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α-Synuclein aggregation and transmission in Parkinson's disease: a link to mitochondria and lysosome

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The presence of intraneuronal Lewy bodies (LBs) and Lewy neurites (LNs) in the substantia nigra (SN) composed of aggregated α-synuclein (α-syn) has been recognized as a hallmark of pathological changes in Parkinson's disease (PD). Numerous studies have shown that aggregated α-syn is necessary for neurotoxicity. Meanwhile, the mitochondrial and lysosomal dysfunctions are associated with α-syn pathogenicity. The hypothesis that α-syn transmission in the human brain contributes to the instigation and progression of PD has provided insights into PD pathology. This review will provide a brief overview of increasing researches that shed light on the relationship of α-syn aggregation with mitochondrial and lysosomal dysfunctions, and highlight recent understanding of α-syn transmission in PD pathology.

α-synuclein, Lewy pathology, mitochondria, lysosome, aggregation, transmission

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease characterized by the progressive degeneration of dopaminergic (DA) neurons in substantia nigral pars compacta (SNpc) (Hu and Wang, 2016). The onset of the disease usually occurs over 60 years old, and the clinical symptoms manifest as a movement disorder of bradykinesia, tremor, rigidity, and postural instability, as well as a number of non-motor symptoms, such as hyposmia, constipation, cognitive and rapid eye move (REM) sleep disorders (Corti et al., 2011; de Lau and Breteler, 2006; Dong et al., 2019a; Lee and Trojanowski, 2006). To date, the etiology of PD remains unclear and there still lacks effective therapies for PD. Although most of the PD cases are sporadic, about 5%–10% of the PD cases are familial (Corti et al., 2011; Deng et al., 2018). Most notably, Lewy bodies (LBs) and Lewy neurites (LNs), which are referred to as Lewy pathology (LP), the main pathological hallmarks in PD, are presented in neurons at the brainstem and cortex in most familial and sporadic PD patients.

LBs are mainly composed of aggregated α-synuclein (α-syn) assemblies and other proteins (Goedert, 2015). Point mutations of *SNCA* gene that encodes α-syn as well as duplications or triplications in *SNCA* gene result in familial forms of PD (Nuytemans et al., 2010; Polymeropoulos et al., 1997; Singleton et al., 2003). The presence of α-syn aggregation in LBs in most cases of PD supports the hypothesis that α-syn plays a critical role in disease pathogenesis. α-Syn is a ~14 kD protein (140 amino acid residues) that is mainly enriched in presynaptic terminal. The physiological functions of α-syn remain unclear, although it may be involved in synaptic transmission (Bendor et al., 2013; Wang et al., 2014). Under physiological conditions, α-syn can exist as a compact state with monomer to avoid the exposure of its

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aggregation-prone NAC (non-Aβ component) domain to the cytoplasm (Burré et al., 2013; Theillet et al., 2016; Weinreb et al., 1996), or form a helically fold tetramer mediated by its KTKEGV repeats to resist aggregation (Bartels et al., 2011; Kim et al., 2018) (Figure 1). Once the native structure is broken by pathogenic factors, α-syn will increase tendency to form misfolded oligomers and β-sheet rich fibrils that are toxic assemblies for α-syn pathogenicity (Cremades et al., 2012). Many of PD-associated genes identified by genome-wide association studies (GWAS), including *DJ-1*, *parkin*, *PINK1*, *LRRK2*, *GBA*, *VPS35*, *ATP13A2* and *TMEM175*, have been reported to be associated with the regulation of mitochondrial and lysosomal functions (Brás et al., 2015; Corti et al., 2011; Grünewald et al., 2019; Hu and Wang, 2016; Krohn et al., 2020). Most recently, it has been identified that there are abundant disrupted mitochondria and lysosomes in LP inclusions in brain tissues from PD patients using correlative light and electron microscopy (CLEM) (Shahmoradian et al., 2019). These findings provide strong evidence that mitochondrial and lysosomal damages are associated with α-syn aggregation and LP formation, which play a key role in the PD pathogenesis. Recent studies support that misfolded α-syn seeds α-syn aggregates by recruiting endogenous native monomers, and initiates propagation in a prion-like manner from neuron to neuron and one region of brain to another (Henderson et al., 2019b; Vargas et al., 2019). The transmission of α-syn provides reasonable explanations for the progressions of α-syn pathology and disease symptoms in PD patients (Henderson et al., 2019b; Vargas et al., 2019). In this review, we will discuss: (i) the role of mitochondrial and lysosomal dysfunction in α-syn aggregation, (ii) the toxicity of aggregated α-syn on mitochondria and lysosome, (iii) the contribution of α-syn transmission to PD pathology.

Mitochondrial dysfunction and α-syn aggregation

Mitochondria are known as double membrane-bound organelles that play a key role in cell processes, including supply of cellular energy, participating in cellular metabolism, and maintaining cellular homeostasis (Benard et al., 2007; Perier and Vila, 2012). Neurons have a high energy demand to maintain their basic physiological activities, therefore mitochondrial homeostasis is crucial for neuron survival (Attwell and Laughlin, 2001). The basic bioenergetic function of mitochondria is to provide ATP through the mitochondrial respiratory chain for cellular function. The respiratory chain is located in the inner mitochondrial membrane (IMM), which is composed of complex I, II, III, IV and V. Complex I, II, III and IV can transfer electrons to molecular oxygen; at the same time, the protons in the matrix can be pumped into the inter membrane space (IMS) to produce an electrochemical gradient, which drives ATP generation through complex V (also called ATP synthase) (Benard et al., 2007; Dawson and Dawson, 2017; Perier and Vila, 2012). If the respiratory chain is disturbed, the electrons will escape from the respiratory chain, which produces reactive oxygen species (ROS). The main sites for ROS production in mitochondria are mitochondrial complexes I and III, and ROS produced by mitochondria is a primary cause of oxidative stress in cells (Dawson and Dawson, 2017; Guo et al., 2013; Starkov, 2008; Zhou et al., 2008).

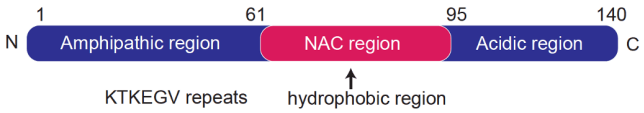

Figure 1 α-Syn assemblies in PD pathology. α-Syn protein can be divided into three different regions. The N-terminal domain contains multiple amino acid repeats with a motif of KTKEGV that are key mediators for α-syn tetramerization. The central NAC (non-Aβ component) region is associated with an increased propensity to form α-syn aggregation. The C-terminal region is involved in post-translational modifications of α-syn, such as phosphorylation at serine 129.

Mitochondrial dysfunction mediates α-syn aggregation

Mitochondrial dysfunction is tightly associated with various neurodegenerative diseases, including Alzheimer's disease (AD), PD, amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD) (Cabral-Costa and Kowaltowski, 2020; Dong et al., 2019b; Johri and Beal, 2012; Lin and Beal, 2006; Zhang et al., 2019a). Contribution of mitochondrial dysfunction to pathogenic α-syn aggregation has been reported in the studies on the role of some environmental toxins in PD pathology. A well-known neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has been widely used as a tool drug for modeling PD symptoms in animal studies (Ghosh et al., 2016; Gu et al., 2017; Panaro et al., 2018; Ren et al., 2018; Wang et al., 2015). MPTP, itself is not toxic, but is lipid-soluble and easy to cross the blood-brain barrier into central nervous system (CNS). It is then taken up by astrocyte and converted into 1-methyl-4-phenylpyridinium (MPP^+). By the dopamine transporter (DAT), MPP^+ selectively enters into DA neurons and inhibits the activity of mitochondrial complex I (Nicklas et al., 1985; Ramsay et al., 1986). MPTP causes the degeneration of DA neurons and induces motor symptoms in animals similar to some pathological features in PD patients. However, in the MPTP PD mouse models, animals lack typical LBs that exist in most PD patients (Alvarez-Fischer et al., 2008; Muñoz-Manchado et al., 2016; Shimoji et al., 2005). Although LBs are absent in MPTP-induced rodent PD models, an administration of MPTP to nonhuman primates can induce LB-like pathology and DA neuronal degeneration in SN, which are similar to the pathological changes in PD patients (Huang et

al., 2018; Li et al., 2020). In epidemiological studies, the pesticides paraquat and rotenone that inhibit mitochondrial respiratory chain induce PD pathological changes in patients (Jackson-Lewis et al., 2012; Nisticò et al., 2011; Tieu, 2011), including α-syn aggregation and LBs formation, which provides direct evidence that mitochondrial dysfunction may lead to α-syn pathology in PD. Most importantly, increasing the vulnerability of DA neurons to oxidative stress by DA oxidation has been commonly recognized as a factor in association with α-syn pathology (Burbulla et al., 2017; Mor et al., 2017; Surmeier et al., 2017; Zhang et al., 2019b). DA oxidative metabolism and large oscillations of Ca^{2+} concentration in DA neurons are closely related to mitochondrial damage, which is responsible for the higher levels of oxidative stress in DA neurons (Burbulla et al., 2017; Goldberg et al., 2012; Guzman et al., 2010; Song and Xie, 2018; Surmeier et al., 2017; Zhang et al., 2019b; Zucca et al., 2017). Oxidative stress caused by the damage of mitochondrial respiratory chain may be involved in the modification of α-syn aggregation. Indeed, α-syn can be directly modified by nitrating agents (oxidative products), which promotes α-syn aggregation (Chavarría and Souza, 2013; Giasson et al., 2000). Moreover, oxidative stress caused by mitochondrial dysfunction can induce DNA damage (Tapias et al., 2017), which subsequently induces poly(adenosine 5′-diphosphate-ribose) (PAR) polymerase-1 (PARP-1) activation (Dawson and Dawson, 2017). PAR, a product generated by PARP-1, accelerates α-syn fibrillization *in vitro* and *in vivo* (Kam et al., 2018). PAR modified α-syn species increase the neurotoxicity to DA neurons (Kam et al., 2018). Interestingly, PAR levels are increased in the cerebrospinal fluid in PD patients (Kam et al., 2018). In addition, an increase of oxidized DA is presented in PD (*DJ-1* mutant) induced pluripotent stem cell (iPSC)-derived DA neurons, and a chronic feeding of levodopa increases α-syn accumulation in *DJ-1* knockout mice (Burbulla et al., 2017). The mitochondrial antioxidants can significantly decrease DA oxidation and α-syn accumulation in homozygous *DJ-1* mutant neurons (Burbulla et al., 2017). These data suggest that the oxidative stress from mitochondrial dysfunction is associated with DA oxidation and α-syn accumulation (Figure 2).

α-Syn aggregation causes mitochondrial dysfunction

It is well documented that α-syn aggregation also triggers mitochondrial dysfunction, evidenced by many observations that the accumulation of α-syn is presented within mitochondria, and disturbs the function of mitochondrial respiration and dynamics (Di Maio et al., 2016; Luth et al., 2014; Martin et al., 2006; Reeve et al., 2015; Tapias et al., 2017). Recently, it was reported that α-syn oligomers interact with the mitochondrial ATP synthase and induce ROS production, which induces neuronal death by opening the permeability transition pore (PTP) in primary mouse cells (Ludtmann et al., 2018). This interaction also occurs in iPSC-derived cortical neurons from a PD patient with a triplication of *SNCA* (Ludtmann et al., 2018). Interestingly, the different pathogenic α-syn species, including oligomeric, dopamine-modified and S129E phosphomimetic α-syn, damage mitochondria by interaction with TOM20 (TOM, the translocase of outer mitochondrial membrane) to impair mitochondrial protein import, which leads to a decrease of mitochondrial respiration and an induction of oxidative stress in cells (Di Maio et al., 2016). In addition, aggregated α-syn interferes with the function of key elements involved in maintaining mitochondrial dynamics such as Miro, Opa1 and Drp1, leading to abnormalities of the mitochondrial dynamics (Ordonez et al., 2018; Shaltouki et al., 2018; Tapias et al., 2017). Thus, mitochondrial dysfunction and α-syn aggregation are mutually dependent and interactive, which contribute to PD pathogenesis (Figure 2).

Lysosomal dysfunction and α-syn aggregation

Lysosomes are single membrane-bound organelles containing about 60 different hydrolases (such as nucleases, proteases, phosphatases, lipases and others), which are responsible for degradation of cell components and macromolecules (Ballabio and Bonifacino, 2020; Perera and Zoncu, 2016). Some products from substrate degradation can be transported out of lysosomes for recycling in cells. Lysosome maturation involves the fusion of transport vesicles formed by budding from the membrane of the trans-Golgi network, with membrane vesicles derived from endocytosis (phagocytosis) or autophagy (di Ronza et al., 2018; Perera and Zoncu, 2016). Lysosomal hydrolases are active at an acidic internal pH, which is maintained through the activity of a vacuolar-type proton adenosine triphosphatase (v-ATPase) (Saftig and Klumperman, 2009). Lysosomes play important roles in maintaining cellular homeostasis by removing damaged components, recycling degraded products and transporting nutrients in cells (Ballabio and Bonifacino, 2020). Lysosomal dysfunction leads to accumulations of dysfunctional organelles and undegraded substrates in cells, contributing to the occurrence of diseases (Ballabio and Bonifacino, 2020).

Lysosomal dysfunction mediates α-syn aggregation

Many of the PD-associated genes, including *SNCA*, *LRKK2*, *GBA1* and *ATP13A2*, have been reported to be associated with the regulation of lysosome and autophagy functions (Corti et al., 2011). Most recently, several of new PD candidate risk genes from GWASs are also enriched in lysosomal and autophagic functions, indicating that lysosome

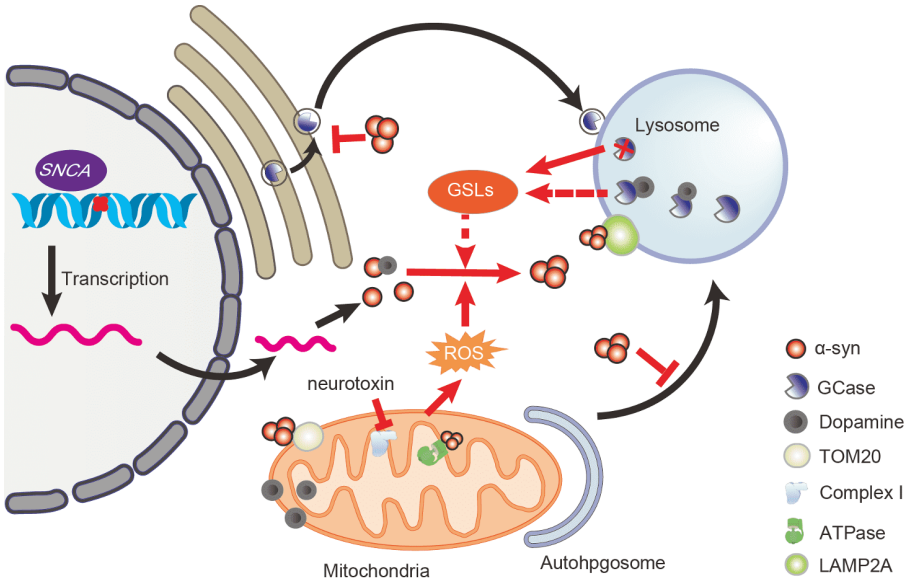

Figure 2 Schematic representation of the interactions between α-syn aggregation and mitochondrial and lysosomal dysfunction. Mitochondrial and lysosomal dysfunctions accelerate the production of ROS and the accumulation of GSLs, which promotes α-syn aggregation. Moreover, α-syn aggregates also disturb mitochondrial and lysosomal dysfunction, and contribute to PD pathology.

dysfunction may be involved in the pathogenies of PD (Blauwendraat et al., 2019; Chang et al., 2017; Pihlstrom et al., 2017). Lysosomal dysfunction is typically presented in lysosomal storage diseases (LSDs), a heterogeneous group of inherited lysosomal disorders (Marques and Saftig, 2019; Parenti et al., 2015; Platt et al., 2018). Gaucher disease (GD), one of LSDs, has been characterized by the accumulation of glycosphingolipids (GSLs), including glucosylceramide (GlcCer), glucosylsphingosine (GlcSph), sphingosine (Sph) and sphingosine-1-phosphate (S1P), within lysosomes due to the mutation in *GBA1* that encodes the glucocerebrosidase (GCase) (Mistry et al., 2014; Platt, 2018). Mutations in *GBA1* gene increase the risk for developing PD and dementia with Lewy bodies (DBL) (Mazzulli et al., 2011; Sidransky, 2005). Lines of evidence indicate that the accumulation of GSLs caused by *GBA1* mutation can stabilize intermediate α-syn oligomers, and promote pathological α-syn aggregation (Mazzulli et al., 2011; Murphy et al., 2014; Smith et al., 2014; Taguchi et al., 2017). For example, the GlcCer accumulation by depletion of GCase results in the formation of soluble and insoluble toxic α-syn species in cellular models, similar to the changes observed in GD mice and GD patients (Mazzulli et al., 2011). On the other hand, an increase of α-syn in cell lines or primary mouse neurons, in turn, inhibits the activity of GCase and damages lysosomes by disturbing lysosomal maturation (Mazzulli et al., 2011). Subsequent studies in human iPSC-derived midbrain DA neurons showed that the increase of GSLs will break down the structure of physiological α-syn conformers and induce pathological α-syn aggregates (Kim et al., 2018; Zunke et al., 2018). The fact is that destruction of physiological α-syn conformers might increase α-syn monomers that contribute to pathogenic α-syn aggregation. Furthermore, the deficiency of GCase activity and lysosomal dysfunction due to DA oxidation have been further confirmed in iPSC-derived neurons from patients with idiopathic and familial PD (Burbulla et al., 2017). In addition, α-syn aggregation is tightly associated with autophagy dysfunction. α-Syn monomers are degraded by CMA (chaperone-mediated autophagy) pathway, but aggregated α-syn is degraded via the macro-autophagy pathway (Cuervo et al., 2004). PD-associated genes *LRKK2* and *TMEM175* are involved in the autophagosome-lysosome pathway, which further regulates the degradation of aggregated α-syn (Cang et al., 2015; Giaime et al., 2017; Tong et al., 2012; Wallings et al., 2019). Therefore, the dysfunction of autophagy contributes to α-syn aggregation (Figure 2).

α-Syn aggregation causes the dysfunction of autophagy and lysosome

It has been reported that the aggregated α-syn can impair the autophagy-lysosomal pathway (Tanik et al., 2013). As a result of DA oxidation, DA-modified α-syn is prone to form oligomers that inhibit the activity of the CMA (Martinez-Vicente et al., 2008). In addition, the pathogenic A30P and A53T α-syn can block the lysosomal uptake and degradation of CMA substrates (including mutant α-syn) through the inactivation of lysosomal receptor LAMP2A, which in turn induce a further accumulation of pathogenic α-syn species (Cuervo et al., 2004). In addition, α-syn aggregates also impair macro-autophagy pathway due to a decrease of au-

tophagosome clearance, although the formation of autophagosome keeps normal (Tanik et al., 2013), which suggests a failure of the fusion between autophagosome and lysosome. Importantly, the impairment of autophagy and the accumulation of autophagosome, along with the occurrence of α-syn aggregation, are commonly presented in multiple PD models (Giaime et al., 2017; Schöndorf et al., 2014). In iPSC-derived midbrain DA neurons, α-syn aggregates induce defective ER-to-Golgi trafficking of hydrolase, which contributes to a reduced activity of lysosomal hydrolases, such as GCase, β-galactosidase (β-gal), cathepsin B and hexosaminidase (Mazzulli et al., 2016). Therefore, it is conceivable that there are bilateral effects between lysosomal dysfunction and α-syn aggregation, which play a crucial role in the PD pathogenies (Figure 2).

Although the mitochondrial damage, lysosomal damage, as well as α-syn aggregation play roles in PD pathogenesis, and they interact with each other, it is still unclear which factor initiates the pathological changes in PD, and how serial reactions occur and ultimately lead to irreversible neuronal dysfunction.

α-Syn transmission in PD

In addition to mitochondrial and lysosomal dysfunction, the accumulation of α-syn aggregates is driven as a result of cell-to-cell spreading of pathogenic α-syn species between neurons. In the past two decades, many neurodegenerative diseases-relevant proteins such as amyloid-β (amyloid plaques in AD), α-syn (LBs in PD and LDB), TAR DNA-binding protein-43 (inclusions in ALS) and huntingtin (nuclear inclusions in HD) have been reported to be transmitted between neurons and/or glia by a prion-like manner (Jucker and Walker, 2013; Ren et al., 2009). Prions are proteinaceous infectious particles, they are composed of misfolded prion proteins (PrP) produced by forcing cellular native prion proteins (PrP-cellular, PrP^{C}) into misfolded prion proteins (PrP-scrapie, or PrP^{Sc}) by their prion domain. The prion domain enriched for glutamine or asparagine in the amino acid sequences can exist in a natively unfold conformation or a misfolding cross-β conformation (Jucker and Walker, 2013; King et al., 2012). Prions will induce aggregates, fragment to new seeds and propagate in the CNS, leading to progressive neuronal death of the affected individual and eventually dysfunction of the nervous system (Aguzzi and Calella, 2009; Caughey et al., 2009; Soto and Pritzkow, 2018). A growing body of evidence has uncovered the prion-like properties of neurodegenerative diseases-relevant proteins, these proteins spread the pathogenic forms in brains, which is responsible for the pathogenesis of diseases (Soto and Pritzkow, 2018; Walker and Jucker, 2015). These pathogenic proteins have been shown to contain an aggregation-prone domain in their amino acid sequences (King et al., 2012; Weinreb et al., 1996). Under some conditions, the changes of this domain make these proteins prone to misfolding (Jucker and Walker, 2013; Jucker and Walker, 2018; King et al., 2012). Like prions, these misfolded proteins will generate amyloid conformation through a polymerized process, in which native monomers are converted into misfolded oligomeric intermediates and eventually fibrillar aggregates (β-sheet-rich structures) (Jucker and Walker, 2013). The mature fibrils can be fragmented to form short profibrils that serve as seeds to further propagate fibrillar aggregates, which contributes to the spread of neuropathological lesions in brains (Goedert, 2015; Soto and Pritzkow, 2018; Walker and Jucker, 2015). It has been reported that NAC domain of α-syn is essential for the formation of pathologic α-syn aggregates (Weinreb et al., 1996). Similar to prion domain, NAC sequences can switch between a natively unfolded state and misfolded form due to their hydrophobic properties (Weinreb et al., 1996). However, analysis of amino acid sequence of NAC domain does not reveal that it was rich in glutamine or asparagine like prion domain, and even the proportion of its hydrophobic residues to total residues is normal (Weinreb et al., 1996). Currently, it is still unclear by which mechanism the sequence of NAC domain determines its hydrophobic properties.

It is well accepted that in the CNS, the α-syn pathology is developed from lower brain stem to SN, and further to the thalamus and prefrontal association field (Braak et al., 2003). Most interestingly, the transmission of α-syn pathology can undergo the same way, even from peripheral to the CNS (Braak et al., 2003). First evidence that α-syn might have the prion-like properties to propagate in neurons comes from the observation that the embryonic mesencephalic neurons grafted into the brain of PD patients develop LBs over a decade after transplant surgery (Kordower et al., 2008; Li et al., 2008). Later, clear experimental evidence shows that transmission of α-syn aggregates can occur from host to grafted neurons both *in vitro* and *in vivo* (Desplats et al., 2009). Moreover, exogenous introduction of α-syn preformed-fibrils (PFFs) into cultured cells induces intracellular LB pathology by the recruitment of endogenous α-syn (Luk et al., 2009), and causes cell death of primary mouse neurons (Volpicelli-Daley et al., 2011). Furthermore, an intracerebral injection of α-syn fibrils induces aggregation of endogenous α-syn and transmission of LB pathology among anatomically interconnected brain regions (Luk et al., 2012; Peelaerts et al., 2018; Rey et al., 2016) (Figure 3). In addition to intracerebral inoculation, a peripheral administration of α-syn fibrils also causes pathogenic α-syn propagation that is able to spread to the brain (Kim et al., 2019; Peelaerts et al., 2015; Ulusoy et al., 2013). It has been shown that α-syn fibrils can cross the blood-brain barrier and distribute to brain regions intravenously (Peelaerts et al., 2015). The injection of α-syn

PFFs in gastrointestinal tract induces a gut-to-brain transmission of pathologic α-syn via the vagus nerve, which also provides direct evidence that the transmission of α-syn pathology depends on the recruitment of endogenous α-syn to seed aggregation *in vivo* (Kim et al., 2019). These results indicate that the pathogenic α-syn aggregates in PD patients are not necessarily initiated in the brain but might come from the periphery.

The transmission of α-syn involves secretion in cells and the uptake of neighboring cells. The mechanisms of α-syn secretion in cells may be associated with multiple pathways (Abounit et al., 2016; Ejlerskov et al., 2013; Emmanouilidou et al., 2010; Lee et al., 2005). Some studies have reported that α-syn located in some vesicles is prone to aggregation or secretion to extracellular space (Jang et al., 2010; Lee et al., 2005). Those vesicles containing α-syn have exosome properties (Danzer et al., 2012; Emmanouilidou et al., 2010), therefore it is possible that exosome release is involved in α-syn secretion and transmission. Moreover, those exosomes containing pathological α-syn aggregates have been identified in the cerebrospinal fluid of PD patients (Stuendl et al., 2016). The dysfunction of mitochondria caused by rotenone may accelerate the secretion process (Lee et al., 2005). Lysosomal disorders induced by the vacuolar H^+ ATPase inhibitor bafilomycin A1 or GBA1 deficiency can also increase the release and transmission of α-syn (Alvarez-Erviti et al., 2011; Bae et al., 2014). Thus, these data provide robust evidence that the increase of α-syn secretion caused by lysosomal dysfunction plays a role in α-syn transmission. After secretion, extracellular α-syn aggregates might be internalized by surrounding cells through clathrin-dependent endocytosis (Lee et al., 2008; Oh et al., 2016). Indeed, clathrin-dependent endocytosis has been shown to mediate the uptake of other neurodegenerative diseases-relevant proteins, including amyloid-β in AD (Domínguez-Prieto et al., 2018) and dipeptide repeat protein in ALS (Wang et al., 2019). Recently, several receptors have been identified to be involved in α-syn endocytosis, which demonstrates the internalization of α-syn aggregates through different receptors in multiple cell types (Choi et al., 2018; Holmes et al., 2013; Lee et al., 2008; Mao et al., 2016; Panicker et al., 2019). Three receptors, including heparan sulfate proteoglycans (HSPGs), FcγRIIB and LAG3, are able to mediate the α-syn fibril endocytosis into neurons (Choi et al., 2018; Holmes et al., 2013; Mao et al., 2016), suggesting that extracellular α-syn can enter the neighboring neurons through different receptors on neurons. However, it is still an open question whether a blockage of a single receptor can completely inhibit the uptake of α-syn aggregates into neurons.

Interestingly, the surrounding glia can uptake α-syn aggregates (Loria et al., 2017; Panicker et al., 2019). Glial membrane receptor proteins CD36 and TLR2 have been recently identified to be involved in glial uptake of α-syn aggregates (Panicker et al., 2019). However, it is still unclear whether glia phagocytosis of α-syn benefits neurons through the clearance of α-syn aggregates or contributes to the dysfunction of glia, which in turn triggers neuroinflammation or increases the spreading of α-syn to other regions (Loria et al., 2017; Panicker et al., 2019; Tremblay et al., 2019). Further studies are needed to explore the effects of glial phagocytosis of α-syn aggregates on PD pathology (Figure 3).

Overall, the cell-to-cell transmission of pathogenic α-syn may be a complex process that involves multiple cell types and different mechanisms, which is regulated by multiple factors. In addition to transmission of α-syn by the manner of secretion-uptake, the transfer of pathological α-syn can also occur through tunneling nanotubes (TNTs) between neurons or neuron-glia (Abounit et al., 2016). Interestingly, oxidative stress caused by α-syn aggregates may increase in the number of TNTs, which further contributes to α-syn transmission (Abounit et al., 2016). Moreover, trans-synaptic transmission of α-syn aggregates may occur due to anato-

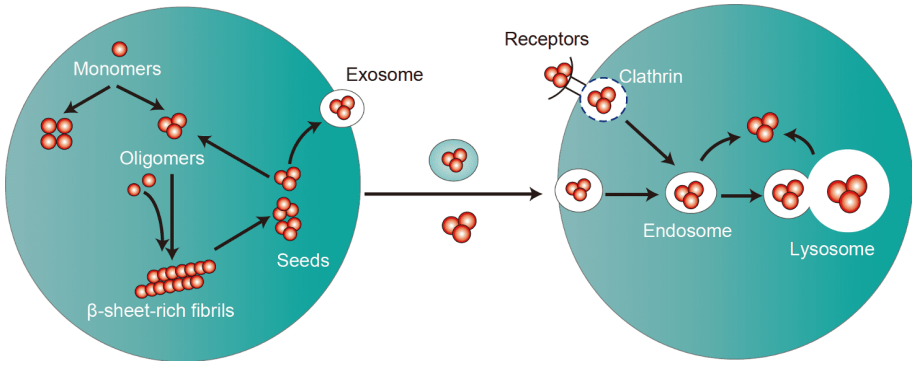

Figure 3 Under physiological conditions, α-synuclein can exist as both stable monomers and folded tetramers; however, under pathological conditions, α-syn monomers are converted into misfolded oligomeric intermediates and eventually fibrils (β-sheet-rich structures) by recruitment of endogenous α-syn. Moreover, the mature fibrils can be fragmented to seeds to propagate this process, which contributes to the spread of neuropathological lesions in brains. α-Syn aggregates can be secreted to the extracellular space by exosome, while extracellular α-syn aggregates can enter adjacent cells through receptor-mediated endocytosis. Once entering the cells, α-syn aggregates reach lysosomes through endosomes and are degraded by lysosomes. The undegraded α-syn aggregates and aggregates escaped from endosomes in turn form new seeds for propagation.

mical connections of the synapses within neuron, which also occurs in tau transmission (Henderson et al., 2019a; Yamada et al., 2014).

Conclusion

In the past two decades, there has been dramatic progress on researches of LBs in PD pathology. It has been widely recognized that LBs mainly consist of aggregated α-syn assemblies, which reflects the progression of pathology in association with PD symptoms in LB-positive patients. Therefore, exploring the mechanisms of α-syn aggregation and cell damage caused by aggregated α-syn is important for the development of therapeutic approaches that target pathogenic α-syn. The current researches on the PD-related genes provide a clear clue that mitochondrial and lysosomal dysfunctions, as well as α-syn aggregation, play a central role in PD pathogenesis. The dysfunctions of mitochondria and lysosome may facilitate the α-syn transmission. Increasing evidence from the animal models indicates that the aggregation of α-syn can initially occur in different regions even in periphery. The aggregated α-syn further spreads to vulnerable neurons and contributes to LB pathology spreading. Further studies on the mechanisms of α-syn transmission will provide a perspective for understanding pathogenesis of PD and exploring treatment strategies for diseases.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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