α-Synuclein pathology from the body to the brain: so many seeds so close to the central soil

Yunying Yang[1], Zhentao Zhang[1, 2, *]

https://doi.org/10.4103/1673-5374.387967

Date of submission: April 6, 2023

Date of decision: July 11, 2023

Date of acceptance: August 24, 2023

Date of web publication: November 8, 2023

From the Contents

Abstract

α-Synuclein is a protein that mainly exists in the presynaptic terminals. Abnormal folding and accumulation of α-synuclein are found in several neurodegenerative diseases, including Parkinson's disease. Aggregated and highly phosphorylated α-synuclein constitutes the main component of Lewy bodies in the brain, the pathological hallmark of Parkinson's disease. For decades, much attention has been focused on the accumulation of α-synuclein in the brain parenchyma rather than considering Parkinson's disease as a systemic disease. Recent evidence demonstrates that, at least in some patients, the initial α-synuclein pathology originates in the peripheral organs and spreads to the brain. Injection of α-synuclein preformed fibrils into the gastrointestinal tract triggers the gut-to-brain propagation of α-synuclein pathology. However, whether α-synuclein pathology can occur spontaneously in peripheral organs independent of exogenous α-synuclein preformed fibrils or pathological α-synuclein leakage from the central nervous system remains under investigation. In this review, we aimed to summarize the role of peripheral α-synuclein pathology in the pathogenesis of Parkinson's disease. We also discuss the pathways by which α-synuclein pathology spreads from the body to the brain.

Key Words: aggregation; autonomic nervous system; barrier receptors; body fluid circulation; in situ generation; Parkinson's disease; phosphorylation; propagation; synucleinopathies; α-synuclein; α-synuclein fibrils

Introduction

α-Synuclein: genes, protein characteristics, and protein behaviors

α-Synuclein (α-Syn) is encoded by the SNCA gene, which is located on the long arm of chromosome 4 (Mizuno et al., 1999). Mutations in the SNCA gene, including A53T, A30P, E46K, G51D, H50Q, duplication, triplication, multiplication, etc., result in their carriers being susceptible to α-Syn pathology, among which A53T carriers exhibit the strongest tendency to form α-Syn pathology in the brain (Ikeuchi et al., 2008; Byers et al., 2011; Porcari et al., 2015; Zhang et al., 2019; Boyer et al., 2020; Joshi et al., 2023; Lau et al., 2023). Compared to healthy controls, A53T carriers had lower levels of serum α-Syn, indicating dysregulated homeostasis of α-Syn caused by SNCA mutation (Emmanouilidou et al., 2020). A53T carriers also show early and persistent accumulation of phosphorylated α-Syn in the enteric nervous system as well as an altered profile of peripheral immune cells, suggesting the potential influence of SNCA mutation on peripheral α-Syn pathology (Bencsik et al., 2014; Idova et al., 2021).

α-Syn has three major domains: N-terminal domain [amino acid (a.a.) 1–60], central domain (a.a. 61–95), and C-terminal domain (a.a. 96–140) (Wang et al., 2019). The N-terminal domain is highly hydrophobic, containing a consensus sequence (a.a. sequence: KTKEGV) consisting of seven imperfect repeats (a.a. 7–87). Deletion of the 13 residues in the N-terminus accelerates the fibrillization of α-Syn (McGlinchey et al., 2021). The central domain is called the non-amyloid-β component, which is indispensable for α-Syn aggregation (Xu et al., 2016). The C-terminus is negatively charged and flexible, which resists aggregation of the protein (Kumari et al., 2021). *In vitro* and intracellular nuclear magnetic resonance evidence showed that in the normal cellular environment, α-Syn appears as monomeric and disordered (Theillet et al., 2016). Other evidence showed that α-Syn can also form helically folded tetramers that resist aggregation (Selkoe et al., 2014). The aggregation propensity of α-Syn is regulated by the extent of N-terminus exposure (Stephens et al., 2020).

As a synaptic protein, α-Syn regulates synaptic vesicle trafficking and neurotransmitter release. The exact physiological behaviors of α-Syn need to be further investigated (Burré et al., 2010; Butler et al., 2015). The accumulation and hyperphosphorylation of α-Syn play a pivotal role in the pathogenesis of Parkinson's disease (PD) and other synucleinopathies. The already aggregated pathological α-Syn acts as "seeds" to template the aggregation of the remaining soluble counterparts. This abnormal behavior endows it with the characteristics of prion-like proteins (Fink, 2006; Peng et al., 2018; Lau et al., 2020). Aggregated α-Syn is also highly phosphorylated in the brain in PD. The phosphorylation of α-Syn is believed to be mediated by protein kinases including casein kinase 2 and death-associated protein kinase 1. Other kinases may also contribute to the phosphorylation of α-Syn (Fujiwara et al., 2002; Su et al., 2019; Hu et al., 2020; Yu et al., 2022a). The processes of α-Syn aggregation and phosphorylation interact with each other in an ambiguous order of occurrence. Phosphorylation of α-Syn at Ser129, the most commonly observed phosphorylation site, promotes the formation of fibrils, which reversely act on the "soil" of α-Syn monomers and subsequently induce the formation of α-Syn-enriched insoluble inclusions in the cytoplasm of brain cells (Chen and Feany, 2005; Helwig et al., 2016; Froula et al., 2019; Leitão et al., 2021; Yang et al., 2021; Ghanem et al., 2022). Intracerebral injection of α-Syn preformed fibrils (α-Syn PFFs), an artificial analog of α-Syn fibrils, into wild-type mice gave rise to typical α-Syn pathology in the brain, along with loss of dopaminergic neurons, blood-brain barrier (BBB) dysfunction, glial activation, neuroinflammation, and PD-like behavioral deficits (Luk et al., 2012b; Kim et al., 2018; Yun et al., 2018; Bieri et al., 2019; Ding et al., 2021; Butler et al., 2022). Pathological α-Syn can be detected not only in the brain but also in other peripheral organs, body fluids, and autonomic nerves, indicating the flowability and cell-to-cell transmission of pathological α-Syn (Mollenhauer et al., 2011; Wood, 2016; Iranzo et al., 2021; Sharabi et al., 2021; Lobanova et al., 2022; Poggiolini et al., 2022).

Synucleinopathies

PD

Synucleinopathies cover a series of neurodegenerative diseases with α-Syn aggregates, including Lewy body (LB) diseases [including PD, PD with dementia (PDD), and dementia with LBs (DLB)] and multiple system atrophy (MSA) (Koga et al., 2021). PD is the second most common neurodegenerative disease and one of the most studied synucleinopathies, with growing prevalence, disability, and lethality over the years (Pagonabarraga et al., 2015; Bloem et al., 2021). The pathological hallmark of PD is the loss of dopaminergic neurons in the substantia nigra (SN) and the formation of Lewy neurites and LBs consisting mainly of aggregated hyperphosphorylated α-Syn (Spillantini et al., 1997; Yang et al., 2022). Both genetic and environmental

[1]Department of Neurology, Renmin Hospital of Wuhan University, Wuhan, Hubei Province, China; [2]TaiKang Center for Life and Medical Sciences, Wuhan University, Wuhan, Hubei Province, China

*Correspondence to: Zhentao Zhang, MD, PhD, zhentaozhang@whu.edu.cn.

https://orcid.org/0000-0001-6708-1472 (Zhentao Zhang)

Funding: This work was supported by the National Natural Science Foundation of China, Nos. 82271447, 81771382; the National Key Research and Development Program of China, No. 2019YFE0115900; and the "New 20 Terms of Universities in Jinan", No. 202228022 (all to ZZ).

How to cite this article: Yang Y, Zhang Z (2024) α-Synuclein pathology from the body to the brain: so many seeds so close to the central soil. Neural Regen Res 19(7):1463-1472.

factors contribute to the onset of PD (Goldsmith et al., 1997; Polymeropoulos et al., 1997; Menegon et al., 1998; Healy et al., 2008; Tysnes and Storstein, 2017; Blauwendraat et al., 2020). To date, over 8.5 million people have been affected worldwide by PD (Rocca, 2018; GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators, 2019; World Health Organization, 2022).

PD is characterized by both motor and non-motor symptoms (Alarcón et al., 2023). The motor symptoms of PD include static tremor, rigidity, bradykinesia, and changes in posture and gait, resulting from hyperactivity of the acetylcholinergic system relative to deficiency of dopamine (de Bie et al., 1999; Tolosa et al., 2006; Li et al., 2012; Bai and Li, 2021; Nawaz et al., 2022). The non-motor features of PD include sleep disorders, constipation, dysfunction of autonomic nerves, cognitive decline, and depression, which usually occur as atypical symptoms in early stages of PD (Cooper et al., 1992; Wakabayashi and Takahashi, 1997; Williams and Lees, 2005; Camilleri et al., 2022; De Cock et al., 2022; Zhang et al., 2022b).

Other synucleinopathies

In addition to PD, LB diseases also include PDD and DLB. LB diseases share common neuropathological changes: Parkinsonism, cognitive decline, hallucinations, sleep disorders, and fluctuating attention (Donaghy et al., 2018). PD pathology is more confined to the brainstem and limbic regions, while PDD and DLB pathology is more diffuse in the neocortex (Colosimo et al., 2003). Huang et al. (2021) reported that in PDD, α-Syn predominantly causes dementia, while in DLB cases, the cooperation of α-Syn and amyloid β exert the effect. It has been reported that the α-Syn level in the cerebrospinal fluid (CSF) of DLB patients is higher than that of PDD patients (Bougea et al., 2018, 2020). MSA has two major clinical subtypes, MSA-C (MSA with predominant cerebellar ataxia) and MSA-P (MSA with predominant Parkinsonism) (Kalia et al., 2015; Guo et al., 2023). MSA is characterized by the presence of α-Syn-positive glial cytoplasmic inclusions (Papp and Lantos, 1994; Huang et al., 2008; Teil et al., 2022). α-Syn-positive inclusions also invade neurons in MSA, resulting in neuronal cytoplasmic inclusions (Wakabayashi et al., 1998; Hass et al., 2021). The direct correlation between neuronal cytoplasmic inclusions and glial cytoplasmic inclusions remains largely unknown. The density of accumulative glial cytoplasmic inclusions is positively correlated with the clinical manifestations of MSA, typical of which is early and severe autonomic failure, presenting as urinary urge incontinence or retention and orthostatic hypotension (Ozawa et al., 2004; Swaminath et al., 2010; Squair et al., 2022). α-Syn aggregates were also found in the urinary system and correlated with urinary symptoms in MSA (Peelaerts et al., 2023).

'Brain-first' and 'body-first' transmission mode of α-Syn pathology

The accumulation and propagation patterns of α-Syn have been extensively studied in synucleinopathies. Pathological analysis performed by Braak et al. (2003) showed that α-Syn pathology initially occurs in the dorsal motor nucleus of the glossopharyngeal nerve and the anterior olfactory nucleus, medulla, pontine tegmentum, and midbrain, and finally invades the neocortex, leading to the hypothesis that α-Syn pathology may spread through the nervous system. In some patients with prodromal symptoms of PD, ^{123}I-metaiodobenzylguanidine scintigraphy showed fully developed pathology in the peripheral autonomic nervous system and the locus coeruleus, equal to that in diagnosed PD cases. This peripheral dysfunction of the autonomic nervous system supports that PD pathology initiates from peripheral autonomic nerves and then spreads rostrally to the brainstem in some cases (Knudsen et al., 2018). In addition, using a multimodal imaging method, Jacob Horsager and colleagues further validated the existence of both subtypes of PD pathology: brain-first parkinsonism (pathology found sequentially in the amygdala, SN, locus coeruleus, dorsal motor nucleus, and heart) and body-first parkinsonism (pathology found sequentially in the intestine, heart, dorsal motor nucleus, locus coeruleus, and SN) (Horsager et al., 2020). However, the mechanisms underlying the propagation of α-Syn throughout the body remain under investigation.

In this review, we aimed to summarize the existence and production of α-Syn pathology in the peripheral organs and their possible role as a source of peripheral and central α-Syn pathology. Furthermore, the propagation modes of peripheral α-Syn pathology, including the autonomic nerve pathway and body fluid pathway, and the fibrillization microenvironment in which these two pathways are conducive to the formation of peripheral α-Syn pathology were discussed to provide a peripheral and systemic view of α-Syn pathology as a supplement for recognizing the pathogenesis of synucleinopathies.

Search Strategy

Articles published from the year 1992 to 2023 included in this narrative review were screened and selected from the PubMed database. The search keywords included, but were not limited to, Parkinson's disease (and) α-synuclein (and) synucleinopathy; peripheral α-synuclein; α-synuclein (and) brain; α-synuclein (and) heart; α-synuclein (and) liver; α-synuclein (and) spleen; α-synuclein (and) spleen; α-synuclein (and) intestinal; α-synuclein (and) skin; α-synuclein (and) glands; α-synuclein (and) autonomic nerve; α-synuclein (and) blood. The articles that did not correspond to peripheral α-Syn pathology were excluded.

The Source of Peripheral α-Synuclein Pathology

Solid viscera and glands

α-Syn is abundantly expressed in the central nervous system (Agliardi et al., 2022; Alam et al., 2022a; Pena-DIaz and Ventura, 2022). Thus, most previous studies have focused on α-Syn pathology in the brain (Luk et al., 2012a; Masuda-Suzukake et al., 2013). Pathological α-Syn aggregates can also be detected in peripheral organs, such as the liver and heart, which have a high distribution density of nerves and blood vessels (Navarro-Otano et al., 2013; Javanshiri et al., 2022). Studies have indicated that the liver may help to clear pathological α-Syn, while overexpression of α-Syn in the perivascular nerve fiber lowered norepinephrin-induced contraction of the mouse aorta (Marrachelli et al., 2010; Reyes et al., 2021). In these cases, pathological α-Syn may come from brain-originated α-Syn leakage across the BBB and blood-CSF circulation, which communicates with the autonomic nerve system, or possibly from *in situ* generation within these solid viscera. The neuroendocrine organs and glands are also affected by α-Syn pathology, which is related to symptoms such as depression in PD. For example, phosphorylated α-Syn can be detected in the posterior pituitary lobe and salivary glands (Homma et al., 2012). Therefore, a biopsy of the salivary glands may facilitate the early diagnosis of PD (Del Tredici et al., 2010; Gelpi et al., 2014; Vilas et al., 2016). According to these findings, the solid viscera and glands can be a potential source of peripheral α-Syn pathology.

Gastrointestinal tract

In the early stage of PD, intestinal inflammation induces dysregulation of the gut microbiota. Gut microbiota dysbiosis is closely related to motor phenotypes observed in PD (Dodiya et al., 2020). The gut microbiota and their secretions may directly promote the aggregation of α-Syn. It is possible that the formation of α-Syn pathology in the gut may alter the gut microbiota (Scheperjans et al., 2015; Sampson et al., 2016, 2020; Wang et al., 2021a). The intestinal bacteria Enterobacteriaceae can secrete the functional amyloid protein major fimbrial subunit of thin curled fimbriae, which is believed to contribute to α-Syn aggregation. Inhibiting the expression of the intestinal major fimbrial subunit of thin curled fimbriae alleviates α-Syn pathology (Sampson et al., 2020; Wang et al., 2021a). Antibiotic-treated mice display less α-Syn pathology; in contrast, recolonization of the microbiota will aggravate α-Syn pathology (Sampson et al., 2016). This is consistent with the observation that the density of Enterobacteriaceae is positively associated with the severity of postural instability and gait difficulty in PD patients (Scheperjans et al., 2015). α-Syn pathology observed in other parts of the digestive tract, such as the esophagus, is also correlated with disease progression (Tanei et al., 2021). Hits from these digestive tract pathological α-Syn and the pathological reactions it causes together contribute to prodromal enteric nervous system dysfunctions, which manifest clinically as hydrostomia, dysphagia, gastroparesis, and constipation (Manfredsson et al., 2018). These observations support the presence of pathological α-Syn in the gastrointestinal tract and its potential in generating *in situ* α-Syn pathology.

Skin and mucosal tissues

PD is genetically associated with various skin diseases such as melanoma, sweating disorders, dermatophytosis, and seborrheic dermatitis (Dube et al., 2020; Scott et al., 2021). Antemortem skin biopsies conducted by Wang et al. (2020) revealed the existence of pathological α-Syn deposits with seeding activity within the skin among PD and other synucleinopathy cases. Phosphorylated, oligomeric, and aggregated forms of α-Syn are also commonly seen in various skin cells, such as cutaneous nerve cells, indicating communication of PD pathology between the cutaneous nerves and the central nervous system (Spehlmann, 1975; Doppler et al., 2017; Israel and Asch, 2020; Mazzetti et al., 2020; Marano et al., 2022; Nolano et al., 2022; Park et al., 2022). Therefore, detection of pathological α-Syn in the skin and olfactory mucosa is used to diagnose prodromal PD symptoms (Doppler et al., 2022). These results revealed the possibility of pathological α-Syn in the skin and mucosal tissues as a source of peripheral synucleinopathy.

Transmission Pathways of α-Synuclein Pathology from Peripheral Organs to the Brain

The autonomic nerve pathway

Pathological α-Syn accumulates in peripheral tissues many years before the appearance of motor symptoms in synucleinopathies (Palma et al., 2018; Yamada et al., 2020; Camacho et al., 2021; Van Den Berge et al., 2021). Braak et al. (2003) hypothesized that synucleinopathic lesions originate from the peripheral nervous system and spread via the autonomic nerves to the dorsal motor nucleus of the vagus nerve and to the cerebral cortex. Kim et al. (2019) injected α-Syn fibrils into the duodenal and pyloric muscularis layers, which are densely innervated by the vagus nerve, and detected α-Syn lesions in the brain. As expected, pathological changes were first found in the dorsal motor nucleus and then in the caudal portions of the hindbrain. Vagotomy of the autonomic nerve pathway almost completely blocked the propagation from the gastrointestinal tract to the brain (Kim et al., 2019; Chen et al., 2021). Similarly, pathological α-Syn is also enriched in the appendix, and appendectomy may delay PD onset (Killinger et al., 2018). The widespread distribution of α-Syn deposits in autonomic nerves and their upward communication with the central nervous system provide solid evidence supporting the hypothesis that α-Syn may initiate from peripheral tissues. However, considering that α-Syn pathology is predominant in the brain rather than in other tissues, peripheral α-Syn deposits may originate from central nervous system leakage rather than in situ generation. Under *in vivo* conditions, aggregated α-Syn in the brain may spread to the autonomic nerves, which is then transferred to autonomic nerve-enriched peripheral tissues via mechanisms including macromolecule transport, endocytosis, exocytosis, or neuroendocrine processes (Li et al., 2022). Pathological α-Syn may be further processed in the peripheral organ environment or retained *in situ* for a long time, thus accounting for nonmotor autonomic symptoms,

including hydrostomia, dysphagia, gastroparesis, and constipation (Barboza et al., 2015). Conversely, peripheral pathological α-Syn also crosses the BBB and is transported to the central nervous system, becoming part of the sources leading to central α-Syn pathology. This dual transmission forms a vicious circle between central and peripheral α-Syn pathology (Arotcarena et al., 2020).

The body fluid circulation pathway

The autonomic nerve pathway that pathological α-Syn relies on to propagate between the central nervous system and enteric nervous system could result in PD being considered as a systematic disease. However, the autonomic nervous system is not the only pathway that contributes to the flowability of pathological α-Syn. Early in 2006, El-Agnaf et al. (2006) validated the existence of pathological α-Syn in the CSF. High levels of α-Syn in the CSF are associated with PD symptoms and progression (Mollenhauer et al., 2013; Wurster et al., 2022; Coutinho et al., 2023). In addition to the CSF, pathological α-Syn has also been detected in other bodily fluids, including the saliva, lymph, and blood (Sergeyeva et al., 2011; Kluge et al., 2022; Luan et al., 2022). For instance, plasma α-Syn levels are also reported to be related to some signs of PD (Malec-Litwinowicz et al., 2018). Similar to the autonomic nervous system pathway, the circulation of intracellular bodily fluids, including the plasma, CSF, interstitial fluids, and lymph, also results in the transmission of pathological α-Syn between the brain and the peripheral organs (Kim et al., 2012; Matsui and Matsui, 2017; Bartl et al., 2022).

α-Syn expression in the blood is most abundant in red blood cells (Liu et al., 2021). Erythrocytic α-Syn is expressed at both the mRNA and protein levels throughout the lifetime of red blood cells; therefore, α-Syn possibly influences the hemopoietic system (Nakai et al., 2007). It has been reported that erythrocytic α-Syn levels are linked to the occurrence of constipation, a common autonomic symptom of PD (Martínez-Rodríguez and Rey-Buitrago, 2020). In addition, the level of hemoglobin-binding α-Syn is elevated in patients with α-Syn pathology, which is also reported to be related to some sympathetic symptoms observed in PD (Umehara et al., 2020; Zhang et al., 2022a). In the brain parenchyma, α-Syn is located on the presynaptic membrane, showing high proximity in spatial position with membrane lipid rafts, which may participate in its transmission among brain cells (Perissinotto et al., 2020); in contrast, α-Syn in the blood binds to lipoproteins, thus influencing lipid transport (Emamzadeh and Allsop, 2017; Sinclair et al., 2021).

Phosphorylation is a widely studied post-translational modification of α-Syn that promotes α-Syn aggregation. The levels of phosphorylated α-Syn both inside red blood cells and on the erythrocytic membranes of patients with PD are much higher than those of healthy controls (Tian et al., 2019). Moreover, the level of oligomeric α-Syn in erythrocytes was increased in the early stage of PD (Liu et al., 2022). There is evidence that higher erythrocytic oligomeric α-Syn levels predict accelerated disease progression (Yu et al., 2022b). These blood-oriented phosphorylated α-Syn proteins resist digestion by protein kinase K, similar to α-Syn inclusions extracted from the brain, and are capable of binding phospholipids and plasma proteins (Abd-Elhadi et al., 2015; Iyer et al., 2016). In addition to being transported by plasma proteins, these pathological phosphorylated α-Syn proteins may also be transmitted from the blood to the brain by erythrocytic extracellular vesicles via membrane fusion with the BBB (Matsumoto et al., 2017). Additionally, phosphorylation is not the only post-translational modification found in erythrocytic α-Syn; it has been reported that the lysine residues in erythrocytic α-Syn can be modified by acetylation, glycation, ubiquitination, SUMOylation, and even nitration and acylation, similar to that found in the brain of PD patients. In conclusion, this data supports that erythrocytic α-Syn may play a role in the peripheral formation and propagation of synucleinopathies (Amagai et al., 2023).

On the one hand, the abovementioned erythrocytic normal and pathological α-Syn may originate from the leakage of brain-oriented pathological α-Syn through the BBB or blood-CSF circulation. Many experiments have validated this brain-to-blood propagation. When radio-labeled α-Syn fibrils are injected into certain brain regions or directly into the lateral ventricle, they can be detected in the CSF, peripheral blood, and even in some peripheral tissues (Sui et al., 2014). On the other hand, from the peripheral perspective, other peripheral administration routes of α-Syn PFFs, including oral, intranasal, intraperitoneal, and intramuscular administration, as well as tail vein injection, can also lead to brain α-Syn pathology similar to that induced by intracerebral injection of α-Syn PFFs, proving the existence of α-Syn propagation between the blood and brain through the circulation of bodily fluids (Ayers et al., 2017; Earls et al., 2019; Macdonald et al., 2021; Masuda-Suzukake et al., 2021; Awa et al., 2022).

Multiple Factors Mediate the Propagation of Peripheral α-Synuclein Pathology to the Brain

BBB receptors

The BBB is the main barrier and the most pivotal structural basis blocking the entry of peripheral pathological α-Syn into the brain. The BBB is altered in the brain of PD patients, which results from hits of pathological α-Syn (Dohgu et al., 2019; Tsunemi et al., 2020; Xia et al., 2021; Huang et al., 2022a). Brain microvascular endothelial cells, astrocytes, and pericytes are the main components of the BBB and blood-CSF barrier (Campisi et al., 2018). Peripheral pathological α-Syn is most likely transported across the BBB via interaction with receptors on these cells and extracellular vesicles. These receptors can be divided into three categories according to their affinity to pathological α-Syn: transporters mediating α-Syn transmission by direct binding, facilitators regulating vesicle trafficking of pathological α-Syn, and receptors affecting BBB permeability conducive to α-Syn propagation (**Table 1**; Calderón-Garcidueñas et al., 2008; Kanekiyo et al., 2011; Jangula and Murphy, 2013; Chen et al., 2015; Mao et al., 2016; Masaracchia et al., 2018; Phillips et al., 2018; Bae and Lee, 2020; Rauch et al., 2020; Emmenegger et al., 2021; Gasca-Salas et al., 2021; Gu et al., 2021; Kim et al., 2021; Pediaditakis et al., 2021; Streubel-Gallasch et al., 2021; Wang et al., 2021b, c; Zhang et al., 2021, 2023a, c; Alam et al., 2022b; Chen et al., 2022; Feng et al., 2022; Huang et al., 2022a; Lan et al., 2022; Prieto Huarcaya et al., 2022; Roshanbin et al., 2022; Ruan et al., 2022; Salman et al., 2022; Shin et al., 2022; Vellingiri et al., 2022). Direct binding was found between α-Syn fibrils and lymphocyte-activation gene 3, as well as amyloid precursor-like protein 1, which are widely expressed in blood, immune, and endothelial cells, thus mediating the transmission of α-Syn fibrils (Mao et al., 2016; Zhang et al., 2021). The second category includes astrocytic vascular endothelial growth factor A (VEGFA), low-density lipoprotein receptor-related protein 1, Ras-related in brain 7 (Rab7), and leucine-rich repeat kinase 2 (LRRK2), which are reported to regulate vesicle trafficking of pathological α-Syn. Blocking astrocyte VEGFA signaling in the *in vitro* BBB model effectively protects the barrier against the harmful effects of oligomeric α-Syn, while dysregulation of Rab7 signaling and LRRK2 signaling causes abortive clearance of pathological α-Syn, leading to α-Syn accumulation and propagation (Bae and Lee, 2020; Wang et al., 2021b; Alam et al., 2022b; Chen et al., 2022; Lan et al., 2022). When treating *in vitro* models of the BBB with α-Syn fibrils, a series of targets, including lipoprotein receptor-related protein 1 and LRRK2, have been proven to undergo alterations (Pediaditakis et al., 2021). Physical and environmental hits, such as ultrasound, air pollution, heavy metals, and a ketogenic diet, and chemical factors, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, lipopolysaccharide, cerebrolysin, and tissue plasminogen activator, are also reported to affect other BBB receptors, such as aquaporin 4, thus enhancing BBB permeability and contributing to the entry of pathological α-Syn into the brain (Calderón-Garcidueñas et al., 2008; Jangula and Murphy, 2013; Chen et al., 2015; Phillips et al., 2018; Gasca-Salas et al., 2021; Wang et al., 2021c; Feng et al., 2022; Ruan et al., 2022; Salman et al., 2022; Vellingiri et al., 2022).

However, it is controversial whether these interactions between pathological α-Syn and the receptors can actually aggravate the α-Syn pathology (Emmenegger et al., 2021; Gu et al., 2021). Often, these receptors have poor selectivity for α-Syn monomers, oligomers, and fibrils, as well as other aggregated proteins (Rauch et al., 2020). Even when confronted with the same protein fibrils, these receptors exhibit distinct binding affinities. α-Syn fibrils with post-translational modifications, such as phosphorylation at Ser129, are believed to have a higher bonding affinity with lymphocyte-activation gene 3 than pure fibrils (Zhang et al., 2023a). Except for poor selectivity, the widespread distribution and functional diversity of these receptors also limits their weight in regulating α-Syn propagation. For instance, lipoprotein receptor-related protein 1 is expressed on various cell types, including neurons, astrocytes, microglia, macrophages, fibroblasts, and smooth muscle cells, and cooperates with other endocytosis-related receptors, such as heparin sulfate proteoglycan, regulating cell-to-cell propagation of not only pathological α-Syn, but also pathological proteins typical of Alzheimer's disease (Kanekiyo et al., 2011). Likewise, in addition to promoting transmission, the LRRK2 and Rab7 pathways are also responsible for normal phagocytosis and clearance of pathological α-Syn (Masaracchia et al., 2018; Streubel-Gallasch et al., 2021). When peripheral pathological α-Syn is attached to a BBB receptor, clearance via lysosomal degradation and autophagy may occur first before it can enter the exocytosis pathway and then be transmitted among brain cells. It can be speculated that there is a receptor-mediated balance among endo- and exocytosis, and the clearance and propagation of pathological proteins, the disturbance of which ultimately leads to successful propagation of α-Syn pathology from the periphery to the central nervous system (Volpicelli-Daley et al., 2011; Rodrigues et al., 2022). Therefore, there is an urgent need to identify the key receptors with specificity that mediate the spreading of pathological α-Syn.

Properties of α-Syn fibrils

The main forms in which pathological α-Syn exists in PD brains are α-Syn oligomers, fibrils, and ribbons (Peelaerts et al., 2015; Rodriguez et al., 2015). The highly aggregated form, α-Syn ribbons, has the strongest seeding activity, while the oligomer and fibril are prone to cause cell toxicity and cell-to-cell transmission, respectively (Mahul-Mellier et al., 2015; Uemura et al., 2023). In different synucleinopathies, aggregated α-Syn possesses different properties. Both insoluble and soluble fractions of α-Syn-enriched brain extracts derived from MSA patients can induce the accumulation of normal α-Syn, while only insoluble fractions derived from patients with PD retain this seeding ability (Yamasaki et al., 2019; Van der Perren et al., 2020). Phosphorylation at Ser129 of α-Syn is another point distinguishing PD from other synucleinopathies (Sonustun et al., 2022). Approximately 90% of α-Syn in LBs in PD is hyperphosphorylated. Ubiquitination, acetylation, nitrification, palmitoylation, etc. also occupy a minority of modifications of α-Syn, influencing the properties of α-Syn fibrils (Sevcsik et al., 2011; Kunadt et al., 2015; Rott et al., 2017; Ho et al., 2023; Zhang et al., 2023b). Among these, phosphorylation of serine, ubiquitination, nitrification, glycation, etc. are believed to promote α-Syn aggregation and propagation (**Table 2**; Nonaka et al., 2005; Kim et al., 2006; Danielson et al., 2009; Lee et al., 2009; Waxman et al., 2010; Liu et al., 2011; Padmaraju et al., 2011; Izawa et al., 2012; Binolfi et al., 2016; Arawaka et al., 2017; Vicente Miranda et al., 2017; Zhang et al., 2017a, b; Wen et al., 2018; Barinova et al., 2019; Chavarría et al., 2019;

Table 1 | **BBB receptors interacting with α-Syn and α-Syn fibrils**

Receptor name	Interaction type with α-Syn	Effect on α-Syn transportation
LAG3	Direct binding	Transmission
APLP1		
TLR2	Direct interaction	
LRP1	Indirect interaction	Vesicle trafficking, BBB permeability
	Changed gene expression by α-Syn monomer	
HSPG	Indirect interaction, synergies with LRP1	Vesicle trafficking
Rab7	Indirect interaction	
VEGFA		
LRRK2	Indirect interaction	
	Changed gene expression by α-Syn monomer	
IGF1R	Indirect interaction	Molecular shuttle
TfR		
NEK		BBB permeality
AQP4		
Nurr1		
M6PR		
LRP2	Changed gene expression by α-Syn monomer	BBB function
ABCB1		
CLDN4	Changed gene expression by α-Syn fibril	BBB function
CLDN9		
CLDN1		
SLC2A6		
SLC16A6		
GJA4		

Data were from studies Calderón-Garcidueñas et al., 2008; Kanekiyo et al., 2011; Jangula and Murphy, 2013; Chen et al., 2015; Mao et al., 2016; Masaracchia et al., 2018; Phillips et al., 2018; Bae and Lee, 2020; Rauch et al., 2020; Emmenegger et al., 2021; Gasca-Salas et al., 2021; Gu et al., 2021; Kim et al., 2021; Pediaditakis et al., 2021; Streubel-Gallasch et al., 2021; Wang et al., 2021b, c; Zhang et al., 2021, 2023a, c; Alam et al., 2022b; Chen et al., 2022; Feng et al., 2022; Huang et al., 2022a; Lan et al., 2022; Prieto Huarcaya et al., 2022; Roshanbin et al., 2022; Ruan et al., 2022; Salman et al., 2022; Shin et al., 2022; Vellingiri et al., 2022. ABCB1: Adenosine triphosphate-binding cassette subfamily B member 1; APLP1: amyloid precursor-like protein 1; AQP4: aquaporin-4; CLDN1: claudin-1; CLDN4: claudin-4; CLDN9: claudin-9; GJA4: gap junction protein alpha 4; SLC2A6: facilitated glucose transporter member 6; HSPG: heparan sulfate proteoglycan; IGF1R: insulin like growth factor 1 receptor; LRRK2: leucine-rich repeat kinase 2; LRP1: low-density lipoprotein receptor-related protein 1; LRP2: low-density lipoprotein receptor-related protein 2; LAG3: lymphocyte activation gene-3; M6PR: mannose-6-phosphate receptor; SLC16A6: monocarboxylate transporter 6; NEK: NimA related kinase; Nurr1: nuclear receptor-related factor 1; Rab7: Ras-related in brain 7; TLR2: Toll-like receptor 2; TfR: transferrin receptor-1; VEGFA: vascular endothelial growth factor A; α-Syn: α-synuclein.

Table 2 | **Posttranslational modifications that affect α-Syn properties**

Modification	Sites	Modification effects
Phosphorylation	Ser129	Promoting α-Syn aggregation
	Ser87	
	Tyr39	
	Tyr136	
	Tyr125	Suppressing α-Syn aggregation
O-GlcNAcylation	Thr72	Suppressing α-Syn aggregation
	Ser87	
Ubiquitination	Lys6	Promoting α-Syn aggregation
	Lys10	
	Lys12	
Nitrification	Tyr125	Promoting α-Syn aggregation
	Tyr133	
	Tyr136	
	Tyr39	
Glycation	Not applicable	Promoting α-Syn aggregation
Arginylation	Glu83	Suppressing α-Syn aggregation
Acetylation	Not applicable	Postponing α-Syn aggregation
SUMOylation	Not applicable	Suppressing α-Syn aggregation
Nitroalkylation	Not applicable	Suppressing α-Syn aggregation
Adenylylation	Not applicable	Suppressing α-Syn aggregation
N-homocysteinylation (chemical modification)	Lys80	Promoting α-Syn aggregation
Pyroglutamate (pGlu)79 (chemical modification)	Gln79	Promoting α-Syn aggregation
Glyceraldehyde-3-phosphate (chemical modification)	Not applicable	Preventing α-Syn aggregation
4-Hydroxy-2-nonenal (chemical modification)	His50	Promoting α-Syn aggregation
Dicarbonyl compounds (chemical modification)	Not applicable	Suppressing α-Syn aggregation
Tyrosine hydroxylase (chemical modification)	Tyr136	Promoting α-Syn aggregation
Docosahexaenoic acid (chemical modification)	Not applicable	Promoting α-Syn aggregation
Asparagine endopeptidase (proteolysis)	Asn103	Promoting α-Syn aggregation

Data were from studies Nonaka et al., 2005; Kim et al., 2006; Danielson et al., 2009; Lee et al., 2009; Waxman et al., 2010; Liu et al., 2011; Padmaraju et al., 2011; Izawa et al., 2012; Binolfi et al., 2016; Arawaka et al., 2017; Vicente Miranda et al., 2017; Zhang et al., 2017a, b; Wen et al., 2018; Barinova et al., 2019; Chavarría et al., 2019; Sanyal et al., 2019; Semenyuk et al., 2019; Zhao et al., 2020; Andersen et al., 2021; Dhakal et al., 2021; Hartlage-Rübsamen et al., 2021; Bell et al., 2022; Farzadfard et al., 2022; Jin et al., 2022; Kam et al., 2022; Panigrahi et al., 2023; Zhou et al., 2023. α-Syn: α-Synuclein.

Sanyal et al., 2019; Semenyuk et al., 2019; Zhao et al., 2020; Andersen et al., 2021; Dhakal et al., 2021; Hartlage-Rübsamen et al., 2021; Bell et al., 2022; Farzadfard et al., 2022; Jin et al., 2022; Kam et al., 2022; Panigrahi et al., 2023; Zhou et al., 2023). α-Syn can also be modified by other proteins, lipids, and small molecular compounds, which enhance or suppress its propagation or seeding activity (Masaracchia et al., 2018; Kim et al., 2021; Streubel-Gallasch et al., 2021). For example, asparagine endopeptidase cleaves α-Syn at N103, generating the α-Syn (1–103) fragment, which forms aggregates with higher pathogenicity, suggesting that fragmentation of α-Syn influences the properties of fibrils (Zhang et al., 2017b). Furthermore, chemical substances, such as homocysteine derivatives, can also modify α-Syn on the K80 residue, thus forming more toxic fibrils with higher seeding and propagation activity (Zhou et al., 2023). Most of these modified α-Syn proteins are more resistant to digestion by proteinases and are more likely to undergo fibrillation and aggregation; therefore, they are less easily engulfed and degraded by their host cells. In addition, they are more prone to undergo neuron–neuron, glia–neuron, and peripheral cell-brain cell propagation, forming the spreading mechanism of pathological α-Syn among the central nervous system and from the peripheral tissues to the central nervous system (Pluvinage et al., 2019; Yuan et al., 2022).

Microenvironment promotes the formation of peripheral α-Syn pathology

The aggregation and propagation of α-Syn requires a specific microenvironment. Thus, we propose that there is a fibrillization microenvironment (FME) composed of pathological α-Syn, the peripheral immune system, the erythrocytic intracellular environment, the autonomic nerve system, soluble and insoluble cytokines, ionic concentration, pH, temperature, hemodynamics, and the BBB (**Figure 1**). These elements together contribute to the focal enrichment of pathological α-Syn, isolating it from the liquid phase of the intracellular fluid and irreversibly forming agglutinative fibrils and ribbons (Huang et al., 2022b). For instance, dysfunction of ionic homeostasis, disturbance of BBB receptors, acidic pH, and dysregulation of phosphatases promote the formation and cell-to-cell transmission of α-Syn pathology (Bhak et al., 2014; Li et al., 2020, 2023a; Yu et al., 2021). From the peripheral view, the peripheral blood provides an immunity-centered FME that promotes the generation and propagation of peripheral pathological α-Syn. In addition, the adjacency in location between the blood and the autonomic nerves further enhances the effect of FME on the transmissibility of α-Syn pathology throughout the body.

Once pathological α-Syn is agglutinated in erythrocytes (possibly taking several decades before the observation of clinical manifestations caused by acute ischemic stroke, thoracic trauma, infection, etc.), it can activate and recruit peripheral immune cells, including B lymphocytes for antibody production and T lymphocytes for antigen presentation prior to neurodegeneration, in line with the clinical detection of α-Syn antibodies in the peripheral blood of PD patients (Xiao et al., 2014; Sulzer et al., 2017; Harms et al., 2018; Tulisiak et al., 2019; Wu et al., 2019; Karikari et al., 2022; Ruf et al., 2022; Li et al., 2023b). Although α-Syn antibodies help to eliminate pathological α-Syn in the peripheral blood and the activated autophagic and lysosomal proteins within these immune cells also promote an active process of proteasomal degradation of pathological α-Syn, the reaction of pathological α-Syn and its antibody still activates the complement system (Papagiannakis et al., 2015; Miki et al., 2018; Gregersen et al., 2021). Thorough activation of the peripheral immune and inflammatory system can directly promote the propagation of α-Syn pathology (Kim et al., 2022). Simultaneously, penetration of active T lymphocytes across the BBB into the brain has also been proven to cause neuroinflammation and aggravation of central α-Syn pathology, again proving the influence of the immune environment on α-Syn transmission (Williams et al., 2021). This *in vivo* regulation between the peripheral immune system and α-Syn pathology provides an explanation for the failure of antibody therapy in treating PD, owing to the counterforce of the immune system on promoting α-Syn pathology, indicating an immunity-centered FME

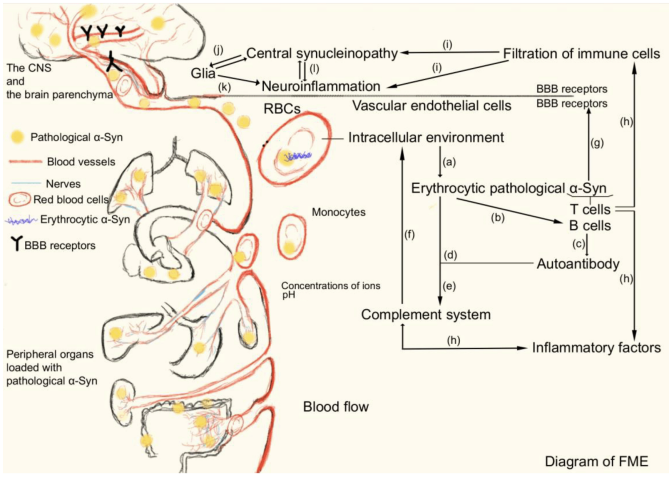

Figure 1 | **Diagram of FME and the propagation mode of pathological α-Syn from peripheral organs to the brain.**
The FME is composed of pathological α-Syn, the peripheral immune system, members of the BBB, the erythrocytic intracellular environment, and soluble and insoluble cytokines. (a) The erythrocytic intracellular environment contributes to the generation of pathological α-Syn. (b) Erythrocytic pathological α-Syn recruits B cells. (c) B cells secrete autoantibodies against α-Syn. (d) Autoantibodies of α-Syn promote clearance of erythrocytic pathological α-Syn. (e) A combination of α-Syn and its antibody leads to activation of the complement system. (f) Members of the complement system reversely aggravate α-Syn pathology. (g) T cells discriminate peptides of α-Syn and perform antigen presentation. (h) Recruiting of B and T cells and vesicle trafficking of pathological α-Syn give rise to infiltration of inflammatory factors and peripheral pathological α-Syn across the BBB. (i–l) Penetration of peripheral immune cells and peripheral pathological α-Syn causes central synucleinopathy and neuroinflammation. Created with Adobe Illustrator. BBB: Blood-brain barrier; CNS: central nervous system; FME: fibrillization microenvironment; RBC: red blood cell; α-Syn: α-synuclein.

contributing to the formation and propagation of peripheral α-Syn pathology (Lang et al., 2022; Pagano et al., 2022).

Conclusion

The production of pathological α-Syn in peripheral organs, the crosstalk between the body fluid and autonomic nervous system, the participation of BBB receptors, and the peripheral FME that affects α-Syn properties support peripheral organs as the source of PD pathology and even the initiation of α-Syn pathology. The existence of reverse diffusion from the blood to brain, from peripheral to central tissues, and the circulatory aggravation of α-Syn pathology on either side of the BBB urges us to understand the pathogenesis of PD from a systemic and global perspective. Therapies facilitating the clearance of peripheral α-Syn and inhibiting the forward and reverse transportation of peripheral and central α-Syn, early intervention of peripheral FME, and prevention of the circulatory spread of α-Syn pathology may alleviate the propagation of PD pathology. To date, the autonomic nerve pathway has been the most recognized route that mediates the transmission of pathological α-Syn from the periphery to the brain. Although emerging evidence has proven the existence of the body fluid pathway, there is a lack of feasibility in cutting off the body fluid connection as in the autonomic nerve pathway, bringing difficulties to further studies centering on humoral transmission of α-Syn pathology. In this review, we discussed the autonomic nerve pathway and body fluid circulation pathway as two separate mechanisms; however, we have not extended α-Syn pathology transmission to the crosstalk between the abovementioned two pathways. Whether pathological α-Syn in the bodily fluids can directly reach the brain parenchyma relying on body fluid circulation, or first interact with peripheral autonomic nerves and then indirectly reach the brain parenchyma needs further investigation.

Author contributions: *Both authors contributed to conceptualization, reference review, and preparation of the manuscript and have read and approved the final version of the manuscript.*
Conflicts of interest: *The authors declare no competing interest.*
Data availability statement: *The data are available from the corresponding author on reasonable request.*

References

Abd-Elhadi S, Honig A, Simhi-Haham D, Schechter M, Linetsky E, Ben-Hur T, Sharon R (2015) Total and proteinase K-resistant α-synuclein levels in erythrocytes, determined by their ability to bind phospholipids, associate with Parkinson's disease. Sci Rep 5:11120.
Agliardi C, Guerini FR, Meloni M, Clerici M (2022) Alpha-synuclein as a biomarker in Parkinson's disease: focus on neural derived extracelluar vesicles. Neural Regen Res 17:1503-1504.
Alam MM, Yang D, Li XQ, Liu J, Back TC, Trivett A, Karim B, Barbut D, Zasloff M, Oppenheim JJ (2022a) Alpha synuclein, the culprit in Parkinson disease, is required for normal immune function. Cell Rep 38:110090.
Alam P, Holst MR, Lauritsen L, Nielsen J, Nielsen SSE, Jensen PH, Brewer JR, Otzen DE, Nielsen MS (2022b) Polarized α-synuclein trafficking and transcytosis across brain endothelial cells via Rab7-decorated carriers. Fluids Barriers CNS 19:37.
Alarcón TA, Presti-Silva SM, Simões APT, Ribeiro FM, Pires RGW (2023) Molecular mechanisms underlying the neuroprotection of environmental enrichment in Parkinson's disease. Neural Regen Res 18:1450-1456.
Amagai R, Yoshioka S, Otomo R, Nagano H, Hashimoto N, Sakakibara R, Tanaka T, Okado-Matsumoto A (2023) Post-translational modification of lysine residues in erythrocyte α-synuclein. J Biochem 173:177-184.
Andersen C, Grønnemose AL, Pedersen JN, Nowak JS, Christiansen G, Nielsen J, Mulder FAA, Otzen DE, Jørgensen TJD (2021) Lipid peroxidation products HNE and ONE promote and stabilize alpha-synuclein oligomers by chemical modifications. Biochemistry 60:3644-3658.
Arawaka S, Sato H, Sasaki A, Koyama S, Kato T (2017) Mechanisms underlying extensive Ser129-phosphorylation in α-synuclein aggregates. Acta Neuropathol Commun 5:48.
Arotcarena ML, Dovero S, Prigent A, Bourdenx M, Camus S, Porras G, Thiolat ML, Tasselli M, Aubert P, Kruse N, Mollenhauer B, Trigo Damas I, Estrada C, Garcia-Carrillo N, Vaikath NN, El-Agnaf OMA, Herrero MT, Vila M, Obeso JA, Derkinderen P, et al. (2020) Bidirectional gut-to-brain and brain-to-gut propagation of synucleinopathy in non-human primates. Brain 143:1462-1475.
Awa S, Suzuki G, Masuda-Suzukake M, Nonaka T, Saito M, Hasegawa M (2022) Phosphorylation of endogenous α-synuclein induced by extracellular seeds initiates at the pre-synaptic region and spreads to the cell body. Sci Rep 12:1163.
Ayers JI, Brooks MM, Rutherford NJ, Howard JK, Sorrentino ZA, Riffe CJ, Giasson BI (2017) Robust central nervous system pathology in transgenic mice following peripheral injection of α-synuclein fibrils. J Virol 91:e02095-16.
Bae EJ, Lee SJ (2020) The LRRK2-RAB axis in regulation of vesicle trafficking and α-synuclein propagation. Biochim Biophys Acta Mol Basis Dis 1866:165632.
Bai F, Li X (2021) Association of Helicobacter pylori treatment with Parkinsonism and related disorders: a systematic review and meta-analysis. Life Sci 281:119767.
Barboza JL, Okun MS, Moshiree B (2015) The treatment of gastroparesis, constipation and small intestinal bacterial overgrowth syndrome in patients with Parkinson's disease. Expert Opin Pharmacother 16:2449-2464.
Barinova K, Serebryakova M, Sheval E, Schmalhausen E, Muronetz V (2019) Modification by glyceraldehyde-3-phosphate prevents amyloid transformation of alpha-synuclein. Biochim Biophys Acta Proteins Proteom 1867:396-404.
Bartl M, Xylaki M, Bähr M, Weber S, Trenkwalder C, Mollenhauer B (2022) Evidence for immune system alterations in peripheral biological fluids in Parkinson's disease. Neurobiol Dis 170:105744.
Bell R, Thrush RJ, Castellana-Cruz M, Oeller M, Staats R, Nene A, Flagmeier P, Xu CK, Satapathy S, Galvagnion C, Wilson MR, Dobson CM, Kumita JR, Vendruscolo M (2022) N-terminal acetylation of α-synuclein slows down its aggregation process and alters the morphology of the resulting aggregates. Biochemistry 61:1743-1756.
Bencsik A, Muselli L, Leboidre M, Lakhdar L, Baron T (2014) Early and persistent expression of phosphorylated α-synuclein in the enteric nervous system of A53T mutant human α-synuclein transgenic mice. J Neuropathol Exp Neurol 73:1144-1151.
Bhak G, Lee J, Kim TH, Lee S, Lee D, Paik SR (2014) Molecular inscription of environmental information into protein suprastructures: temperature effects on unit assembly of α-synuclein oligomers into polymorphic amyloid fibrils. Biochem J 464:259-269.
Bieri G, Brahic M, Bousset L, Couthouis J, Kramer NJ, Ma R, Nakayama L, Monbureau M, Defensor E, Schüle B, Shamloo M, Melki R, Gitler AD (2019) LRRK2 modifies α-syn pathology and spread in mouse models and human neurons. Acta Neuropathol 137:961-980.
Binolfi A, Limatola A, Verzini S, Kosten J, Theillet FX, Rose HM, Bekei B, Stuiver M, van Rossum M, Selenko P (2016) Intracellular repair of oxidation-damaged α-synuclein fails to target C-terminal modification sites. Nat Commun 7:10251.
Blauwendraat C, Nalls MA, Singleton AB (2020) The genetic architecture of Parkinson's disease. Lancet Neurol 19:170-178.
Bloem BR, Okun MS, Klein C (2021) Parkinson's disease. Lancet 397:2284-2303.
Bougea A, Stefanis L, Emmanouilidou E, Vekrelis K, Kapaki E (2020) High discriminatory ability of peripheral and CFSF biomarkers in Lewy body diseases. J Neural Transm (Vienna) 127:311-322.
Bougea A, Stefanis L, Paraskevas GP, Emmanouilidou E, Efthymiopoulou E, Vekrelis K, Kapaki E (2018) Neuropsychiatric symptoms and α-Synuclein profile of patients with Parkinson's disease dementia, dementia with Lewy bodies and Alzheimer's disease. J Neurol 265:2295-2301.
Boyer DR, Li B, Sun C, Fan W, Zhou K, Hughes MP, Sawaya MR, Jiang L, Eisenberg DS (2020) The α-synuclein hereditary mutation E46K unlocks a more stable, pathogenic fibril structure. Proc Natl Acad Sci U S A 117:3592-3602.
Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E (2003) Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 24:197-211.
Burré J, Sharma M, Tsetsenis T, Buchman V, Etherton MR, Südhof TC (2010) Alpha-synuclein promotes SNARE-complex assembly in vivo and in vitro. Science 329:1663-1667.

Butler B, Saha K, Rana T, Becker JP, Sambo D, Davari P, Goodwin JS, Khoshbouei H (2015) Dopamine transporter activity is modulated by α-synuclein. J Biol Chem 290:29542-29554.

Butler YR, Liu Y, Kumbhar R, Zhao P, Gadhave K, Wang N, Li Y, Mao X, Wang W (2022) α-Synuclein fibril-specific nanobody reduces prion-like α-synuclein spreading in mice. Nat Commun 13:4060.

Byers B, Cord B, Nguyen HN, Schüle B, Fenno L, Lee PC, Deisseroth K, Langston JW, Pera RR, Palmer TD (2011) SNCA triplication Parkinson's patient's iPSC-derived DA neurons accumulate α-synuclein and are susceptible to oxidative stress. PLoS One 6:e26159.

Calderón-Garcidueñas L, Solt AC, Henríquez-Roldán C, Torres-Jardón R, Nuse B, Herritt L, Villarreal-Calderón R, Osnaya N, Stone I, García R, Brooks DM, González-Maciel A, Reynoso-Robles R, Delgado-Chávez R, Reed W (2008) Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. Toxicol Pathol 36:289-310.

Camacho M, Greenland JC, Williams-Gray CH (2021) The gastrointestinal dysfunction scale for Parkinson's disease. Mov Disord 36:2358-2366.

Camilleri M, Subramanian T, Pagan F, Isaacson S, Gil R, Hauser RA, Feldman M, Goldstein M, Kumar R, Truong D, Chhabria N, Walter BL, Eskenazi J, Riesenberg R, Burdick D, Tse W, Molho E, Robottom B, Bhatia P, Kadimi S, et al. (2022) Oral ENT-01 targets enteric neurons to treat constipation in Parkinson disease: a randomized controlled trial. Ann Intern Med 175:1666-1674.

Campisi M, Shin Y, Osaki T, Hajal C, Chiono V, Kamm RD (2018) 3D self-organized microvascular model of the human blood-brain barrier with endothelial cells, pericytes and astrocytes. Biomaterials 180:117-129.

Chavarría C, Trostchansky A, Durán R, Rubbo H, Souza JM (2019) Nitroalkylation of α-synuclein by nitro-oleic acid: implications for Parkinson's disease. Adv Exp Med Biol 1127:169-179.

Chen C, Zhou Y, Wang H, Alam A, Kang SS, Ahn EH, Liu X, Jia J, Ye K (2021) Gut inflammation triggers C/EBPβ/δ-secretase-dependent gut-to-brain propagation of Aβ and Tau fibrils in Alzheimer's disease. EMBO J 40:e106320.

Chen K, Martens YA, Meneses A, Ryu DH, Lu W, Raulin AC, Li F, Zhao J, Chen Y, Jin Y, Linares C, Goodwin M, Li Y, Liu CC, Kanekiyo T, Holtzman DM, Golde TE, Bu G, Zhao N (2022) LRP1 is a neuronal receptor for α-synuclein uptake and spread. Mol Neurodegener 17:57.

Chen L, Feany MB (2005) Alpha-synuclein phosphorylation controls neurotoxicity and inclusion formation in a Drosophila model of Parkinson disease. Nat Neurosci 8:657-663.

Chen T, Hou R, Li C, Wu C, Xu S (2015) MPTP/MPP+ suppresses activation of protein C in Parkinson's disease. J Alzheimers Dis 43:133-142.

Colosimo C, Hughes AJ, Kilford L, Lees AJ (2003) Lewy body cortical involvement may not always predict dementia in Parkinson's disease. J Neurol Neurosurg Psychiatry 74:852-856.

Cooper JA, Sagar HJ, Doherty SM, Jordan N, Tidswell P, Sullivan EV (1992) Different effects of dopaminergic and anticholinergic therapies on cognitive and motor function in Parkinson's disease. A follow-up study of untreated patients. Brain 115 (Pt 6):1701-1725.

Coutinho AM, Ghilardi MG, Campos ACP, Etchebehere E, Fonoff FC, Cury RG, Pagano RL, Martinez RCR, Fonoff ET (2023) Does TRODAT-1 SPECT uptake correlate with cerebrospinal fluid α-synuclein levels in mid-stage Parkinson's disease? Biomedicines 11:296.

Danielson SR, Held JM, Schilling B, Oo M, Gibson BW, Andersen JK (2009) Preferentially increased nitration of alpha-synuclein at tyrosine-39 in a cellular oxidative model of Parkinson's disease. Anal Chem 81:7823-7828.

de Bie RM, de Haan RJ, Nijssen PC, Rutgers AW, Beute GN, Bosch DA, Haaxma R, Schmand B, Schuurman PR, Staal MJ, Speelman JD (1999) Unilateral pallidotomy in Parkinson's disease: a randomised, single-blind, multicentre trial. Lancet 354:1665-1669.

De Cock VC, Dodet P, Leu-Semenescu S, Aerts C, Castelnovo G, Abril B, Drapier S, Olivet H, Corbillé AG, Leclair-Visonneau L, Sallansonnet-Froment M, Lebouteux M, Anheim M, Ruppert E, Vitello N, Eusebio A, Lambert I, Marques A, Fantini ML, Devos D, et al. (2022) Safety and efficacy of subcutaneous night-time only apomorphine infusion to treat insomnia in patients with Parkinson's disease (APOMORPHEE): a multicentre, randomised, controlled, double-blind crossover study. Lancet Neurol 21:428-437.

Del Tredici K, Hawkes CH, Ghebremedhin E, Braak H (2010) Lewy pathology in the submandibular gland of individuals with incidental Lewy body disease and sporadic Parkinson's disease. Acta Neuropathol 119:703-713.

Dhakal S, Saha J, Wyant CE, Rangachari V (2021) αS oligomers generated from interactions with a polyunsaturated fatty acid and a dopamine metabolite differentially interact with Aβ to enhance neurotoxicity. ACS Chem Neurosci 12:4153-4161.

Ding XB, Wang XX, Xia DH, Liu H, Tian HY, Fu Y, Chen YK, Qin C, Wang JQ, Xiang Z, Zhang ZX, Cao QC, Wang W, Li JY, Wu E, Tang BS, Ma MM, Teng JF, Wang XJ (2021) Impaired meningeal lymphatic drainage in patients with idiopathic Parkinson's disease. Nat Med 27:411-418.

Dodiya HB, Forsyth CB, Voigt RM, Engen PA, Patel J, Shaikh M, Green SJ, Naqib A, Roy A, Kordower JH, Pahan K, Shannon KM, Keshavarzian A (2020) Chronic stress-induced gut dysfunction exacerbates Parkinson's disease phenotype and pathology in a rotenone-induced mouse model of Parkinson's disease. Neurobiol Dis 135:104352.

Dohgu S, Takata F, Matsumoto J, Kimura I, Yamauchi A, Kataoka Y (2019) Monomeric α-synuclein induces blood-brain barrier dysfunction through activated brain pericytes releasing inflammatory mediators in vitro. Microvasc Res 124:61-66.

Donaghy PC, Taylor JP, O'Brien JT, Barnett N, Olsen K, Colloby SJ, Lloyd J, Petrides G, McKeith IG, Thomas AJ (2018) Neuropsychiatric symptoms and cognitive profile in mild cognitive impairment with Lewy bodies. Psychol Med 48:2384-2390.

Doppler K, Mammadova S, Kuzkina A, Reetz K, Michels J, Hermann W, Sommerauer M, Volkmann J, Oertel WH, Janzen A, Sommer C (2022) Association between probable REM sleep behavior disorder and increased dermal alpha-synuclein deposition in Parkinson's disease. Parkinsonism Relat Disord 99:58-61.

Doppler K, Jentschke HM, Schulmeyer L, Vadasz D, Janzen A, Luster M, Höffken H, Mayer G, Brumberg J, Booij J, Musacchio T, Klebe S, Sittig-Wiegand E, Volkmann J, Sommer C, Oertel WH (2017) Dermal phospho-alpha-synuclein deposits confirm REM sleep behaviour disorder as prodromal Parkinson's disease. Acta Neuropathol 133:535-545.

Dube U, Ibanez L, Budde JP, Benitez BA, Davis AA, Harari O, Iles MM, Law MH, Brown KM, Cruchaga C (2020) Overlapping genetic architecture between Parkinson disease and melanoma. Acta Neuropathol 139:347-364.

Earls RH, Menees KB, Chung J, Barber J, Gutekunst CA, Hazim MG, Lee JK (2019) Intrastriatal injection of preformed alpha-synuclein fibrils alters central and peripheral immune cell profiles in non-transgenic mice. J Neuroinflammation 16:250.

El-Agnaf OM, Salem SA, Paleologou KE, Curran MD, Gibson MJ, Court JA, Schlossmacher MG, Allsop D (2006) Detection of oligomeric forms of alpha-synuclein protein in human plasma as a potential biomarker for Parkinson's disease. FASEB J 20:419-425.

Emamzadeh FN, Allsop D (2017) α-Synuclein interacts with lipoproteins in plasma. J Mol Neurosci 63:165-172.

Emmanouilidou E, Papagiannakis N, Kouloulia S, Galaziou A, Antonellou R, Papadimitriou D, Athanasiadou A, Bozi M, Koros C, Maniati M, Vekrellis K, Ioannou PC, Stefanis L (2020) Peripheral alpha-synuclein levels in patients with genetic and non-genetic forms of Parkinson's disease. Parkinsonism Relat Disord 73:35-40.

Emmenegger M, De Cecco E, Hruska-Plochan M, Eninger T, Schneider MM, Barth M, Tantardini E, de Rossi P, Bacioglu M, Langston RG, Kaganovich A, Bengoa-Vergniory N, Gonzalez-Guerra A, Avar M, Heinzer D, Reimann R, Häsler LM, Herling TW, Matharu NS, Landeck N, et al. (2021) LAG3 is not expressed in human and murine neurons and does not modulate α-synucleinopathies. EMBO Mol Med 13:e14745.

Farzadfard A, König A, Petersen SV, Nielsen J, Vasili E, Dominguez-Meijide A, Buell AK, Outeiro TF, Otzen DE (2022) Glycation modulates alpha-synuclein fibrillization kinetics: a sweet spot for inhibition. J Biol Chem 298:101848.

Feng D, Zhou J, Liu H, Wu X, Li F, Zhao J, Zhang Y, Wang L, Chao M, Wang Q, Qin H, Ge S, Liu Q, Zhang J, Qu Y (2022) Astrocytic NDRG2-PPM1A interaction exacerbates blood-brain barrier disruption after subarachnoid hemorrhage. Sci Adv 8:eabq2423.

Fink AL (2006) The aggregation and fibrillation of alpha-synuclein. Acc Chem Res 39:628-634.

Froula JM, Castellana-Cruz M, Anabtawi NM, Camino JD, Chen SW, Thrasher DR, Freire J, Yazdi AA, Fleming S, Dobson CM, Kumita JR, Cremades N, Volpicelli-Daley LA (2019) Defining α-synuclein species responsible for Parkinson's disease phenotypes in mice. J Biol Chem 294:10392-10406.

Fujiwara H, Hasegawa M, Dohmae N, Kawashima A, Masliah E, Goldberg MS, Shen J, Takio K, Iwatsubo T (2002) alpha-Synuclein is phosphorylated in synucleinopathy lesions. Nat Cell Biol 4:160-164.

Gasca-Salas C, Fernández-Rodríguez B, Pineda-Pardo JA, Rodríguez-Rojas R, Obeso I, Hernández-Fernández F, Del Álamo M, Mata D, Guida P, Ordás-Bandera C, Montero-Roblas JI, Martínez-Fernández R, Foffani G, Rachmilevitch I, Obeso JA (2021) Blood-brain barrier opening with focused ultrasound in Parkinson's disease dementia. Nat Commun 12:779.

GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators (2019) Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 18:56-87.

Gelpi E, Navarro-Otano J, Tolosa E, Gaig C, Compta Y, Rey MJ, Martí MJ, Hernández I, Valldeoriola F, Reñé R, Ribalta T (2014) Multiple organ involvement by alpha-synuclein pathology in Lewy body disorders. Mov Disord 29:1010-1018.

Ghanem SS, Majbour NK, Vaikath NN, Ardah MT, Erskine D, Jensen NM, Fayyad M, Sudhakaran IP, Vasili E, Melachroinou K, Abdi IY, Poggiolini I, Santos P, Dorn A, Carloni P, Vekrellis K, Attems J, McKeith I, Outeiro TF, Jensen PH, et al. (2022) α-Synuclein phosphorylation at serine 129 occurs after initial protein deposition and inhibits seeded fibril formation and toxicity. Proc Natl Acad Sci U S A 119:e2109617119.

Goldsmith JR, Herishanu YO, Podgaietski M, Kordysh E (1997) Dynamics of parkinsonism-Parkinson's disease in residents of adjacent kibbutzim in Israel's Negev. Environ Res 73:156-161.

Gregersen E, Betzer C, Kim WS, Kovacs G, Reimer L, Halliday GM, Thiel S, Jensen PH (2021) Alpha-synuclein activates the classical complement pathway and mediates complement-dependent cell toxicity. J Neuroinflammation 18:177.

Gu H, Yang X, Mao X, Xu E, Qi C, Wang H, Brahmachari S, York B, Sriparna M, Li A, Chang M, Patel P, Dawson VL, Dawson TM (2021) Lymphocyte activation gene 3 (Lag3) contributes to α-synucleinopathy in α-synuclein transgenic mice. Front Cell Neurosci 15:656426.

Guo Y, Shen XN, Huang SY, Chen SF, Wang HF, Zhang W, Zhang YR, Cheng W, Cui M, Dong Q, Yu JT (2023) Head-to-head comparison of 6 plasma biomarkers in early multiple system atrophy. NPJ Parkinsons Dis 9:40.

Harms AS, Thome AD, Yan Z, Schonhoff AM, Williams GP, Li X, Liu Y, Qin H, Benveniste EN, Standaert DG (2018) Peripheral monocyte entry is required for alpha-Synuclein induced inflammation and Neurodegeneration in a model of Parkinson disease. Exp Neurol 300:179-187.

Hartlage-Rübsamen M, Bluhm A, Moceri S, Machner L, Köppen J, Schenk M, Hilbrich I, Holzer M, Weidenfeller M, Richter F, Coras R, Serrano GE, Beach TG, Schilling S, von Hörsten S, Xiang W, Schulze A, Roßner S (2021) A glutaminyl cyclase-catalyzed α-synuclein modification identified in human synucleinopathies. Acta Neuropathol 142:399-421.

Hass EW, Sorrentino ZA, Lloyd GM, McFarland NR, Prokop S, Giasson BI (2021) Robust α-synuclein pathology in select brainstem neuronal populations is a potential instigator of multiple system atrophy. Acta Neuropathol Commun 9:80.

Healy DG, Falchi M, O'Sullivan SS, Bonifati V, Durr A, Bressman S, Brice A, Aasly J, Zabetian CP, Goldwurm S, Ferreira JJ, Tolosa E, Kay DM, Klein C, Williams DR, Marras C, Lang AE, Wszolek ZK, Berciano J, Schapira AH, et al. (2008) Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. Lancet Neurol 7:583-590.

Helwig M, Klinkenberg M, Rusconi R, Musgrove RE, Majbour NK, El-Agnaf OM, Ulusoy A, Di Monte DA (2016) Brain propagation of transduced α-synuclein involves non-fibrillar protein species and is enhanced in α-synuclein null mice. Brain 139:856-870.

Ho GPH, Wilkie EC, White AJ, Selkoe DJ (2023) Palmitoylation of the Parkinson's disease-associated protein synaptotagmin-11 links its turnover to α-synuclein homeostasis. Sci Signal 16:eadd7220.

Homma T, Mochizuki Y, Mizutani T (2012) Phosphorylated α-synuclein immunoreactivity in the posterior pituitary lobe. Neuropathology 32:385-389.

Horsager J, Andersen KB, Knudsen K, Skjærbæk C, Fedorova TD, Okkels N, Schaeffer E, Bonkat SK, Geday J, Otto M, Sommerauer M, Danielsen EH, Bech E, Kraft J, Munk OL, Hansen SD, Pavese N, Göder R, Brooks DJ, Berg D, et al. (2020) Brain-first versus body-first Parkinson's disease: a multimodal imaging case-control study. Brain 143:3077-3088.

Hu S, Hu M, Liu J, Zhang B, Zhang Z, Zhou FH, Wang L, Dong J (2020) Phosphorylation of Tau and α-Synuclein Induced Neurodegeneration in MPTP Mouse Model of Parkinson's Disease. Neuropsychiatr Dis Treat 16:651-663.

Huang J, Ding J, Wang X, Gu C, He Y, Li Y, Fan H, Xie Q, Qi X, Wang Z, Qiu P (2022a) Transfer of neuron-derived α-synuclein to astrocytes induces neuroinflammation and blood-brain barrier damage after methamphetamine exposure: Involving the regulation of nuclear receptor-associated protein 1. Brain Behav Immun 106:247-261.

Huang S, Xu B, Liu Y (2022b) Calcium promotes α-synuclein liquid-liquid phase separation to accelerate amyloid aggregation. Biochem Biophys Res Commun 603:13-20.

Huang X, Wang C, Chen L, Zhang T, Leung KL, Wong G (2021) Human amyloid beta and α-synuclein co-expression in neurons impair behavior and recapitulate features for Lewy body dementia in Caenorhabditis elegans. Biochim Biophys Acta Mol Basis Dis 1867:166203.

Huang Y, Song YJ, Murphy K, Holton JL, Lashley T, Revesz T, Gai WP, Halliday GM (2008) LRRK2 and parkin immunoreactivity in multiple system atrophy inclusions. Acta Neuropathol 116:639-646.

Idova GV, Al'perina EL, Gevorgyan MM, Tikhonova MA, Zhanaeva SY (2021) Content of peripheral blood T- and B-cell subpopulations in transgenic A53T mice of different age (a model of Parkinson's disease). Bull Exp Biol Med 170:401-404.

Ikeuchi T, Kakita A, Shiga A, Kasuga K, Kaneko H, Tan CF, Idezuka J, Wakabayashi K, Onodera O, Iwatsubo T, Nishizawa M, Takahashi H, Ishikawa A (2008) Patients homozygous and heterozygous for SNCA duplication in a family with parkinsonism and dementia. Arch Neurol 65:514-519.

Iranzo A, Fairfoul G, Ayudhaya ACN, Serradell M, Gelpi E, Vilaseca I, Sanchez-Valle R, Gaig C, Santamaria J, Tolosa E, Riha RL, Green AJE (2021) Detection of α-synuclein in CSF by RT-QuIC in patients with isolated rapid-eye-movement sleep behaviour disorder: a longitudinal observational study. Lancet Neurol 20:203-212.

Israel Z, Asch N (2020) Reversing a model of Parkinson's disease with in situ converted nigral neurons. Mov Disord 35:1955.

Iyer A, Roeters SJ, Schilderink N, Hommersom B, Heeren RM, Woutersen S, Claessens MM, Subramaniam V (2016) The impact of N-terminal acetylation of α-synuclein on phospholipid membrane binding and fibril structure. J Biol Chem 291:21110-21122.

Izawa Y, Tateno H, Kameda H, Hirakawa K, Hato K, Yagi H, Hongo K, Mizobata T, Kawata Y (2012) Role of C-terminal negative charges and tyrosine residues in fibril formation of α-synuclein. Brain Behav 2:595-605.

Jangula A, Murphy EJ (2013) Lipopolysaccharide-induced blood brain barrier permeability is enhanced by alpha-synuclein expression. Neurosci Lett 551:23-27.

Javanshiri K, Drakenberg T, Haglund M, Englund E (2022) Cardiac alpha-synuclein is present in alpha-synucleinopathies. J Parkinsons Dis 12:1125-1131.

Jin M, Matsumoto S, Ayaki T, Yamakado H, Taguchi T, Togawa N, Konno A, Hirai H, Nakajima H, Komai S, Ishida R, Chiba S, Takahashi R, Takao T, Hirotsune S (2022) DOPAnization of tyrosine in α-synuclein by tyrosine hydroxylase leads to the formation of oligomers. Nat Commun 13:6880.

Joshi N, Sarhadi TR, Raveendran A, Nagotu S (2023) Sporadic SNCA mutations A18T and A29S exhibit variable effects on protein aggregation, cell viability and oxidative stress. Mol Biol Rep 50:5547-5556.

Kalia LV, Lang AE, Hazrati LN, Fujioka S, Wszolek ZK, Dickson DW, Ross OA, Van Deerlin VM, Trojanowski JQ, Hurtig HI, Alcalay RN, Marder KS, Clark LN, Gaig C, Tolosa E, Ruiz-Martínez J, Marti-Masso JF, Ferrer I, López de Munain A, Goldman SM, et al. (2015) Clinical correlations with Lewy body pathology in LRRK2-related Parkinson disease. JAMA Neurol 72:100-105.

Kam TI, Park H, Chou SC, Van Vranken JG, Mittenbühler MJ, Kim H, A M, Choi YR, Biswas D, Wang J, Shin Y, Loder A, Karuppagounder SS, Wrann CD, Dawson VL, Spiegelman BM, Dawson TM (2022) Amelioration of pathologic α-synuclein-induced Parkinson's disease by irisin. Proc Natl Acad Sci U S A 119:e2204835119.

Kanekiyo T, Zhang J, Liu Q, Liu CC, Zhang L, Bu G (2011) Heparan sulphate proteoglycan and the low-density lipoprotein receptor-related protein 1 constitute major pathways for neuronal amyloid-beta uptake. J Neurosci 31:1644-1651.

Karikari AA, McFleder RL, Ribechini E, Blum R, Bruttel V, Knorr S, Gehmeyr M, Volkmann J, Brotchie JM, Ahsan F, Haack B, Monoranu CM, Keber U, Yeghiazaryan R, Pagenstecher A, Heckel T, Bischler T, Wischhusen J, Koprich JB, Lutz MB, et al. (2022) Neurodegeneration by α-synuclein-specific T cells in AAV-A53T-α-synuclein Parkinson's disease mice. Brain Behav Immun 101:194-210.

Killinger BA, Madaj Z, Sikora JW, Rey N, Haas AJ, Vepa Y, Lindqvist D, Chen H, Thomas PM, Brundin P, Brundin L, Labrie V (2018) The vermiform appendix impacts the risk of developing Parkinson's disease. Sci Transl Med 10:eaar5280.

Kim C, Kwon S, Iba M, Spencer B, Rockenstein E, Mante M, Adame A, Shin SJ, Fields JA, Rissman RA, Lee SJ, Masliah E (2021) Effects of innate immune receptor stimulation on extracellular α-synuclein uptake and degradation by brain resident cells. Exp Mol Med 53:281-290.

Kim D, Yoo JM, Hwang H, Lee J, Lee SH, Yun SP, Park MJ, Lee M, Choi S, Kwon SH, Lee S, Kwon SH, Kim S, Park YJ, Kinoshita M, Lee YH, Shin S, Paik SR, Lee SJ, Lee S, et al. (2018) Graphene quantum dots prevent α-synucleinopathy in Parkinson's disease. Nat Nanotechnol 13:812-818.

Kim EJ, Sung JY, Lee HJ, Rhim H, Hasegawa M, Iwatsubo T, Min do S, Kim J, Paik SR, Chung KC (2006) Dyrk1A phosphorylates alpha-synuclein and enhances intracellular inclusion formation. J Biol Chem 281:33250-33257.

Kim KS, Choi YR, Park JY, Lee JH, Kim DK, Lee SJ, Paik SR, Jou I, Park SM (2012) Proteolytic cleavage of extracellular α-synuclein by plasmin: implications for Parkinson disease. J Biol Chem 287:24862-24872.

Kim S, Kwon SH, Kam TI, Panicker N, Karuppagounder SS, Lee S, Lee JH, Kim WR, Kook M, Foss CA, Shen C, Lee H, Kulkarni S, Pasricha PJ, Lee G, Pomper MG, Dawson VL, Dawson TM, Ko HS (2019) Transneuronal propagation of pathologic α-synuclein from the gut to the brain models Parkinson's disease. Neuron 103:627-641.e7.

Kim TK, Bae EJ, Jung BC, Choi M, Shin SJ, Park SJ, Kim JT, Jung MK, Ulusoy A, Song MY, Lee JS, Lee HJ, Di Monte DA, Lee SJ (2022) Inflammation promotes synucleinopathy propagation. Exp Mol Med 54:2148-2161.

Kluge A, Bunk J, Schaeffer E, Drobny A, Xiang W, Knacke H, Bub S, Lückstädt W, Arnold P, Lucius R, Berg D, Zunke F (2022) Detection of neuron-derived pathological α-synuclein in blood. Brain 145:3058-3071.

Knudsen K, Fedorova TD, Hansen AK, Sommerauer M, Otto M, Svendsen KB, Nahimi A, Stokholm MG, Pavese N, Beier CP, Brooks DJ, Borghammer P (2018) In-vivo staging of pathology in REM sleep behaviour disorder: a multimodality imaging case-control study. Lancet Neurol 17:618-628.

Koga S, Sekiya H, Kondru N, Ross OA, Dickson DW (2021) Neuropathology and molecular diagnosis of Synucleinopathies. Mol Neurodegener 16:83.

Kumari P, Ghosh D, Vanas A, Fleischmann Y, Wiegand T, Jeschke G, Riek R, Eichmann C (2021) Structural insights into α-synuclein monomer-fibril interactions. Proc Natl Acad Sci U S A 118:e2012171118.

Kunadt M, Eckermann K, Stuendl A, Gong J, Russo B, Strauss K, Rai S, Kügler S, Falomir Lockhart L, Schwalbe M, Krumova P, Oliveira LM, Bähr M, Möbius W, Levin J, Giese A, Kruse N, Mollenhauer B, Geiss-Friedlander R, Ludolph AC, et al. (2015) Extracellular vesicle sorting of α-synuclein is regulated by sumoylation. Acta Neuropathol 129:695-713.

Lan G, Wang P, Chan RB, Liu Z, Yu Z, Liu X, Yang Y, Zhang J (2022) Astrocytic VEGFA: an essential mediator in blood-brain-barrier disruption in Parkinson's disease. Glia 70:337-353.

Lang AE, Siderowf AD, Macklin EA, Poewe W, Brooks DJ, Fernandez HH, Rascol O, Giladi N, Stocchi F, Tanner CM, Postuma RB, Simon DK, Tolosa E, Mollenhauer B, Cedarbaum JM, Fraser K, Xiao J, Evans KC, Graham DL, Sapir I, et al. (2022) Trial of cinpanemab in early Parkinson's disease. N Engl J Med 387:408-420.

Lau A, So RWL, Lau HHC, Sang JC, Ruiz-Riquelme A, Fleck SC, Stuart E, Menon S, Visanji NP, Meisl G, Faidi R, Marano MM, Schmitt-Ulms C, Wang Z, Fraser PE, Tandon A, Hyman BT, Wille H, Ingelsson M, Klenerman D, et al. (2020) α-Synuclein strains target distinct brain regions and cell types. Nat Neurosci 23:21-31.

Lau HHC, Martinez-Valbuena I, So RWL, Mehra S, Silver NRG, Mao A, Stuart E, Schmitt-Ulms C, Hyman BT, Ingelsson M, Kovacs GG, Watts JC (2023) The G51D SNCA mutation generates a slowly progressive α-synuclein strain in early-onset Parkinson's disease. Acta Neuropathol Commun 11:72.

Lee D, Park CW, Paik SR, Choi KY (2009) The modification of alpha-synuclein by dicarbonyl compounds inhibits its fibril-forming process. Biochim Biophys Acta 1794:421-430.

Leitão ADG, Rudolffi-Soto P, Chappard A, Bhumkar A, Lau D, Hunter DJB, Gambin Y, Sierecki E (2021) Selectivity of Lewy body protein interactions along the aggregation pathway of α-synuclein. Commun Biol 4:1124.

Li F, Harmer P, Fitzgerald K, Eckstrom E, Stock R, Galver J, Maddalozzo G, Batya SS (2012) Tai chi and postural stability in patients with Parkinson's disease. N Engl J Med 366:511-519.

Li J, Zhao N, Zhang W, Li P, Yin X, Zhang W, Wang H, Tang B (2023a) Assessing the progression of early atherosclerosis mice using a fluorescence nanosensor for the simultaneous detection and imaging of pH and phosphorylation. Angew Chem Int Ed Engl 62:e202215178.

Li S, Yue L, Chen S, Wu Z, Zhang J, Hong R, Xie L, Peng K, Wang C, Lin A, Jin L, Guan Q (2022) High clinical diagnostic accuracy of combined salivary gland and myocardial metaiodobenzylguanidine scintigraphy in the diagnosis of Parkinson's disease. Front Aging Neurosci 14:1066331.

Li Y, Yang C, Wang S, Yang D, Zhang Y, Xu L, Ma L, Zheng J, Petersen RB, Zheng L, Chen H, Huang K (2020) Copper and iron ions accelerate the prion-like propagation of α-synuclein: a vicious cycle in Parkinson's disease. Int J Biol Macromol 163:562-573.

Li Y, Wang T, Meng L, Jin L, Liu C, Liang Y, Ren L, Liu Y, Liu Y, Liu S, Li T, Liang Y, Chen X, Zhang Z (2023b) Novel naturally occurring autoantibodies attenuate α-synuclein pathology in a mouse model of Parkinson's disease. Neuropathol Appl Neurobiol 49:e12860.

Liu G, Yu Z, Gao L, Zheng Y, Feng T (2022) Erythrocytic alpha-synuclein in early Parkinson's disease: A 3-year longitudinal study. Parkinsonism Relat Disord 104:44-48.

Liu X, Wang Q, Yang Y, Stewart T, Shi M, Soltys D, Liu G, Thorland E, Cilento EM, Hou Y, Liu Z, Feng T, Zhang J (2021) Reduced erythrocytic CHCHD2 mRNA is associated with brain pathology of Parkinson's disease. Acta Neuropathol Commun 9:37.

Liu Y, Qiang M, Wei Y, He R (2011) A novel molecular mechanism for nitrated {alpha}-synuclein-induced cell death. J Mol Cell Biol 3:239-249.

Lobanova E, Whiten D, Ruggeri FS, Taylor CG, Kouli A, Xia Z, Emin D, Zhang YP, Lam JYL, Williams-Gray CH, Klenerman D (2022) Imaging protein aggregates in the serum and cerebrospinal fluid in Parkinson's disease. Brain 145:632-643.

Luan M, Sun Y, Chen J, Jiang Y, Li F, Wei L, Sun W, Ma J, Song L, Liu J, Liu B, Pei Y, Wang Z, Zhu L, Deng J (2022) Diagnostic value of salivary real-time quaking-induced conversion in Parkinson's disease and multiple system atrophy. Mov Disord 37:1059-1063.

Luk KC, Kehm VM, Zhang B, O'Brien P, Trojanowski JQ, Lee VM (2012a) Intracerebral inoculation of pathological α-synuclein initiates a rapidly progressive neurodegenerative α-synucleinopathy in mice. J Exp Med 209:975-986.

Luk KC, Kehm V, Carroll J, Zhang B, O'Brien P, Trojanowski JQ, Lee VM (2012b) Pathological α-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice. Science 338:949-953.

Macdonald JA, Chen JL, Masuda-Suzukake M, Schweighauser M, Jaunmuktane Z, Warner T, Holton JL, Grossman A, Berks R, Lavenir I, Goedert M (2021) Assembly of α-synuclein and neurodegeneration in the central nervous system of heterozygous M83 mice following the peripheral administration of α-synuclein seeds. Acta Neuropathol Commun 9:189.

Mahul-Mellier AL, Vercruysse F, Maco B, Ait-Bouziad N, De Roo M, Muller D, Lashuel HA (2015) Fibril growth and seeding capacity play key roles in α-synuclein-mediated apoptotic cell death. Cell Death Differ 22:2107-2122.

Malec-Litwinowicz M, Plewka A, Plewka D, Bogunia E, Morek M, Szczudlik A, Szubiga M, Rudzińska-Bar M (2018) The relation between plasma α-synuclein level and clinical symptoms or signs of Parkinson's disease. Neurol Neurochir Pol 52:243-251.

Manfredsson FP, Luk KC, Benskey MJ, Gezer A, Garcia J, Kuhn NC, Sandoval IM, Patterson JR, O'Mara A, Yonkers R, Kordower JH (2018) Induction of alpha-synuclein pathology in the enteric nervous system of the rat and non-human primate results in gastrointestinal dysmotility and transient CNS pathology. Neurobiol Dis 112:106-118.

Mao X, Ou MT, Karuppagounder SS, Kam TI, Yin X, Xiong Y, Ge P, Umanah GE, Brahmachari S, Shin JH, Kang HC, Zhang J, Xu J, Chen R, Park H, Andrabi SA, Kang SU, Gonçalves RA, Liang Y, Zhang S, et al. (2016) Pathological α-synuclein transmission initiated by binding lymphocyte-activation gene 3. Science 353:aah3374.

Marano M, Anzini G, Musumeci G, Magliozzi A, Pozzilli V, Capone F, Di Lazzaro V (2022) Transcutaneous auricular vagus stimulation improves gait and reaction time in Parkinson's disease. Mov Disord 37:2163-2164.

Marrachelli VG, Miranda FJ, Alabadí JA, Milán M, Cano-Jaimez M, Kirstein M, Alborch E, Fariñas I, Pérez-Sánchez F (2010) Perivascular nerve fiber α-synuclein regulates contractility of mouse aorta: a link to autonomic dysfunction in Parkinson's disease. Neurochem Int 56:991-998.

Martínez-Rodríguez TY, Rey-Buitrago M (2020) Alpha sinuclein expression in blood and its relationship with chronic constipation in a population from Bogotá, D.C., with problems of alcohol consumption. Biomedica 40:309-321.

Masaracchia C, Hnida M, Gerhardt E, Lopes da Fonseca T, Villar-Pique A, Branco T, Stahlberg MA, Dean C, Fernández CO, Milosevic I, Outeiro TF (2018) Membrane binding, internalization, and sorting of alpha-synuclein in the cell. Acta Neuropathol Commun 6:79.

Masuda-Suzukake M, Nonaka T, Hosokawa M, Oikawa T, Arai T, Akiyama H, Mann DM, Hasegawa M (2013) Prion-like spreading of pathological α-synuclein in brain. Brain 136:1128-1138.

Masuda-Suzukake M, Shimozawa A, Hashimoto M, Hasegawa M (2021) Common marmoset model of α-synuclein propagation. Methods Mol Biol 2322:131-139.

Matsui H, Matsui N (2017) Cerebrospinal fluid injection into adult zebrafish for disease research. J Neural Transm (Vienna) 124:1627-1633.

Matsumoto J, Stewart T, Sheng L, Li N, Bullock K, Song N, Shi M, Banks WA, Zhang J (2017) Transmission of α-synuclein-containing erythrocyte-derived extracellular vesicles across the blood-brain barrier via adsorptive mediated transcytosis: another mechanism for initiation and progression of Parkinson's disease? Acta Neuropathol Commun 5:71.

Mazzetti S, Basellini MJ, Ferri V, Cassani E, Cereda E, Paolini M, Calogero AM, Bolliri C, De Leonardis M, Sacilotto G, Cilia R, Cappelletti G, Pezzoli G (2020) α-Synuclein oligomers in skin biopsy of idiopathic and monozygotic twin patients with Parkinson's disease. Brain 143:920-931.

McGlinchey RP, Ni X, Shadish JA, Jiang J, Lee JC (2021) The N terminus of α-synuclein dictates fibril formation. Proc Natl Acad Sci U S A 118:e2023487118.

Menegon A, Board PG, Blackburn AC, Mellick GD, Le Couteur DG (1998) Parkinson's disease, pesticides, and glutathione transferase polymorphisms. Lancet 352:1344-1346.

Miki Y, Shimoyama S, Kon T, Ueno T, Hayakari R, Tanji K, Matsumiya T, Tsushima E, Mori F, Wakabayashi K, Tomiyama M (2018) Alteration of autophagy-related proteins in peripheral blood mononuclear cells of patients with Parkinson's disease. Neurobiol Aging 63:33-43.

Mizuno Y, Hattori N, Mori H (1999) Genetics of Parkinson's disease. Biomed Pharmacother 53:109-116.

Mollenhauer B, Locascio JJ, Schulz-Schaeffer W, Sixel-Döring F, Trenkwalder C, Schlossmacher MG (2011) α-Synuclein and tau concentrations in cerebrospinal fluid of patients presenting with parkinsonism: a cohort study. Lancet Neurol 10:230-240.

Mollenhauer B, Trautmann E, Taylor P, Manninger P, Sixel-Döring F, Ebentheuer J, Trenkwalder C, Schlossmacher MG (2013) Total CSF α-synuclein is lower in de novo Parkinson patients than in healthy subjects. Neurosci Lett 532:44-48.

Nakai M, Fujita M, Waragai M, Sugama S, Wei J, Akatsu H, Ohtaka-Maruyama C, Okado H, Hashimoto M (2007) Expression of alpha-synuclein, a presynaptic protein implicated in Parkinson's disease, in erythropoietic lineage. Biochem Biophys Res Commun 358:104-110.

Navarro-Otano J, Gelpi E, Mestres CA, Quintana E, Rauek S, Ribalta T, Santiago V, Tolosa E (2013) Alpha-synuclein aggregates in epicardial fat tissue in living subjects without parkinsonism. Parkinsonism Relat Disord 19:27-31; discussion 27.

Nawaz H, Sargent L, Quilon H, Cloud LJ, Testa CM, Snider JD, Lageman SK, Baron MS, Berman BD, Zimmerman K, Price ET, Mukhopadhyay ND, Barrett MJ (2022) Anticholinergic medication burden in Parkinson's disease outpatients. J Parkinsons Dis 12:599-606.

Nolano M, Caporaso G, Manganelli F, Stancanelli A, Borreca I, Mozzillo S, Tozza S, Dubbioso R, Iodice R, Vitale F, Koay S, Vichayanrat E, da Silva FV, Santoro L, Iodice V, Provitera V (2022) Phosphorylated α-synuclein deposits in cutaneous nerves of early Parkinsonism. J Parkinsons Dis 12:2453-2468.

Nonaka T, Iwatsubo T, Hasegawa M (2005) Ubiquitination of alpha-synuclein. Biochemistry 44:361-368.

Ozawa T, Paviour D, Quinn NP, Josephs KA, Sangha H, Kilford L, Healy DG, Wood NW, Lees AJ, Holton JL, Revesz T (2004) The spectrum of pathological involvement of the striatonigral and olivopontocerebellar systems in multiple system atrophy: clinicopathological correlations. Brain 127:2657-2671.

Padmaraju V, Bhaskar JJ, Prasada Rao UJ, Salimath PV, Rao KS (2011) Role of advanced glycation on aggregation and DNA binding properties of α-synuclein. J Alzheimers Dis 24 Suppl 2:211-221.

Pagano G, Taylor KI, Anzures-Cabrera J, Marchesi M, Simuni T, Marek K, Postuma RB, Pavese N, Stocchi F, Azulay JP, Mollenhauer B, López-Manzanares L, Russell DS, Boyd JT, Nicholas AP, Luquin MR, Hauser RA, Gasser T, Poewe W, Ricci B, et al. (2022) Trial of prasinezumab in early-stage Parkinson's disease. N Engl J Med 387:421-432.

Pagonabarraga J, Kulisevsky J, Strafella AP, Krack P (2015) Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment. Lancet Neurol 14:518-531.

Palma JA, Norcliffe-Kaufmann L, Kaufmann H (2018) Orthostatic hypotension as a prodromal marker of α-synucleinopathies. JAMA Neurol 75:1154.

Panigrahi R, Krishnan R, Singh JS, Padinhateeri R, Kumar A (2023) SUMO1 hinders α-Synuclein fibrillation by inducing structural compaction. Protein Sci 32:e4632.

Papagiannakis N, Xilouri M, Koros C, Stamelou M, Antonelou R, Maniati M, Papadimitriou D, Moraitou M, Michelakakis H, Stefanis L (2015) Lysosomal alterations in peripheral blood mononuclear cells of Parkinson's disease patients. Mov Disord 30:1830-1834.

Papp MI, Lantos PL (1994) The distribution of oligodendroglial inclusions in multiple system atrophy and its relevance to clinical symptomatology. Brain 117 (Pt 2):235-243.

Park H, Kam TI, Peng H, Chou SC, Mehrabani-Tabari AA, Song JJ, Yin X, Karuppagounder SS, Umanah GK, Rao AVS, Choi Y, Aggarwal A, Chang S, Kim H, Byun J, Liu JO, Dawson TM, Dawson VL (2022) PAAN/MIF nuclease inhibition prevents neurodegeneration in Parkinson's disease. Cell 185:1943-1959.e21.

Pediaditakis I, Kodella KR, Manatakis DV, Le CY, Hinojosa CD, Tien-Street W, Manolakos ES, Vekrellis K, Hamilton GA, Ewart L, Rubin LL, Karalis K (2021) Modeling alpha-synuclein pathology in a human brain-chip to assess blood-brain barrier disruption. Nat Commun 12:5907.

Peelaerts W, Bousset L, Van der Perren A, Moskalyuk A, Pulizzi R, Giugliano M, Van den Haute C, Melki R, Baekelandt V (2015) α-Synuclein strains cause distinct synucleinopathies after local and systemic administration. Nature 522:340-344.

Peelaerts W, Mercado G, George S, Villumsen M, Kasen A, Aguileta M, Linstow C, Sutter AB, Kuhn E, Stetzik L, Sheridan R, Bergkvist L, Meyerdirk L, Lindqvist A, Gavis MLE, Van den Haute C, Hultgren SJ, Baekelandt V, Pospisilik JA, Brudek T, et al. (2023) Urinary tract infections trigger synucleinopathy via the innate immune response. Acta Neuropathol 145:541-559.

Pena-DIaz S, Ventura S (2022) One ring is sufficient to inhibit α-synuclein aggregation. Neural Regen Res 17:508-511.

Peng C, Gathagan RJ, Covell DJ, Medellin C, Stieber A, Robinson JL, Zhang B, Pitkin RM, Olufemi MF, Luk KC, Trojanowski JQ, Lee VM (2018) Cellular milieu imparts distinct pathological α-synuclein strains in α-synucleinopathies. Nature 557:558-563.

Perissinotto F, Stani C, De Cecco E, Vaccari L, Rondelli V, Posocco P, Parisse P, Scaini D, Legname G, Casalis L (2020) Iron-mediated interaction of alpha synuclein with lipid raft model membranes. Nanoscale 12:7631-7640.

Phillips MCL, Murtagh DKJ, Gilbertson LJ, Asztely FJS, Lynch CDP (2018) Low-fat versus ketogenic diet in Parkinson's disease: A pilot randomized controlled trial. Mov Disord 33:1306-1314.

Pluvinage JV, Haney MS, Smith BAH, Sun J, Iram T, Bonanno L, Li L, Lee DP, Morgens DW, Yang AC, Shuken SR, Gate D, Scott M, Khatri P, Luo J, Bertozzi CR, Bassik MC, Wyss-Coray T (2019) CD22 blockade restores homeostatic microglial phagocytosis in ageing brains. Nature 568:187-192.

Poggiolini I, Gupta V, Lawton M, Lee S, El-Turabi A, Querejeta-Coma A, Trenkwalder C, Sixel-Döring F, Foubert-Samier A, Pavy-Le Traon A, Plazzi G, Biscarini F, Montplaisir J, Gagnon JF, Postuma RB, Antelmi E, Meissner WG, Mollenhauer B, Ben-Shlomo Y, Hu MT, et al. (2022) Diagnostic value of cerebrospinal fluid alpha-synuclein seed quantification in synucleinopathies. Brain 145:584-595.

Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, Pike B, Root H, Rubenstein J, Boyer R, Stenroos ES, Chandrasekharappa S, Athanassiadou A, Papapetropoulos T, Johnson WG, Lazzarini AM, Duvoisin RC, Di Iorio G, Golbe LI, Nussbaum RL (1997) Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science 276:2045-2047.

Porcari R, Proukakis C, Waudby CA, Bolognesi B, Mangione PP, Paton JF, Mullin S, Cabrita LD, Penco A, Relini A, Verona G, Vendruscolo M, Stoppini M, Tartaglia GG, Camilloni C, Christodoulou J, Schapira AH, Bellotti V (2015) The H50Q mutation induces a 10-fold decrease in the solubility of α-synuclein. J Biol Chem 290:2395-2404.

Prieto Huarcaya S, Drobny A, Marques ARA, Di Spiezio A, Dobert JP, Balta D, Werner C, Rizo T, Gallwitz L, Bub S, Stojkovska I, Belur NR, Fogh J, Mazzulli JR, Xiang W, Fulzele A, Dejung M, Sauer M, Winner B, Rose-John S, et al. (2022) Recombinant pro-CTSD (cathepsin D) enhances SNCA/α-synuclein degradation in α-Synucleinopathy models. Autophagy 18:1127-1151.

Rauch JN, Luna G, Guzman E, Audouard M, Challis C, Sibih YE, Leshuk C, Hernandez I, Wegmann S, Hyman BT, Gradinaru V, Kampmann M, Kosik KS (2020) LRP1 is a master regulator of tau uptake and spread. Nature 580:381-385.

Reyes JF, Ekmark-Léwen S, Perdiki M, Klingstedt T, Hoffmann A, Wiechec E, Nilsson P, Nilsson KPR, Alafuzoff I, Ingelsson M, Hallbeck M (2021) Accumulation of alpha-synuclein within the liver, potential role in the clearance of brain pathology associated with Parkinson's disease. Acta Neuropathol Commun 9:46.

Rocca WA (2018) The burden of Parkinson's disease: a worldwide perspective. Lancet Neurol 17:928-929.

Rodrigues PV, de Godoy JVP, Bosque BP, Amorim Neto DP, Tostes K, Palameta S, Garcia-Rosa S, Tonoli CCC, de Carvalho HF, de Castro Fonseca M (2022) Transcellular propagation of fibrillar α-synuclein from enteroendocrine to neuronal cells requires cell-to-cell contact and is Rab35-dependent. Sci Rep 12:4168.

Rodriguez JA, Ivanova MI, Sawaya MR, Cascio D, Reyes FE, Shi D, Sangwan S, Guenther EL, Johnson LM, Zhang M, Jiang L, Arbing MA, Nannenga BL, Hattne J, Whitelegge J, Brewster AS, Messerschmidt M, Boutet S, Sauter NK, Gonen T, et al. (2015) Structure of the toxic core of α-synuclein from invisible crystals. Nature 525:486-490.

Roshanbin S, Julku U, Xiong M, Eriksson J, Masliah E, Hultqvist G, Bergström J, Ingelsson M, Syvänen S, Sehlin D (2022) Reduction of αSYN pathology in a mouse model of PD using a brain-penetrating bispecific antibody. Pharmaceutics 14:1412.

Rott R, Szargel R, Shani V, Hamza H, Savyon M, Abd Elghani F, Bandopadhyay R, Engelender S (2017) SUMOylation and ubiquitination reciprocally regulate α-synuclein degradation and pathological aggregation. Proc Natl Acad Sci U S A 114:13176-13181.

Ruan Z, Zhang D, Huang R, Sun W, Hou L, Zhao J, Wang Q (2022) Microglial activation damages dopaminergic neurons through MMP-2/-9-mediated increase of blood-brain barrier permeability in a Parkinson's disease mouse model. Int J Mol Sci 23:2793.

Ruf WP, Palmer A, Dörfer L, Wiesner D, Buck E, Grozdanov V, Kassubek J, Dimou L, Ludolph AC, Huber-Lang M, Danzer KM (2022) Thoracic trauma promotes alpha-Synuclein oligomerization in murine Parkinson's disease. Neurobiol Dis 174:105877.

Salman MM, Kitchen P, Halsey A, Wang MX, Törnroth-Horsefield S, Conner AC, Badaut J, Iliff JJ, Bill RM (2022) Emerging roles for dynamic aquaporin-4 subcellular relocalization in CNS water homeostasis. Brain 145:64-75.

Sampson TR, Challis C, Jain N, Moiseyenko A, Ladinsky MS, Shastri GG, Thron T, Needham BD, Horvath I, Debelius JW, Janssen S, Knight R, Wittung-Stafshede P, Gradinaru V, Chapman M, Mazmanian SK (2020) A gut bacterial amyloid promotes α-synuclein aggregation and motor impairment in mice. Elife 9:e53111.

Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE, Challis C, Schretter CE, Rocha S, Gradinaru V, Chesselet MF, Keshavarzian A, Shannon KM, Krajmalnik-Brown R, Wittung-Stafshede P, Knight R, Mazmanian SK (2016) Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. Cell 167:1469-1480.e12.

Sanyal A, Dutta S, Camara A, Chandran A, Koller A, Watson BG, Sengupta R, Ysselstein D, Montenegro P, Cannon J, Rochet JC, Mattoo S (2019) Alpha-synuclein is a target of Fic-mediated adenylylation/AMPylation: possible implications for Parkinson's disease. J Mol Biol 431:2266-2282.

Scheperjans F, Aho V, Pereira PA, Koskinen K, Paulin L, Pekkonen E, Haapaniemi E, Kaakkola S, Eerola-Rautio J, Pohja M, Kinnunen E, Murros K, Auvinen P (2015) Gut microbiota are related to Parkinson's disease and clinical phenotype. Mov Disord 30:350-358.

Scott GD, Lim MM, Drake MG, Woltjer R, Quinn JF (2021) Onset of skin, gut, and genitourinary prodromal Parkinson's disease: a study of 1.5 million veterans. Mov Disord 36:2094-2103.

Selkoe D, Dettmer U, Luth E, Kim N, Newman A, Bartels T (2014) Defining the native state of α-synuclein. Neurodegener Dis 13:114-117.

Semenyuk P, Barinova K, Muronetz V (2019) Glycation of α-synuclein amplifies the binding with glyceraldehyde-3-phosphate dehydrogenase. Int J Biol Macromol 127:278-285.

Sergeyeva TN, Sergeyev VG, Tolstolytskaya TO (2011) Effects of bacterial endotoxin on α-synuclein expression in the lymph node leukocytes of rats. Bull Exp Biol Med 150:348-351.

Sevcsik E, Trexler AJ, Dunn JM, Rhoades E (2011) Allostery in a disordered protein: oxidative modifications to α-synuclein act distally to regulate membrane binding. J Am Chem Soc 133:7152-7158.

Sharabi Y, Vatine GD, Ashkenazi A (2021) Parkinson's disease outside the brain: targeting the autonomic nervous system. Lancet Neurol 20:868-876.

Shin JW, An S, Kim D, Kim H, Ahn J, Eom J, You WK, Yun H, Lee B, Sung B, Jung J, Kim S, Son Y, Sung E, Lee H, Lee S, Song D, Pak Y, Sandhu JK, Haqqani AS, et al. (2022) Grabody B, an IGF1 receptor-based shuttle, mediates efficient delivery of biologics across the blood-brain barrier. Cell Rep Methods 2:100338.

Sinclair E, Trivedi DK, Sarkar D, Walton-Doyle C, Milne J, Kunath T, Rijs AM, de Bie RMA, Goodacre R, Silverdale M, Barran P (2021) Metabolomics of sebum reveals lipid dysregulation in Parkinson's disease. Nat Commun 12:1592.

Sonustun B, Altay MF, Strand C, Ebanks K, Hondhamuni G, Warner TT, Lashuel HA, Bandopadhyay R (2022) Pathological relevance of post-translationally modified alpha-synuclein (pSer87, pSer129, nTyr39) in idiopathic Parkinson's disease and multiple system atrophy. Cells 11:906.

Spehlmann R (1975) The effects of acetylcholine and dopamine on the caudate nucleus depleted of biogenic amines. Brain 98:219-230.

Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M (1997) Alpha-synuclein in Lewy bodies. Nature 388:839-840.

Squair JW, Berney M, Castro Jimenez M, Hankov N, Demesmaeker R, Amir S, Paley A, Hernandez-Charpak S, Dumont G, Asboth L, Allenbach G, Becce F, Schoettker P, Wuerzner G, Bally JF, Courtine G, Bloch J (2022) Implanted system for orthostatic hypotension in multiple-system atrophy. N Engl J Med 386:1339-1344.

Stephens AD, Zacharopoulou M, Moons R, Fusco G, Seetaloo N, Chiki A, Woodhams PJ, Mela I, Lashuel HA, Phillips JJ, De Simone A, Sobott F, Schierle GSK (2020) Extent of N-terminus exposure of monomeric alpha-synuclein determines its aggregation propensity. Nat Commun 11:2820.

Streubel-Gallasch L, Giusti V, Sandre M, Tessari I, Plotegher N, Giusto E, Masato A, Iovino L, Battisti I, Arrigoni G, Shimshek D, Greggio E, Tremblay ME, Bubacco L, Erlandsson A, Civiero L (2021) Parkinson's disease-associated LRRK2 interferes with astrocyte-mediated alpha-synuclein clearance. Mol Neurobiol 58:3119-3140.

Su Y, Deng MF, Xiong W, Xie AJ, Guo J, Liang ZH, Hu B, Chen JG, Zhu X, Man HY, Lu Y, Liu D, Tang B, Zhu LQ (2019) MicroRNA-26a/death-associated protein kinase 1 signaling induces synucleinopathy and dopaminergic neuron degeneration in Parkinson's disease. Biol Psychiatry 85:769-781.

Sui YT, Bullock KM, Erickson MA, Zhang J, Banks WA (2014) Alpha synuclein is transported into and out of the brain by the blood-brain barrier. Peptides 62:197-202.

Sulzer D, Alcalay RN, Garretti F, Cote L, Kanter E, Agin-Liebes J, Liong C, McMurtrey C, Hildebrand WH, Mao X, Dawson VL, Dawson TM, Oseroff C, Pham J, Sidney J, Dillon MB, Carpenter C, Weiskopf D, Phillips E, Mallal S, et al. (2017) T cells from patients with Parkinson's disease recognize α-synuclein peptides. Nature 546:656-661.

Swaminath PV, Ragothaman M, Koshy S, Sarangmath N, Adhyam M, Subbakrishna DK, Mathias CJ, Muthane UB (2010) Urogenital symptoms in Parkinson's disease and multiple system atrophy-Parkinsonism: at onset and later. J Assoc Physicians India 58:86-90.

Tanei ZI, Saito Y, Ito S, Matsubara T, Motoda A, Yamazaki M, Sakashita Y, Kawakami I, Ikemura M, Tanaka S, Sengoku R, Arai T, Murayama S (2021) Lewy pathology of the esophagus correlates with the progression of Lewy body disease: a Japanese cohort study of autopsy cases. Acta Neuropathol 141:25-37.

Teil M, Dovero S, Bourdenx M, Arotcarena ML, Camus S, Porras G, Thiolat ML, Trigo-Damas I, Perier C, Estrada C, Garcia-Carrillo N, Morari M, Meissner WG, Herrero MT, Vila M, Obeso JA, Bezard E, Dehay B (2022) Brain injections of glial cytoplasmic inclusions induce a multiple system atrophy-like pathology. Brain 145:1001-1017.

Theillet FX, Binolfi A, Bekei B, Martorana A, Rose HM, Stuiver M, Verzini S, Lorenz D, van Rossum M, Goldfarb D, Selenko P (2016) Structural disorder of monomeric α-synuclein persists in mammalian cells. Nature 530:45-50.

Tian C, Liu G, Gao L, Soltys D, Pan C, Stewart T, Shi M, Xie Z, Liu N, Feng T, Zhang J (2019) Erythrocytic α-synuclein as a potential biomarker for Parkinson's disease. Transl Neurodegener 8:15.

Tolosa E, Wenning G, Poewe W (2006) The diagnosis of Parkinson's disease. Lancet Neurol 5:75-86.

Tsunemi T, Ishiguro Y, Yoroisaka A, Valdez C, Miyamoto K, Ishikawa K, Saiki S, Akamatsu W, Hattori N, Krainc D (2020) Astrocytes protect human dopaminergic neurons from α-synuclein accumulation and propagation. J Neurosci 40:8618-8628.

Tulisiak CT, Mercado G, Peelaerts W, Brundin L, Brundin P (2019) Can infections trigger alpha-synucleinopathies? Prog Mol Biol Transl Sci 168:299-322.

Tysnes OB, Storstein A (2017) Epidemiology of Parkinson's disease. J Neural Transm (Vienna) 124:901-905.

Uemura N, Marotta N, Ara J, Meymand E, Zhang B, Kameda H, Koike M, Luk K, Trojanowski J, Lee V (2023) Distinct biological activity of Lewy body α-Synuclein strain in mice. Res Sq doi: 10.21203/rs.3.rs-2579805/v1.

Umehara T, Oka H, Nakahara A, Shiraishi T, Sato T, Matsuno H, Komatsu T, Omoto S, Murakami H, Iguchi Y (2020) Sympathetic nervous activity and hemoglobin levels in de novo Parkinson's disease. Clin Auton Res 30:273-278.

Van Den Berge N, Ferreira N, Mikkelsen TW, Alstrup AKO, Tamgüney G, Karlsson P, Terkelsen AJ, Nyengaard JR, Jensen PH, Borghammer P (2021) Ageing promotes pathological alpha-synuclein propagation and autonomic dysfunction in wild-type rats. Brain 144:1853-1868.

Van der Perren A, Gelders G, Fenyi A, Bousset L, Brito F, Peelaerts W, Van den Haute C, Gentleman S, Melki R, Baekelandt V (2020) The structural differences between patient-derived α-synuclein strains dictate characteristics of Parkinson's disease, multiple system atrophy and dementia with Lewy bodies. Acta Neuropathol 139:977-1000.

Vellingiri B, Suriyanarayanan A, Abraham KS, Venkatesan D, Iyer M, Raj N, Gopalakrishnan AV (2022) Influence of heavy metals in Parkinson's disease: an overview. J Neurol 269:5798-5811.

Vicente Miranda H, Szego É M, Oliveira LMA, Breda C, Darendelioglu E, de Oliveira RM, Ferreira DG, Gomes MA, Rott R, Oliveira M, Munari F, Enguita FJ, Simões T, Rodrigues EF, Heinrich M, Martins IC, Zamolo I, Riess O, Cordeiro C, Ponces-Freire A, et al. (2017) Glycation potentiates α-synuclein-associated neurodegeneration in synucleinopathies. Brain 140:1399-1419.

Vilas D, Iranzo A, Tolosa E, Aldecoa I, Berenguer J, Vilaseca I, Martí C, Serradell M, Lomeña F, Alós L, Gaig C, Santamaria J, Gelpi E (2016) Assessment of α-synuclein in submandibular glands of patients with idiopathic rapid-eye-movement sleep behaviour disorder: a case-control study. Lancet Neurol 15:708-718.

Volpicelli-Daley LA, Luk KC, Patel TP, Tanik SA, Riddle DM, Stieber A, Meaney DF, Trojanowski JQ, Lee VM (2011) Exogenous α-synuclein fibrils induce Lewy body pathology leading to synaptic dysfunction and neuron death. Neuron 72:57-71.

Wakabayashi K, Takahashi H (1997) The intermediolateral nucleus and Clarke's column in Parkinson's disease. Acta Neuropathol 94:287-289.

Wakabayashi K, Hayashi S, Kakita A, Yamada M, Toyoshima Y, Yoshimoto M, Takahashi H (1998) Accumulation of alpha-synuclein/NACP is a cytopathological feature common to Lewy body disease and multiple system atrophy. Acta Neuropathol 96:445-452.

Wang C, Sharma SK, Olaluwoye OS, Alrashdi SA, Hasegawa T, Leblanc RM (2019) Conformation change of α-synuclein(61–95) at the air-water interface and quantitative measurement of the tilt angle of the axis of its α-helix by multiple angle incidence resolution spectroscopy. Colloids Surf B Biointerfaces 183:110401.

Wang C, Lau CY, Ma F, Zheng C (2021a) Genome-wide screen identifies curli amyloid fibril as a bacterial component promoting host neurodegeneration. Proc Natl Acad Sci U S A 118:e2106504118.

Wang H, Qi W, Zou C, Xie Z, Zhang M, Naito MG, Mifflin L, Liu Z, Najafov A, Pan H, Shan B, Li Y, Zhu ZJ, Yuan J (2021b) NEK1-mediated retromer trafficking promotes blood-brain barrier integrity by regulating glucose metabolism and RIPK1 activation. Nat Commun 12:4826.

Wang R, Zhu Y, Liu Z, Chang L, Bai X, Kang L, Cao Y, Yang X, Yu H, Shi MJ, Hu Y, Fan W, Zhao BQ (2021c) Neutrophil extracellular traps promote tPA-induced brain hemorrhage via cGAS in mice with stroke. Blood 138:91-103.

Wang Z, Becker K, Donadio V, Siedlak S, Yuan J, Rezaee M, Incensi A, Kuzkina A, Orrú CD, Tatsuoka C, Liguori R, Gunzler SA, Caughey B, Jimenez-Capdeville ME, Zhu X, Doppler K, Cui L, Chen SG, Ma J, Zou WQ (2020) Skin α-synuclein aggregation seeding activity as a novel biomarker for Parkinson disease. JAMA Neurol doi: 10.1001/jamaneurol.2020.3311.

Waxman EA, Emmer KL, Giasson BI (2010) Residue Glu83 plays a major role in negatively regulating alpha-synuclein amyloid formation. Biochem Biophys Res Commun 391:1415-1420.

Wen L, Zhang QS, Heng Y, Chen Y, Wang S, Yuan YH, Chen NH (2018) NLRP3 inflammasome activation in the thymus of MPTP-induced Parkinsonian mouse model. Toxicol Lett 288:1-8.

Williams DR, Lees AJ (2005) Visual hallucinations in the diagnosis of idiopathic Parkinson's disease: a retrospective autopsy study. Lancet Neurol 4:605-610.

Williams GP, Schonhoff AM, Jurkuvenaite A, Gallups NJ, Standaert DG, Harms AS (2021) CD4 T cells mediate brain inflammation and neurodegeneration in a mouse model of Parkinson's disease. Brain 144:2047-2059.

Wood H (2016) Parkinson disease: Peripheral α-synuclein deposits- prodromal markers for Parkinson disease? Nat Rev Neurol 12:249.

World Health Organization (2022) Parkinson disease. https://www.who.int/news-room/fact-sheets/detail/parkinson-disease. Accessed June 13, 2022.

Wu Z, Li X, Zeng M, Qiu H, Feng H, Xu X, Yu S, Wu J (2019) Alpha-synuclein alterations in red blood cells of peripheral blood after acute ischemic stroke. Int J Clin Exp Pathol 12:1757-1763.

Wurster I, Quadalti C, Rossi M, Hauser AK, Deuschle C, Schulte C, Waniek K, Lachmann I, la Fougere C, Doppler K, Gasser T, Bender B, Parchi P, Brockmann K (2022) Linking the phenotype of SNCA triplication with PET-MRI imaging pattern and alpha-synuclein CSF seeding. NPJ Parkinsons Dis 8:117.

Xia Y, Zhang G, Kou L, Yin S, Han C, Hu J, Wan F, Sun Y, Wu J, Li Y, Huang J, Xiong N, Zhang Z, Wang T (2021) Reactive microglia enhance the transmission of exosomal α-synuclein via toll-like receptor 2. Brain 144:2024-2037.

Xiao W, Shameli A, Harding CV, Meyerson HJ, Maitta RW (2014) Late stages of hematopoiesis and B cell lymphopoiesis are regulated by α-synuclein, a key player in Parkinson's disease. Immunobiology 219:836-844.

Xu L, Nussinov R, Ma B (2016) Coupling of the non-amyloid-component (NAC) domain and the KTK(E/Q)GV repeats stabilize the α-synuclein fibrils. Eur J Med Chem 121:841-850.

Yamada M, Komatsu J, Nakamura K, Sakai K, Samuraki-Yokohama M, Nakajima K, Yoshita M (2020) Diagnostic criteria for dementia with Lewy bodies: updates and future directions. J Mov Disord 13:1-10.

Yamasaki TR, Holmes BB, Furman JL, Dhavale DD, Su BW, Song ES, Cairns NJ, Kotzbauer PT, Diamond MI (2019) Parkinson's disease and multiple system atrophy have distinct α-synuclein seed characteristics. J Biol Chem 294:1045-1058.

Yang X, Wang B, Hoop CL, Williams JK, Baum J (2021) NMR unveils an N-terminal interaction interface on acetylated-α-synuclein monomers for recruitment to fibrils. Proc Natl Acad Sci U S A 118:e2017452118.

Yang Y, Shi Y, Schweighauser M, Zhang X, Kotecha A, Murzin AG, Garringer HJ, Cullinane PW, Saito Y, Foroud T, Warner TT, Hasegawa K, Vidal R, Murayama S, Revesz T, Ghetti B, Hasegawa M, Lashley T, Scheres SHW, Goedert M (2022) Structures of α-synuclein filaments from human brains with Lewy pathology. Nature 610:791-795.

Yu D, Zarate N, White A, Coates D, Tsai W, Nanclares C, Cuccu F, Yue JS, Brown TG, Mansky RH, Jiang K, Kim H, Nichols-Meade T, Larson SN, Gundry K, Zhang Y, Tomas-Zapico C, Lucas JJ, Benneyworth M, Öz G, et al. (2022a) CK2 alpha prime and alpha-synuclein pathogenic functional interaction mediates synaptic dysregulation in huntington's disease. Acta Neuropathol Commun 10:83.

Yu X, Persillet M, Zhang L, Zhang Y, Xiuping S, Li X, Ran G, Breger LS, Dovero S, Porras G, Dehay B, Bezard E, Qin C (2021) Evaluation of blood flow as a route for propagation in experimental synucleinopathy. Neurobiol Dis 150:105255.

Yu Z, Liu G, Li Y, Arkin E, Zheng Y, Feng T (2022b) Erythrocytic α-synuclein species for Parkinson's disease diagnosis and the correlations with clinical characteristics. Front Aging Neurosci 14:827493.

Yuan J, Liu H, Zhang H, Wang T, Zheng Q, Li Z (2022) Controlled activation of TRPV1 channels on microglia to boost their autophagy for clearance of alpha-synuclein and enhance therapy of Parkinson's disease. Adv Mater 34:e2108435.

Yun SP, Kam TI, Panicker N, Kim S, Oh Y, Park JS, Kwon SH, Park YJ, Karuppagounder SS, Park H, Kim S, Oh N, Kim NA, Lee S, Brahmachari S, Mao X, Lee JH, Kumar M, An D, Kang SU, et al. (2018) Block of A1 astrocyte conversion by microglia is neuroprotective in models of Parkinson's disease. Nat Med 24:931-938.

Zhang J, Lei H, Chen Y, Ma YT, Jiang F, Tan J, Zhang Y, Li JD (2017a) Enzymatic O-GlcNAcylation of α-synuclein reduces aggregation and increases SDS-resistant soluble oligomers. Neurosci Lett 655:90-94.

Zhang S, Liu YQ, Jia C, Lim YJ, Feng G, Xu E, Long H, Kimura Y, Tao Y, Zhao C, Wang C, Liu Z, Hu JJ, Ma MR, Liu Z, Jiang L, Li D, Wang R, Dawson VL, Dawson TM, et al. (2021) Mechanistic basis for receptor-mediated pathological α-synuclein fibril cell-to-cell transmission in Parkinson's disease. Proc Natl Acad Sci U S A 118:e2011196118.

Zhang S, Li J, Xu Q, Xia W, Tao Y, Shi C, Li D, Xiang S, Liu C (2023a) Conformational dynamics of an α-synuclein fibril upon receptor binding revealed by insensitive nuclei enhanced by polarization transfer-based solid-state nuclear magnetic resonance and cryo-electron microscopy. J Am Chem Soc 145:4473-4484.

Zhang S, Zhu R, Pan B, Xu H, Olufemi MF, Gathagan RJ, Li Y, Zhang L, Zhang J, Xiang W, Kagan EM, Cao X, Yuan C, Kim SJ, Williams CK, Magaki S, Vinters HV, Lashuel HA, Garcia BA, James Petersson E, et al. (2023b) Post-translational modifications of soluble α-synuclein regulate the amplification of pathological α-synuclein. Nat Neurosci 26:213-225.

Zhang X, Wang S, Li X, Li X, Ran W, Liu C, Tian W, Yu X, Wu C, Li P, Li N, Wei Y, Wang Y, Yu S, Chen Z (2022a) Hemoglobin-binding α-synuclein levels in erythrocytes are elevated in patients with multiple system atrophy. Neurosci Lett 789:136868.

Zhang XM, Anwar S, Kim Y, Brown J, Comte I, Cai H, Cai NN, Wade-Martins R, Szele FG (2019) The A30P α-synuclein mutation decreases subventricular zone proliferation. Hum Mol Genet 28:2283-2294.

Zhang Y, Roy DS, Zhu Y, Chen Y, Aida T, Hou Y, Shen C, Lea NE, Schroeder ME, Skaggs KM, Sullivan HA, Fischer KB, Callaway EM, Wickersham IR, Dai J, Li XM, Lu Z, Feng G (2022b) Targeting thalamic circuits rescues motor and mood deficits in PD mice. Nature 607:321-329.

Zhang Y, Zhang C, He XZ, Li ZH, Meng JC, Mao RT, Li X, Xue R, Gui Q, Zhang GX, Wang LH (2023c) Interaction between the glymphatic system and α-synuclein in Parkinson's disease. Mol Neurobiol 60:2209-2222.

Zhang Z, Kang SS, Liu X, Ahn EH, Zhang Z, He L, Iuvone PM, Duong DM, Seyfried NT, Benskey MJ, Manfredsson FP, Jin L, Sun YE, Wang JZ, Ye K (2017b) Asparagine endopeptidase cleaves α-synuclein and mediates pathologic activities in Parkinson's disease. Nat Struct Mol Biol 24:632-642.

Zhao K, Lim YJ, Liu Z, Long H, Sun Y, Hu JJ, Zhao C, Tao Y, Zhang X, Li D, Li YM, Liu C (2020) Parkinson's disease-related phosphorylation at Tyr39 rearranges α-synuclein amyloid fibril structure revealed by cryo-EM. Proc Natl Acad Sci U S A 117:20305-20315.

Zhou L, Guo T, Meng L, Zhang X, Tian Y, Dai L, Niu X, Li Y, Liu C, Chen G, Liu C, Ke W, Zhang Z, Bao A, Zhang Z (2023) N-homocysteinylation of α-synuclein promotes its aggregation and neurotoxicity. Aging Cell 22:e13745.

C-Editors: Li JY, Zhao M; S-Editors: Yu J, Li CH; L-Editors: Yu J, Song LP; T-Editor: Jia Y