Cellular and Molecular Neurobiology (2025) 45:30
https://doi.org/10.1007/s10571-025-01544-2

REVIEW PAPER

Alpha-Synuclein Pathophysiology in Neurodegenerative Disorders: A Review Focusing on Molecular Mechanisms and Treatment Advances in Parkinson's Disease

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Received: 11 February 2025 / Accepted: 10 March 2025

Abstract
Worldwide aging has contributed to the growth of prevalence of neurodegenerative diseases (NDDs), including Parkinson's disease among the elderlies. The advanced destruction of dopaminergic neurons in the substantia nigra, due to many accelerator factors in the brain is the main mechanism of Parkinson's disease. The pathological aggregated alpha-synuclein (α-syn), a protein implicated in multiple neurodegenerative disorders, is one of the critical factors in this neurodegenerative disease and other similar disorders. The misfolding and aggregation of α-syn may interrupt critical processes, including functions of synaptic vesicles and can lead to neuronal death. This protein is encoded by Alpha-Synuclein Gene (SNCA) and mutation in this gene can lead to dysfunctions of the protein structure. Since, therapeutic policies that aim α-syn are promising approaches. Advances in immunotherapies, molecular chaperones, gene therapy targeting SNCA, and DNA aptamers are some examples of this strategy. This review aims to comprehensively assess the current knowledge and evidence on α-syn pathology, genetic determinants, and novel therapeutic methods in Parkinson,'s disease and other synucleinopathies. Continued investigation to discover interventions in this system could result in finding of effective and safe treatments for NDDs.

Keywords Neurodegenerative diseases · Parkinson's disease · Alpha-synuclein · Alpha- synucleinopathy

Background

Nowadays, among the general population, aging in aging is a critical concern (United Nations 2023). The risk of developing age-related neurodegenerative diseases (NDDs), such as Parkinson's disease, increases in the elderly. The prevalence of Parkinson's disease has been estimated nearby 1.51 cases per 1000 cases in all-age group. This prevalence increased from 1980 to 2023 and achieved its climax from 2010 to 2023 (Zhu et al. 2024). Some of the risk factors include genetic predisposition, female gender, and contact with pesticides or heavy metals (Dorsey et al. 2018; Kalia and Lang 2015; Lill and Klein 2017). In Parkinson's disease, there is a destruction in the dopaminergic neurons located in the substantia nigra pars compacta (Bloem et al. 2021; Kalia and Lang 2015; Lill and Klein 2017). Moreover, the activity of dopaminergic neurons located in the basal ganglia faded, and motor manifestations, including bradykinesia, resting tremor, and muscular rigidity, were observed (Bloem et al. 2021; Kalia and Lang 2015; Lill and Klein 2017).

From a histopathological perspective, in these patients, the accumulation of aggregated cytoplasmic proteins,

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Published online: 26 March 2025

especially neurofibrillary alpha-synuclein (α-syn) located in the substantia nigra (TretiakoffC 1919; Spillantini et al. 1997, 1998). Alpha-syn is a protein with 140 amino acids and it is one of the family members of small acidic proteins and it is encoded by Alpha-Synuclein Gene (SNCA) (Cookson 2009; Snead and Eliezer 2014). β-synuclein (β-syn) and γ-synuclein (γ-syn) are also other members of the synuclein subtypes (Spillantini et al. 1995). The α- and β-syn are basically expressed in the presynaptic terminals of the brain (George 2001).

The neurofibrillary α-syn aggregation also was observed in other neurodegenerative diseases, like dementia with lewy bodies (DLB), pure autonomic failure (PAF), rapid eye movement (REM) sleep behavior disorder (RBD) and multiple systems atrophy (MSA) (Kaufmann et al. 2001; Goldstein et al. 2021; Krismer and Wenning 2017; McKeith et al. 2017). Because of limitations of the regeneration capacity in the brain, the reduction of neurons, principally due to protein aggregation and misfolding, can accelerate the development of strong neurotoxic forms of the proteins (Sweeney et al. 2017).

Despite many developments in this filed, the significant gaps is in the overall mechanisms and pathogenesis of these disorders' and finding new treatment strategies. The new treatment of neurodegenerative disease, especially Parkinson's disease, targeting dysfunctional neurons to prolong disease, halt neuronal loss, and shorten the disease duration plays a crucial role (Sardi et al. 2018).

Here, we inclusively review information on neural dysfunction caused by a-syn, focusing on Parkinson's disease, new possible mechanisms to overcome protein aggregation, and trending approaches in terms of treatments.

Main Text

Structure, Characteristics and Roles of a-Synuclein

Alpha-syn contains three parts, including a N-terminus (1–60) with the amphipathic feature that binds to cellular membranes and has an alpha-helical structure, a hydrophobic domain in its median named non-amyloid component (NAC) (61–95) that usually folded as an alpha helix; however, it can also transfers to a beta-sheet structure; and also a hydrophilic C-terminus (96–140) (Bendor et al. 2013). This protein is mainly restricted to the cytosol of synapses, but it may be found in the nuclear and synaptic partitions. Alpha-syn interacts with lipid membranes and histones in the cell nucleus that can control of the levels of its own expression (Snead and Eliezer 2014; Cookson 2009; Xu et al. 2015). As in the hydrated solution, a well-known three-dimensional configuration for α-syn has not been developed, it is called "natively unfolded" (Weinreb et al. 1996).

In Alzheimer's disease, the NAC region was first discovered in the plaques of amyloid that is the most interesting motif in Parkinson's disease PD research. It is assumed that the highly hydrophobic center domain mainly leads to the fibril maturation of aggregation and amyloidogenic. To confirm this hypothesis, it is discovered that isolated NAC forms amyloid fibrils (Du et al. 2003; Giasson et al. 2001; Han et al. 1995; Ueda et al. 1993). The final C-terminus (96–140) has a negative charge and can be involved in Ca2 + binding and chaperone-like activity. This binding regulates the α-syn—synaptic membranes interactions (Lautenschläger et al. 2018; Nielsen et al. 2001). In α-syn, a transient interaction has been shown between N-terminal and C-terminal (Kumari et al. 2021). The unfolding process of proteins with the exposure of the accumulation aggregation-prone components of the protein occur as the results of intermolecular interaction. This situation serves as a critical condition for the aggregation of proteins, with the increase in formation of α-syn and new monomers of amyloids on their surface, a process named secondary nucleation (Virdi et al. 2022).

The strict role of α-syn has not been completely discovered. As α-syn can bind to the lipid membranes on synaptic vesicles, Golgi apparatus or mitochondria, these features have well-known related roles. Alpha-syn is a molecular chaperone that can promote the collection of SNARE complexes at the synapse (Burré et al. 2014, 2015, 2010). Moreover, it manages the dynamics of neurotransmitters, clathrin-dependent refilling of the group of synaptic vesicles, besides the maintenance of mitochondrial membrane proteins (Abeliovich et al. 2000; Cabin et al. 2002; Devi et al. 2008; Vargas et al. 2014). The physiologically decrease in the α-syn can lead to reduction in the amount of synaptic vesicles at the distal pools, and the high expression of this leads to increase of vesicles docked at the membranes. Based on this, α-syn can restrict the vesicle collapse within kiss-and-run exocytosis and limit the mechanisms of progress of fast membrane retrieval (Larsen et al. 2006; Murphy et al. 2000; Vargas et al. 2014).

Researches also show that human α-syn can regulate dopamine neurotransmission. Based on studies, this effect is dose-dependent on dopamine neurotransmission, and this can collaborate with the manifestations of Parkinson's disease (Janezic et al. 2013; Plaas et al. 2008). The dopamine storage in synaptic vesicles along with the expression of vesicular monoamine transporter 2 (VMAT2) and activation in nigral neurons are managed by a-syn. It has been shown that VMAT2 is necessary for the reduction of unfairly oxidative side-effects due to the metabolites of dopamine located in the cytosol (González-Hernández et al. 2004). The N-terminal field of α-syn has interaction with mitochondria, and the signal of putative mitochondrial localization can promote by its first 32 amino acids of α-syn. Alpha-syn is also been on the external membrane of mitochondrial, and

via the TOM40 transporter, it can be displaced to the inner membrane (Devi et al. 2008).

Although the function of the α-syn and mitochondria interaction is not fully revealed, it is revealed that the relation of membranes with α-syn is strongly rely on the lipid conformation. The α -syn and the mitochondrial membrane interaction is simplified by cardiolipin which is a diphosphatidylglycerol lipid with a scaffold chaperone for the apparatuses of the electron transport chain (ETC) (Chicco and Sparagna 2007; Guardia-Laguarta et al. 2015). The stability of the ETC complex is the result of α-syn and mitochondrial membrane binding (Snead and Eliezer 2014).

SNCA Gene

SNCA gene, at chromosome 4, is responsible for encoding of α-syn (Spillantini et al. 1995). The gene has seven exons, and five of them code the protein (Lavedan 1998). The transcription process of SNCA is controlled by the zinc finger proteins types including ZSCAN21 and ZNF219, GATA2 as the transcription elements, methylation and microRNAs (miRNAs) nerve and basic fibroblast growth factors (NGF; bFGF) (Brenner et al. 2015; Clough et al. 2009; Kantor et al. 2018; Recasens et al. 2016).

The major location for point mutations that occurs in α-syn is its N-terminus. These mutations can lead to diseases like Parkinson's disease or dementia with Lewy bodies (these mutations are: A30P, A53E, A53T, E46K, G51D, and H50Q) (Tanaka et al. 2019). The promotion of α-syn oligomerization is the result of A30P and A53T mutations, the increase in the level of fibrillar aggregation and toxicity cause as the result E46K, G51D, A53E, and H50Q mutations (Boyer et al. 2019; Conway et al. 2000; Lázaro et al. 2014; Rutherford and Giasson 2015). The phosphorylation and truncation are generally found at the C-terminal. This domain that is prone to phosphorylation contains one serine (129) and also three tyrosine residues (125, 133, and 136) (Sano et al. 2021). Moreover, truncation of this site can enlarged aggregation tendency besides harmfulness of α-syn (Zhang et al. 2022). The phosphorylated and truncated forms of α-syn were found in Parkinson's disease and also dementia with Lewy bodies (Muntané et al. 2012).

All of missense mutations that happened and reproductions of SNCA increase the risk factors in the autosomal dominant form of Parkinson's disease. The increase in these repeats lead to progress of growth the α-syn level, and the worsening of the symptoms (Book 2018). Consequently, the wild-type proteins induce the disease. Basically, the single nucleotide polymorphisms (SNPs) and also reduction of the epigenetic silencing of SNCA are the main risk factors for the induction of Parkinson's disease (Edwards et al. 2010; Jowaed et al. 2010). There is a recommendation that by decreasing the expression of α-syn, the risk of adopting atypical structure by the protein and oligomerization may be lower. It should be considered that, however, SNCA silencing does not have a mortal impact; the decline in the level of α-syn is harmful and impairs the dopaminergic and neural synaptic (Benskey et al. 2018).

Various clinical studies discussed information about the presence of abnormalities related to this gene. For instance, a study evaluates the SNCA-positive cells in the epidermis, pilosebaceous units (PSU), and eccrine glands from the skin biopsy of patients and normal individuals. To detect and quantify SNCA, the biopsies were assessed using immunohistochemistry (IHC) and immunofluorescence (IF). Results showed significant α-Syn positivity in Parkinson's patients, while the healthy patients showed no immunoreaction (Rodríguez-Leyva et al. 2014). A case study also reported that the SNCA p.A53T variant led to premature onset, rapid development, and severe cognitive disease (Nishioka et al. 2020). Recently, studies regarding epigenetic mechanisms have been conducted (Surguchov 2023). In a clinical study on Parkinson's disease, patients that had multiple system atrophy, besides a control group, they assessed the methylation levels of both CpG and non-CpG sites in controlling locations of the SNCA gene. They reported the low level of methylation in CpG sites of the SNCA intron 1 in the group of Parkinson's disease was associated with primary onset of syndrome, and the high level of methylation in predominantly non-CpG of SNCA promoter section in MSA was associated with shorter disease time (Fedotova et al. 2023). From a cross-sectional retrospective report, the main outcome of SNCA gene SNPs in patients was observed by imaging analysis. Based on the results, in patients the unprompted activity of the brain in the right superior cerebellum, left supplementary motor area and vermis was weaker than in healthy people. For rs11931074 of SNPs, the key genotypic objects were seen in the paracingulate gyri, the left inferior cerebellum and right anterior cingulate. The main effects of other SNPs, rs356219, and rs356165, were presented in the left caudate nucleus. An interaction also presented in the right inferior parietal gyrus for rs356219 (Chen et al. 2024).

Other Genes

The glucosylceramidase beta 1 (GBA) gene mutation, which occurs in Gaucher disease, also can increase the risk of Parkinson's disease (Sidransky et al. 2009). GBA gene can encode the lysosomal enzyme of glucocerebrosidase (GCase), that catalyzes glucocerebroside into two parts of glucose and ceramide (Granek et al. 2023). From CSF sampling of patients, a significant low-activity and protein concentrations of GCase 1 has been observed (Parnetti et al. 2017; Rocha et al. 2015). The exact mechanism that connected the GBA mutation to Parkinson's disease is poorly

understood, but an animal study reveals that GBA1L444P mutation can cause malfunction in the hippocampal function, a reduction in the hippocampal excitatory synaptic protein, and predisposed the hippocampus for the generation of α-syn inclusion (Mahoney-Crane et al. 2023).

The leucine-rich repeat kinase 2 (LRRK2) gene is one of the family members from the leucine-rich repeat kinase family, which encodes a protein of an armadillo repeat region, and also an ankyrin repeat region, a leucine-rich repeat domain, a kinase domain, a GTPase domain, a RAS domain, and a WD40 domain. This gene has a considerable role in different physiological processes within neurons. A mutation of exon 41, which is responsible for encoding the kinase domain of LRRK2, can increase the kinase activity of LRRK2 and, thereby, neurological deficiency observe in patients with Parkinson's disease (Li et al. 2014; Rideout and Stefanis 2014). The mutations in LRRK2 can lead to an increase in kinase activity, dysfunction in GTPase, or dimerization of the protein (Daher 2017). The aggregation of α-syn is due to gain-of-function mutations in LRRK2 gene (Schulte and Gasser 2011).

Alpha-Synucleinopathy

Here, data about types of a-synucleinopathy and its toxicity will be discussed.

A simple system to demonstrate the toxicity of α-syn is a yeast model, where overexpression of this protein limits cell growth during both the logarithmic and stationary phases (Brandis et al. 2006). Some experiments were evaluated the harmfulness of α-syn in mammalian models. In the model of midbrain cultures, α-syn toxicity in dopamine neurons is higher than other cells, and this finding can be related to the relative susceptibility of nigral neurons in simulations with Parkinson's disease (Petrucelli et al. 2002). Based on some studies, the variations between mutant and wild-type proteins are dose related, and the regular protein can become as toxic as the dominant mutants in increasing expression levels (Xu et al. 2002).

Alpha-synucleinopathies are associated abnormal aggregations of α-syn that can induce neurodegenerative diseases including idiopathic Parkinson's disease, DLB, MSA, RBD, and PAF (Goldstein et al. 2021; Krismer and Wenning 2017; McKeith et al. 2017). At the mitochondrial level, pathological α-syn can damage function, morphology and also cause mitochondria accumulation, and reduce the basal oxygen consumption rate (Di Maio et al. 2016; Ludtmann et al. 2018; Plotegher et al. 2014). Evidence also shows a vicious circle of cellular damage due to oxidative reactions, accumulation of toxic α-syn, and neuronal loss (Gu et al. 2005). While these facts show the age-related damage of α-syn to mitochondrial activity, the aggregated α-syn is not discovered in the central nervous system (CNS) in Parkinson's disease. Vulnerable neurons characterize the effects of structural and practical features in a better way (Beach et al. 2009; Surmeier et al. 2017).

As data supported that a-syn, malfunction in mitochondrial, and interruption of Ca2 + homeostasis are strongly implicated in Parkinson's disease, the outcomes of α-syn on the mitochondrial functions were evaluated. It is reported that α-syn is a tether between Endoplasmic reticulum (ER) and mitochondria. It means α-syn also can prevent the salvage of cellular damages from mitochondrial malfunction (by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP/MPP +) and carbonyl cyanide m-chlorophenyl hydrazone (CCCP)), which can introduce as a pathological character of α-syn (Ramezani et al. 2023).

To better understand, in the mouse brain, they conducted a quantitative pathology mapping that showed the spatiotemporal spread pattern was related to the anatomical connection and internal α-syn expression in a specified area (Henderson et al. 2019). In addition to animal studies, cohort study results indicate three disease modes: typical, mild and severe progression. In the severe progression, they saw faster disease propagation to limbic and prefrontal areas. The tremor-dominant form is mild that had low cognitive impairments, and innervations of dopaminergic neurons are protected longer (Fereshtehnejad et al. 2017). Beta-sheet conformation monomers form fibrillar α-synucleins (F-αsyns). F-αsyns are considered like disease-causing prions in studies (Olanow and Brundin 2013). F-αSyn also spreads the pathology cell-to-cell during the process of F-αsyn internalization, bypassing the cellular protection mechanism, acting in a prion-like mode, cell transportation, and transferring F-αsyn to other cells (Kim et al. 2019; Bieri et al. 2018).

The roles of inflammatory system in the Parkinson's disease pathophysiology and further synucleinopathies, along with their mechanisms and factors contributing to disease progression, are also suggested. Missense mutation of SNCA that leads to the increase of α-syn protein and microglia activation also causes inflammation in the neurologic system and deterioration of the striatal neurons. The modulatory effects that lead to cell death like nitric oxide (NO), reactive oxygen species (ROS), tumor necrosis factor (TNF)-alpha(α), and interleukin (IL)-1beta(β) were also reported (Glass et al. 2010; Hirsch and Hunot 2009; Orr et al. 2005).

The neuroinflammation can activates microglia, adaptive immune, and interrupts mitochondrial (Ferreira and Romero-Ramos 2018). Many studies showed that α-syn activates microglia and generates a pathological inflammatory response (Rocha et al. 2018). The mutant monomeric form of α-syn leads to a significant immune system response. Also, there is a relation between the α-syn oligomers molecular weight and the response severity (Grozdanov et al. 2019).

As the correlation exists between inflammation and Parkinson's disease, α-syn malfunction and inflammatory response play role in the Parkinson's disease severity. CSF and serum of patients with Parkinson's, have greater levels of inflammatory biomarkers like TNF-α, interleukins, TGF-β, and IFN-γ, that explained the activation of α-syn-mediated microglial (Chen et al. 2005; Hamza et al. 2010; Karpenko et al. 2018). Microgliosis can have roles in the phagocytosis of damaged synapses, like events in Alzheimer's disease (Hong et al. 2016). The adaptive immune system in Parkinson's disease, may lead to T cells infiltrations in the SNPC of patients, which relate to adaptive immune responses (Baba et al. 2005; Brochard et al. 2009; Saunders et al. 2012).

Based on evidence, cytokines in Parkinson's disease, can direct effect on neural cells by the exacerbation of α-syn. A study showed that human induced pluripotent stem cells (iPSC) from healthy volunteers' cortical neurons (CNs) and participants with duplication at α-syn gene locus were accelerated with IL-17A cytokines. The patients with duplication at the α-syn gene locus showed an over-expression of the IL-17A receptor and an increase in regulation of impaired IL-17A-mediated receptor. Moreover, Tau pathology in this group was provoked by IL-17A and cytokines. They also observed that inhibition of α-syn oligomerization prevented IL-17A-mediated neuronal impairment (Sigutova et al. 2024).

The links between the CD4 + T-helper cells and α-syn in an animal study were assessed. They examined α-syn61-75 in this study to induce infiltration of CD4 + T-cell to the brain. Results showed that the immunization due to α-syn61-75 is caused immunologic responses, α-synuclein aggregation, and loss of dopaminergic cells located in the substantia nigra of the brain. Also, symptoms related to Levodopa-sensitive motor were detected after 8 weeks in mice (Parkinson et al. 2024).

Another study about the autoimmune response of T-cell according to α-syn in mice revealed that autoimmune responses due to α-syn peptide-mediated caused primary neuronal cell loss and the microglia and A1-type astrocytes activation. This study injected 50 µg of candidate peptides combined with 100 µg of whole adjuvant into two altered hind flank sites. After that, they harvested primary cortical neurons and splenocytes from the sample. These cells were cocultured within 2–3 days at 37 °C, and then, they analyzed cell death. Results showed that autoimmune T-cell responses occurred due to α-syn monomers (M-α-syn) and α-syn preformed fibrils (PFFs). Interestingly, the high numbers of IL-17A-producing CD4 + T cells and IFN-γ-producing CD4 + T cells and were presented in these mice models. They also reported that pep#1 and pep#5 trigger T cells and (Choe et al. 2024).

About the potential character of natural killer (NK) cells in pathophysiology of Parkinson's disease, data showed that they localize in the nigra and they can respond to α-syn and also, suggesting that these immunologic cells possibly are stimulate by both monomeric and aggregated of α-syn (Earls et al. 2020). To investigation of the protection role of NK cells in neuroinflammation, more studies should be conducted (Kasen et al. 2022). A study also showed that the NK cells and macrophages that can destroy α-syn, in two environments with phosphatidylserine and cholesterol (PS/Cho) and investigated the potential roles in the start and also the progression of Parkinson's disease. Results showed that PS/Cho vesicles developed the harmfulness of α-syn fibrils along with the degradation of α-syn (Matveyenka et al. 2024).

Regarding the function of B cells in α-syn-related neurodegenerative diseases, data are still debatable. In studies, peripheral IgG + B cells that can produce antibodies against to α-syn were found in patients with Parkinson disease, and some types of antibodies had α-syn aggregation inhibiting features. These facts present a possible protective influence of IgG in patients with Parkinson's disease (Li et al. 2019).

Chaperones and Alpha-Syn

Chaperones correct the miss folding of protein chains and interact with miss folded protein to inhibit aggregation (Ellis 1997; Sharma and Priya 2017). They also ease the folding of multi-part proteins by temporary sequestration of the folding intermediates (Powers et al. 2009). Chaperones can prevent the seeding of new aggregations and fibrillization (Hartl et al. 2011).

Heat-shock proteins (Hsps) are a large class of chaperones with important roles in proteastasis. They play roles in both typical physiological and under stress conditions (Jäättelä 1999). Studies showed that Hsp40, Hsp70, and Hsp110 chaperones can undo α-syn aggregation in vitro (Gao et al. 2015; Duennwald et al. 2012). About the roles of these chaperones, Hsp90 leads to stabilization in its substances, and Hsp70 transfers these agents for proteasomal degradation upon Hsp90 detachment. In animal and cellular simulations of Parkinson's disease they found that Hsp90 activity inhibiting or Hsp70 activity stimulating and its collaborator Hsp40 decreased toxicity of α-syn (Putcha et al. 2010; Klucken et al. 2004; Auluck et al. 2005; Auluck and Bonini 2002; McLean et al. 2002; Batelli et al. 2008; Fan et al. 2006; Outeiro et al. 2008; Shin et al. 2005; Yu et al. 2005; Zhou et al. 2004).

One of the groups of Hsp is small heat-shock proteins (sHsps) which are the prime security against aggregation of proteins. This inhibitory function to protein aggregation has been evaluated in pathogenic and physiologic proteins, like α-syn (Binger et al. 2013; Carver et al. 2002; Rekas et al.

2004, 2007; Bruinsma et al. 2011; Pivovarova et al. 2007). Ten human small heat-shock proteins (sHsps) were found, and amongst them, Hsp20 (HSPB6), Hsp27, αA-crystallin (HSPB4, αA-c), and αB-c are the most famous of them (Carra et al. 2013; Kampinga et al. 2009). The sHsps have quite small (compared to other types of Hsps) monomeric weights (12–43 kDa) (Stamler et al. 2005; van Montfort et al. 2001). Hsp27 is main induced protein of the brain in Parkinson's disease (Zhang et al. 2005). When dopaminergic neurons express low basal of Hsp27, the start of α-syn aggregation may be facilitated (Carra et al. 2013; Chen and Brown 2007). A recent study revealed that HSPB6 shows a lipid-dependent activity as it could limit the α-syn aggregation just in the existence of lipid membranes (Secco et al. 2024).

F-αsyns somehow surpass the regulation of protein quality control, containing activity of the lysosomes, the autophagosomes, the proteasomes, and the chaperones (Bieri et al. 2018; Saibil 2013). They also can escape from membranous structures (Bieri et al. 2018). This can lead to the interaction of Free F-αsyns with intracellular α-syns and trigger their nucleation (Aulić et al. 2014). Here, the roles of the HSPs can be explained, especially since F-αsyns prevent the ubiquitin–proteasome system (UPS) located in the dopaminergic cells (Zondler et al. 2017). In a study, the intracellular response of HSP to F-αsyn was explored by exposing them to F-αsyn and measuring the intracellular amounts of HSPs. They revealed that during the first 6 h of internalization, there was an surge in the levels of Hsc70 and Hsp90, and following 12 h later, F-αsyn suppressed the intracellular chaperone levels (Çamoğlu et al. 2024).

New Insights for Treatments and Drug Developments

Modulation of α-syn transcription is a known approach. For instance, agonists of the Beta2 adrenoreceptor (β2AR) such as metaproterenol, clenbuterol, and salbutamol, mostly in a dose- and time-dependent method, can reduce transcription of the SNCA gene (Mittal et al. 2017; Qian et al. 2011). Yet, there is deficiency of evidence-based clinical studies. Another approach uses small molecules that target α-syn mRNA, leading to downregulating expression. Synucleozoid was the most effective candidate that inhibited the translation of α-syn (Zhang et al. 2020).

Small molecules that prevent α-syn aggregation were also investigated. SynuClean-D reduced the aggregation of α-syn and rescued the degradation of dopaminergic cells. UCB0599 is an anti-aggregant agent for Parkinson's disease with a tolerable safety profile based on the pharmacokinetic study (Pujols et al. 2018; Smit et al. 2022).

A thorough evaluation of recent trends in developing new molecules and the investigation of new effects of existing drugs on alpha-synucleinopathy is detailed in Fig. 1, Table 1.

Immunotherapy

One of the principles in immunotherapy is the direct administration of antibodies that target α-syn. This method can control factors such as binding affinities and side-effects. Here, some examples were discussed (Bergström et al. 2016).

BIIB054/cinpanemab, as a monoclonal antibody, can link to the aggregated form α-syn protein, and it has been evaluated in a clinical setting. They discovered in early Parkinson's disease, receiving BIIB054 up to a 72-week period showed improvements in the assessment of Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) total score and other assessments (Brys et al. 2019). However, in another study, the results were not desirable (Lang et al. 2021, 2022). Another monoclonal antibody, ABBV-0805, can bind to C-terminal of aggregated of α-syn with a faire profile of safety (Nordström et al. 2021). Experiments showed that the substitution of arginine ligands to the C-terminus of α-syn accelerated the aggregation on the C-terminus, which is an important part of α-syn for therapeutic aims (Jha et al. 2018). PRX002/prasinezumab was developed based on this theory of the targeting C-terminus (Games et al. 2014). This humanized monoclonal antibody can highly bind to aggregated α-syn (Bergström et al. 2016). PRX002/prasinezumab as the most innovative treatment, reported good safety and tolerability in Parkinson disease and decreased free α-syn in the serum in a dose-dependent way (Jankovic et al. 2018; Schenk et al. 2017). However, the PASADENA study tested PRX002/prasinezumab by directing the C-terminal of α-syn, had promising outcomes, BIIB054/cinpanemab with its epitope residue of side chains located at the N-terminus in the recent study showed unwilling results (Schenk et al. 2017; Weihofen et al. 2019). BIIB054 and prasinezumab showed preferable affinity to target aggregated α-syn and could bind to monomeric serum α-syn (Brys et al. 2019; Schenk et al. 2017).

The MEDI1341 monoclonal antibody binds to both monomeric and aggregated α-syn and also it inhibits the uptake of aggregated α-syn to the cells, and reduces α-syn levels (Schofield et al. 2019).

Lu AF82422 is a humanize immunoglobulin G1 (IgG1) monoclonal antibody which can bind to the C-terminal truncated α-syn, preferably to aggregated α-syn. Lu AF82422 antibody can bind to extracellular and pathological α-syn and also it inhibits the seeding and spreading of them to the other cells. Results from the phase 1 study demonstrated that this antibody is safe and tolerable (Buur et al. 2024).

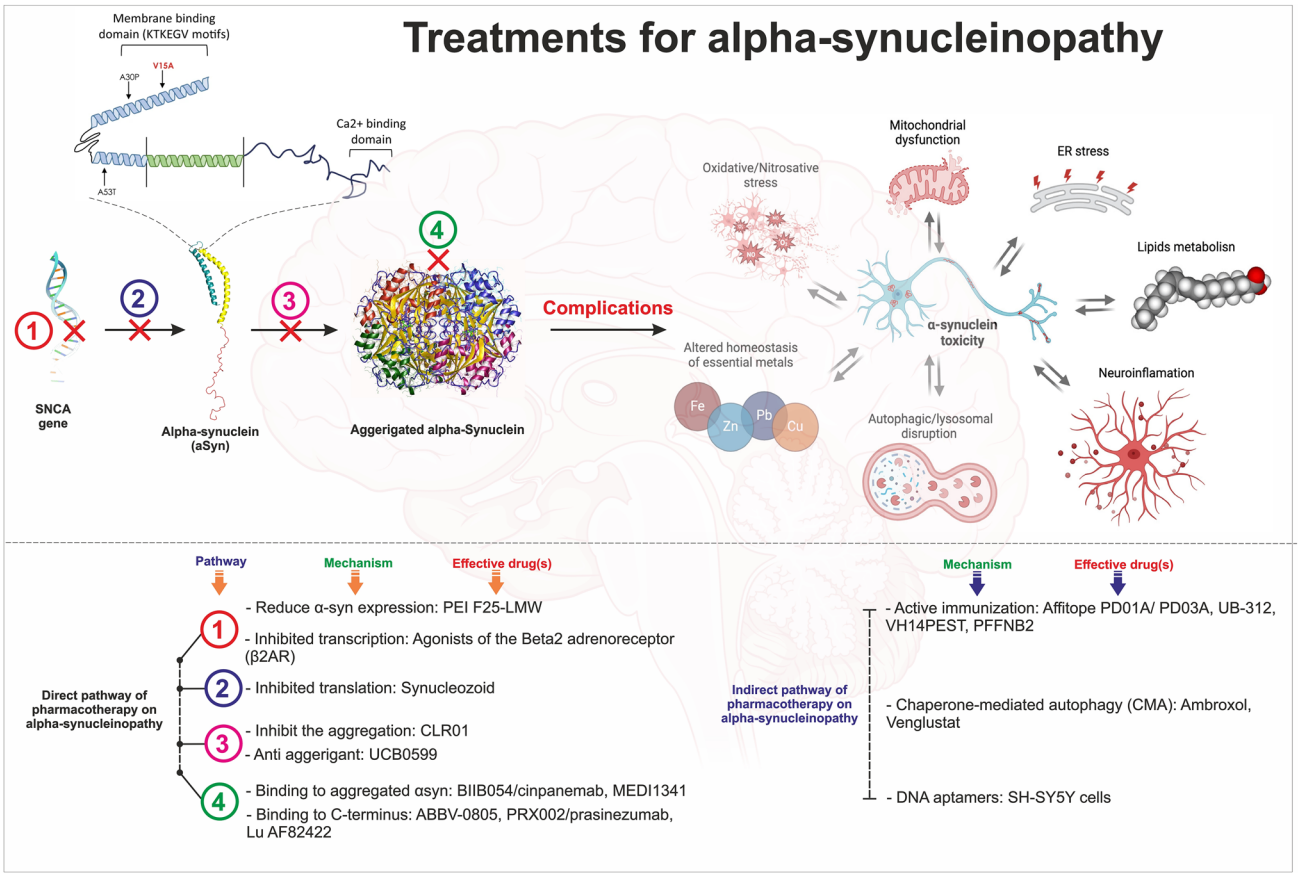

Fig. 1 Treatments for alpha-synucleinopathy

A property of antibodies that matter is the origin. Both aducanumab (for Alzheimer's disease) and BIIB054/cinpanemab are produced from memory B-cell libraries of humans. MEDI1341 and Lu AF82422 are also of humanized antibodies, and PRX002/prasinezumab is a humanized version of murine based antibodies (Bergström et al. 2016; Braczynski et al. 2017; Schofield et al. 2019; Sevigny et al. 2016).

Within various strategies for immunotherapy, inhibition of cell-to-cell communication and cellular uptake, and sequestration of α-syn to lower oligomerization would be a strong approach. AF82422 targets all main species, mono- and oligomeric, and also both N- and C-terminal truncated forms of α-syn (Fjord-Larsen et al. 2021).

Another approach of immunotherapy is active immunization, in which this system responds following the exposure of a specific antigen. The depending of the immune response on the patients could be a disadvantage of this approach (Nikolich-Žugich 2018; Schneeberger et al. 2016).

Affitope PD01A/ PD03A and UB-312 are aimed for Parkinson's disease. Affitope PD01A and PD03A are small peptides and they mimic α-syn epitopes (mimotopes) with eight amino acids, and they are unfamiliar to the immune system (Schneeberger et al. 2010, 2012). The keyhole limpet hemocyanin (KLH) carrier of vaccines and the aluminum hydroxide parts play roles as the immunological adjuvant (Schneeberger et al. 2016).

UB-312 -311 was developed based on the UBITh® technique by which various subtypes of T-helper cell epitopes are linked to a short B-cell epitope directly or indirectly and it can promote the immune response (Wang 2014, 2022; Wang and Walfield 2005).

VH14PEST targets NAC of α-syn and it is a bifunctional nanobody fused to a proteasome targeting signal that is critical for initial aggregation. Compared to NbSyn87PEST that binds to the C-terminus, VH14PEST is more effective (Butler et al. 2016). PFFNB2 is the alternative nanobody-based treatment that can identify the α-syn preformed fibrils. The binding of PFFNB2 throughout an adeno-associated virus (AAV) can limit the aggregated α-syn (Butler et al. 2022).

DNA Aptamers

Recent studies reveal that DNA aptamers tend to the monomeric α-syn and can successfully preclude its aggregation. This could be a favorable approach for treating Parkinson's

Table 1 Recent trends in developing new molecules and the investigation of new effects of existing drugs on alpha-synucleinopathy

NCT Code	Year	Phase	Agent	Mechanism	Outcomes
NCT02281474	2015	Phase 1	Nilotinib	Kinase Inhibitor	Nilotinib is safe and tolerated in advanced Parkinson's disease (Pagan et al. 2016)
NCT05931575 (Wolff et al. 2024)	2023	Phase 2	Fasudil	ROCK-inhibitor	–
NCT02914366	2015	Phase 2	Ambroxol	Chaperon of GCase	Ambroxol is effective and safe as a one of the first disease-modifying treatments for Parkinson disease (Silveira et al. 2019)
NCT02270489	2014	Phase 1	PD01A and PD03A	Therapeutic vaccines	Both of them are safe well-tolerated. PD01A has a rapid and long-lasting antibody response (Meissner et al. 2020)
NCT06015841	2023	Phase 2	ACI-7104.056	Anti-α-synuclein active immunotherapy (del Giudice et al. 2024)	–
NCT05424276	2023	Phase 2	Risvodetinib (IkT-148009)	c-Abl inhibitor	IkT-148009 is safe over 7-day dosing (Werner et al. 2024)
NCT03022799	2016	Phase 1	KM-819	FAS-associated factor 1 (FAF1) inhibitor	KM-819 has a favorable pharmacokinetic and safety profiles elderlies (Shin et al. 2019)
NCT06175767	2022	Phase 2	MT101-5	Neuroprotective herbal medicine (Kim et al. 2022)	–
NCT02046434	2014	Phase 1	Phenylbutyrate	Increase the removal of α-syn from the brain into the bloodstream (Phenylbutyrate Response As a Biomarker for Alpha-Synuclein Clearance From Brain 2014)	–
NCT04449484	2020	Phase 1	MEDI341	A monoclonal antibody that binds to the C-terminal region of human alpha-synuclein (Padmanabhan et al. 2023)	–

disease. In cellular models, results showed that a-syn-1 decreased intracellular α-syn aggregation. Systemic transfer of a-syn-1 by a liposome vehicle in transgenic animal models (mice) reduced aggregated α-syn in vital brain regions. Aptamers have several benefits, such as ease of synthesis, specificity, and the ability for chemical justifications. A better understanding of the long-standing effects and potential harms of aptamers needs more investigation (Berezovski 2024).

Gene Therapy

The reduction in the SNCA gene expression to control α-syn is another interesting method. In a mouse model, polyethyleneimine with low molecular weight, PEI F25-LMW, decreased SNCA mRNA by up to 67% and led to a 31% reduction of α-syn (Helmschrodt et al. 2017). Other study in the mouse model was the conjugation of short interfering RNA (siRNA) or antisense oligonucleotide (ASO) compounds with indatraline (IND) lowered α-syn expression (Alarcón-Arís et al. 2018). In a novel technique, the transportation of short hairpin RNA mini circles by rabies virus glycoprotein (RVG) considerably decreased α-syn levels (Izco et al. 2019).

One of the challenges in delivery for these conditions is the limitation of the blood–brain barrier (BB). The carriage of a siRNA in order to targeting α-syn was eased throughout the binding to a sequence of 11-amino acid from the apoB protein (ApoB11) and an arginine linker, and this resulted in the reduction of α-syn (Spencer et al. 2019). CLR01 is a short molecule that can obstruct the protein aggregation and toxicity in many neurodegenerative syndromes such as Parkinson's disease with a good safety profile along with appropriate permeability to the brain for the therapeutic uses (Attar et al. 2012; Bengoa-Vergniory et al. 2020; Di et al. 2021; Malik et al. 2018; Shahpasand-Kroner et al. 2023).

Chaperone-Mediated Autophagy (CMA)

Based on the evidence, autophagy considered as a crucial contributing factor to the advancement of Parkinson's disease and the significance of Chaperone-mediated autophagy (CMA) (Hardy 2004). In the CMA procedure, cytoplasmic proteins are targets by a distinctive recognition motif. The motif is recognized by the cytoplasmic companion Hsc70 and considered the gateway for the introduction of proteins into the lysosomes (Mizushima 2007; Settembre et al. 2007). Moreover, it has been discovered that mutant GCase leads to dysfunction in chaperone-mediated autophagy. The impaired autophagy can increase α-syn accumulation (Settembre et al. 2007; Yun et al. 2018). Observations in neuronal cells reveal that targeting wild-type α-syn for degradation by CMA is a proper approach; however, the lack of 95VKKDQ99 sequence in α-syn can impair this process (Cuervo et al. 2004).

Two main methods are presented in order to improvement of low GCase activity. One strategy is using small-molecule chaperones to elevate GCase activity. Ambroxol is an example of this method, and it is a GCase chaperone. Ambroxol promoted the activity of GCase and decreased α-syn (Magalhaes et al. 2018; Migdalska-Richards et al. 2016). It also showed effective outcomes in clinical studies with favorable safety and tolerability profiles and fair permeability through the blood–brain barrier (McNeill et al. 2014; Mullin et al. 2020). Another strategy is the inhibition of the growth of glucosylceramide, which occurs in Parkinson's disease due to GBA1 mutation (Sardi et al. 2017). Venglustat is an inhibitor of glucosylceramide synthase with brain penetration, and it can reduce the level of glycosphingolipids. To prove its effectiveness, other studies should be conducted (Giladi et al. 2023). Development of treatments that are related to the control system of the endoplasmic reticulum could be a promising method for the elimination of aggregated proteins through pathways like protein kinase RNA-like ER kinase (PERK), inositol-requiring protein 1 (IRE1), and activating transcription factor 6 (ATF6) (Koszła and Sołek 2024).

Conclusion

In conclusion, α-synuclein's multifaceted role in neurodegenerative disorders, particularly Parkinson's disease, highlights its valuable roles as a crucial biomarker for diagnosis and therapeutic targeting. While challenges remain in using of α-syn as a therapeutic approch, ongoing research focusing on α-synuclein's specific isoforms, modifications, and interactions with other proteins shows promising result for the development of novel strategies in Parkinson disease. Further investigation into the complicated interplay between α-synuclein pathology and disease progression is crucial should be consider to advancing our information and management of Parkinson's disease and related neurodegenerative conditions.

Authors Contribution SY: conception and design, organization, execution, manuscript preparation and writing, editing of final version of the manuscript. MA: conception and design, execution, manuscript preparation and writing, editing of final version of the manuscript. KM: conception and design, execution, manuscript preparation and writing, editing of final version of the manuscript, review and critique, final approval.

Funding None.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

Ethical Approval This manuscript is a review paper, and no new data collection involving human participants was conducted. As such, no ethics approval was required.

Research Involving Human and Animal Participants Not applicable.

Consent to Participate Not applicable.

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