013/415078 PMID: 23983898

[111] Taylor M, Alessi DR. Advances in elucidating the function of leucine-rich repeat protein kinase-2 in normal cells and Parkinson's disease. Curr Opin Cell Biol 2020; 63: 102-13. http://dx.doi.org/10.1016/j.ceb.2020.01.001 PMID: 32036294

[112] Thakur G, Kumar V, Lee KW, Won C. Structural insights and development of lrrk2 inhibitors for Parkinson's disease in the last decade. Genes 2022; 13(8): 1426. http://dx.doi.org/10.3390/genes13081426 PMID: 36011337

[113] Wang D, Tai PWL, Gao G. Adeno-associated virus vector as a platform for gene therapy delivery. Nat Rev Drug Discov 2019; 18(5): 358-78. http://dx.doi.org/10.1038/s41573-019-0012-9 PMID: 30710128

[114] Wang J, Sun X, Cheng L, *et al.* What we know about TMEM175 in Parkinson's disease. CNS Neurosci Ther 2025; 31(1): 70195. http://dx.doi.org/10.1111/cns.70195 PMID: 39834146

[115] Wang J, Zhu M, Sun J, *et al.* Gene therapy of adeno-associated virus (AAV) vectors in preclinical models of ischemic stroke. CNS Neurosci Ther 2023; 29(12): 3725-40. http://dx.doi.org/10.1111/cns.14392 PMID: 37551863

[116] Wojewska DN, Kortholt A. LRRK2 targeting strategies as potential treatment of Parkinson's disease. Biomolecules 2021; 11(8): 1101. http://dx.doi.org/10.3390/biom11081101 PMID: 34439767

[117] Williams ET, Chen X, Otero PA, Moore DJ. Understanding the contributions of VPS35 and the retromer in neurodegenerative disease. Neurobiol Dis 2022; 170: 105768. http://dx.doi.org/10.1016/j.nbd.2022.105768 PMID: 35588987

[118] Zhao HT, John N, Delic V, *et al.* LRRK2 antisense oligonucleotides ameliorate α-synuclein inclusion formation in a Parkinson's disease mouse model. Mol Ther Nucleic Acids 2017; 8: 508-19. http://dx.doi.org/10.1016/j.omtn.2017.08.002 PMID: 28918051

[119] Lim SY, Klein C. Parkinson's disease is predominantly a genetic disease. J Parkinsons Dis 2024; 14(3): 467-82. http://dx.doi.org/10.3233/JPD-230376 PMID: 38552119

[120] Imbriani P, Martella G, Bonsi P, Pisani A. Oxidative stress and synaptic dysfunction in rodent models of Parkinson's disease. Neurobiol Dis 2022; 173: 105851. http://dx.doi.org/10.1016/j.nbd.2022.105851 PMID: 36007757

[121] Dong-Chen X, Yong C, Yang X, Chen-Yu S, Li-Hua P. Signaling pathways in Parkinson's disease: Molecular mechanisms and therapeutic interventions. Signal Transduct Target Ther 2023; 8(1): 73. http://dx.doi.org/10.1038/s41392-023-01353-3 PMID: 36810524

[122] Jennings D, Huntwork-Rodriguez S, Vissers MFJM, *et al.* LRRK2 Inhibition by BIIB122 in healthy participants and patients with Parkinson's disease. Mov Disord 2023; 38(3): 386-98. http://dx.doi.org/10.1002/mds.29297 PMID: 36807624

[123] Ding Y, Klomparens EA. The neuroprotective mechanisms and effects of sulforaphane. Brain Circ 2019; 5(2): 74-83. http://dx.doi.org/10.4103/bc.bc_7_19 PMID: 31334360

[124] Lee S, Lee S, Lee SJ, Chung SW. Inhibition of mitoNEET induces Pink1-Parkin-mediated mitophagy. BMB Rep 2022; 55(7): 354-9. http://dx.doi.org/10.5483/BMBRep.2022.55.7.040 PMID: 35725011

[125] Liu L, de Leeuw K, van Goor H, Westra J. The role of antioxidant transcription factor NRF2 and its activating compounds in systemic lupus erythematosus. Antioxidants 2024; 13(10): 1224. http://dx.doi.org/10.3390/antiox13101224 PMID: 39456477

[126] Madsen HB, Navarro C, Gasparini E, *et al.* Urolithin A and nicotinamide riboside differentially regulate innate immune defenses and metabolism in human microglial cells. Front Aging Neurosci 2024; 16: 1503336. http://dx.doi.org/10.3389/fnagi.2024.1503336 PMID: 39665042

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