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Review

Targeted protein degradation for the treatment of Parkinson's disease: Advances and future perspective

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ABSTRACT

Parkinson's disease (PD) is a progressive disorder that belongs to a class of neurodegenerative disorders (NDs) called Synucleinopathies. It has characterized by the misfolding and aggregation of a-synuclein. Our understanding of PD continues to evolve, and so does our approach to treatment. including therapies aimed at delaying pathology, quitting neuronal loss, and shortening the course of the disease by selectively targeting essential proteins suspected to play a role in PD pathogenesis. One emerging approach that is generating significant interest is Targeted Protein Degradation (TPD). TPD is an innovative method that allows us to specifically break down certain proteins using specially designed molecules or peptides, like PROteolysis-TArgeting-Chimera (PROTACs). This approach holds great promise, particularly in the context of NDs. In this review, we will briefly explain PD and its pathogenesis, followed by discussing protein degradation systems and TPD strategy in PD by reviewing synthesized small molecules and peptides. Finally, future perspectives and challenges in the field are discussed.

1. Introduction

Parkinson's disease (PD) is the world's second most prevalent neurological ailment, trailing only Alzheimer's disease (AD). It falls into the neurological classification of synucleinopathies, characterized by abnormal fibers and a-synuclein accumulation, affecting countless individuals worldwide. Reported PD adults up to 60 years of age and back in the United States reached 1%. Worldwide, PD is believed to exhibit an

Abbreviations: AD,, Alzheimer's Disease; AUTOTAC, AUTOphagy TArgeting Chimera; AUTAC, Autophagy Targeting Chimera; ATTEC, Autophagosome Tethering Compound; ATF4, Activating Transcription Factor; ALP, Autophagy Lysosomal Pathways; Aβ42, Amyloid Beta 42; BBB, Blood Brain Barrier; BDNF, Brain Derived Neurotrophic Factor; BAG5, Bcl-2 Associated Athanogene 5; BiP, Immunoglobulin Protein; CMA, Chaperone Mediated Autophagy; CHIP, Chromatin Immunoprecipitation; E1, Ubiquitin Activating Enzyme; E2, Ubiquitin Conjugating Enzymes; ER, Endoplasmic Reticulum FTD, Fas, Fatty AcidsFrontotemporal Dementia; GBA, Glucocerebrosidase; Hsp70, Heat Shock Protein 70; LBs, Lewy bodies; LRRK2, Leucine-rich repeat kinase 2; LYTAC, Lysosome Targeting Chimera; MFN, Mitofusin; MAPT, Microtubule Associated Protein Tau; MAO-B, Monoamine Oxidase-B; MAO-A, Monoamine Oxidase-A; MSA, Multiple system atrophy; NFATs, ND, Neurodegenerative DiseaseNuclear Factor of Activated T cells; NFTs, Neurofibrillary Tangles; PD, Parkinson Disease; PINK1, PTEN-induced putative kinase; PGC-1α, Peroxisome Proliferator Activated Receptor Gamma Coactivator 1-alpha; PROTAC, PROteolysis-Targeting Chimera; RAB, Ras-associated Binding; hTau, human Tau; TRKB, Tropomyosin receptor kinase B; TOI, Target Of Interest; p Tau, Phosphorylated Tau; TPD, Targeted Protein Degradation; t Tau, Total Tau; TUFm, Elongation Factor Tu; TXNIP, Thioredoxin Interacting Protein; UPR, Unfolded Protein Response; UPS, Ubiquitin Proteasome System; UCHL1, Ubiquitin Carboxy Terminal Hydrolase L1.

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annual incidence rate ranging from 5 to 35 cases per 100,000 population [108]. The global preponderance, evaluated at 0.3%, increases dramatically with age, reaching > 3% in people over 80 [114]. According to the Global Hurdle of Disease Study, the number of people living with PD will be duplicated from around 7 million in 2015 to about 13 million in 2040 [43]. PD is a progressive neurodegenerative disease (NDs) represented by bradykinesia(relates to the delay of *a* voluntary movement, which may be related to slow programming to generate instructions and/or slow processing of such commands), rest tremor (limb, hand, or foot) is not deliberately engaged and fully sustained against gravity, it exhibits a repetitive, reflexive oscillatory movement), and rigidity(characterized as enhanced difficulty felt when passively moving body components), as well as postural instability(Impaired balance jeopardizes the ability to maintain pose), a variety of other minor motor symptoms, and a variety of non-motor abnormalities such as cognitive impairment, autonomic dysfunction, disorders of sleep, depression and hyposmia [108,149]. PD is presently diagnosed as a multifaceted ailment regarding genetic variables, either causal or susceptibility editions, some environmental pollutants including pesticides, metals, industrial chemical substances, and the possibly interaction of each [149]. The current medical care of PD attempts to preserve the manipulation of signs and symptoms while decreasing aspect effects to halt the sickness's continuous route are urgently desired [27]. PD is defined by neuronal loss in particular regions of the substantia nigra and expansive accumulation of the intracellular protein α-synuclein. In the early stages of the disease, dopaminergic neuron loss is localized to the ventrolateral substantia nigra, with other midbrain dopaminergic neurons remaining relatively unaffected but becoming more widespread by the end stages [39,45]. Another important neuropathology is the abnormal accumulation of α-synuclein in the cytoplasm of specific neurons in many brain regions as Lewy bodies (LBs). Lewy pathology is initially patterned in cholinergic and monoaminergic brain stem cells, as well as neurons of the olfactory system, but progresses to limbic and neocortical brain regions [22].

As our understanding of the etiology of PD progresses, treatment strategies are being developed. These include therapies aimed at prolonging disease, halting neuronal loss, and shortening the disease course by targeting important proteins thought to play a role in PD pathogenesis, such as α selective upregulation of α-synuclein and leucine-rich repeat kinase 2 (LRRK2) [117].

Targeted Protein Degradation (TPD) is a novel drug discovery method lately gaining tremendous interest. This approach will enable selective degradation of the desired goal by using synthesizing heterobifunctional small molecules or peptides. TPD has an exceedingly high ability for drug discovery in NDs. In neurodegenerative conditions, proteins along with tau protein and α-synuclein are involved, which are undruggable in conventional modalities. TPD, then again, can pass this trouble. Therefore, TPD can also supply proper insights into the evolution of recent drugs for PD (Fig. 1).

We will explain PD and its pathogenesis briefly in this review. Following that, we're going to speak about protein degradation systems in PD. Finally, we look at the TPD strategy in PD by reviewing synthesized small molecules and peptides and comparing the sector's destiny perspective and demanding situations.

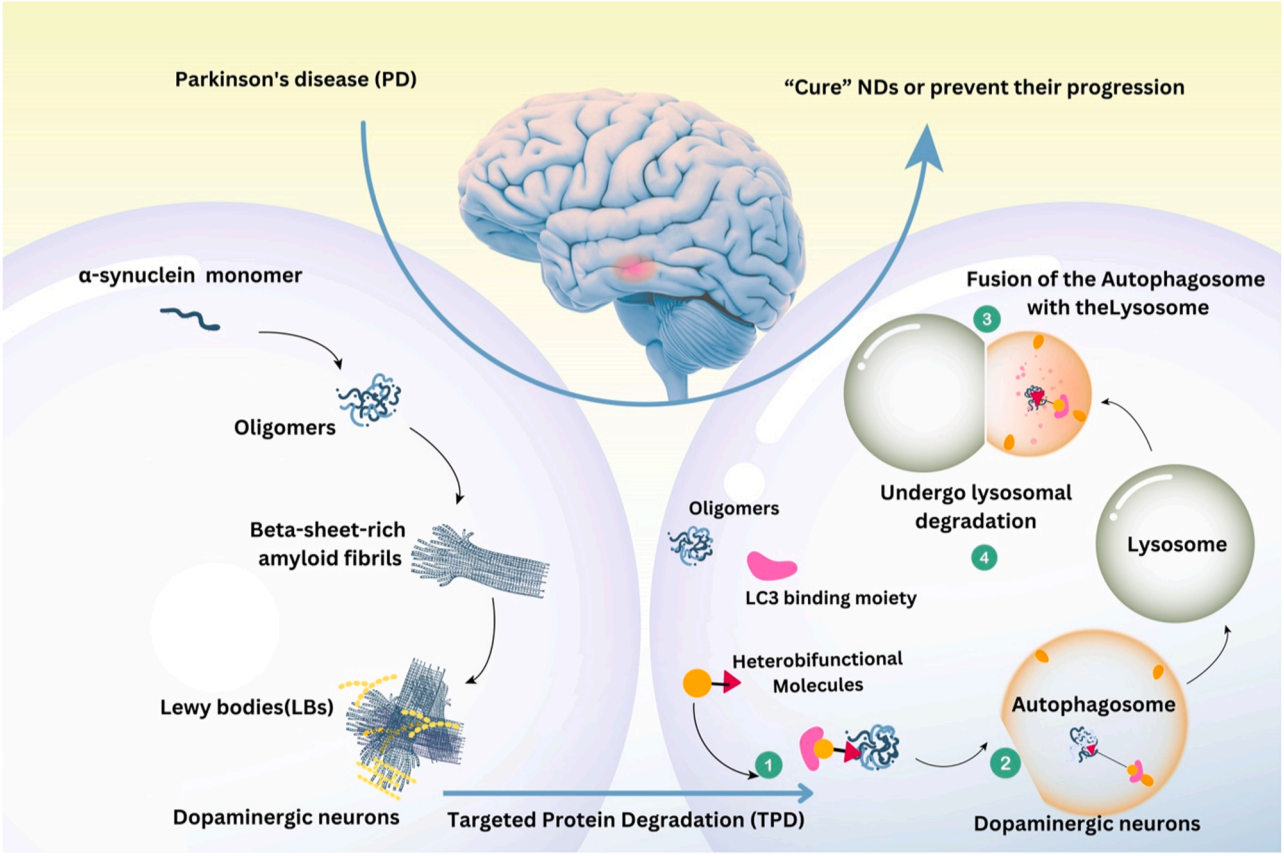

Fig. 1. The schematic illustration of the primary role of alpha-synuclein in the evolution of Parkinson's disease. Instability in the protein structure and moving towards the composition of toxic aggregates, particularly in the form of oligomers, and eventually the formation of Lewy bodies in the neurons. The right side showed that via the Targeted Protein Degradation (TPD) approach, toxic oligomer accumulations can be targeted and then degraded by the cellular degradation system such as the autophagy-lysosome system, which eventually prevents the progression of Parkinson's disease or ultimately treated the disorder.

2. Parkinson's disease

The past centuries proceed in comprehension of the pathophysiology of PD and the molecular, neurophysiological, and behavioral approaches that underpin the disorder and its signs have advanced our expertise and capability to deal with the condition [10,110].

The primary etiology of PD is not completely comprehended. Neuronal loss in some regions of the substantia nigra and intracellular assemblage of α-synuclein is the pathological hallmark of PD. Losing dopaminergic neurons in the substantia nigra and the deposit of α-synuclein in neurons are not precise to PD, which can be observed in synucleinopathies diseases like dementia LBs, Multiple system atrophy (MSA) [45]. However, when applied together, they are typical for a decisive diagnosis of idiopathic PD. Heritable types of PD showed point mutations (Ala53Thr, Ala30Pro, and Glu46Lys) and upsurges in the α-synuclein (SNCA) gene, which codes for α-synuclein; also, a single-nucleotide variation at the SNCA gene modifies the risk of developing sporadic PD and is related with more significant α-synuclein accumulation [57].

2.1. α-Synuclein

As a ubiquitous neuronal protein α-synuclein is localized mainly on presynaptic terminals and regulates synaptic vesicle trafficking - an essential function for neural activity regulation. The conserved protein family that includes alpha-, beta- and gamma-synuclein first identified α-synuclein as the precursor for non-amyloid components found in AD senile plaques [133]. It exists predominantly within the brain but can also be located within red blood cells and other tissues throughout the body. α-synuclein attaches to membranes and interacts with synaptic vesicles generating membrane curvature while contributing crucially toward brain lipid metabolism - vital for neuron survival [24].

Mutations found within α-synuclein genes linked to familial PD have aimed at understanding how hyperphosphorylated α-synuclein contributes towards PD pathogenesis. α-synuclein's structure or degradation can be prompted via other genes linked with familial PD. Research indicates that this protein has a tendency toward misfolding and binds with lipids at the same time as interacting with phospholipids and fatty acids (FAs), finally aggregating in intracytoplasmic as LBs [124]. Relations between specific α-synuclein conformations and dopamine metabolism strength provoke particular degeneration of dopamine neurons [18]. Recent findings indicate it occurs due to assembling monomers into oligomers before creating beta-sheet-rich amyloid fibrils during aggregation as a result of the interplay of this protein with cells [18]. Assessing how α-synuclein impacts overall cell function from different perspectives. Such as vesicle trafficking dysfunction affects small GTPases called Ras-associated binding (RAB) proteins involved in membrane fusion and vesicle trafficking necessary for proper cellular functioning. The association between RAB proteins and vesicle trafficking of α-synuclein has been investigated via recent research findings [15,19]. Furthermore, RAB proteins have also been linked to regulating mitochondrial function and autophagy. Additionally, Tropomyosin receptor kinase B (TRKB) has emerged as a key participant in vesicle trafficking disorder related to α-synuclein. TRKB binds to neurotrophins, such as brain-derived neurotrophic component (BDNF) [70,91] which plays a vital role in retaining dopaminergic neurons and impairment of BDNF/TRKB signaling, is suggested as an underlying motive of dopaminergic neuron degeneration in PD [13,147]. Enriching TRKB signaling has been proven to defend dopaminergic neurons from degeneration in PD animal studies with the aid of modulating α-synuclein aggregation and toxicity [48,93]. Likewise, α-synuclein intervenes with Golgi functions involved in processing and packaging proteins within cells, major to an accumulation of misfolded proteins. When Golgi apparatus malfunctions occur, processing and trafficking α-synuclein could cause a buildup of the protein. The Unfolded Protein Response (UPR) is a great participant in managing the buildup of misfolded proteins within the endoplasmic reticulum (ER). The affiliation creates a bidirectional relationship between UPR and α-synuclein, as UPR regulates the expression of α-synuclein[95,129]. The ER stress induced by α-synuclein activates the UPR at the cellular level, stimulating responses facilitated by the interaction between α-synuclein and binding immunoglobulin protein (BiP), an ER-resident chaperone [125] [87]. BiP, within the ER, binds to misfolded proteins, subsequently activating the UPR to alleviate the stress associated with protein folding. Intriguingly, this process also plays a role in regulating the expression of α-synuclein [116]. By inhibiting transcription factor 4 (ATF4) activity in pathways associated with the UPR, α-synuclein levels can be modulated [42,55]. Over the latest years, studies have shed light on the impact that α-synuclein has within cellular nuclei by way of interacting with other nuclear-based total proteins like histones and DNA. Interactions with histones slow down acetylation mainly in the end to adverse adjustments in gene expression which negatively affect proper cell characteristics [40,132]. α-synuclein notably hampers normal nucleocytoplasmic shipping by way of trapping RNA molecules inside cellular nuclei leading to similar disruption in regular cellular function. One instance is proven inside the necessity of the nuclear issue of activated T cells (NFATs) for regulating both gene expression and immune responses. Within the nuclear surroundings, α-synuclein's capability to interact with NFAT has a long way-attaining effects [90,122]. Its ability to either activate or inhibit NFAT-dependent genes results in immune responses; in particular its potential to avert T cell activation [25]. Through binding with calcineurin - a regulatory protein for NFAT – α-synuclein can negatively affect signaling activity associated with this factor. Ultimately such impact could lead not only to changes in gene expression but also impairments such as DNA damage and complications within the nucleocytoplasmic transport efficacy [90]. Mitochondrial dysfunction is another consequential hallmark associated with PD through autophagy lysosomal pathway (ALP) and ubiquitin-proteasome system all under α-synuclein influence (Fig. 3) [28]. Research highlights disturbances in multiple enzymes within the autophagy dysfunction concept. Specifically, studies show how crucial enzyme ATG9's interaction with α-synuclein significantly affects its function [80,82]. The inhibition of transportation from Golgi to an autophagosome is a crucial step leading to this effect on the α-synuclein part. The complex relationship between this protein and another called protein kinase CK2 is responsible for regulating trafficking by phosphorylating ATG9. Moreover, subsequent research has unveiled a connection between the lysosomal protein LAMP2A and α-synuclein, resulting in the exacerbation of autophagic impairment. LAMP2A facilitates the regulation and degradation of the protein ATG9, but this interaction is disrupted by α-synuclein [105,140]. This disruption negatively affects the autophagy process by way of interfering with the characteristic of SNAP29, a protein involved in the fusion of autophagosomes with lysosomes. Correspondingly, overexpression of SNAP29 can recover the impairment of autophagy caused by α-synuclein [59,128,128]. The discovery that α-synuclein aggregates may be transmitted among neuronal cells has led to the hypothesis that the mechanism of aggregate propagation resembles that of prion propagation. The accumulation of α-synuclein has also been correlated to AD. Nevertheless, researchers have found remarkable patterns of pathology in individuals with AD, broadly conveying affecting localized limbic mind regions. Regarding all the above information and the association of those findings to dopaminergic neural death, Conway et al. researching rats with oligomerization-promoting mutations, observed how α- synuclein acts while attached to lipid membranes; they discovered that multimers were generated and protofibril conversion was partially blocked by dopamine and its metabolites, which could promote protofibril accumulation. This process might explain why dopamine neurons are more susceptible to toxicity caused by α-synuclein [35]. In conclusion, the need to explore the complicated interaction between α-synuclein and different signaling pathways concerned with NDs, It is also vital to recall the heterogeneity of those disorders, as they present a complex quandary in terms of

interventions, and take years to expand in consequence of different factors, making it hard to decide precise remedy goals. Still, there is desire as researchers make advances in genetic and molecular technologies and accumulate extra nuanced statistics about the vital role of α-synuclein in the improvement of these debilitating disorders.

2.2. Tau protein

Microtubule balance depends on the tau protein, that is produced through a single human gene, microtubule-associated protein tau (MAPT) located on chromosome 17. Tau proteins exist in a soluble shape inside the everyday state when unfolded and sure to microtubules. Conversely, underneath positive situations, they emerge as insoluble and related to diverse NDs including AD. Álmos et al., ($year$) [2].

Investigations indicate concurrent deposition of both tau and α-synuclein in PD patient brains due to their crosstalk resulting from physiological dysfunction and axonal transport failure, which leads to toxic fibril deposition ending up with cell death [6,7,53]. Mutations within MAPT are likely responsible for the process of tau assembly. A recent study suggests that misfolded Tau spread among cells similarly to prion disease [33]. One possible outcome of the hyperphosphorylation process is the accumulation of filaments leading to neurofibrillary tangles (NFTs) formation. This scenario happens since it impacts how the protein attaches itself to microtubules thus influencing how they all connect, hence culminating in these problematic clusters [118]. In PD patients, examination of the cerebrospinal fluid is beneficial to set up a clear dating among cognitive performance and tau. Studies have proven that people with cognitive impairment from PD had multiplied tiers of general tau (t tau) and phosphorylated tau (p tau), whilst ranges of amyloid beta forty-two (Aβ42) have been lower than those without tau [34]. In postmortem examinations conducted by Buongiorno Arima et al. and Ishizaw respectively, there was an accumulation of both tau and α-synuclein within LBs in PD or dementia with LBs individuals (Fig. 2) [23]. Likewise, Ishizawa et al. confirmed tau and α-synuclein aggregation in LBs indicated that tau-immunoreactive LBs were located in neurons susceptible to NFTs, such as the locus coeruleus and Meynert's basal nucleus [61]. More research is needed to acquire a complete understanding of the PD pathogenesis due to tau and α-synuclein interactions which can identify effective therapies targeting these molecular and cellular pathways.

2.3. LRRK2

LRRK2 is an inherited gene that has received much attention among PD patients in recent times due to its significant association with the disorder. In particular, various studies have demonstrated that mutations in this gene cause PD. Interestingly LRRK2 plays critical roles in different cellular processes such as vesicular trafficking and endosomal transport while also regulating mitochondrial morphology and calcium levels within the mitochondria [29,62,123,134]. Also, there is a direct connection between this gene product's kinase activity and cytoskeleton dynamics evidenced by LRRK2 phosphorylation of some key substrates like moesin ezrin and radixin among others. The role of this protein also includes constraining microtubule dynamics essential for maintaining neuronal structures' structural integrity, enabling efficient communication among brain cells. Gillardon ($year$) [51,62]. When mutations arise within the genetic code for LRRK2 proteins, it results in autophagy dysfunction that leads to problems breaking down α-synuclein. This causes an accumulation of proteins and creates a negative impact on various diseases. Through examining transgenic mice expressing specific

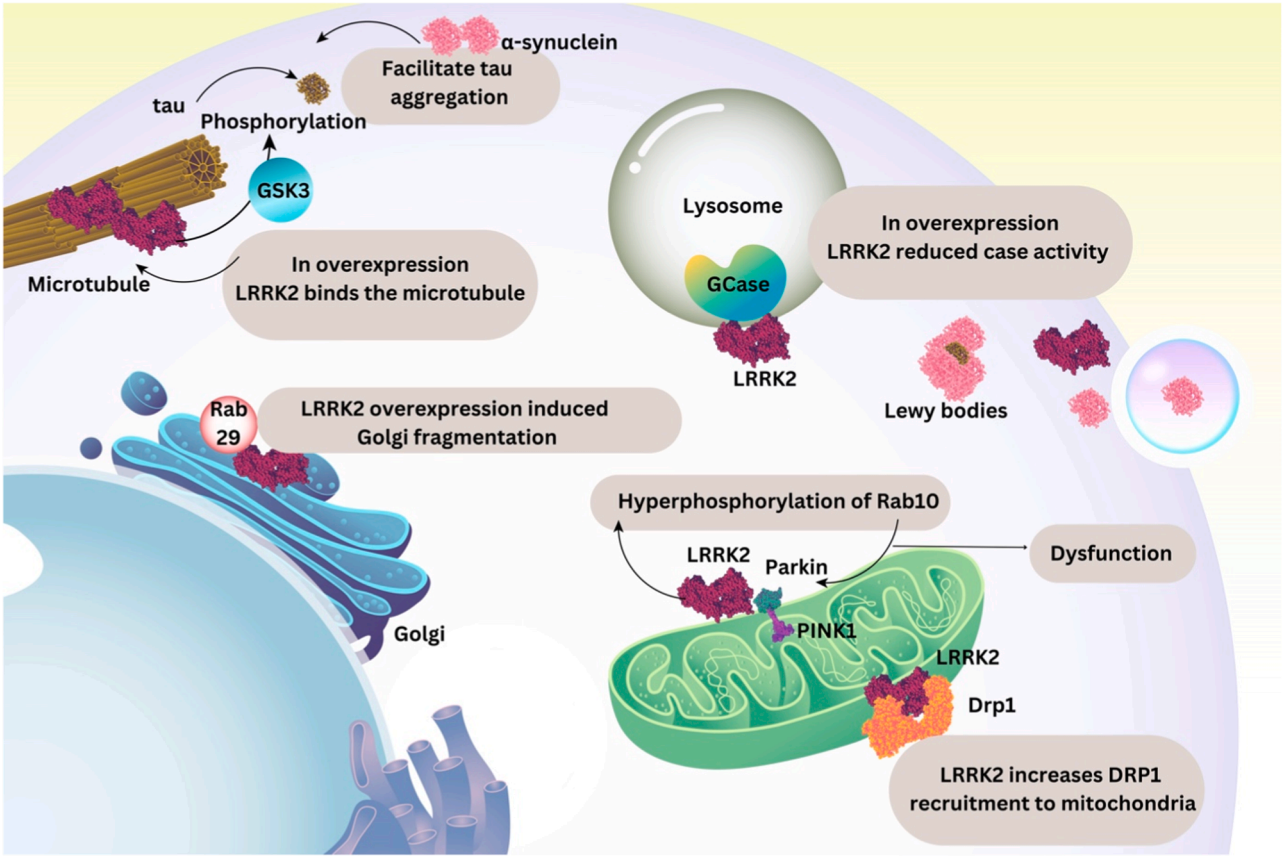

Fig. 2. Schematic illustration of PDs pathways between α-synuclein, tau, and LRRK2 connections become apparent. Specifically implicated is the role that LRRk2 plays in both GSK-induced tau hyperphosphorylation and α-synuclein inducing tau aggregates. Furthermore overexpressing LRRk2 results in mitochondrial dysfunction via Drp1 and Rab10 while also impacting Golgi fragmentation.

mutations scientists were able to obtain a more profound understanding of how α-synuclein and LRRK2 are interconnected functionally [148].

Their research also showed that when overexpressed, both wild-type (WT) and mutant forms of LRRK2 exacerbated neuropathological changes caused by α-synuclein; while animals deficient in LRRK2 had only moderate alterations accompanied by elevated levels of accumulated α-synuclein when the Ala53Thr mutation was present. Besides pathologic conditions linked with altered genes of LRRKs, that have been associated with abnormal tau aggregates through several recent studies implying its fundamental role under healthy scenarios and under normal situations involving mutant forms of LRRKs genes responsible for NDs processes like PDs. Taken together, the available data points firmly towards LRRK2's ability to directly impact microtubule resilience [86]. Evidence revealed that the Ala53Thr mutation generated moderate neuropathological alterations in animals deficient in LRRK2. The means by which this is achieved include increasing tau phosphorylation through GSK3 or Ste20 kinases as well as expanding the tubulin phosphorylation (Fig. 2) [84,143]. Discoveries linking LRRK2 to PD-targeted therapies for treating or preventing this condition are gaining traction among researchers. Current treatments only address symptoms without focusing on the underlying issue of toxic protein accumulation within the brain. Targeted approaches such as manipulating interactions between signaling pathways or regulating LRRK2 activities had more promising results in effectively treating PD. Small molecule inhibitors that block kinase activity of LRRK2 have undergone preclinical studies displaying encouraging outcomes by reducing toxic protein buildup [63,64]. Besides investigating interactions between LRRK2 and signaling pathways exploring other proteins involved may offer insight into discovering novel path-breaking strategies to address NDs. With researchers dedicated to studying its molecular mechanisms, a picture has emerged of promising protein targets that may offer viable options for therapeutic intervention. If successful such approaches may cause transformative strides against conditions like PD and other debilitating diseases that rob people of their health and quality of life.

3. Protein degradation machinery in PD disease

Protein degradation constitutes a pivotal physiological process, the disruption or dysregulation of which can precipitate diverse pathological conditions. s. This regulated protein catabolism is primarily orchestrated through two fundamental pathways: the ubiquitin-proteasome system (UPS) and the autophagy-lysosomal system. The UPS assumes a central role in the degradation of short-lived proteins, distinguished by its capacity to confer precise specificity and temporal control. This precision is instrumental in governing the homeostatic levels of numerous regulatory proteins. Additionally, UPS-mediated catabolism assumes a vital role in conserving amino acid resources during periods of critical nutrient deprivation and contributes to the degradation of malfunctioning proteins [103]. Conversely, autophagy represents a highly efficient intracellular mechanism tailored for the degradation and recycling of long-lived proteins and organelles. The initiation of autophagic vacuole formation is prompted by a spectrum of extracellular and intracellular triggers. These triggers encompass nutritional deprivation, hormonal or pharmacological interventions, bacterial infections, the presence of aggregated or misfolded proteins, and organelle damage [74].

3.1. The ubiquitin proteasome system

The UPS serves as the primary machinery liable for the degradation of a wide range of intracellular proteins, with the notable exception of membrane and extracellular proteins, which can be routed for degradation through the lysosomal pathway following endocytosis.

The process of UPS-mediated protein degradation commences with the attachment of a polyubiquitin chain to a specific lysine residue on the target protein. This ubiquitination marks the protein for degradation, and it is subsequently recognized and processed by the 26 S proteasome, a sophisticated proteolytic complex [17,102]. The UPS system plays a pivotal role in maintaining protein quality control and reducing the accumulation of misfolded and aggregated proteins associated with NDs [109]. This polyubiquitination process entails a series of enzyme-mediated steps to activate ubiquitin, resulting in a thiol ester bond formation with a cysteine residue through ATP-dependent glycine conjugation in ubiquitin (Hochstrasser, 1996). Active ubiquitin is then transported to ubiquitin-conjugating enzymes (E2s), and in concert with a specific E3 ligase, it is appended to the substrate protein, thereby marking it for subsequent degradation by the 26 S proteasome. Notably, a minimum of four ubiquitin moieties is required for efficient proteasome targeting. E3s recreate a consequential function in the selectivity of ubiquitination and substrate recognition [102]. Several studies show that UPS disruption is critical in initiating and aggravating the pathophysiology of NDs. The accumulation of α-synuclein, ubiquitin, and additional proteins buildup the LBs, which promotes languishing dopaminergic neurons in the substantia nigra in idiopathic PD. This accumulation suggests that impaired protein degradation, whether due to insufficient processing or abnormal aggregation, may contribute to neuronal demise. In fact, research dating back to 2001 indicated that inhibition of the ubiquitin-proteasome system could lead to altered protein handling and LB formation, potentially elucidating the degeneration of the nigrostriatal pathway in idiopathic PD [94].

Genetic evidence strongly supports UPS dysfunction as an underlying factor in PD pathogenesis. Variants associated with PD have been identified in genes such as PARK2 and Ubiquitin carboxy-terminal hydrolase L1 (UCHL1), which encode the ubiquitin E3 ligase parkin and the deubiquitinating enzyme UCHL1, respectively [76,92]. Mutations in DJ-1 and PINK1 genes also lead to a recessively inherited form of PD, likely through loss-of-function mechanisms [20,130]. Parkin, an E3 ubiquitin ligase, plays a pivotal role in polyubiquitinating various protein substrates, marking them for degradation by the 26 S proteasomal complex [99].

Furthermore, Parkin, PINK1, and DJ-1 were shown to form a complex known as the PPD complex, facilitating the degradation of Parkin substrates via ubiquitination. Deficiency in Pink1 or Dj-1 results in decreased ubiquitination of endogenous Parkin substrates, leading to their accumulation [144]. This investigation recognized an applicable ubiquitin E3 ligase complex composed of PD disease-associated Parkin, PINK1, and DJ-1 that promotes the destruction of unfolded and misfolded proteins and implies that their PD-pathogenic mutations damage the complex's E3 ligase activity, which may represent a mechanism underlying PD pathogenesis. To enhance the UPS function, C-terminus of HSC70-interacting protein (CHIP), an E3 ligase, can stimulate Parkin E3 function by inhibiting the HSP90 chaperone [60]. By increasing the activity of the CHIP E3 ligase and inhibiting the HSP90 chaperone, the harmful consequences of LRRK2 can be avoided [77]. Kalia et al. Kalia et al., ($year$) [69] established that CHIP was found to ubiquitinate α-synuclein in vitro, and its interaction with Bcl-2-associated athanogene 5 (BAG5) via heat shock protein 70 (Hsp70) inhibits CHIP's E3 ubiquitin ligase activity, ultimately reducing α-synuclein ubiquitination. These collective findings underscore the pivotal role of UPS dysfunction in PD pathogenesis and hint at potential therapeutic targets.

3.2. Autophagy

Autophagy constitutes a pivotal catabolic process accountable for the sequestration and shipping of misfolded proteins and aberrant cytoplasmic components to the lysosome for degradation. This intricate autophagic method manifests in 3 distinct subtypes, every delineating a particular pathway for shipping to the lysosome: Macroautophagy, Microautophagy, and chaperone-mediated autophagy (CMA) [75].

Macroautophagy, the most prominent among these autophagic subtypes, is characterized by the formation of a flattened membrane structure known as the phagophore. This phagophore undergoes a multi-

step transformation driven by specific signaling pathways, ultimately culminating in the formation of the autophagosome, a double-membraned vesicle [54]. Notably, this process necessitates coordinated interactions among the ER, Golgi apparatus, and mitochondria, orchestrating the assembly of essential autophagy-related proteins such as Beclin1. Concurrently, the lysosome assumes its role in engulfing the sequestered cytosolic components. Macro and microautophagy mechanisms efficiently eliminate bulky and redundant cellular structures. In tandem with micro and macroautophagy, CMA operates with the primary objective of disposing of misfolded proteins. CMA accomplishes this mission by specifically ferrying these aberrant proteins to the lysosome for degradation [52].

Furthermore, the intricate ultrastructural analysis of autophagosomes in the brains of individuals with PD was meticulously undertaken by Anglade et al. Anglade et al., ($year$) [4]. Their findings illuminated a substantial presence of phospho-ERK-tagged mitochondria, signifying an aberrant mitophagy process associated with the disease. Intriguingly, the study also revealed a reduction in autophagy, CMA, and mitophagy activities within vulnerable brain regions of PD patients.

In the realm of hereditary PD, mutations represent the predominant causative factors, with a significant proportion attributed to genetic aberrations within the LRRK2 (PARK8) and SNCA genes. These genetic anomalies, either in the form of mutations or as risk factors predisposing individuals to the disorder, exhibit finely tuned involvement in regulating the autophagy pathway. Specifically, among the LRRK2 gene mutations, G2019S and R1441C have emerged as focal points of investigation due to their recurrent occurrence. These mutations have demonstrated a pronounced association with autophagy processes, characterized by heightened kinase activity and alterations in GTPase activity. Intriguingly, the LRRK2 protein boasts eight discernible putative motifs associated with chaperone-mediated autophagy (CMA). Consequently, LRRK2 experiences degradation within lysosomes via CMA or through the ubiquitin-proteasome system, delineating a distinctive route that bypasses macroautophagy [104]. Conversely, the G2019S mutation exerts a distinct influence by enhancing macroautophagy, ushering in a sustained surge in autophagosome formation via a calcium-dependent pathway. This augmentation is further underscored by elevated levels of the autophagy receptor p62, which effectively compensates for the compromised CMA pathway.

The macroautophagic enhancement spans across both somatic and neuritic compartments, prominently involving the pivotal autophagy gene Atg7. This orchestrated sequence of events culminates in the rescue of neurons from neurite abbreviation, and the deactivation of LC3 serves as a potent mechanism for safeguarding primary neurons against dendritic degeneration catalyzed by the G2019S mutation [30,107].

Further substantiating the role of LRRK2 in augmenting macroautophagy, recent research has unveiled that LRRK2 exacerbates cytotoxicity by intervening in aggresome formation and the autophagic clearance of accumulated protein aggregates. This revelation was underscored by experiments involving dopaminergic neurons derived from pluripotent cells of PD patients carrying LRRK2 mutations, which showcased noteworthy alterations in macroautophagy and heightened levels of α-synuclein protein [115].

Another noteworthy gene implicated in the modulation of the autophagy system within the context of PD is PINK1, which fulfills a dual role in this intricate process. PINK1 gene mutations have been distinctly associated with both the recessively inherited and sporadic onsets of PD, characterized as PARK6. In essence, PINK1 contributes significantly to the rigorous oversight of the organelle network, a function primarily centered on the precise elimination of dysfunctional mitochondria. PINK1 operates as a mitophagy stimulator, orchestrating the targeted removal of impaired mitochondria. Conversely, it can assume the role of a mitophagy inhibitor through the phosphorylation of the translation elongation factor Tu (TUFm) at Ser222, thereby shielding mitochondria from wholesale degradation [85].

Another critical player in PINK1's involvement in autophagy dysfunction is Drp1. The underlying mechanism revolves around PKA, a PINK1 substrate, with the dephosphorylation of Drp1 at this site triggering enhanced fission and mitophagy. The activation of PKA by PINK1 serves to displace PKA from the mitochondria, facilitating Drp1-mediated mitochondrial cleavage [56]. Furthermore, PINK1-mediated phosphorylation at Ser156 enhances mitophagy by promoting the degradation of RhoT1/2, while phosphorylation at Thr298/299 curtails the degradation of RhoT1/2 [98,120].

PINK1 assumes a pivotal role in orchestrating the trafficking of parkin to dysfunctional mitochondria, which subsequently undergo autophagic degradation. Parkin labels these malfunctioning mitochondria via ubiquitination of the outer mitochondrial membrane, encompassing proteins like mitofusin (MFN), VDAC, Fis1, and TOM20. This ubiquitination marks them for recognition by macroautophagy/autophagy receptors, subsequently facilitating their integration into phagophores. This well-coordinated process culminates in their eventual incorporation into phagophores, with LC3 serving as a key facilitator in this complex autophagic cascade [50,151]. The interplay of PINK1 and parkin genes serves as a safeguard against mitochondrial degradation and profoundly impacts the persistence of impaired mitochondria, which would otherwise precipitate cellular demise. Notably, mutations in several genes implicated in PD pathogenesis can lead to a deficiency in mitophagy through similar mechanistic pathways [58].

Furthermore, the DJ-1 (Park7) gene also falls under scrutiny, with mutations in this gene associated with PD, characterized by mitochondrial dysfunction and heightened oxidative stress levels. DJ-1 encodes a protective protein within the C56 family, which acts as a peptidase. These proteins are highly responsive to oxidative stress and are instrumental in shielding dopaminergic neurons from the perils of mitochondrial dysfunction and oxidative stress. Research has illuminated DJ-1's role as a regulator of the autophagic process, thus corroborating its significance in PD pathogenesis (V Bonifati et al.). Mutations within the DJ-1 gene lead to the misalignment of its protein function, resulting in the dysregulation of reactive oxygen species and culminating in stress-induced Parkin mobilization and mitophagy [67,79]. Andres-Mateos et al. have elucidated the intricate involvement of DJ-1 within the mitochondrial thioredoxin/apoptosis signal-regulating kinase 1 (Trx/Ask1) complex, revealing its role as an atypical peroxiredoxin-like peroxidase that effectively scavenges H2O2 through Cys-10 oxidation. Notably, CMA selectively orchestrates the removal of oxidatively damaged DJ-1. Consequently, mutations in the DJ-1 motif have the potential to disrupt the CMA-mediated degradation of DJ-1. The CMA-DJ-1 pathway emerges as a pivotal regulator of mitochondrial morphology, effectively counteracting cytotoxicity arising from PD-related neurotoxins. This signifies that any disturbance in this pathway could shed light on the neuronal deficits witnessed during PD progression [150].

Insights garnered from in-vitro and in-vivo studies on flies underscore a significant elevation in DJ-1 modification. Aged flies exhibit heightened vulnerability to oxidative stress, coupled with a noticeable augmentation in DJ-1b alterations triggered by oxidative stimuli [97].

Turning to the subsequent protagonist in PD pathology, the neurotoxic α-synuclein, it's important to highlight its role in neurodegeneration and lysosomal dysfunction. In sporadic PD, mutations in the α-synuclein gene, particularly the Ala53Thr and Ala30Pro mutations associated with PD, alongside the wild-type α-synuclein protein's dopamine modification, curtail CMA function, impeding the degradation of pertinent substrates [36]. Yang et al. Yang et al., ($year$) [145] further delved into α-synuclein's influence on autophagy dysfunction, elucidating how CMA inhibition leads to the accumulation of inactive MEF2D in the cytoplasm. Importantly, their findings unveil that both the wild-type α-synuclein and its mutant forms disrupt the MEF2D-Hsc70 interaction, ultimately triggering neuronal demise.

A significant body of evidence highlights the intricate interplay between α-synuclein's pathobiology and mitochondrial damage, particularly at the outer mitochondrial membrane. Extensive in vitro and in

vivo studies have demonstrated that α-synuclein overexpression culminates in mitochondrial enlargement, perturbed membranes or cristae, and impaired mitochondrial complex I and IV activity. Notably, these structural aberrations persist even with relatively low α-synuclein overexpression. Interestingly, these structural irregularities are not observed in other intracellular organelles [141] [37,100,111] Su et al. have underscored the role of Thioredoxin-interacting protein (TXNIP) in stimulating oxidative stress and promoting LC3-II presentation while failing to degrade p62, a crucial autophagy substrate. This TXNIP-induced enhancement in α-synuclein aggregation is further compounded by the reduction in the expression of ATP13A2, a lysosomal membrane protein. Intriguingly, overexpression of ATP13A2 mitigates the impairment of autophagic flux and α-synuclein aggregation induced by TXNIP, ultimately contributing to the preservation of dopaminergic (DA) neurons in the substantia nigra [126]. Erviti et al.'s research underscores that the reduction in CMA is closely linked to the A53T mutation and elevated levels of wild-type α-synuclein expression. This dysregulation results in reduced LAMP2A or Hsc70 levels, ultimately leading to elevated α-synuclein levels [3].

Notably, silencing the CMA pathway through genetic downregulation of the LAMP-2a receptor in mature rat substantia nigra is associated with intracellular α-synuclein aggregation, the formation of autophagic vacuoles, and lysosomal impairment. Moreover, the mutations in Glucocerebrosidase (GBA), the lysosomal enzyme responsible for digesting the fatty substance glucocerebroside, carry an elevated risk for typical LBs-related PD. These mutations are particularly prevalent in individuals of Ashkenazi Jewish ancestry [8,49]. Also, patients with GBA mutations exhibit more severe disease progression and intensified motor symptoms compared to those without GBA mutations. This positions GBA mutations as promising biomarkers for predicting disease severity and progression in individuals with PD [11,146]. Dysfunctions within the autophagic/lysosomal device were notably found in several GCase-deficient models of the PD [1,9]. The speculation that GCase deficiency may also contribute to PD pathogenesis with the aid of compromising the autophagic system, in general, stems from the elaborate interaction between GCase activity and α-synuclein, in which reduced GCase interest leads to aberrant α-synuclein accumulation, and conversely, improved α-synuclein interferes with proper glucocerebrosidase characteristic. Notably, a study by Schondrof et al. [119] highlights the difficult affiliation between GBA1 mutations, changes in the autophagic/lysosomal device, and perturbed intracellular calcium homeostasis, all of which collectively make a contribution to the neurodegenerative panorama. Interestingly, small molecule inhibitors focused on GBA have demonstrated the ability to minimize α-synuclein aggregation and beautify motor characteristics in in-vivo PD fashions [38,46].

As we navigate through the intricate web of autophagy's involvement in PD, the convergence of multiple pathologies presents a complex challenge in fully comprehending its role. While current investigations highlight the disruptive potential of autophagic dysregulation in PD, a deeper understanding of the specific mechanisms involved demands further exploration before potential therapeutic strategies can be formulated. Despite this uncertainty, the imperative of effectively addressing PD remains undiminished. A thorough analysis of the intricate nexus between neurodegenerative pathology and dysregulated autophagic activity within neurons, influenced by disease-associated mutations or toxic insults arising from α-synuclein proteinopathies and aging processes alike, remains a crucial avenue to explore (Fig. 3).

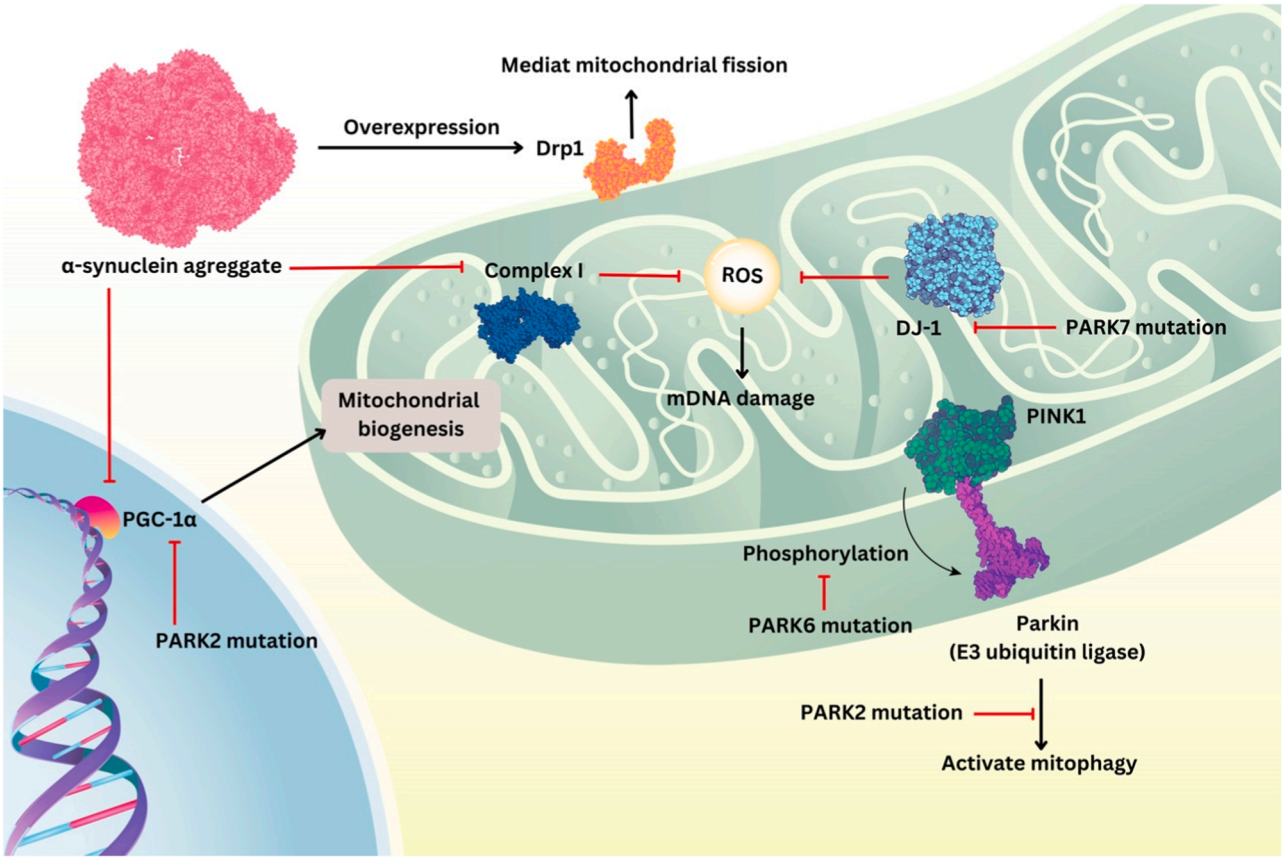

Fig. 3. The schematic illustration of interrelated contributors to compromised cellular function due to disrupted mitophagy caused by factors such as ROS accumulation inducing mDNA damage coupled with overexpression of Drp1 functions resulting in elevated fission of mitochondria. Mutations within PARK6, PARK2, and PARK7 genes reduce mitochondria's ability to trigger mitophagy through its critical pathway -PINK1/Parkin-pathway resulting in additional damage. PGC-α1 functioning negatively impacts the on-homeostasis of mitochondria which is influenced by PARK2 and α-synuclein aggregates.

4. Targeted protein degradation (TPD)

TPD represents an innovative approach in drug discovery, utilizing autophagy or the Ubiquitin-Proteasome System (UPS) to selectively degrade specific target proteins. This unique mechanism of action positions TPD as a promising strategy for addressing non-enzymatic and structurally challenging proteins that are typically beyond the scope of conventional inhibitors. Notably, TPD holds significant potential in tackling proteins associated with NDs, such as tau protein and α-synuclein. One of the most well-recognized TPD strategies is the use of PROteolysis-TArgeting-Chimeras (PROTACs). PROTACs are heterobifunctional small molecules or peptides designed to interact with both the E3 ubiquitin ligase and the target of interest (TOI). This interaction results in the formation of a ternary complex (TOI-PROTAC-UPS), triggering ubiquitination of the TOI, followed by its subsequent degradation through the UPS mechanism (Fig. 4).

The efficacy of PROTAC extends across diverse fields, including the treatment of various cancers, autoimmune diseases, and NDs [14]. In recent years, several synthesized PROTACs have advanced to the phase of clinical trials (NCT03888612, NCT04072952, NCT04886622, NCT04772885). Since the UPS is limited to monomer and oligomer proteins, larger proteins and non-protein inclusions are out of PROTAC's application. Therefore, autophagy-harnessing platforms were developed to respond to this growing need. These platforms are heterobifunctional molecules that use autophagy to selectively degrade the TOI, which can be a protein or other intracellular inclusions like lipid droplets or damaged mitochondria (Fig. 5). So far, three different small-molecule-based techniques for harnessing autophagy have developed: 1) Takahashi et al. Takahashi, Arimoto ($year$) [127] developed a novel strategy called autophagy-targeting chimera (AUTAC), which destinated the TOI for degradation by selective autophagy through ubiquitination. 2) Fu et al. Fu et al., ($year$) [47] designed heterobifunctional small molecules that bind to the inner surface of forming autophagosomes. Then the TOI will be trapped in the autophagosome and undergo degradation. They named it autophagosome-tethering compound (ATTEC. 3) Chang Hoon Ji and colleagues [65] developed a general platform AUTOphagy-TArgeting Chimera (AUTOTAC) of heterobifunctional molecules that selectively degrade the TOI via the interaction with the ZZ domain of the autophagy receptor p62/Sequestosome-1/SQSTM1.

While these versatile platforms empower researchers to selectively target intracellular proteins or inclusions for degradation, they remain limited in their ability to address extracellular proteins. Introducing the Lysosome-targeting chimera (LYTAC) as another distinct TPD platform with exceptional attributes [12]. LYTAC is designed to effectively target extracellular and transmembrane proteins for degradation within the lysosome, thereby expanding the scope of TPD into both the extracellular and intracellular domains.

5. Targeted protein degradation in PD

Building upon TPD technology, a range of PROTACs and AUTOTACs have emerged with the potential to address NDs like PD, HD, and AD. This section delves into the examination of these small molecules and peptides, which hold promise for applications in PD. Specifically, it explores the development of small molecules and peptides designed for targeting α-synuclein, LRRK2, and tau protein, leveraging PROTAC and other TPD methodologies.

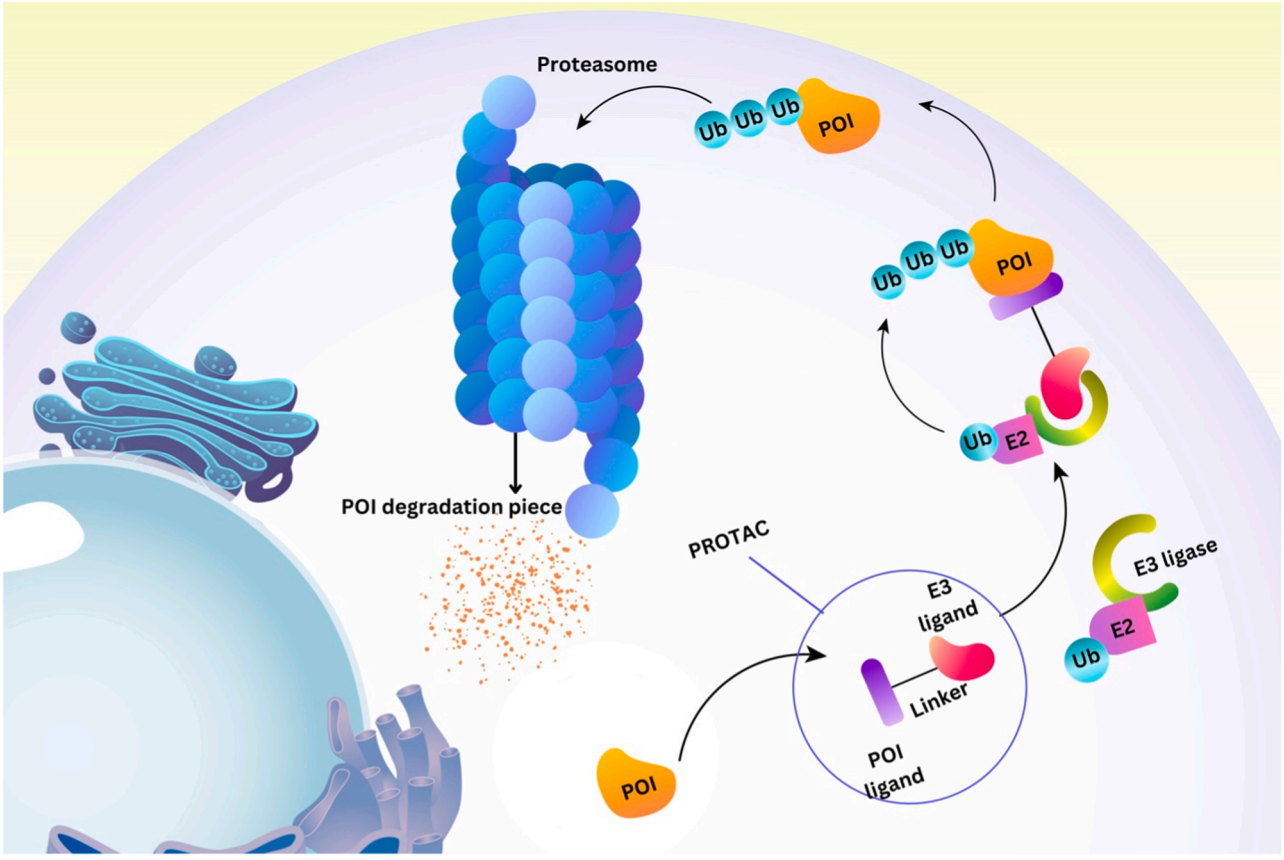

Fig. 4. PROteolysis-TArgeting-Chimera (PROTAC): The schematic illustration of PROTAC and its mechanism of action. Heterobifunctional small-molecule or peptide (red object) that attaches to the E3 ubiquitin ligase from one side and by a linker attached to the other part which binds to the target of interest (TOI) which here is a protein of interest (POI). The next steps resulted in numerous ubiquitylation reactions, constructing ubiquitin chains on substrate ubiquitination. The poly-ubiquitinated POI is recognized by the subsequent 26 S proteasome and will be degraded in further steps.

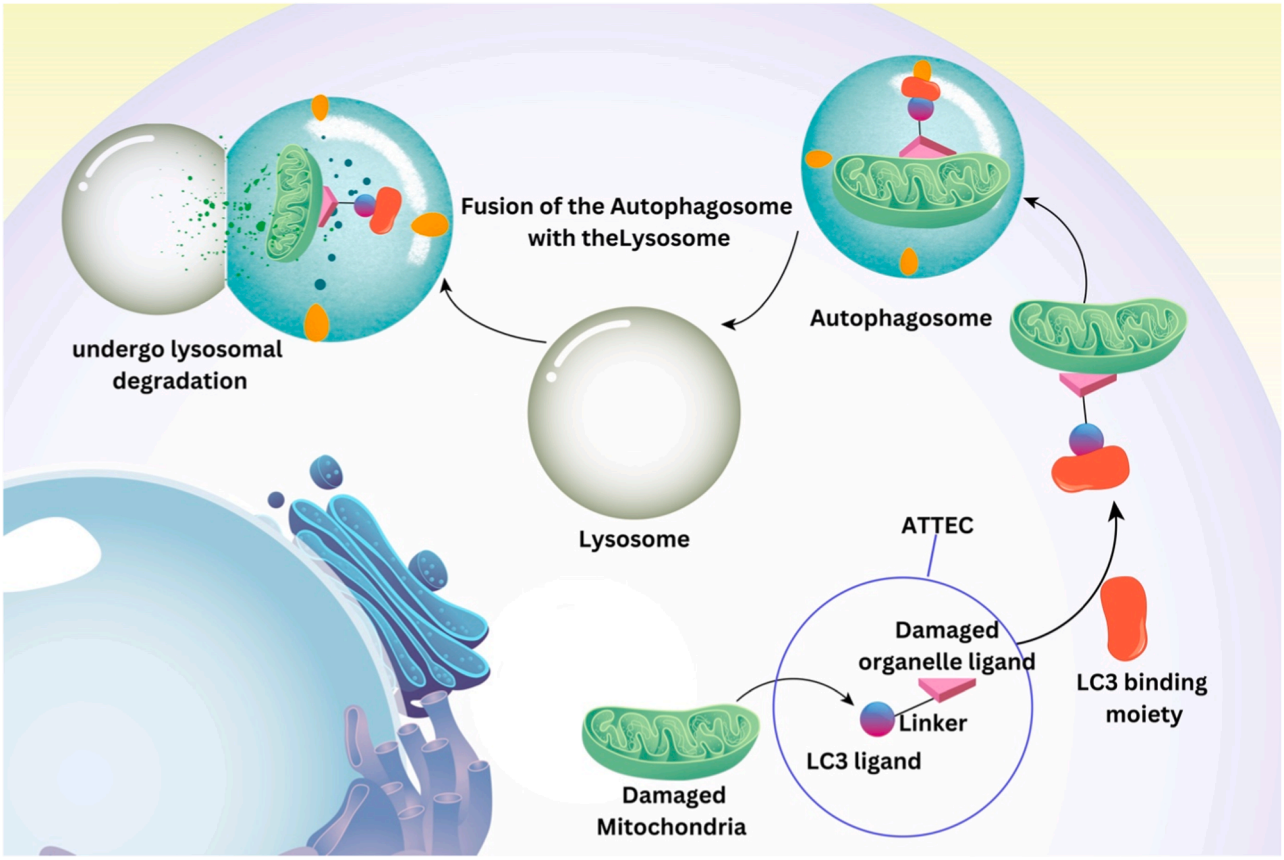

Fig. 5. Autophagy-Lysosomal-System: The schematic illustration of Heterobifunctional molecules that use autophagy to selectively degrade the target of interest (TOI). Here we describe autophagy-targeting chimera (AUTAC), including a degradation tag and a degron to equip target specificity. As predicted from the substrate extent of autophagy, AUTAC degraded impaired organelles such as mitochondria or protein aggregations. In this fig, Mitochondria-targeted AUTAC revved the disposal of dysfunctional fragmented mitochondria. Double-membrane autophagosome forms around the cell contents. Then autophagosome fuses with the lysosome and forms an autolysosome. Then lysosomal environment degrades autolysosome contents.

5.1. Targeting α-synuclein

In Section 2.1, we discussed in element the paramount role of α-synuclein in the pathogenesis of PD. With the rationalization of the essence of this protein, numerous therapeutic techniques which include inhibitors, antibodies, gene modification [96], and many other techniques have been investigated, each of which has its interest and obstacles, which are not blanketed in the subject matter of this assessment. In this regard, TPD has been studied. In 2014, Xuelai Fan and colleagues [44] pioneered a membrane-permeant targeting peptide-based approach for degrading the Target of Interest (TOI) by harnessing Chaperone-Mediated Autophagy (CMA). Their creation, TAT-βsyn-CTM, comprised three essential components: TAT serves as a cell-penetrating peptide. βsyn, acting as a specific binder to α-synuclein. CTM, a tag designed for CMA recognition. Their work demonstrated the efficacy of this method both in vitro and in vivo.

In a further attempt in 2021, Tat-βsyn-degron was developed for selective degradation of α-synuclein by harnessing the UPS [66]. This peptide contains three distinct domains, including 1)TAT to facilitate the peptide's passage through the BBB and plasma membrane, 2) βsyn, serving as a precise α-synuclein binder, and 3) Degron, a peptide signal guiding tagged proteins to proteasomes for degradation. Remarkably, proteasomal degradation of this peptide efficaciously decreased α-synuclein ranges in both in vitro and in vivo studies. Tat-βsyn-degron now not simplest dwindled α-synuclein accumulations and microglial hyperactivity in transgenic mice overexpressing human A53T α-synuclein, mimicking synucleinopathies, however, additionally alleviated neuronal impairment and motor dysfunction related to PD in a mouse model of PD toxicity. Beyond degrader peptides, the field has also seen the development of small-molecule degraders targeting α-synuclein [73], in which six distinct α-synuclein PROTAC compounds are introduced (Fig. 6-a). In a distinct endeavor, Pedrini et al. Pedrini et al., ($year$) [106] directed their focus toward synucleinopathies. Their study delves into the potential effectiveness of intervening by targeting α-synuclein aggregates. They accomplished this by designing six putative PROTACs based on Anle138b, which interact with these aggregates, inducing polyubiquitination, and culminating in proteasomal degradation. The standout compound from their research, Anle138b-PROTAC 8a, exhibited a noteworthy reduction in cellular α-synuclein levels. This compound holds promise for addressing pathologies arising from misfolded or aggregated proteins. As outlined in this manuscript, efforts have been undertaken to target proteins implicated in PD, with α-synuclein emerging as a primary focal point due to its established role. The degradation of α-synuclein relies significantly on the UPS and autophagy pathways [142]. As a result, diverse TPD modalities such as PROTACs and AUTOTACs can be leveraged for this purpose. Notably, autophagy takes a more prominent role in degrading oligomeric forms of α-synuclein [142]. In this context, Fan et al. successfully developed two peptides targeting monomeric α-synuclein for degradation through CMA and the UPS, respectively [44,66]. However, monomeric α-synuclein plays physiological roles, while recent research suggests that oligomeric α-synuclein may have a more significant impact on PD [16].

This insight highlights the potential benefit of targeting oligomeric α-synuclein for a more precise therapeutic approach. Wagner et al.[135] identified Anle138b as a selective modulator of oligomeric α-synuclein, with minimal interaction with monomeric α-synuclein and other species. Building upon this molecule, Chang Hoon Ji et al. Wagner et al., ($year$) [135] revised an AUTOTAC targeting oligomeric α-synuclein

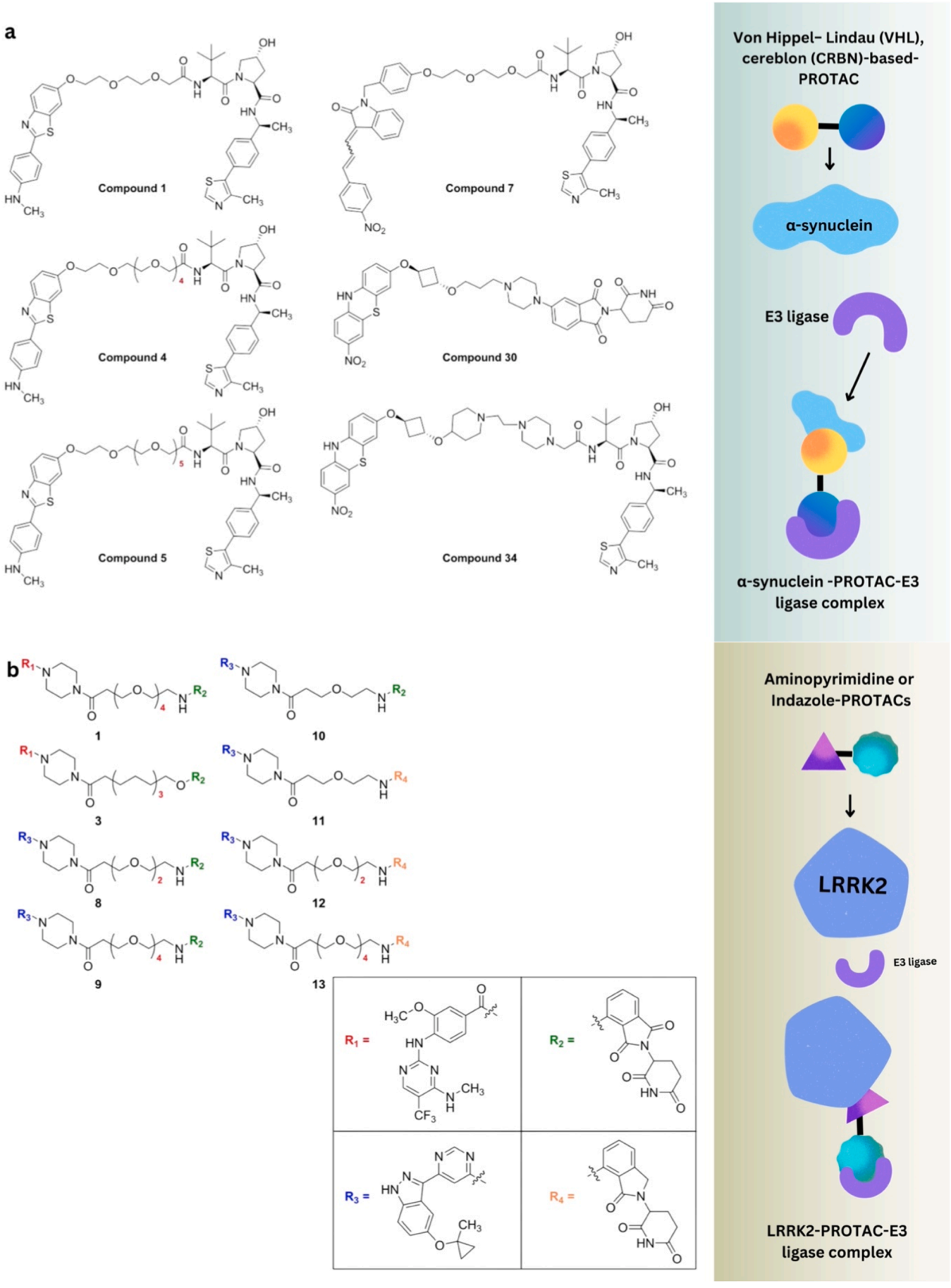

Fig. 6. (a) PROteolysis-TArgeting-Chimera (PROTAC) based on degrader peptides, small-molecule degraders developed to target α-synuclein Robert B [73]. (b) PROTAC is based on aminopyrimidine or indazole. Compounds 1 and 3 did not degrade LRRK2, but, compounds 8 −13 decreased the level of LRRK2 Robert B [72].

for autophagic degradation. Another avenue involves targeting intraneural Lewy bodies (LBs) using AUTAC, ATTEC, or AUTOTAC strategies. The debate over whether these inclusions are protective (by sequestering harmful species) or detrimental creates an intriguing area for exploration. Targeting them not only offers potential therapeutic benefits but also deepens our comprehension of PD's pathophysiology. The prion-like hypothesis of α-synuclein proposes that α-synuclein oligomers and aggregates propagate in a prion-like manner, affecting neighboring healthy neurons [5]. In a recent study, Lee et al. embarked on an investigation centered around designing an AUTOTAC platform to target α-synuclein aggregates. They employed Anle138b, baicalein (a flavonoid compound binding to Tyr residues of α-synuclein), resveratrol (a natural phenol binding to α-synuclein amyloids and β-sheet rich structures), and PBA (4-phenylbutyric acid, exhibiting anti-aggregating properties to α-synuclein). This strategy successfully implemented TPD in PD, demonstrating p62-activating and target-binding efficacy. Among the compounds tested as α-synuclein binders, Anle138b, designed as AUTOTAC (ATC161), proved highly effective in degrading α-synuclein aggregates in cellular and mouse models of PD. Notably, ATC161 most efficiently induced p62 oligomerization compared to other AUTOTAC compounds [81]. Consequently, addressing the propagation of extracellular α-synuclein oligomers holds the potential to halt disease progression. LYTAC could offer a promising avenue for targeting extracellular α-synuclein and preventing its dissemination.

5.2. Targeting LRRK2

Elevated LRRK2 activity within the brain triggers a cascade of pathways, resulting in both the activation and deactivation of various cellular processes. Ultimately, this disruption culminates in the accumulation of neuronal dysfunctions and the onset of PD [26]. The primary therapeutic objective revolves around mitigating the kinase activity of LRRK2 within the brain. Extensive research has explored the Targeted Protein Degradation (TPD) approach as a means to target LRRK2. Konstantinidou et al. Konstantinidou et al., ($year$) [78] examined the potential of four PROTACs based on PF-06447475/CRBN and three PROTACs based on GNE-7915/CRBN (refer to Fig. 6-b). These compounds were designed to facilitate cellular penetration and binding to the LRRK kinase pocket. However, western blot analysis revealed no significant difference in LRRK2 protein levels between cells treated with PROTACs and those treated with the original kinase inhibitors. This suggests that the PROTACs did not induce LRRK2 degradation. In a patent search conducted by Kargbo [72], small molecules targeting LRRK2 were identified. These molecules comprised an aminopyrimidine or indazole as the LRRK2 binder, a linker, and an E3 ubiquitin ligase component. Compounds 1 and 3 effectively inhibited S935 and Rab10 phosphorylation but did not facilitate LRRK2 degradation. In contrast, compound 813 not only inhibited S935 phosphorylation but also reduced the abundance of LRRK2. This underscores the critical role of ligand selection in determining the efficacy of PROTACs. In 2022, Liu X et al. embarked on the discovery of an LRRK2-targeting PROTAC. They initiated their efforts by designing and synthesizing a small set of PROTACs based on HG-10–102–01, a BBB-penetrant type 1 LRRK2 inhibitor. This choice was grounded in the ligand's small molecular size and favorable physicochemical properties. For the E3 ubiquitin ligases, CRBN and VHL were enlisted. This endeavor resulted in the identification of a highly effective degrader, XL01126. Notably, XL01126 displayed significant oral bioavailability (F = 15%) and the capability to penetrate the Blood-Brain Barrier (BBB) following either oral or parenteral administration in mouse models [88].

Looking ahead, future studies aimed at targeting LRRK2 via autophagy-based platforms may yield promising outcomes. This approach takes into account that E3 ligase accessibility, ternary complex formation, and the cellular location of LRRK2 may not be as critical in these platforms.

5.3. Targeting Tau protein

Tau is a favorite target for researchers in ND's drug discovery. Since the introduction of the TPD concept, many efforts have been conducted to develop new drugs based on this modality. Chu et al. Chu et al., ($year$) [32] developed and synthesized for the first time a set of multifunctional compounds containing Tau-recognition and E3 ligase-binding moieties with a cell-penetrating moiety to specifically degrade endogenous Tau protein via peptide-directed ubiquitin-proteasome degradation. TH006 has a considerable efficacious in generating Tau degradation by expanding its polyubiquitination. The degradation of Tau by TH006 significantly detracts from the cytotoxicity spread by Aβ. Additionally, it It restrained the Tau level in the brain of a mouse model of AD. A peptide PROTAC via recruiting Keap1-Cul3 ubiquitin E3 ligase was synthesized and employed to degrade intracellular Tau by Lu et al.et alLu et al. Lu et al., ($year$) [89]. Peptide 1 showed a highhigh interaction with Keap1 and Tau and led to Keap1-dependent Tau degradation via increasing the ubiquitination of the Tau in-vitro model. This peptide could diminish the intracellular Tau level in both times- and concentration-dependent ways. Silva and colleagues developed 25 heterobifunctional small molecules to develop a small-molecule base PROTAC against the tau protein[121]. QC-01–175 showed the most promising results. QC-01–175 is a heterobifunctional small molecule composed of Pomalidomide serving as an E3 recruiter, a linker, and 18 F-T807 operating as a tau binder. Regarding in vivo analyses, 18 F-T807 (or 18 F-AV-1451) is the most advanced PET tracer for tau protein. It does, however, exhibit some off-target activity toward monoamine oxidase-B (MAO-B) and monoamine oxidase-A (MAO-A) [83].

However, QC-01–175 had fewer off-target effects. QC-01–175 induced tau poly-ubiquitination and subsequent UPS degradation in frontotemporal dementia (FTD) patient-derived neuronal cell models in a concentration-dependent method and recovered tau-mediated neuronal stress defenselessness. Additionally, it had a minimal impact on tau in neurons from healthy controls, stating that it was specific for disease-relevant forms.

Kargbo has summarized patented small-molecule PROTACs for tau [71]. Rather, the combinations in this patent view degraded hyperphosphorylated tau and entire tau proteins in human tau-A152T and tau-P301L neurons. Tau degradation assays revealed the capacity of the compounds in this Patent Highlight to degrade tau proteins in human cells. These compounds were also examined in an in vivo assay to see whether they could cross the BBB. Wang et al. [139] evolved a novel, PROTAC, C004019, that recruits tau and VHL E3-ligase concurrently, increasing tau protein ubiquitination and proteolysis by UPS. C004019 promoted a robust tau elimination in HEK293 cells overexpressing human tau (hTau) and in SH-SY5Y cells constituting overexpressed hTau. Additionally, the intracerebral ventricular infusion of C004019 significantly increased tau degradation in vivo. Most notably, both single-dose and multiple-dose subcutaneous injections of C004019 (once every six days for a total of five times) significantly depleted tau levels in the brains of WT, hTau-transgenic, and 3xTg-AD mice while improving synaptic and cognitive abilities. Chang Hoon Ji et al. Ji et al., ($year$) [65].

developed PBA-1105 and PBA-1106 based on their AUTOTAC platform. These heterobifunctional small-molecules could induce perdurable expressed mutant tau degradation at DC50 of ~1–10 nM via autophagy.

As previously discussed, hyperphosphorylated tau is the primary culprit in NDs and, as such, has earned considerable attention as a potential therapeutic target. Jangampalli Adi Pradeepkiran and Hemachandra Reddy [113] are working on a patent for a small molecule PROTAC that targets pathological tau specifically. A pharmacophore screening for possible hyperphosphorylated tau ligands based on 7-Phosphoomethyl-naphthalene-1-carboxylic acid was used to identify a suitable ligand with the highest docking score conducted [112]. They

are specifying and conjugating vowing small molecules (ligands) that mainly bind to a target protein (p-tau) at Ser 285 (S23) and Tyr 310 (Y44), restraining GSK3 and CDK5, linking this small molecule with a PEG-based linker and binding to E3-ubiquitin ligase results in a specific PROTAC for pathogenic tau protein. These studies will cause more selective and specific drug molecules for treating NDs. Tau protein is a valuable target in AD, but, as discussed previously, it also plays a role in PD. Tau protein has been the favorite target in ND drug discovery; therefore, more studies are on it. However, more specific studies are needed for the selective targeting of toxic tau oligomers. PROTAC and AUTOTAC have been recruited for selective tau degradation and reducing their levels in cells. Similar efforts can be made by AUTAC and ATTEC, which, at least in theory, should have more potency at targeting oligomers and insoluble tau than PROTAC. Another possible intervention is to develop LYTACs to specifically target tau propagation which induces tau aggregation in healthy neurons [41].

Mitochondria is a double membrane organelle responsible for energy production and redox homeostasis [31]. Mitochondria dysfunction has been reported in different cancers and age-related diseases, and mitochondrial fragmentation has been seen in PD and AD [68]; [137]; [138]. There is no therapeutic intervention to eliminate damaged mitochondria. Thus, targeting injured mitochondria is a promising approach that autophagy-based platforms can achieve. In developing the AUTAC platform, Takahashi et al. Takahashi, Arimoto ($year$) [127] designed AUTAC4, which could improve mitochondria functions in Down Syndrome cells by degradation of fragmented mitochondria. Still, it did not affect healthy mitochondria because of its larger size. It improved mitochondrial quality control and restored energy production. Further studies need to clarify whether ATTEC and AUTOTAC can degrade healthy or injured mitochondria.

6. Conclusion and future perspective

NDs afflict millions annually, yet the absence of effective curative interventions to halt their progression underscores an urgent need for innovative approaches. A pivotal challenge in PD drug discovery emanates from the non-enzymatic nature of implicated proteins, posing a formidable hurdle in conventional drug development. This roadblock, however, can be circumvented by the TPD technology. Consequently, harnessing TPD methodologies to engineer small molecules or peptides for ND treatment or prevention is within closer reach. However, several challenges merit consideration along this trajectory:TPD empowers the selective degradation of target proteins via cellular clearance mechanisms, holding particular promise for PD treatment. The diverse landscape of PD pathology offers insight into potential targets for degradation, yet the field of TPD-based PD interventions remains nascent, leaving ample room for exploration. Nonetheless, the development of a discerning ligand that exclusively targets pathological proteins while sparing physiological counterparts is a critical necessity. Presently, a scarcity of selective ligands tailored to specific proteins and ND targets underscores the urgency for further research in this domain. Additionally, the perturbation of the UPS or autophagy in PD mandates astute platform selection for TPD. Among the challenges is the precise identification of disease-driving proteins warranting degradation, while evading the unintended degradation of non-disease-related proteins. In the context of PD, the focus resides on alpha-synuclein. Ensuring the precise targeting of alpha-synuclein while preserving essential proteins is imperative for therapeutic success.

Furthermore, the transit of TPD agents across the BBB presents an enduring hurdle. These agents, often larger than typical small molecules, accentuate the intricacies of CNS drug delivery. Thus, concerted efforts are required to optimize their physicochemical attributes to enhance BBB permeability.

Moreover, the long-term repercussions of sustained protein degradation necessitate comprehensive exploration. The potential for off-target effects or unintended consequences arising from prolonged TPD agent usage underscores the significance of ensuring their safety and tolerance in extended therapeutic contexts.

Considering the multifaceted nature of PD, wherein distinct mechanisms converge, integrating TPD with therapeutic modalities such as neuroprotective agents or symptomatic relief medications becomes paramount. A holistic approach that fuses TPD with diverse treatment strategies offers a comprehensive solution to address the complexity of PD.

In summary, the TPD paradigm offers a promising avenue for ND treatment, notably in PD. The challenges outlined, including precise ligand design, BBB penetration, long-term effects, and the integration of multifaceted treatments, must be thoughtfully navigated to realize the full potential of TPD-based interventions for NDs.

CRediT authorship contribution statement

Roshanak Amirian: Conceptualization, Writing – original draft. **Mehdi Azadi Badrbani:** Conceptualization, Writing – original draft. **Hossein Derakhshankhah:** Writing – original draft. **Zhila Izadi:** Conceptualization, Supervision, Writing – original draft. **Mohammad-Ali Shahbazi:** Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

Authors declare no conflict of interest in the present work.

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References

[1] R. Alcalay, P. Wolf, O. Levy, U. Kang, C. Waters, S. Fahn, H. Shah, Alpha galactosidase A activity in Parkinson's disease, Neurobiol. Dis. 112 (2018) 85–90.
[2] P.Z. Álmos, S. Horváth, Á. Czibula, I. Raskó, B. Sipos, P. Bihari, J. Kálmán, H1 tau haplotype-related genomic variation at 17q21. 3 as an Asian heritage of the European Gypsy population, Heredity 101 (5) (2008) 416–419.
[3] L. Alvarez-Erviti, M.C. Rodriguez-Oroz, J.M. Cooper, C. Caballero, I. Ferrer, J. A. Obeso, A.H. Schapira, Chaperone-mediated autophagy markers in Parkinson disease brains, Arch. Neurol. 67 (12) (2010) 1464–1472.
[4] P. Anglade, S. Vyas, F. Javoy-Agid, M.T. Herrero, P.P. Michel, J. Marquez, Y. Agid, Apoptosis and autophagy in nigral neurons of patients with Parkinson's disease, Histol. Histopathol. 12 (1) (1997) 25–31.
[5] E. Angot, J.A. Steiner, C. Hansen, J.-Y. Li, P. Brundin, Are synucleinopathies prion-like disorders, Lancet Neurol. 9 (11) (2010) 1128–1138.
[6] K. Arima, S. Hirai, N. Sunohara, K. Aoto, Y. Izumiyama, K. Uéda, M. Kawai, Cellular co-localization of phosphorylated tau-and NACP/α-synuclein-epitopes in Lewy bodies in sporadic Parkinson's disease and in dementia with Lewy bodies, Brain Res. 843 (1–2) (1999) 53–61.
[7] K. Arima, T. Mizutani, M.A. Alim, H. Tonozuka-Uehara, Y. Izumiyama, S. Hirai, K. Uéda, NACP/α-synuclein and tau constitute two distinctive subsets of filaments in the same neuronal inclusions in brains from a family of parkinsonism and dementia with Lewy bodies: double-immunolabeling fluorescence and electron microscopic studies, Acta Neuropathol. 100 (2) (2000) 115–121.
[8] M. Avenali, F. Blandini, S. Cerri, Glucocerebrosidase defects as a major risk factor for Parkinson's disease, Front. Aging Neurosci. 12 (2020) 97.
[9] E.-J. Bae, N.Y. Yang, C. Lee, H.-J. Lee, S. Kim, S.P. Sardi, S.-J. Lee, Loss of glucocerebrosidase 1 activity causes lysosomal dysfunction and α-synuclein aggregation, Exp. Mol. Med. 47 (3) (2015) e153-e153.
[10] R. Balestrino, A. Schapira, Parkinson disease, Eur. J. Neurol. 27 (1) (2020) 27–42.
[11] R. Balestrino, A.H. Schapira, Glucocerebrosidase and Parkinson disease: molecular, clinical, and therapeutic implications, Neuroscientist 24 (5) (2018) 540–559.
[12] S.M. Banik, K. Pedram, S. Wisnovsky, G. Ahn, N.M. Riley, C.R. Bertozzi, Lysosome-targeting chimaeras for degradation of extracellular proteins, Nature 584 (7820) (2020) 291–297.
[13] S. Bawari, D. Tewari, S. Argüelles, A.N. Sah, S.F. Nabavi, S. Xu, S. Shirooie, Targeting BDNF signaling by natural products: novel synaptic repair therapeutics for neurodegeneration and behavior disorders, Pharmacol. Res. 148 (2019), 104458.

[14] M. Békés, D.R. Langley, C.M. Crews, PROTAC targeted protein degraders: the past is prologue, Nat. Rev. Drug Discov. (2022) 1–20.
[15] A. Bellucci, F. Longhena, M.G. Spillantini, The role of Rab proteins in Parkinson's disease synaptopathy, Biomedicines 10 (8) (2022) 1941.
[16] N. Bengoa-Vergniory, R.F. Roberts, R. Wade-Martins, J. Alegre-Abarrategui, Alpha-synuclein oligomers: a new hope, Acta Neuropathol. 134 (6) (2017) 819–838, https://doi.org/10.1007/s00401-017-1755-1.
[17] R. Betarbet, T.B. Sherer, J.T. Greenamyre, Ubiquitin–proteasome system and Parkinson's diseases, Exp. Neurol. 191 (2005) S17–S27.
[18] A.J. Bindas, K.N. Nichols, N.J. Roth, R. Brady, A.N. Koppes, R.A. Koppes, Aggregation of alpha-synuclein in enteric neurons does not impact function in vitro, Sci. Rep. 12 (1) (2022) 22211.
[19] L. Bonet-Ponce, M.R. Cookson, The role of Rab GTPases in the pathobiology of Parkinson'disease, Curr. Opin. Cell Biol. 59 (2019) 73–80.
[20] V. Bonifati, P. Rizzu, M. van Baren, O. Schaap, G. Breedveld, E. Krieger, M. Joosse, J.W. can Dongen, N. Vanacore, J.C. van Swieten, A. Brice, G. Meco, C. M. van Duijn, B.A. Oostra, P. Heutink, Mutations in the DJ-1 gene associated with autosomal recessive earlyonset parkinsonism, Science 299 (2003) 256–259.
[22] H. Braak, K. Del Tredici, U. Rüb, R.A. De Vos, E.N.J. Steur, E. Braak, Staging of brain pathology related to sporadic Parkinson's disease, Neurobiol. Aging 24 (2) (2003) 197–211.
[23] M. Buongiorno, Y. Compta, M.J. Martí, Amyloid-β and τ biomarkers in Parkinson's disease–dementia, J. Neurol. Sci. 310 (1–2) (2011) 25–30.
[24] J. Burré, M. Sharma, T. Tsetsenis, V. Buchman, M.R. Etherton, T.C. Südhof, α-synuclein promotes SNARE-complex assembly in vivo and in vitro, Science 329 (5999) (2010) 1663–1667, https://doi.org/10.1126/science.1195227.
[25] G. Caraveo, P.K. Auluck, L. Whitesell, C.Y. Chung, V. Baru, E.V. Mosharov, P. Picotti, Calcineurin determines toxic versus beneficial responses to α-synuclein, Proc. Natl. Acad. Sci. 111 (34) (2014) E3544–E3552.
[26] E.E.S. Chang, P.W.-L. Ho, H.-F. Liu, S.Y.-Y. Pang, C.-T. Leung, Y. Malki, S.-L. Ho, LRRK2 mutant knock-in mouse models: therapeutic relevance in Parkinson's disease, Transl. Neurodegener. 11 (1) (2022) 10.
[27] D. Charvin, R. Medori, R.A. Hauser, O. Rascol, Therapeutic strategies for Parkinson disease: beyond dopaminergic drugs, Nat. Rev. Drug Discov. 17 (11) (2018) 804–822.
[28] B. Chen, X. Wen, H. Jiang, J. Wang, N. Song, J. Xie, Interactions between iron and α-synuclein pathology in Parkinson's disease, Free Radic. Biol. Med. 141 (2019) 253–260.
[29] M.-L. Chen, R.-M. Wu, LRRK 2 gene mutations in the pathophysiology of the ROCO domain and therapeutic targets for Parkinson's disease: a review, J. Biomed. Sci. 25 (1) (2018) 1–11.
[30] S.J. Cherra III, E. Steer, A.M. Gusdon, K. Kiselyov, C.T. Chu, Mutant LRRK2 elicits calcium imbalance and depletion of dendritic mitochondria in neurons, Am. J. Pathol. 182 (2) (2013) 474–484.
[31] P.F. Chinnery, E.A. Schon, Mitochondria, J. Neurol. Neurosurg. Psychiatry 74 (9) (2003) 1188–1199.
[32] T.-T. Chu, N. Gao, Q.-Q. Li, P.-G. Chen, X.-F. Yang, Y.-X. Chen, Y.-M. Li, Specific knockdown of endogenous tau protein by peptide-directed ubiquitin-proteasome degradation, Cell Chem. Biol. 23 (4) (2016) 453–461, https://doi.org/10.1016/j.chembiol.2016.02.016.
[33] F. Clavaguera, M. Tolnay, M. Goedert, The prion-like behavior of assembled tau in transgenic mice, Cold Spring Harb. Perspect. Med. 7 (10) (2017), https://doi.org/10.1101/cshperspect.a024372.
[34] Y. Compta, L. Parkkinen, S.S. O'Sullivan, J. Vandrovcova, J.L. Holton, C. Collins, R. de Silva, Lewy-and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important, Brain 134 (5) (2011) 1493–1505.
[35] K.A. Conway, J.-C. Rochet, R.M. Bieganski, P.T. Lansbury, Kinetic Stabilization of the α-Synuclein Protofibril by a Dopamine-α-Synuclein Adduct, science 294 (5545) (2001) 1346–1349, https://doi.org/10.1126/science.1063522.
[36] A.M. Cuervo, Autophagy: many paths to the same end, Mol. Cell. Biochem. 263 (1) (2004) 55–72.
[37] A.M. Cuervo, L. Stefanis, R. Fredenburg, P.T. Lansbury, D. Sulzer, Impaired degradation of mutant α-synuclein by chaperone-mediated autophagy, Science 305 (5688) (2004) 1292–1295, https://doi.org/10.1126/science.1101738.
[38] V. Cullen, S.P. Sardi, J. Ng, Y.H. Xu, Y. Sun, J.J. Tomlinson, J. Woulfe, Acid β-glucosidase mutants linked to Gaucher disease, Parkinson disease, and Lewy body dementia alter α-synuclein processing, Ann. Neurol. 69 (6) (2011) 940–953.
[39] P. Damier, E. Hirsch, Y. Agid, A. Graybiel, The substantia nigra of the human brain: II. Patterns of loss of dopamine-containing neurons in Parkinson's disease, Brain 122 (8) (1999) 1437–1448.
[40] D. Davidi, M. Schechter, S. Abd Elhadi, A. Matatov, L. Nathanson, R. Sharon, α-Synuclein translocates to the nucleus to activate retinoic-acid-dependent gene transcription, IScience 23 (3) (2020), 100910.
[41] A. De Calignon, M. Polydoro, M. Suárez-Calvet, C. William, D.H. Adamowicz, K. J. Kopeikina, G.A. Carlson, Propagation of tau pathology in a model of early Alzheimer's disease, Neuron 73 (4) (2012) 685–697.
[42] M.D. Demmings, E.C. Tennyson, G.N. Petroff, H.E. Tarnowski-Garner, S. P. Cregan, Activating transcription factor-4 promotes neuronal death induced by Parkinson's disease neurotoxins and α-synuclein aggregates, Cell Death Differ. 28 (5) (2021) 1627–1643.
[43] E.R. Dorsey, A. Elbaz, E. Nichols, N. Abbasi, F. Abd-Allah, A. Abdelalim, J.-Y. J. Choi, Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016, Lancet Neurol. 17 (11) (2018) 939–953.
[44] X. Fan, W.Y. Jin, J. Lu, J. Wang, Y.T. Wang, Rapid and reversible knockdown of endogenous proteins by peptide-directed lysosomal degradation, Nat. Neurosci. 17 (3) (2014) 471–480.
[45] J.M. Fearnley, A.J. Lees, Ageing and Parkinson's disease: substantia nigra regional selectivity, Brain 114 (5) (1991) 2283–2301.
[46] I. Fishbein, Y.-M. Kuo, B.I. Giasson, R.L. Nussbaum, Augmentation of phenotype in a transgenic Parkinson mouse heterozygous for a Gaucher mutation, Brain 137 (12) (2014) 3235–3247.
[47] Y. Fu, N. Chen, Z. Wang, S. Luo, Y. Ding, B. Lu, Degradation of lipid droplets by chimeric autophagy-tethering compounds, Cell Res. 31 (9) (2021) 965–979.
[48] R.M. Furlong, G.W. O'Keeffe, C. O'Neill, A.M. Sullivan, Alterations in α-synuclein and PINK1 expression reduce neurite length and induce mitochondrial fission and Golgi fragmentation in midbrain neurons, Neurosci. Lett. 720 (2020), 134777.
[49] M.E. Gegg, E. Menozzi, A.H. Schapira, Glucocerebrosidase-associated Parkinson disease: pathogenic mechanisms and potential drug treatments, Neurobiol. Dis. (2022), 105663.
[50] S. Geisler, K.M. Holmström, D. Skujat, F.C. Fiesel, O.C. Rothfuss, P.J. Kahle, W. Springer, PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1, Nat. Cell Biol. 12 (2) (2010) 119–131.
[51] F. Gillardon, Leucine-rich repeat kinase 2 phosphorylates brain tubulin-beta isoforms and modulates microtubule stability–a point of convergence in Parkinsonian neurodegeneration, J. Neurochem. 110 (5) (2009) 1514–1522.
[52] D. Glick, S. Barth, K.F. Macleod, Autophagy: cellular and molecular mechanisms, J. Pathol. 221 (1) (2010) 3–12, https://doi.org/10.1002/path.2697.
[53] M. Goedert, C.M. Wischik, R.A. Crowther, J.E. Walker, A. Klug, Cloning and sequencing of the cDNA encoding a core protein of the paired helical filament of Alzheimer disease: identification as the microtubule-associated protein tau, Proc. Natl. Acad. Sci. 85 (11) (1988) 4051–4055, https://doi.org/10.1073/pnas.85.11.4051.
[54] C.J. Griffey, A. Yamamoto, Macroautophagy in CNS health and disease, Nat. Rev. Neurosci. 23 (7) (2022) 411–427.
[55] S. Ham, J.H. Kim, H. Kim, J.-Y. Shin, Y. Lee, ATF4-activated parkin induction contributes to deferasirox-mediated cytoprotection in Parkinson's disease, Toxicol. Res. (2022) 1–9.
[56] H. Han, J. Tan, R. Wang, H. Wan, Y. He, X. Yan, S. Shang, PINK 1 phosphorylates Drp1S616 to regulate mitophagy-independent mitochondrial dynamics, EMBO Rep. 21 (8) (2020), e48686.
[57] J. Hardy, P. Lewis, T. Revesz, A. Lees, C. Paisan-Ruiz, The genetics of Parkinson's syndromes: a critical review, Curr. Opin. Genet. Dev. 19 (3) (2009) 254–265.
[58] J. Haskin, R. Szargel, V. Shani, L.N. Mekies, R. Rott, G.G. Lim, S. Engelender, AF-6 is a positive modulator of the PINK1/parkin pathway and is deficient in Parkinson's disease, Hum. Mol. Genet. 22 (10) (2013) 2083–2096.
[59] A.-C. Hoffmann, G. Minakaki, S. Menges, R. Salvi, S. Savitskiy, A. Kazman, J. Winkler, Extracellular aggregated alpha synuclein primarily triggers lysosomal dysfunction in neural cells prevented by trehalose, Sci. Rep. 9 (1) (2019) 544.
[60] Y. Imai, M. Soda, S. Hatakeyama, T. Akagi, T. Hashikawa, K.-I. Nakayama, R. Takahashi, CHIP is associated with Parkin, a gene responsible for familial Parkinson's disease, and enhances its ubiquitin ligase activity, Mol. Cell 10 (1) (2002) 55–67, https://doi.org/10.1016/S1097-2765(02)00583-X.
[61] T. Ishizawa, P. Mattila, P. Davies, D. Wang, D.W. Dickson, Colocalization of tau and alpha-synuclein epitopes in Lewy bodies, J. Neuropathol. Exp. Neurol. 62 (4) (2003) 389–397.
[62] M. Jaleel, R.J. Nichols, M. Deak, D.G. Campbell, F. Gillardon, A. Knebel, D. R. Alessi, LRRK2 phosphorylates moesin at threonine-558: characterization of how Parkinson's disease mutants affect kinase activity, Biochem. J. 405 (2) (2007) 307–317.
[63] D. Jennings, S. Huntwork-Rodriguez, A.G. Henry, J.C. Sasaki, R. Meisner, D. Diaz, M.D. Troyer, Preclinical and clinical evaluation of the LRRK2 inhibitor DNL201 for Parkinson's disease, Sci. Transl. Med. 14 (648) (2022) eabj2658, https://doi.org/10.1126/scitranslmed.abj2658.
[64] D. Jennings, S. Huntwork-Rodriguez, M.F.J.M. Vissers, V.M. Daryani, D. Diaz, M. S. Goo, M.D. Troyer, LRRK2 Inhibition by BIIB122 in healthy participants and patients with Parkinson's disease, Mov. Disord. 38 (3) (2023) 386–398, https://doi.org/10.1002/mds.29297.
[65] C.H. Ji, H.Y. Kim, M.J. Lee, A.J. Heo, D.Y. Park, S. Lim, K.Y. Kim, The Autotac chemical biology platform for targeted protein degradation via the autophagy-lysosome system, Nat. Commun. 13 (1) (2022) 1–14.
[66] J.W. Jin, X. Fan, E. del Cid-Pellitero, X.-X. Liu, L. Zhou, C. Dai, X. Wu, Development of an α-synuclein knockdown peptide and evaluation of its efficacy in Parkinson's disease models, Commun. Biol. 4 (1) (2021) 1–15.
[67] A.P. Joselin, S.J. Hewitt, S.M. Callaghan, R.H. Kim, Y.-H. Chung, T.W. Mak, D. S. Park, ROS-dependent regulation of Parkin and DJ-1 localization during oxidative stress in neurons, Hum. Mol. Genet. 21 (22) (2012) 4888–4903.
[68] A.U. Joshi, P.S. Minhas, S.A. Liddelow, B. Haileselassie, K.I. Andreasson, G. W. Dorn, D. Mochly-Rosen, Fragmented mitochondria released from microglia trigger A1 astrocytic response and propagate inflammatory neurodegeneration, Nat. Neurosci. 22 (10) (2019) 1635–1648.
[69] L.V. Kalia, S.K. Kalia, H. Chau, A.M. Lozano, B.T. Hyman, P.J. McLean, Ubiquitinylation of α-synuclein by carboxyl terminus Hsp70-interacting protein (CHIP) is regulated by Bcl-2-associated athanogene 5 (BAG5), PloS One 6 (2) (2011), e14695.
[70] S.S. Kang, Z. Zhang, X. Liu, F.P. Manfredsson, M.J. Benskey, X. Cao, K. Ye, TrkB neurotrophic activities are blocked by α-synuclein, triggering dopaminergic cell death in Parkinson's disease, Proc. Natl. Acad. Sci. 114 (40) (2017) 10773–10778.

[71] R.B. Kargbo, Treatment of Alzheimer's by PROTAC-Tau protein degradation, ACS Med. Chem. Lett. 10 (5) (2019) 699–700, https://doi.org/10.1021/acsmedchemlett.9b00083.

[72] R.B. Kargbo, Degradation of LRRK2 in the Treatment of Parkinson's Disease. In, Vol. 11, ACS Publications,, 2020, pp. 2070–2071.

[73] R.B. Kargbo, PROTAC compounds targeting α-synuclein protein for treating neurogenerative disorders: Alzheimer's and Parkinson's diseases. In, Vol. 11, ACS Publications,, 2020, pp. 1086–1087.

[74] A. Kelekar, Autophagy, Ann. N. Y. Acad. Sci. 1066 (1) (2006) 259–271.

[75] K.H. Kim, M.-S. Lee, Autophagy—a key player in cellular and body metabolism, Nat. Rev. Endocrinol. 10 (6) (2014) 322–337.

[76] T. Kitada, S. Asakawa, N. Hattori, H. Matsumine, Y. Yamamura, S. Minoshima, N. Shimizu, Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism, Nature 392 (6676) (1998) 605–608, https://doi.org/10.1038/33416.

[77] H.S. Ko, R. Bailey, W.W. Smith, Z. Liu, J.-H. Shin, Y.-I. Lee, D.J. Moore, CHIP regulates leucine-rich repeat kinase-2 ubiquitination, degradation, and toxicity, Proc. Natl. Acad. Sci. 106 (8) (2009) 2897–2902.

[78] M. Konstantinidou, A. Oun, P. Pathak, B. Zhang, Z. Wang, F. Ter Brake, A. Dömling, The tale of proteolysis targeting chimeras (PROTACs) for Leucine-Rich Repeat Kinase 2 (LRRK2), ChemMedChem 16 (6) (2021) 959–965.

[79] G. Krebiehl, S. Ruckerbauer, L.F. Burbulla, N. Kieper, B. Maurer, J. Waak, D. Woitalla, Reduced basal autophagy and impaired mitochondrial dynamics due to loss of Parkinson's disease-associated protein DJ-1, PloS One 5 (2) (2010), e9367.

[80] H.-J. Lee, E.-D. Cho, K.W. Lee, J.-H. Kim, S.-G. Cho, S.-J. Lee, Autophagic failure promotes the exocytosis and intercellular transfer of α-synuclein, Exp. Mol. Med. 45 (5) (2013) e22-e22.

[81] J. Lee, K.W. Sung, E.J. Bae, D. Yoon, D. Kim, J.S. Lee, Y.T. Kwon, Targeted degradation of α-synuclein aggregates in Parkinson's disease using the Autotac technology, Mol. Neurodegener. 18 (1) (2023) 41, https://doi.org/10.1186/s13024-023-00630-7.

[82] Z. Lei, G. Cao, G. Wei, A30P mutant α-synuclein impairs autophagic flux by inactivating JNK signaling to enhance ZKSCAN3 activity in midbrain dopaminergic neurons, Cell Death Dis. 10 (2) (2019) 133.

[83] L. Lemoine, A. Leuzy, K. Chiotis, E. Rodriguez-Vieitez, A. Nordberg, Tau positron emission tomography imaging in tauopathies: the added hurdle of off-target binding, Alzheimer'S. Dement. Diagn. Assess. Dis. Monit. 10 (1) (2018) 232–236, https://doi.org/10.1016/j.dadm.2018.01.007.

[84] C.-H. Lin, P.-I. Tsai, R.-M. Wu, C.-T. Chien, LRRK2 G2019S mutation induces dendrite degeneration through mislocalization and phosphorylation of tau by recruiting autoactivated GSK3β, J. Neurosci. 30 (39) (2010) 13138–13149.

[85] J. Lin, K. Chen, W. Chen, Y. Yao, S. Ni, M. Ye, C. Gao, Paradoxical mitophagy regulation by PINK1 and TUFm, Mol. Cell 80 (4) (2020) 607–620, e612.

[86] X. Lin, L. Parisiadou, X.-L. Gu, L. Wang, H. Shim, L. Sun, J. Ding, Leucine-rich repeat kinase 2 regulates the progression of neuropathology induced by Parkinson's-disease-related mutant α-synuclein, Neuron 64 (6) (2009) 807–827.

[87] M. Liu, L. Qin, L. Wang, J. Tan, H. Zhang, J. Tang, C. Wang, α-synuclein induces apoptosis of astrocytes by causing dysfunction of the endoplasmic reticulum-Golgi compartment, Mol. Med. Rep. 18 (1) (2018) 322–332.

[88] X. Liu, A.F. Kalogeropulou, S. Domingos, N. Makukhin, R.S. Nirujogi, F. Singh, A. Ciulli, Discovery of XL01126: a potent, fast, cooperative, selective, orally bioavailable, and blood-brain barrier penetrant protac degrader of leucine-rich repeat kinase 2, J. Am. Chem. Soc. 144 (37) (2022) 16930–16952, https://doi.org/10.1021/jacs.2c05499.

[89] M. Lu, T. Liu, Q. Jiao, J. Ji, M. Tao, Y. Liu, Z. Jiang, Discovery of a Keap1-dependent peptide PROTAC to knockdown Tau by ubiquitination-proteasome degradation pathway, Eur. J. Med. Chem. 146 (2018) 251–259, https://doi.org/10.1016/j.ejmech.2018.01.063.

[90] J. Luo, L. Sun, X. Lin, G. Liu, J. Yu, L. Parisiadou, H. Cai, A calcineurin-and NFAT-dependent pathway is involved in α-synuclein-induced degeneration of midbrain dopaminergic neurons, Hum. Mol. Genet. 23 (24) (2014) 6567–6574.

[91] Z. Ma, K. Liu, X.-R. Li, C. Wang, C. Liu, D.-Y. Yan, B. Xu, Alpha-synuclein is involved in manganese-induced spatial memory and synaptic plasticity impairments via TrkB/Akt/Fyn-mediated phosphorylation of NMDA receptors, Cell Death Dis. 11 (10) (2020) 834.

[92] D. Maraganore, M. Farrer, J. Hardy, S. Lincoln, S. McDonnell, W. Rocca, Case-control study of the ubiquitin carboxy-terminal hydrolase L1 gene in Parkinson's disease, Neurology 53 (8) (1999), 1858-1858.

[93] J.Á. Martínez-Menárguez, M. Tomás, N. Martínez-Martínez, E. Martínez-Alonso, Golgi fragmentation in neurodegenerative diseases: is there a common cause, Cells 8 (7) (2019) 748.

[94] K.S.P. McNaught, P. Jenner, Proteasomal function is impaired in substantia nigra in Parkinson's disease, Neurosci. Lett. 297 (3) (2001) 191–194.

[95] T.Q. Melo, S.J. Copray, M.F. Ferrari, Alpha-synuclein toxicity on protein quality control, mitochondria and endoplasmic reticulum, Neurochem. Res. 43 (2018) 2212–2223.

[96] S. Menon, S. Armstrong, A. Hamzeh, N.P. Visanji, S.P. Sardi, A. Tandon, Alpha-synuclein targeting therapeutics for Parkinson's disease and related synucleinopathies, Front. Neurol. (2022) *13*, https://doi.org/10.3389/fneur.2022.852003.

[97] M.C. Meulener, K. Xu, L. Thomson, H. Ischiropoulos, N.M. Bonini, Mutational analysis of DJ-1 in drosophila implicates functional inactivation by oxidative damage and aging, Proc. Natl. Acad. Sci. 103 (33) (2006) 12517–12522.

[98] S. Michiorri, V. Gelmetti, E. Giarda, F. Lombardi, F. Romano, R. Marongiu, G. Arena, The Parkinson-associated protein PINK1 interacts with Beclin1 and promotes autophagy, Cell Death Differ. 17 (6) (2010) 962–974.

[99] D.J. Moore, Parkin: a multifaceted ubiquitin ligase, Biochem. Soc. Trans. 34 (5) (2006) 749–753, https://doi.org/10.1042/BST0340749.

[100] S. Mullin, A. Schapira, α-Synuclein and mitochondrial dysfunction in Parkinson's disease, Mol. Neurobiol. 47 (2) (2013) 587–597.

[102] D. Nandi, P. Tahiliani, A. Kumar, D. Chandu, The ubiquitin-proteasome system, J. Biosci. 31 (1) (2006) 137–155.

[103] N.B. Nedelsky, P.K. Todd, J.P. Taylor, Autophagy and the ubiquitin-proteasome system: collaborators in neuroprotection, Biochim. Et. Biophys. Acta (BBA)-Mol. Basis Dis. 1782 (12) (2008) 691–699.

[104] S.J. Orenstein, S.-H. Kuo, I. Tasset, E. Arias, H. Koga, I. Fernandez-Carasa, A. Consiglio, Interplay of LRRK2 with chaperone-mediated autophagy, Nat. Neurosci. 16 (4) (2013) 394–406.

[105] S. Pang, D. Chen, A. Zhang, X. Qin, B. Yan, Genetic analysis of the LAMP-2 gene promoter in patients with sporadic Parkinson's disease, Neurosci. Lett. 526 (1) (2012) 63–67.

[106] M. Pedrini, A. Iannielli, L. Meneghelli, D. Passarella, V. Broccoli, P. Seneci, Synthesis and preliminary characterization of putative Anle138b-Centered protacs against α-Synuclein Aggregation, Pharmaceutics 15 (5) (2023) 1467. ⟨https://www.mdpi.com/1999-4923/15/5/1467⟩.

[107] E.D. Plowey, S.J. Cherra III, Y.-J. Liu, C.T. Chu, Role of autophagy in G2019S-LRRK2-associated neurite shortening in differentiated SH-SY5Y cells, J. Neurochem. 105 (3) (2008) 1048–1056, https://doi.org/10.1111/j.1471-4159.2008.05217.x.

[108] W. Poewe, K. Seppi, C.M. Tanner, G.M. Halliday, P. Brundin, J. Volkmann, A. E. Lang, Parkinson disease, Nat. Rev. Dis. Prim. 3 (1) (2017) 1–21.

[109] D. Popovic, D. Vucic, I. Dikic, Ubiquitination in disease pathogenesis and treatment, Nat. Med. 20 (11) (2014) 1242–1253.

[110] R.B. Postuma, D. Berg, M. Stern, W. Poewe, C.W. Olanow, W. Oertel, A.E. Lang, MDS clinical diagnostic criteria for Parkinson's disease, Mov. Disord. 30 (12) (2015) 1591–1601.

[111] V.M. Pozo Devoto, T.L. Falzone, Mitochondrial dynamics in Parkinson's disease: a role for α-synuclein, Dis. Models Mech. 10 (9) (2017) 1075–1087.

[112] J.A. Pradeepkiran, P.H. Reddy, Structure based design and molecular docking studies for phosphorylated tau inhibitors in Alzheimer's disease, Cells 8 (3) (2019) 260.

[113] J.A. Pradeepkiran, P.H. Reddy, Phosphorylated tau targeted small-molecule PROTACs for the treatment of Alzheimer's disease and tauopathies, Biochim. Et. Biophys. Acta (BBA)-Mol. Basis Dis. 1867 (8) (2021), 166162.

[114] T. Pringsheim, N. Jette, A. Frolkis, T.D. Steeves, The prevalence of Parkinson's disease: a systematic review and meta-analysis, Mov. Disord. 29 (13) (2014) 1583–1590.

[115] A. Sánchez-Danés, Y. Richaud-Patin, I. Carballo-Carbajal, S. Jiménez-Delgado, C. Caig, S. Mora, A. Giralt, Disease-specific phenotypes in dopamine neurons from human iPS-based models of genetic and sporadic Parkinson's disease, EMBO Mol. Med. 4 (5) (2012) 380–395.

[116] A. Sanyal, S. Dutta, A. Camara, A. Chandran, A. Koller, B.G. Watson, J. Cannon, Alpha-synuclein is a target of Fic-mediated adenylylation/AMPylation: possible implications for Parkinson's disease, J. Mol. Biol. 431 (12) (2019) 2266–2282.

[117] S.P. Sardi, J.M. Cedarbaum, P. Brundin, Targeted therapies for Parkinson's disease: from genetics to the clinic, Mov. Disord. 33 (5) (2018) 684–696.

[118] J.A. Schneider, J.-L. Li, Y. Li, R.S. Wilson, J.H. Kordower, D.A. Bennett, Substantia nigra tangles are related to gait impairment in older persons, Ann. Neurol. 59 (1) (2006) 166–173, https://doi.org/10.1002/ana.20723.

[119] D.C. Schöndorf, M. Aureli, F.E. McAllister, C.J. Hindley, F. Mayer, B. Schmid, L. K. Schwarz, iPSC-derived neurons from GBA1-associated Parkinson's disease patients show autophagic defects and impaired calcium homeostasis, Nat. Commun. 5 (1) (2014) 1–17.

[120] E. Shlevkov, T. Kramer, J. Schapansky, M.J. LaVoie, T.L. Schwarz, Miro phosphorylation sites regulate Parkin recruitment and mitochondrial motility, Proc. Natl. Acad. Sci. 113 (41) (2016) E6097–E6106.

[121] M.C. Silva, F.M. Ferguson, Q. Cai, K.A. Donovan, G. Nandi, D. Patnaik, B. C. Dickerson, Targeted degradation of aberrant tau in frontotemporal dementia patient-derived neuronal cell models, Elife 8 (2019), e45457.

[122] M. Somayaji, Z. Lanseur, S.J. Choi, D. Sulzer, E.V. Mosharov, Roles for α-synuclein in gene expression, Genes 12 (8) (2021) 1166.

[123] M. Steger, F. Tonelli, G. Ito, P. Davies, M. Trost, M. Vetter, S. Wilson, Phosphoproteomics reveals that Parkinson's disease kinase LRRK2 regulates a subset of Rab GTPases, Elife 5 (2016), e12813.

[124] M. Stöckl, P. Fischer, E. Wanker, A. Herrmann, α-Synuclein selectively binds to anionic phospholipids embedded in liquid-disordered domains, J. Mol. Biol. 375 (5) (2008) 1394–1404.

[125] I. Stojkovska, W.Y. Wani, F. Zunke, N.R. Belur, E.A. Pavlenko, N. Mwenda, J. R. Mazzulli, Rescue of α-synuclein aggregation in Parkinson's patient neurons by synergistic enhancement of ER proteostasis and protein trafficking, Neuron 110 (3) (2022) 436–451, e411.

[126] C.-J. Su, Y. Feng, T.-T. Liu, X. Liu, J.-J. Bao, A.-M. Shi, Y.-L. Yu, Thioredoxin-interacting protein induced α-synuclein accumulation via inhibition of autophagic flux: Implications for Parkinson's disease, CNS Neurosci. Ther. 23 (9) (2017) 717–723, https://doi.org/10.1111/cns.12721.

[127] D. Takahashi, H. Arimoto, Targeting selective autophagy by AUTAC degraders, Autophagy 16 (4) (2020) 765–766.

[128] Q. Tang, P. Gao, T. Arzberger, M. Höllerhage, J. Herms, G. Höglinger, T. Koeglsperger, Alpha-synuclein defects autophagy by impairing SNAP29-mediated autophagosome-lysosome fusion, Cell Death Dis. 12 (10) (2021) 854.
[129] N. Thayanidhi, J.R. Helm, D.C. Nycz, M. Bentley, Y. Liang, J.C. Hay, α-Synuclein delays endoplasmic reticulum (ER)-to-Golgi transport in mammalian cells by antagonizing ER/Golgi SNAREs, Mol. Biol. Cell 21 (11) (2010) 1850–1863.
[130] E.M. Valente, P.M. Abou-Sleiman, V. Caputo, M.M. Muqit, K. Harvey, S. Gispert, D.G. Healy, Hereditary early-onset Parkinson's disease caused by mutations in PINK1, Science 304 (5674) (2004) 1158–1160.
[132] V. Vasquez, J. Mitra, H. Wang, P.M. Hegde, K. Rao, M.L. Hegde, A multi-faceted genotoxic network of alpha-synuclein in the nucleus and mitochondria of dopaminergic neurons in Parkinson's disease: emerging concepts and challenges, Prog. Neurobiol. 185 (2020), 101729.
[133] K. Vekrellis, H.J. Rideout, L. Stefanis, Neurobiology of α-synuclein, Mol. Neurobiol. 30 (1) (2004) 1–21.
[134] M. Verma, J. Callio, P.A. Otero, I. Sekler, Z.P. Wills, C.T. Chu, Mitochondrial calcium dysregulation contributes to dendrite degeneration mediated by PD/LBD-associated LRRK2 mutants, J. Neurosci. 37 (46) (2017) 11151–11165.
[135] J. Wagner, S. Ryazanov, A. Leonov, J. Levin, S. Shi, F. Schmidt, A. Giese, Anle138b: a novel oligomer modulator for disease-modifying therapy of neurodegenerative diseases such as prion and Parkinson's disease, Acta Neuropathol. 125 (6) (2013) 795–813, https://doi.org/10.1007/s00401-013-1114-9.
[137] W. Wang, X. Wang, H. Fujioka, C. Hoppel, A.L. Whone, M.A. Caldwell, X. Zhu, Parkinson's disease–associated mutant VPS35 causes mitochondrial dysfunction by recycling DLP1 complexes, Nat. Med. 22 (1) (2016) 54–63.
[138] W. Wang, F. Zhao, X. Ma, G. Perry, X. Zhu, Mitochondria dysfunction in the pathogenesis of Alzheimer's disease: recent advances, Mol. Neurodegener. 15 (1) (2020) 1–22.
[139] W. Wang, Q. Zhou, T. Jiang, S. Li, J. Ye, J. Zheng, J.-Z. Wang, A novel small-molecule PROTAC selectively promotes tau clearance to improve cognitive functions in Alzheimer-like models, Theranostics 11 (11) (2021) 5279–5295, https://doi.org/10.7150/thno.55680.
[140] A.R. Winslow, D.C. Rubinsztein, The Parkinson disease protein α-synuclein inhibits autophagy, Autophagy 7 (4) (2011) 429–431.
[141] Y.C. Wong, D. Krainc, α-synuclein toxicity in neurodegeneration: mechanism and therapeutic strategies, Nat. Med. 23 (2) (2017) 1–13.
[142] M. Xilouri, O.R. Brekk, L. Stefanis, Alpha-synuclein and protein degradation systems: a reciprocal relationship, Mol. Neurobiol. 47 (2) (2013) 537–551, https://doi.org/10.1007/s12035-012-8341-2.
[143] M. Xilouri, T. Vogiatzi, K. Vekrellis, D. Park, L. Stefanis, Abberant α-synuclein confers toxicity to neurons in part through inhibition of chaperone-mediated autophagy, PloS One 4 (5) (2009), e5515.
[144] H. Xiong, D. Wang, L. Chen, Y.S. Choo, H. Ma, C. Tang, X. Zhuang, Parkin, PINK1, and DJ-1 form a ubiquitin E3 ligase complex promoting unfolded protein degradation, J. Clin. Investig. 119 (3) (2009) 650–660.
[145] Q. Yang, H. She, M. Gearing, E. Colla, M. Lee, J.J. Shacka, Z. Mao, Regulation of neuronal survival factor MEF2D by chaperone-mediated autophagy, Science 323 (5910) (2009) 124–127.
[146] D. Ysselstein, M. Nguyen, T.J. Young, A. Severino, M. Schwake, K. Merchant, D. Krainc, LRRK2 kinase activity regulates lysosomal glucocerebrosidase in neurons derived from Parkinson's disease patients, Nat. Commun. 10 (1) (2019) 5570.
[147] Y. Yuan, J. Sun, M. Zhao, J. Hu, X. Wang, G. Du, N.-H. Chen, Overexpression of α-synuclein down-regulates BDNF expression, Cell. mol. neurobiol. 30 (2010) 939–946.
[148] S. Zach, S. Felk, F. Gillardon, Signal transduction protein array analysis links LRRK2 to Ste20 kinases and PKC zeta that modulate neuronal plasticity, PloS One 5 (10) (2010), e13191.
[149] T.A. Zesiewicz, Parkinson disease, CONTINUUM: Lifelong Learn. Neurol. 25 (4) (2019) 896–918.
[150] E. Andres-Mateos, C. Perier, L. Zhang, L. Blanchard-Fillio, B. Greco, T.M. Thomas, B. Ko, H.S. Sasaki, M. Ischiropoulos, H. Przedborski, S. Dawson, T.M. Dawson, VL. DJ-1 gene deletion reveals that DJ-1 is an atypical peroxiredoxin-like peroxidase, Proc. Natl. Acad. Sci. USA 104 (2007) 14807–14812.
[151] E. Ziviani, R.N. Tao, A.J. Whitworth, Drosophila parkin requires PINK1 for mitochondrial translocation and ubiquitinates mitofusin, Proc. Natl. Acad. Sci. 107 (11) (2010) 5018–5023.