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Review

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Revisiting the advance of age-dependent α-synuclein propagation and aggregation

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Abstract

Aging is a major risk factor for different neurodegenerative diseases (NDDs), including Parkinson's disease (PD). In PD, one of the key neuropathological features is cytoplasmic protein aggregation, named Lewy bodies (LBs) in the cell body, and Lewy neurites (LNs) in neuronal processes and terminals. The protein α-synuclein (α-syn) has been found to be a major component of LBs and LNs, and is considered to play a central role in their formation. α-Syn also increases in healthy aging and in different disease conditions. Evidence has shown that aging promotes α-syn pathological aggregation and propagation and, therefore, may induce and aggravate PD pathogenesis. Here, we aim to highlight recent advances in age-related α-syn aggregation and prion-like propagation and discuss the subsequent consequences to neuronal functions.

Keywords: Parkinson's disease, synucleinopathy, alpha-synuclein, aging, protein aggregation, propagation

INTRODUCTION

Aging is a major risk factor for neurodegenerative diseases (NDDs)[1]. As the aging population grows, the number of patients with NDDs is increasing, creating a rising financial burden on families and society,

making effective prevention and treatment urgently necessary[2]. Parkinson's disease (PD) is a common age-related NDD after Alzheimer's disease (AD), with typical motor symptoms, such as resting tremor, bradykinesia, and rigidity, and various non-motor symptoms, including sleep disorders, constipation, depression, autonomic dysfunction, *etc.*[3]. PD exhibits two major neuropathological characteristics: dopaminergic neuron loss in the substantia nigra pars compacta (SNpc) of the midbrain and the formation of Lewy bodies (LBs) and Lewy neurites (LNs)[4]. The primary protein component in the LBs and LNs is misfolded and aggregated α-synuclein (α-syn)[5,6]. Under physiological conditions, α-syn is widely present in different brain regions and the spinal cord, largely enriched in the presynaptic compartment, and is also present in the nucleus of neurons[7-9]. α-Syn also appears in the peripheral nervous system and is even abundant in different peripheral tissues, such as erythrocytes in the blood[10]. In neurons, α-syn is mainly defused in the cytosol, while a small fraction of the protein correlates with various subcellular organelles, such as synaptic vesicles[11-13], mitochondria[14], lysosomes[15,16], and microtubule[17,18]. Available evidence shows that α-syn may possess various physiological functions. α-Syn is involved in neurotransmission. It maintains the stability of the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex and plays a role in endocytosis[11], and preserves mitochondrial fusion and function[14]. As the key protein component in the LBs and LNs, α-syn stays as monomers in the physiological state, while it undergoes processes of protein aggregation in response to various pathologic stimuli, such as iron deposition and microgliosis[19,20]. Emerging evidence has shown that α-syn accumulation and aggregation are toxic in transgenic animal models that overexpress wild-type or mutant α-syn[21-23]. Here, we will address age-dependent alterations of α-syn in neurons, particularly from increased protein accumulation to pathological aggregation and propagation. At the end, we will briefly highlight how the aging factor affects these processes in PD and different synucleinopathies as a whole.

α-SYN IN DEVELOPMENT AND HEALTHY AGING

α-Syn starts to be present in different neurons during the early neural development in humans. The protein is expressed in the neurons of the SN as early as 15 weeks of gestation; it first appears in the perikarya of neurons and subsequently extends to neuronal processes by 18 weeks of gestation[24]. In other brain regions, the perikaryal presence of α-syn is observed in the cortical plate at 11 weeks of gestation, in the hippocampus and brain stem by 20 weeks of gestation, and in the cerebellum by 21 weeks of gestation[25]. In different types of neurons in humans, α-syn undergoes changes of distribution-redistribution during the development and postnatal stages. Perikaryal α-syn gradually disappears from the neuronal somata in early childhood, relocates to the neuronal processes, and is finally enriched in the presynaptic compartment in adulthood[25,26]. Similar appearances of α-syn in neurons can be observed in other animal species[9,27].

Chu and Kordower reported that α-syn increased in dopaminergic neuronal somata in the SN in humans and monkeys in an age-dependent manner[28]. Human subjects, aged 18 to 102 years, and rhesus monkeys, ranging from 2 to 34 years old, showed a dramatic increase in α-syn accumulation in the cell bodies of dopaminergic neurons with age. The increased α-syn appeared in a soluble and nonaggregated state, in which α-syn can virtually be dissolved with proteinase K treatment, highly contrasting to the insoluble α-syn aggregates in the tissues of the PD patients. The concomitant correlation between increased α-syn and decreased tyrosine hydroxylase (TH) in dopaminergic neurons, suggests that this age-related increase in α-syn may serve as the precursor to α-syn inclusions during the initiation stage of PD pathology[28]. Furthermore, similar findings were also observed in Microcebus murinus lemurs and cynomolgus monkeys; the level of oligomeric and phosphorylated α-syn increases in both the central nervous system and the enteric nervous system with age[29,30]. These results indicate that even soluble α-syn, when the protein level increases to a certain threshold, can negatively impact the function of dopaminergic neurons and, at the same time, may lead the cells into a scenario of initiating pathological protein aggregation. The mechanisms

underlying neurotoxicity induced by soluble α-syn include the following: (i) TH is a rate-limiting enzyme responsible for producing dopamine via the conversion of L-tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA). TH is negatively regulated by increased concentration of α-syn[31]. It has been reported that α-syn decreases TH activity by reducing its phosphorylation and subsequent activation[32]; (ii) L-aromatic amino acid decarboxylase (AADC) is also involved in the final step of dopamine synthesis[33]. Increased α-syn interacts with AADC to reduce its activity, thereby inhibiting dopamine synthesis[33]; (iii) Vesicular monoamine transporter 2 (VMAT2) facilitates the uptake of dopamine from the cytoplasm into synaptic vesicles[34]. The dopamine transporter (DAT) transports extracellular dopamine from the synaptic cleft back into the cytoplasm[35]. Increased α-syn disrupts the activity and function of both VMAT2 and DAT, thereby inhibiting dopamine levels in the synaptic terminal[36,37]; (iv) Age-related lysosomal dysfunction may also impair the clearance of increased α-syn, subsequently leading to misfolded α-syn, forming inclusions, which eventually causes the loss of the dopaminergic neuron[38].

INCREASED α-SYN ACCUMULATION AND AGGREGATION DURING AGING

Emerging evidence shows a dynamic chain of events involving increased α-syn level (i.e., accumulation) - pathological aggregation - cell-to-cell propagation, all of which are dose-dependent processes[39,40].

Aging of intrastriatal transplanted neurons: the lesson learned from the neural transplantation in PD clinical trials

As mentioned above, during the development of neurons, α-syn is first localized to the nucleus and the soma of the immature neuron, and then becomes concentrated in the presynaptic terminals as synapses are being formed[41,42]. Moreover, the expression level of α-syn increases in both neuronal somata and terminal regions with age[28,43]. However, pathological forms of α-syn, such as aggregated, proteinase K-resistant α-syn, appeared earlier in the presynapses than in the cell body[44,45]. A similar phenomenon appeared in the dopaminergic neurons transplanted into the striatum of PD patients. Since the 1980s, fetal nigral transplantation has been reported in several multi-centered, open-labeled trials and two double-blinded trials (for a review, see[46]). Clinical benefits were variable, largely related to the differences in transplantation procedures used, donor cell preparation (gestational stage, cell storage approaches, *etc.*), selection of patients, *etc.* All of these can affect the extent of graft survival, innervation, and local circuit re-establishment, eventually impacting the benefits the patients may acquire[47].

Neural transplantation with fetal dopaminergic neurons provides a unique system to address the issues of how α-syn accumulation and aggregation occur in the grafted cells. The to-be-grafted (donor) cells are usually aged from 6 to 9 weeks post-conception when transplanted into the putamen or/and caudate nucleus of the PD patient brain[48]. Observations have revealed α-syn presence and even α-syn-positive LB-like inclusions in the transplanted cells analogous to those seen in PD patients (See review[47]). Kordower *et al.* also showed clear age-dependent α-syn accumulation and LB/LN formation in the transplanted cells[49-51]. Increased amounts of α-syn appeared in the grafts with age extended from 1.5 to 25 years, accompanied by the forming of typical LBs and LNs in subsets of the grafted cells, and clear functional impacts occurred to the cells. Key dopaminergic neuronal marker proteins or enzymes, such as TH, DAT, and VMAT2, concomitantly declined in the transplanted cells in the 10-year-old grafts and beyond, indicating the functional deterioration of grafted cells over time before cell death occurs[39,40,49,52,53]. On the other hand, age-dependent effects on α-syn spreading may also be attributed to the recipients, i.e., the patients who receive neural transplantation. It is known that after the onset of the disease, PD patients will gradually experience worsening clinical symptoms and neuropathological changes. α-Syn propagation and aggregation are largely dose-dependent. Studies have shown that the difference in the age of the recipients may affect the aggregation of grafted cells, as the loads of aggregated α-syn in the host brains build up over time[40,47,52,54].

Therefore, age has been an important factor in selecting patients who are suitable for neural transplantation[55]. Furthermore, dramatic neuroinflammatory profiles, represented by infiltration of peripheral leukocytes, activated microglia, and astrogliosis, were observed in and around all the grafts[39,53,56]. Nevertheless, PD patients who received transplantation still had substantial clinical improvement, with significant motor improvement, reductions in Unified Parkinson's Disease Rating Scale (UPDRS) motor scores of up to 50%-60%, and recovery of striatal dopaminergic function, particularly in the first decade after transplantation[39,46,57].

When closely exploring the grafted cells in relation to the host Lewy pathology around the grafts, a considerable number of LBs and LNs are found in the close vicinity of the grafts[39,52]. Therefore, we hypothesized that the Lewy pathology, i.e., aggregated α-syn, in the host brain may actively spread from the surroundings to the grafted cells via a "prion-like" mechanism[40,58] and induce high levels of α-syn accumulation in the grafted cells (recipient cells), developing LBs and LNs in the end. This hypothesis has been proven true in a series of follow-up studies in models of PD[59,60] and other NDDs[61-64].

Age-dependent α-syn accumulation and aggregations in animal models

α-Syn aggregation and propagation are a dose-dependent dynamic process, with the level of the protein highly associated with age, as discussed above. The higher the amounts of α-syn are, the more severely the protein aggregation occurs and the more efficiently it spreads to recipient neurons, which form synapses with the donor neurons[39]. On the contrary, the decrease in α-syn level inhibits protein aggregation and neuronal death[65]. Various genetically engineered animal models have been generated in rodents and nonhuman primates[66-68]. The occurrence of PD-like phenotypes in the numerous α-syn-overexpressing mice is broadly correlated with transgene expression. Mouse models have certain limitations. They cannot mimic all the pathological and clinical features of PD patients[22,69-74]. However, nonhuman primates are physiologically, genetically, and morphologically closer to humans than rodents. They are more sophisticated behaviorally and exhibit a brain organization similar to humans, enabling a more accurate assessment of the impact of the pathology on motor outcomes and neuroimaging procedures[75,76].

α-Syn-overexpressing mouse models express either human wild-type α-syn or α-syn with a point mutation, under the control of different expression promoters and exhibit age-dependent α-syn accumulation and aggregation, behavioral deficits, and neuronal dysfunction or neuronal cell death[77-95] [Table 1]. The most commonly used models are made in rodents. Although the transgene may be expressed under different promoters, which drive the transgene expression in distinct brain regions or types of cells, they provide valuable models to study age-associated changes in α-syn accumulation and even aggregation. Among different models, Masliah *et al.* generated a commonly used mouse line in the field[21]. The mice express wild-type human α-syn under the regulatory control of platelet-derived growth factor-β (PDGF-β) promoter. Notably, in line D, the mice develop age-dependent α-syn accumulation and intranuclear and cytoplasmic inclusions in different brain regions, accompanied by dopaminergic terminal loss in the striatum and motor deficits[21]. Another commonly used transgenic mouse line expresses human α-syn with A53T mutation under the control of prion protein (PrP) promoter[96,97]. The mice also develop age-dependent α-syn aggregation, phosphorylation, and behavioral deficits. We generated a transgenic mouse line, expressing wild-type human α-syn under the control of endogenous α-syn promoter; the α-syn is fused with green fluorescent protein (GFP), which provides a possibility to be used for *in vivo* optical imaging[98]. This mouse line also exhibits increased α-syn accumulation, aggregation, and phosphorylation in different brain regions with age, together with impaired dopaminergic neurotransmission and motor deficits, but without significant dopaminergic neuron loss[98]. In addition, the mice also developed age-dependent pathology in the microvasculature[99] and the enteric neurons in the gastrointestinal tract[100,101]. Taken together, different lines of genetically modified mice expressing wild-type or mutant α-syn share some

Table 1. Rodent models overexpressing human α-syn and age-dependent phenotypic development

Transgenes	Promoter	Onset of α-syn pathology	α-Syn pathology	EM features	Brain regions with α-syn aggregates	Neuro-inflammation/mitochondria dysfunction/autophagic impairment	Neuronal dysfunction and cell death	Behavioral alterations	Ref.
WT α-syn (human)	BAC-α-syn (GFP)	2 mo	Phospho-α-syn and α-syn aggregates	N.A.	SNpc; VTA; hippocampus; olfactory bulb; neocortex; thalamus; cerebellum; spinal cord; medulla; oblongata; pons	N.A.	α-Syn-positive SN aggregates, but no dopaminergic neuron loss; altered dopamine release and reuptake	Reductions in amphetamine-induced locomotor activity in the open field; impaired rotarod performance; impaired odor discrimination (7 mo)	[98]
	mPrP	14 mo in homozygous; 24 mo in hemizygous	Increased α-syn levels, but no inclusions	N.A.	Spinal cord; cerebellum; cortex	No	No	No neurological phenotype	[77, 96]
	mThy-1	1 mo	Cytoplasmic accumulation and detergent-insolubility of transgenic human α -syn; swollen α-syn-positive neurites; no compact LBs	N.A.	Telencephalic; brainstem	N.A.	No cell death; but moderate striatal DA loss	N.A.	[78]
		N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	Weight loss; impaired motor performance; coordination; impaired spontaneous activity; sensorimotor deficits; fine motor skill deficits (start from 2 mo)	[79]
	Rat TH	2-3 mo	Diffuse synuclein in TH+ SN neurons; no inclusion bodies	N.A.	Striatum; SN; VTA; locus coeruleus; dorsal striatum; nucleus accumbens; olfactory tubercle; cerebral cortex	N.A.	Increased striatal DAT levels; unremarkable dopaminergic axons and terminals	No neurological abnormalities	[80]
	Human PDGF-β	3 mo	α-Syn-positive inclusions (nuclear and cytoplasmic) and neurites (ubiquitin+)	EM dense deposits in ER; no fibrillar structures	Neocortex; hippocampus; olfactory bulb; substantia nigra	N.A.	No dopaminergic neurons within the substantia nigra; lower striatal levels of TH and TH enzymatic activity (12 mo)	Reduced rotarod performance (12 mo)	[27]
			Phosphorylated-Ser129-α-syn accumulation	Abundant filaments	N.A.	N.A.	N.A.	N.A.	[81]
A53T α-syn	mPrP	7 mo in	Intracytoplasmic	α-Syn inclusions	Spinal cord;	Astrogliosis; muscle atrophy	No cell death	Neglect of grooming; weight	[96]

		homozygous; 22-28 mo in hemizygous	neuronal α-syn inclusions (ubiquitin+); dystrophic neurites; phosphorylated neurofilaments	contained 10-16 nm wide fibrils; axonal degeneration (thioflavin S+) (silvering staining+)	brainstem; cortex; cerebellum; thalamus; striatum; raphe nuclei; pons; locus coeruleus			loss; reduced ambulation; impaired resistance to passive movement; partial paralysis of limbs; accompanied by periods (several seconds) of freezing of a hindlimb; hunched backs; tremulous motion (8-16 mo in homozygous/22-28 mo in hemizygous)	
		N.A.	Intracytoplasmic neuronal α-syn inclusions (ubiquitin+); phosphorylated neurofilaments	Inclusions not like the compact; spherical morphology of LBs; but contain fibrillar inclusions (thioflavin-S+)	Midbrain; cerebellum; brainstem; spinal cord	Astrogliosis in dorsal midbrain, deep cerebellar nuclei, brainstem, and spinal cord	N.A.	Sustained posturing; reduced amplitude; abundance of spontaneous activity; bradykinesia; mild ataxia; dystonia; loss of righting reflex and paralysis; then rapidly progressed to death (9; 11.5;13 mo)	[77]
	mThy-1	4 mo	Diffuse perikaryal α-syn; Lewy-like pathology with ubiquitin immunoreactivity	Dendrites containing electron-dense finely structured granular material; axonal degeneration	Telencephalon; brainstem; spinal cord	Astrogliosis and microgliosis; neurogenic muscular atrophy; neuromuscular denervation in brain stem and motor neurons	No transgene expression in SN	Impaired rotarod performance (5 weeks)	[82]
			Increased Ser129 α-syn phosphorylation						[83]
	Rat TH	2 mo	LB-like α-syn inclusions in TH+ SN neurons; increased Ser129 α-syn phosphorylation	N.A.	SNpc; VTA; striatum; olfactory bulb; nucleus accumbens	N.A.	No dopaminergic neurons loss up to 1 year	No neurological abnormalities	[84]
	CaM-tTA	N.A.	α-Syn aggregates not fibrillar or insoluble (ubiquitin-)	No fibrillary inclusions; nerve fibers filled with electron-dense organelles and condensed mitochondria; lipid droplets	Olfactory bulb; cortex; striatum; hippocampus; thalamus; substantia nigra; brainstem	Reduced neurogenesis and neurodegeneration	Dopaminergic neurons loss; decreased DA transporter binding sites and pre-synaptic terminals; hippocampal neurodegeneration	Cognitive impairment in Morris water maze test (13 mo); impaired rotarod performance and motor learning (4.5 mo)	[85]
A30P α-syn	mPrP	N.A.	Somata accumulation of α-syn (ubiquitin-)	N.A.	Cerebellar nuclei; brainstem; cortex	No	Low level neurodegeneration in brainstem and spinal cord with motor neuron loss; no change in TH or DAT levels; no change in striatal DA levels	No neurological abnormalities	[77]

	mThy-1	12 mo in homozygous; 24 mo in heterozygous	Hyperphospho- and proteinase K-resistant α-syn LB-like inclusions	Electron-dense inclusions contain 9-12 nm wide filaments that were occasionally ubiquitinated (silver staining+) (thioflavin S+)	Zona incerta; the superior colliculus; deep mesencephalic reticular field; pontine and medullary reticular formation; cerebellar nuclei; cortex; brainstem; spinal cord; no striatum and the SN	Oxidized and nitrated α-syn; astrogliosis	Sensorimotor neuronal loss in brainstem and spinal cord; normal DA and metabolite levels	Unsteady gait; weakening extremities; abnormal tail posture and tail movements; hunch-back posture and spastic paralysis at late-stage (8-12 mo)	[86]
		12-13 mo	Insoluble ubiquitin aggregates; altered levels of proteasome subunits	N.A.	Spinal cord	Astrogliosis and microgliosis; activated ubiquitin/proteasome system	Motor neurons loss in spinal cord	Decrease in grip strength; abnormal hind limb movement; atypical limb clasping (10-14 mo)	[87]
		12 mo	Hyperphospho- and PK-resistant α-syn fibrils (ubiquitin+)	N.A.	Amygdala; subthalamic zona incerta; superior colliculus; mesencephalic nuclei; neocortex; hippocampus; thalamus; cerebellum	N.A.	N.A.	Reduced spontaneous locomotor activity (12 mo); impaired rotarod performance (17 mo); cognitive decline (12 mo)	[88]
	Rat TH	N.A.	α-Syn accumulated in TH+ SN neurons; but no LB-like inclusions (ubiquitin-)	(thioflavin S-); (silver staining-)	Striatum; SN	N.A.	No dopaminergic neurons loss and unchanged striatal DA	N.A.	[89]
A30P/A53T α-syn	Rat TH	2-3 mo	No inclusion bodies; but diffuse synuclein in TH+ SN neurons	N.A.	Striatum; SN; VTA; locus coeruleus; dorsal striatum; nucleus accumbens; olfactory tubercle; cerebral cortex	N.A.	Reduced striatal DA and metabolites; dopaminergic neurons terminal failure; increased presynaptic DAT	Reduced spontaneous locomotor activity and coordination (13-23 mo)	[80]
		N.A.	No inclusion bodies in TH+ SN neurons	Neither inclusions; aggregates nor other unique morphological features	Striatum; SN	N.A.	Progressive dopaminergic neurons loss in SNpc	Reduced locomotor activity (2 mo)	[90]
Truncated 1-130 α-syn	Rat TH	2 mo	LB-like α-syn inclusions in TH+ SN neurons	N.A.	SNpc; striatum; VTA; nucleus accumbens	No signs of gliosis	Dopaminergic neurons loss in SN; reduced striatal DA and metabolites; impaired striatal axon terminals	Reduced spontaneous locomotor activity (L-DOPA responsive)	[91]
Truncated 1-120 α-syn	Rat TH	6 weeks	α-Syn inclusions in SN and olfactory bulb	Mixed granular and fibrillary inclusions	SN; striatum; olfactory bulb; locus coeruleus	Microgliosis	No dopaminergic neurons loss in SN; reduced striatal DA;	Reduced spontaneous locomotor activity; increased response to	[92]

				(thioflavin S+)				axons swellings; shrunken perikaryal; dystrophic processes	amphetamine (18 mo)	
Truncated 1-103 α-syn	mThy-1	2-3 mo	Accumulation of pathological α-syn in the central nervous system; phosphorylated-Ser129-α-syn accumulation (ubiquitin+) (thioflavin S+); altered transcriptomics pattern	N.A.	Olfactory bulb; cortex; hippocampus; striatum; SN; cerebellum; pons; spinal cord	N.A.		Loss of dopaminergic neurons in SN; progressive striatal synaptic degeneration	Age-dependent PD-like behavioral impairments in tail suspension test, grid performance test, open field test; weight loss and constipation	[95]

α-syn: α-Synuclein; EM: electron microscope; WT: wildtype; BAC: bcterial artificial chromosome; GFP: green fluorescent protein; mo: month; N.A.: not applicable; SNpc: substantia nigra pars compacta; VTA: ventral tegmental area; SN: substantia nigra; LBs: Lewy bodies; DA: dopamine; TH: tyrosine hydroxylase; DAT: dopamine transporter; PDGF-β: platelet-derived growth factor-β; ER: endoplasmic reticulum; L-DOPA: L-3,4-dihydroxyphenylalanine; PD: Parkinson's disease.

standard features of phenotypes to certain extents, i.e., age-dependent α-syn accumulation, aggregation, and phosphorylation, concomitantly with behavioral impairments and neuronal dysfunction or cell death. Increased levels of α-syn in neurons can also enhance the protein and its aggregated forms to spread from one cell/neuron to another[54]. These similarities implied that similar underlying mechanisms may be involved in regulating the protein build-up in neurons. Considering the increased level of a specific protein, such as α-syn, and increased aggregation, the following mechanisms may contribute alone or jointly: (i) Increased α-syn gene transcription and/or increased α-syn translation (synthesis)[102-104] with age; (ii) With age, increased α-syn accumulation exacerbating age-related mitochondrial dysregulation and impaired mitophagy[105]; (iii) Impaired protein (α-syn) degradation or impaired protein homeostasis also increases with age[106,107], which may involve multiple pathways, for example, dysfunction of ubiquitin-proteosome pathway and/or autophagy-lysosome pathway[108], these dysfunctions further accelerate α-syn accumulation; (iv) when a mutation (such as A30P, A53T, *etc.*) occurs or when pathological posttranslational modifications[109], such as phosphorylation at serine 129, take place, the protein clearance processes are further dampened. Conversely, any therapeutic interventions modulating these points may mitigate α-syn accumulation and reduce its aggregation and propagation, eventually blocking the onset of the disease and/or slowing down the disease progression, such as: (i) Decrease synthesis of α-syn by using siRNA that targets α-syn mRNA[110,111]; (ii) Increase lysosomal or autophagic degradation of α-syn, for example, overexpression of lysosomal proteins promoting α-syn degradation[112,113]; (iii) Decrease α-syn aggregation by using protofibril-selective antibody and small molecules to decrease α-syn protofibrils and α-syn aggregation[114,115]; (iv) Block α-syn propagation by antibodies against C-terminal truncated α-syn to prevent α-syn propagation[116,117]; (v) Immunization to clear up α-syn aggregation, including active immunization for α-syn by vaccines PD01A and PD03A (AFFiRiS) and passive immunization by antibodies against α-syn, including PRX002 (Prothena) and BIIB054 (Biogen)[115,118] [Figure 1].

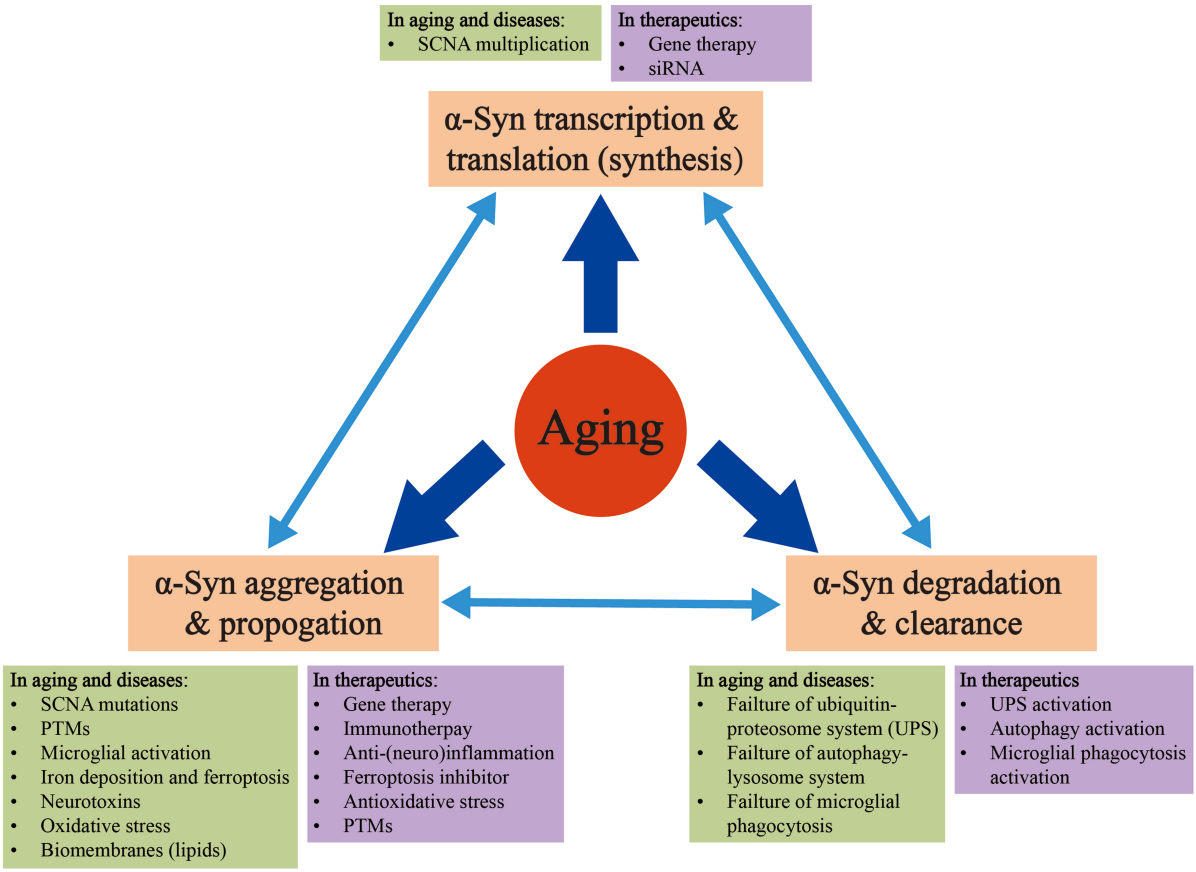

Figure 1. The schematic drawing shows the inter-relationship among increased α-syn level, protein aggregation, and degradation mechanisms in aging and disease conditions and the strategies of potential therapeutic interventions (Modified from[182]). α-syn: α-Synuclein.

The spreading of α-syn pathology within the brain, from the periphery to the brain or vice versa, is also age-dependent. Braak *et al.* reported that Lewy pathology first appears in the peripheral regions of the nervous systems long before PD symptoms are evident. Eventually, pathology gains access to the lower brainstem via the vagal nerve, following an ascending path through vulnerable regions of the basal, mid- and forebrain, until it reaches the cerebral cortex. The temporal appearance of Lewy pathology in PD strongly suggests long-distance transport of the pathology in neurons from peripheral tissues to the brain[119]. Subsequently, they proposed six stages of PD pathology, reflecting different stages of pre- and post-diagnosis of the disease[119]. Since then, a large body of evidence has demonstrated and validated *in vivo* and *in vitro* models that α-syn and its aggregated forms can be spread among neurons and between neurons and non-neuronal cells[120-123]. Despite some skepticism[124], the majority of available evidence favors the prion-like mechanism underlying α-syn spreading from one cell to another, not only in PD but also in PD-related diseases, such as dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). This is particularly true in cell models and animal models[59,61,125,126], compared to humans and nonhuman primates[5,6]. Interestingly, based on different appearances of motor and non-motor symptoms in PD, α-syn pathology may be initiated in the brain or peripheral tissues among different PD cases. This "brain-first *vs.* body-first" phenomenon may reflect the heterogeneity of clinical features in PD and related disorders, which also imply different etiological factors and genetic backgrounds involved[74]. Multiple mechanisms contribute to α-syn cell-to-cell spreading, such as endocytosis, extracellular vesicles (EVs), tunneling nanotubes, *etc.*[59,127,128]. However, the role of aging in these processes remains unclear. Regarding EVs, studies have claimed that EVs carry cell-

state-specific messages that represent the underlying pathology of the disease[128,129]. In PD, it seems that more α-syn packaging occurs in EVs from individuals with PD[130], and EVs may mediate the propagation of misfolded α-syn propagation between cells[131]. When α-syn is transferred into the neighboring cells via EVs, it exerts damaging effects on cells and can even cause cell death[132]. However, other studies argue against the role of EVs in protein propagation[133]. Fussi *et al.* found that silencing autophagy-related gene 5 (ATG5) can elevate EV-mediated α-syn externalization to compensate for the loss of macroautophagy by reducing the intracellular α-syn burden, suggesting the role of EVs in protecting against the neurotoxic effects of α-syn[134].

Modulation of microglia and iron deposition in age-dependent α-syn aggregation

Increasing evidence shows that, in addition to aging, multiple factors such as microglia and iron deposition may regulate α-syn aggregation and propagation. Microglia maintain homeostasis in the brain via phagocytic clearance of misfolded protein aggregates and cellular debris. α-Syn and its aggregated forms can be released and activate microglia, which in turn degrade α-syn by phagocytosis into the autophagosome via selective autophagy[135,136]. Age-dependent microglial impairment of amyloid protein uptake inhibits processes of protein degradation[137,138]. Different molecular mechanisms may be involved, such as modulating a negative regulator CD22[138], lipid and immune aberrations[139], *etc.* With age, significantly increased microglia (IBA1+ cells) in number and alterations in activation were observed in human SN[140]. A similar appearance was observed in animal models overexpressing human α-syn. It is also shown that microglia can form contacts with neurons through tunneling nanotubes to mitigate the neurons from diseased protein accumulation[141]. Using positron emission tomography (PET), two studies indicate the pronounced activated microglia in various regions of the PD brain[142,143]. In various types of PD animal models, activated microglia in the SN and striatum are more common[144], and due to the selective vulnerability of dopaminergic neurons in PD, they are not identical to those elsewhere in the central nervous system[145,146]. The regional heterogeneity of microglia is mainly due to the different microglial cell membrane receptors and the local microenvironment, such as immunomodulators, signaling molecules, electrical properties, and neuronal activity[147-149]. The region-specificity of microglia may play an important role in aggravating differential α-syn pathology between brain regions and neuronal dysfunction during PD.

α-Syn can also be taken up by astrocytes and form inclusion bodies[150]. Excess α-syn in the brain induces neurotoxic reactive astrocytes, triggering an inflammatory response and impaired protein degradative system, aggravating α-syn aggregation and PD neurodegeneration[151-153]. α-Syn aggregation in astrocytes could be transferred to adjacent astrocytes, microglia, and neurons, spreading and aggravating the synucleinopathy[154,155]. Astrocyte properties are also regionally heterogeneous, with striatal astrocytes exhibiting fewer interactions with neurons, K^+ currents, and gap junction coupling than those in the hippocampus[156-158]. Grafting ventral midbrain astrocytes into mouse brains can reduce α-syn accumulation and inflammatory cytokines via numerous mechanisms[159]. The relationship of these region-specific changes with aging and PD progression remains to be further investigated.

Iron is among the most essential trace elements in the human body. Excessive amounts of iron have toxic effects on the nervous system[160]. The factors associated with an increased total iron concentration mainly include aging, the inflammatory response, changes in iron balance, redistribution of iron in the brain, and increased blood-brain barrier permeability[161]. It has been shown that iron-induced α-syn aggregation and cytotoxicity are age-dependent and dose-dependent[162]. In a nonhuman primate model, Guo *et al.* showed that iron deposition was increased in an age-dependent manner from 1 to 17 months in the SN and globus pallidus, highly contrasting to other brain regions after exposure with α-syn preformed fibrils in the olfactory system. At the cellular level, the iron deposits were robustly localized in microglia[163]. How different brain regions maintain iron homeostasis under physiological conditions remains obscure. It has

been shown that iron deposition is present in the main lesion areas in the brains of patients with PD. An abnormal iron content may be associated with dopaminergic neuronal cytotoxicity and degeneration in the SN of the midbrain[164-166]. Recently, Guan *et al.* reported age-dependent and disease-severity-related iron content in different brain regions assessed with a quantitative susceptibility mapping (QSM)[167]. They recruited young and old adults, prodromal PD and clinical PD patients, and mild cognitive impairment (MCI) and AD patients. They quantified the regional magnetic susceptibility, reflecting the iron contents. They observed markedly increased iron deposition in the SN and red nucleus in the old adults (compared to the young ones), clinical PD patients (compared to the prodromal ones), and in the caudate nucleus and putamen in AD patients (compared to MCI ones). These results indicate that increased iron deposition is highly associated with aging and pathogenesis of PD and AD. Considering the increased iron deposition associated with aging and PD, iron chelation or inhibition of iron deposition may be a potential approach for the early prevention and treatment of PD.

CONCLUSION AND PERSPECTIVE

Protein aggregation and propagation are dose-dependent events largely regulated by aging-related events. Aging is a multifactorial process. López-Otín *et al.* proposed as many as twelve hallmarks in aging[168], which are associated with various processes and functions. Among them, loss of proteostasis, disabled autophagy, mitochondrial dysfunction, inflammation, *etc.*, are directly or indirectly associated with protein misfolding, aggregation, and propagation in age-related morbidities, such as AD and PD[169-171]. Moreover, these hallmarks may contribute alone, additively, or synergistically to healthy aging and also to the pathogenesis of diseases. Generally speaking, aging is viewed as the most important risk factor for AD and PD. Considering the hallmarks involved in aging and their association with AD and PD, in practice, it is not easy to mark the border between aging and disease manifestations. Although aging-related events (hallmarks) may contribute to regulating the amounts of α-syn in the brain and periphery, many other factors may also modulate the level of α-syn. These factors include gene mutations, functionality of the protein degradation systems, status of neuroinflammation[172-174], oxidative stress[175], presence/absence of exogenous seeds of α-syn[176-178], and even the involvement of biomembrane[179-181]. These factors that promote accumulation and aggregation of α-syn can be seen as "an aging accelerator", which can also be seen as (part of) processes of disease pathogenesis in PD, reversely, "an aging decelerator". Further understanding of how they are involved in healthy aging and diseases may open novel avenues for the potential therapeutic intervention to modulate α-syn levels, in turn, to interfere with its aggregation and propagation, eventually halting the disease progression of PD and related disorders.

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Authors' contributions

Wrote the paper and approved the final manuscript: Song DY, Li JY

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Conflicts of interest

Li JY is an Editorial Board member of the journal *Ageing and Neurodegenerative Diseases*. Li JY was not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, and decision making. Song DY declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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