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α -synuclein toxicity in neurodegeneration: mechanism and therapeutic strategies

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Abstract

Alterations in α -synuclein dosage lead to familial Parkinson's disease (PD), and its accumulation results in synucleinopathies that include PD, dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). Furthermore, α -synuclein contributes to the fibrilization of amyloid- β and tau, two key proteins in Alzheimer's disease, which suggests a central role for α -synuclein toxicity in neurodegeneration. Recent studies of factors contributing to α -synuclein toxicity and its disruption of downstream cellular pathways have expanded our understanding of disease pathogenesis in synucleinopathies. In this Review, we discuss these emerging themes, including the contributions of aging, selective vulnerability and non-cell-autonomous factors such as α -synuclein cell-to-cell propagation and neuroinflammation. Finally, we summarize recent efforts toward the development of targeted therapies for PD and related synucleinopathies.

α -synuclein (*SNCA*) is a 14-kDa protein that forms a major component of abnormal neuronal aggregates known as Lewy bodies (LBs)¹. It is highly soluble and enriched at presynaptic terminals, where it binds lipids and regulates the release of synaptic vesicles^{2,3}. N-terminal point mutations in α -synuclein (A30P, E46K, H50Q, G51D, A53E and A53T)^{4–10} and genomic duplications or triplications that contain the α -synuclein locus result in autosomal dominant forms of familial PD^{11,12}. In addition, multiple genome-wide association studies (GWASs) have identified single-nucleotide polymorphisms (SNPs) in α -synuclein as risk factors that increase susceptibility to sporadic PD^{13,14}. Among these SNPs is a risk variant in a noncoding distal enhancer element of *SNCA* that leads to increased α -synuclein expression¹⁵. This genetic evidence helps to further highlight a crucial link between increased α -synuclein levels and PD pathogenesis.

α -synuclein also accumulates in other synucleinopathies, including dementia with Lewy bodies (DLB), multiple system atrophy (MSA)^{16,17} and various lysosomal-storage disorders, such as Gaucher's disease¹⁸ (Table 1). Importantly, α -synuclein regulates the fibrilization of both amyloid- β ($a\beta$) and tau, two key proteins in Alzheimer's disease

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(AD) pathophysiology^{19–23}. Thus, delineation of the downstream effects and factors that contribute to α -synuclein toxicity will be crucial for assessing potential therapeutics for both synucleinopathies and AD.

In this Review, we present evidence for various routes to cellular dysfunction caused by α -synuclein toxicity, including synaptic dysfunction, mitochondrial impairment, defective endoplasmic reticulum (ER) function and autophagy–lysosomal pathway and nuclear dysfunction. We discuss additional factors that contribute to α -synuclein toxicity, including the role of aging, selective neuronal vulnerability, non-cell-autonomous factors such as α -synuclein propagation and the role of glia and neuroinflammation, and the interplay of α -synuclein with $a\beta$ and tau. Finally, we compare therapeutic strategies currently being developed to target α -synuclein and minimize its toxicity in disease.

α -synuclein in neurodegenerative diseases

α -synuclein has been implicated in several diseases, which we discuss here to give an impression of the broad reach of its pathogenesis.

In PD, dopaminergic neurons in the substantia nigra pars compacta (SNc) degenerate, which results in dopamine loss in the basal ganglia, an area of the brain responsible for coordinating fine motor control, which ultimately leads to the onset of clinical Parkinson's symptoms such as bradykinesia, muscular rigidity, resting tremors and postural instability²⁴. α -synuclein accumulates in sporadic PD in neuronal cell bodies and processes to form Lewy bodies and Lewy neurites in the brain, spinal cord and peripheral nervous system²⁴. However, Lewy pathology is also observed in a subset of neurologically healthy patients (in a condition called incidental Lewy body disease), which indicates that additional factors other than Lewy pathology alone might be required for α -synuclein's toxicity in patients²⁵. α -synuclein locus duplication results in autosomal dominant forms of PD with late onset (~60 years), typical of patients with sporadic PD. By contrast, α -synuclein locus triplication leads to early PD onset (<40 years)¹¹, demonstrating that increased α -synuclein levels accelerate PD pathogenesis. Of note, patients with familial PD who have mutations in other PD-associated genes, such as leucine-rich repeat kinase 2 (*LRRK2*), can also develop Lewy body pathology^{26–28}. *LRRK2* overexpression was initially found to accelerate neuropathology progression in α -synuclein A53T mice (*tetO-A53T*), whereas *LRRK2* depletion delayed its progression²⁹. Subsequent studies demonstrated that *LRRK2* knockout or inhibition prevented α -synuclein-induced neurodegeneration in animal models^{30,31}, and mutated *LRRK2* increases α -synuclein levels and its recruitment into neuronal inclusions³², which further suggests potential functional interplays between α -synuclein toxicity and other PD-associated genes.

Patients with MSA develop autonomic failure, as well as parkinsonism and cerebellar ataxia, as a result of respective striatonigral and olivopontocerebellar degeneration³³. In contrast to individuals with PD, patients with MSA develop cytoplasmic α -synuclein inclusions in oligodendrocytes. Notably, various α -synuclein mutations result in both Parkinson's and MSA symptoms³³.

Parkinson's disease with dementia (PDD) and DLB occurs in patients who first present with parkinsonism or dementia, respectively, which is followed by onset of other symptoms³⁴. A subset of patients with PDD or DLB develop α -synuclein Lewy pathology and amyloid plaques, although a greater plaque load has been reported in DLB than in PDD³⁴, which suggests an intimate link between α -synuclein and $A\beta$ toxicity. This contributes to a disease spectrum that ranges from PD with α -synuclein pathology to PDD and DLB with mixed pathology and AD with $A\beta$ pathology.

AD is the leading cause of dementia and involves progressive memory loss and cognitive impairment coupled with neurodegeneration of various brain regions, including the hippocampus³⁵. In patients with AD, the microtubule-binding protein tau is hyperphosphorylated and accumulates into intracellular tangles, whereas $A\beta$, an extracellular fragment cleaved from amyloid precursor protein (APP), accumulates into extracellular plaques³⁵. Notably, elevated soluble α -synuclein levels have been observed in the AD-afflicted brain and are correlated with cognitive decline³⁶.

Lysosomal storage disorders (LSD) such as Gaucher's disease have also been linked to α -synuclein toxicity. Gaucher's disease is caused by mutations in *GBA1*, which encodes glucocerebrosidase (GCCase), a lysosomal hydrolase that converts glucosylceramide into ceramide and glucose³⁷. Patients with Gaucher's disease develop thrombocytopenia, anemia, hepatosplenomegaly and bone pain, and seizures and cognitive impairment occur in more severe neuropathic forms. Importantly, some patients develop parkinsonism coincident with α -synuclein Lewy body pathology³⁷, and mutations in *GBA1* are a risk factor for the development of PD³⁸. Recently, several other LSDs, including Sanfilippo syndrome, GM2 gangliosidosis and Niemann–Pick type C, have also been shown to demonstrate α -synuclein pathology¹⁸.

Finally, neurodegeneration with brain iron accumulation (NBIA) is a collection of genetic diseases involving iron accumulation in the globus pallidus and substantia nigra, resulting in parkinsonism, spasticity and dystonia. To date, patients with mutations in the mitochondrial membrane protein *C19orf12* and the A2 phospholipase *PLA2G6* have confirmed Lewy body and neurites. In addition, mutations in *ATP13A2* (also known as *PARK9*), a lysosomal ATPase present in Lewy bodies, also contribute to NBIA, juvenile onset parkinsonism, dementia and neuronal ceroid lipofuscinosis (NCL)³⁹.

Pathways implicated in α -synuclein toxicity

α -synuclein is intrinsically disordered⁴⁰ and forms multiple conformations, including amyloidogenic oligomers⁴¹. α -synuclein contains three distinct regions³: an amino-terminal lipid-binding region, a recently crystalized central NAC (non-amyloid- β component) hydrophobic region⁴², which contributes to its oligomerization, and an intrinsically disordered carboxy-terminal (Box 1).

Although α -synuclein normally localizes to the presynaptic terminal, its oligomers and aggregates localize throughout the cell body and neurites, which suggests that α -synuclein might disrupt cellular function beyond the presynaptic terminal. Indeed, multiple organelles

are implicated in α -synuclein toxicity, including synaptic vesicles, mitochondria, ER and Golgi, lysosomes and autophagosomes and the nucleus (Fig. 1). Moreover, interorganelle contacts and organelle axonal transport are also disrupted by α -synuclein toxicity.

Synaptic-vesicle trafficking.

α -synuclein normally localizes to the presynaptic terminal, where it associates with synaptic vesicles^{43,44}, binds membranes⁴⁵ and induces membrane curvature⁴⁶. α -synuclein regulates soluble NSF attachment protein receptor (SNARE) complex assembly⁴⁷ by binding the SNARE protein synaptobrevin-2/vesicle-associated membrane protein 2 (VAMP2) to promote synaptic-vesicle fusion at the presynaptic terminal². It also potentially regulates additional steps during synaptic-vesicle trafficking^{48–52}.

Large α -synuclein oligomers preferentially bind VAMP2 and disrupt SNARE complex formation, dopamine release⁵³ and synaptic-vesicle motility⁵⁴, and increased α -synuclein levels disrupt neurotransmitter release via decreased synaptic-vesicle recycling-pool size⁵⁵ and mobility⁵⁰. Thus, it has been proposed that α -synuclein's normal function might be disrupted in synucleinopathies. By contrast, other studies have suggested that α -synuclein's physiological role at the synapse is not altered in disease, and have found that α -synuclein oligomers actually promoted SNARE assembly⁵⁶, and that PD-linked mutations (except the lipid-binding-deficient A30P mutation) does not disrupt SNARE assembly⁵⁷ or synaptic-vesicle clustering⁵¹.

Elevated levels of α -synuclein might also disrupt dopamine neurotransmission. Mice lacking α -synuclein show increased dopamine release from nigrostriatal terminals⁵⁸, although α -synuclein deletion does not affect cytosolic dopamine levels⁵⁹. Conversely, transgenic mice overexpressing human α -synuclein show dopaminergic terminal loss⁶⁰, deficient dopamine release and altered synaptic-vesicle distribution⁶¹. Increased α -synuclein expression has also been linked to a reduction in dopamine reuptake and defective dopamine transporter (DAT) function⁶², which suggests several potential mechanisms through which α -synuclein might disrupt dopamine turnover.

Mitochondrial function.

Mitochondria are crucial for ATP synthesis, calcium storage, lipid metabolism and neuronal survival⁶³. α -synuclein toxicity might directly disrupt mitochondrial homeostasis, given that mice with A53T α -synuclein mutations have increased mitochondrial DNA damage⁶⁴ and mitophagy^{65,66}, and increased α -synuclein levels promote dynamin related protein 1 (DRP1)-independent mitochondrial fission in cell lines and mouse models overexpressing α -synuclein^{67,68}. Interestingly, in mice lacking α -synuclein, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced degeneration of dopaminergic neurons is prevented⁶⁹, potentially because α -synuclein oligomers promote mitochondrial dysfunction via increased calcium uptake⁷⁰. Post-translationally modified species of α -synuclein have also recently been suggested to disrupt mitochondrial function by impairing mitochondrial protein import⁷¹. By contrast, mitochondrial dysfunction might also be induced indirectly by α -synuclein toxicity via decreased levels of the mitochondrial biogenesis factor PGC-1 α . This has been observed in cell models that express oligomeric α -synuclein, mice that

express A30P α -synuclein⁷² and the brains of patients with PD, whereas PGC-1 α activation rescued neuronal loss induced by mutant α -synuclein⁷³. Dopaminergic α -synuclein induced pluripotent stem cell (iPSC) models of PD also display inhibition of the MEF2C–PGC-1 α mitochondrial transcription network via increased *S*-nitrosylation of transcription factor MEF2C (ref. 74).

Endoplasmic reticulum and Golgi function, and the endocytic pathway.

The endoplasmic reticulum (ER) is essential for protein folding, trafficking to the Golgi, calcium buffering and the unfolded protein response (UPR). Both wild-type and mutant α -synuclein disrupt ER to Golgi trafficking in yeast⁷⁵ and induce ER stress and early secretory-pathway dysfunction, which is rescued by certain Rab GTPases such as RAB1, RAB3A or RAB8A (refs. 76,77). Increased α -synuclein expression also disrupts endosomal transport events via the E3 ubiquitin ligase yeast RSP5 and its mammalian homologue NEDD4 and endosomal transport can be rescued by the drug *N*-aryl benzimidazole^{78,79}. Moreover, α -synuclein accumulation disrupts GCCase trafficking in PD iPSCs and patient brains; this leads to reduced GCCase lysosomal activity⁸⁰, which in turn might be mediated by the aberrant association of α -synuclein with cis-Golgi–tethering factor GM130 and RAB1A mislocalization⁸¹ or by inhibiting ER to Golgi formation via the R-SNARE ykt6 (ref. 82). Notably, DAT trafficking is also disrupted upon α -synuclein overexpression⁸³. Increased α -synuclein levels also raise cytoplasmic calcium levels, which leads to the activation of a toxic calmodulin–calcineurin cascade^{84,85} and suggests that calcium buffering in the ER might be disrupted by α -synuclein. Finally, α -synuclein has been proposed to bind the ER chaperone GRP78 (also known as BIP)⁸⁶ and interfere with ER folding machinery, which is ameliorated in α -synuclein transgenic mice by decreasing ER stress^{87,88}.

Autophagy or lysosomal pathway.

Autophagy is a dynamic pathway involved in the degradation of damaged organelles and protein aggregates⁸⁹. α -Synuclein overexpression disrupts ER to Golgi trafficking of the autophagic transmembrane protein ATG9 and decreases the formation of omegasomes, a precursor for autophagosome biogenesis⁹⁰. In chaperone-mediated autophagy (CMA), A53T and A30P α -synuclein bind the lysosomal receptor LAMP2A more tightly than wild-type α -synuclein, which prevents their own degradation and cargo loading of other CMA substrates into lysosomes⁹¹. In addition, dopamine-modified α -synuclein also blocks CMA, which might contribute to selective dopaminergic vulnerability in PD⁹². In neuronal models incubated with α -synuclein preformed fibrils (pffs), autophagosomes formed normally but had defective lysosomal fusion and autophagic cargo accumulation⁹³, potentially owing to defective autophagosome axonal transport⁹⁴. Finally, because efficient autophagic degradation relies on lysosomal enzymatic activity, the lysosomal activity of multiple enzymes, including GCCase, cathepsin B, β -galactosidase and hexosaminidase, is reduced in α -synuclein triplication PD iPSCs as compared to control iPSCs as a result of defective ER-to-Golgi trafficking^{80,81,95}.

Nuclear function.

Although α -synuclein was also originally localized to the nucleus⁹⁶, this finding has since been up for debate, potentially because of the use of different antibodies against

cleaved forms of α -synuclein (Box 1). The targeting of α -synuclein to the nucleus has been proposed to be regulated by the nuclear protein TRIM28 (ref. 97) and to inhibit histone acetylation⁹⁸. Moreover, PD-associated mutations (A30P, A53T and G51D) in α -synuclein demonstrate increased nuclear localization as compared to wild-type α -synuclein^{98,99}. Altered activation of various transcription factors has also been observed, including decreased activation of the mitochondrial biogenesis factor PGC-1 α in α -synuclein A53T PD-patient-derived iPSC neurons and PD-afflicted substantia nigra^{72–74}; decreased activation of the autophagy–lysosomal pathway transcription factor TFEB in rats overexpressing α -synuclein via adeno-associated virus (AAV)¹⁰⁰; and increased activation of nuclear factor of activated T cells (NFAT) via calcineurin activation in cell lines that overexpress wild-type or A53T α -synuclein, in dopaminergic neurons from α -synuclein transgenic mice and in brains of patients with PD or DLB^{84,85}.

Disruption of inter-organelle contacts.

In the past few years, multiple inter-organelle contacts have emerged as sites of cellular homeostatic regulation. One such site is the mitochondria-associated ER membrane (MAM), a subdomain of the ER tethered to mitochondria via a group of adaptor proteins, which serves as a critical site for autophagosome biogenesis, mitochondrial fission, calcium homeostasis, phospholipid transport and fatty acid and cholesterol transfer¹⁰¹. Two recent studies have implicated the MAM in α -synuclein toxicity with opposing conclusions; one of these studies found increased numbers of MAM contact sites, resulting in increased mitochondrial calcium uptake from the ER upon α -synuclein overexpression¹⁰², whereas the other study identified α -synuclein in MAM fractions and saw decreased numbers of MAM contact sites upon wild-type, A53T or A30P α -synuclein overexpression¹⁰³. However, in both reports, mitochondrial fragmentation was observed. Thus, further studies to reconcile these differences, as well as experiments in neurons, will be crucial for understanding the interaction of α -synuclein with MAMs, as well as the role of other inter-organelle contacts in the context of α -synuclein toxicity.

Misregulation of organelle dynamics.

The majority of studies on α -synuclein cellular toxicity have been performed at steady state. However, organelles are highly dynamic and undergo axonal transport, fission and fusion events and maturation, and are intricately regulated by numerous signaling pathways mediated by phosphorylation, Rab GTPase activity, calcium signaling and electrical activity. Recently, α -synuclein fibrils were found to impair the axonal transport of autophagosomes and RAB7- and TrkB-receptor-positive endosomes, but not the transport of synaptophysin or mitochondria, which suggests that α -synuclein does not cause a generalized defect in axonal transport⁹⁴. This may be partially due to decreased levels of axonal transport proteins in patients with sporadic PD when compared to age-matched controls¹⁰⁴ or decreased microtubule stability and kinesin-dependent cargo mobility, as observed in cellular models expressing α -synuclein oligomers¹⁰⁵. Transport defects might also be mediated by interactions of α -synuclein with tau, a microtubule-binding protein that stabilizes and promotes microtubule assembly^{20,23}. Neuronal exposure to extracellular α -synuclein also disrupts actin turnover and actin waves along axons, owing to cofilin inactivation¹⁰⁶. By contrast, very little work has examined α -synuclein's regulation of

vesicle fission and fusion and maturation dynamics in neurons, which suggests that further investigation of these processes might advance our understanding of α -synuclein's role in neurodegeneration.

Understanding cellular dysfunction in α -synuclein toxicity

Numerous reports have described multiple pathways of cellular dysfunction in models of α -synuclein toxicity. Why have these different pathways been implicated thus far in α -synuclein toxicity?

One possibility is that distinct pathways might be affected in different synucleinopathies. The pathways affected in familial PD caused by α -synuclein mutations might not be identical to those disrupted by other PD-associated genes or in sporadic PD, and may be different from those involved in MSA or LBD. These differences might be exacerbated by differences in α -synuclein strain characteristics, specific cell types affected and diverse protein interactions.

Moreover, multiple pathways could be affected in synucleinopathies at different time points of disease progression. Some pathways may be disrupted early in disease (presymptomatic) versus late stage (post-symptomatic), whereas others might be compensating for dysfunction in other pathways. In addition, different pathways might have different rates of dysfunction, which may initially be below detection until the cell has already degenerated. Furthermore, additional factors, such as aging and genetic variability, might also affect when and which pathways become dysfunctional.

Finally, the differences in cellular-pathway defects observed across studies might also be in part due to differences in the experimental model of α -synuclein toxicity. α -synuclein toxicity is commonly modeled by the overexpression of wild-type α -synuclein, expression of PD-linked α -synuclein mutations, injection or incubation with α -synuclein preformed oligomers or fibrils or targeted expression of α -synuclein using AAV. These studies are further complicated by differences in the choice of cell type (non-neuronal versus neuronal versus glial), animal model (human versus mouse versus rat) and time point of analysis (2 d versus 200 d versus 2 years). Indeed, using different models of α -synuclein toxicity, different steps in the autophagic pathway have been found to be disrupted, including autophagosome formation⁹⁰, cargo loading in CMA⁹¹, autophagosome fusion with lysosomes and axonal transport^{93,94}, and lysosomal degradative function^{78,80,107}. Moreover, small changes in experimental preparation of α -synuclein oligomers or fibrils can lead to strain differences (Box 1) with distinct seeding, propagation and toxicity-inducing capabilities^{20,108}, which further contributes to potential differences in observed cellular dysfunction. Mouse models of α -synuclein toxicity enable analysis of functional neuronal circuitry, but they do not exhibit accumulation of neuromelanin, a dark pigment that consists of oxidized catechols such as dopamine, which is a key feature of human SNc dopaminergic neurons. By contrast, dopaminergic neurons differentiated from human iPSCs allow for the study, over hundreds of days, of patient-derived cells with endogenous levels of α -synuclein, but lack the complex connections of an intact basal ganglia circuitry. Thus, understanding the capabilities of each model and characteristics such as which synucleinopathy and which

stage of the disease it most accurately reflects will be crucial for designing and interpreting future studies on α -synuclein toxicity.

Steps to α -synuclein toxicity

Although multiple cellular pathways have been implicated downstream of α -synuclein toxicity, several contributing factors might be crucial for the spread, extent and onset of α -synuclein toxicity. Indeed, human postmortem studies have shown that a subset of the population (10–20%) exhibits incidental Lewy body disease but presents as neurologically normal²⁵, so the contributing factors that we discuss below might be crucial for determining which patients will become symptomatic, as well as influence their age of disease onset and rate of disease progression. Of note, different conformations of α -synuclein, as well as differences between α -synuclein strains, might further influence the toxicity of α -synuclein (Box 1). Finally, additional pathways have also been implicated in the augmentation of α -synuclein toxicity in *Drosophila* and mouse models, including loss of the molecular chaperone HSP70 (ref. 109) and presynaptic scaffold protein septin 4 (ref. 110), histone deacetylase sirtuin 2 activation¹¹¹ and α -synuclein S129 phosphorylation¹¹².

Aging.

Aging is the greatest risk factor for multiple neurodegenerative diseases, partially owing to decreased organelle function. Substantia nigra neurons demonstrate higher levels of mitochondrial DNA (mtDNA) deletion with age, which causes mitochondrial dysfunction via respiratory-chain deficiency¹¹³. Proteasome dysfunction in multiple cell types, including neurons, also increases with age owing to disassembly of proteasomes and decreased proteasome subunit expression¹¹⁴, and autophagy is less efficient with age because of decreased levels of autophagy proteins such as beclin 1, ATG5 and ATG7 in human brains⁸⁹. These defects might further contribute to α -synuclein toxicity because defective protein degradation accelerates α -synuclein accumulation. Indeed, α -synuclein levels increase with age in the human substantia nigra^{115,116}.

Oxidative stress also increases with age¹¹⁷, which contributes to pathogenic modifications of α -synuclein, such as nitration of tyrosine residues, which have been observed in the brains of patients afflicted with PD, DLB and MSA¹¹⁸. Importantly, α -synuclein nitration promotes its aggregation¹¹⁹ and decreases its lipid-binding ability¹²⁰. In dopaminergic neurons, autophagic vesicles containing lipofuscin and neuromelanin, generated by iron-catalyzed oxidation and oxidized catecholamines, respectively, accumulate with age¹²¹. α -synuclein has been proposed to associate with the lipid component of neuromelanin in SNc dopaminergic neurons to promote its own aggregation¹²². However, given that neuromelanin may be neuroprotective by sequestering oxidized catecholamines, it remains unclear whether α -synuclein's interaction with neuromelanin is beneficial.

Selective vulnerability.

Synucleinopathies are a diverse group of diseases with disparate affected cell types, including SNc dopaminergic neurons in PD, oligodendrocytes in MSA and cortical neurons in LBD. This suggests that cell-autonomous factors might further augment α -synuclein

toxicity in different populations. Identifying these factors for different cellular populations could thus facilitate targeted treatment development for specific synucleinopathies.

In PD, multiple cellular populations are lost, including neuromelanin-positive catecholamine neurons in the SNc and locus coeruleus, dorsal motor nucleus of the vagus neurons in the majority of patients and norepinephrine and dopaminergic neurons in the enteric nervous system¹²³. Lewy body pathology is present but not limited to these regions, and has been proposed to progress through the brain in a caudo-rostral fashion¹²⁴. Factors that might contribute to the susceptibility of these populations include the use of a monomamine neurotransmitter, highly branched axons with multiple release sites and increased excitability owing to autonomous pacemaking with low intrinsic calcium buffering abilities¹²³.

Specifically, dopamine might also enhance α -synuclein toxicity, because dopamine adducts stabilize α -synuclein protofibrils¹²⁵ by inhibiting α -synuclein aggregation and promoting oligomer formation^{126,127}. Moreover, lowering cytosolic dopamine in cultured midbrain neurons is neuroprotective, and dopaminergic neurons lacking α -synuclein are resistant to L-DOPA-induced cell death⁵⁹. Additionally, neuromelanin, a downstream product of oxidized dopamine, might be toxic, given that neuromelanin-containing neurons are lost in PD¹²⁸. Neuromelanin is a homeostatic byproduct of increased oxidation and catecholamine adducts. However, in cases of excessive oxidation, elevated levels of neuromelanin accumulation in neurons might also contribute to neurodegeneration.

In addition, given that L-DOPA increases dopamine levels and is used to treat PD, and that A10 dopaminergic neurons from the ventral tegmental are spared in PD, dopamine alone might not be sufficient to cause degeneration in the context of α -synuclein toxicity during PD. SNc A9 dopaminergic neurons lost in PD might be more susceptible than A10 neurons owing to their increased cytosolic calcium levels⁵⁹, which drive dopamine metabolism and increase cellular metabolism. Of note, SNc degeneration in PD might also be mediated by non-cell-autonomous mechanisms, such as the expression of cytokines (e.g., interferon (IFN)- γ)¹²⁹.

In MSA, α -synuclein preferentially accumulates in oligodendrocytes, but whether this occurs in a cell-autonomous manner or results from neuronal release and subsequent oligodendrocyte uptake remains unclear. Transgenic mice overexpressing α -synuclein in oligodendrocytes undergo degeneration and myelin autophagocytosis¹³⁰. Selective vulnerability of oligodendrocytes in MSA might be mediated by the accumulation and binding of p25 α , an oligodendrocyte-specific protein, to aggregated α -synuclein¹³¹, or by decreased glial-derived neurotrophic factor (GDNF) levels¹³².

Cell-to-cell spreading of α -synuclein.

α -synuclein spreading was observed initially from host human PD-afflicted brains into grafted nigral neurons over a decade after transplantation^{133,134}. Subsequently, α -synuclein transmission via endocytosis to neighboring neurons was observed in cell culture and mouse models¹³⁵. Exogenous introduction of human α -synuclein fibrils recruited endogenous α -synuclein to form Lewy body-like pathology in human cell lines¹³⁶ and mouse neurons¹³⁷.

Studies *in vivo* subsequently found that mouse α -synuclein fibril inoculation into wild-type mouse brains caused Lewy pathology propagation and progressive dopaminergic SNc loss¹³⁸. α -synuclein intramuscular injection also induced Lewy pathology¹³⁹ and demonstrated efficient crossing of the blood–brain barrier¹⁴⁰, and injection into the olfactory bulb also mimicked the sequential progression of Lewy-body-like pathology¹⁴¹.

One potential mechanism for α -synuclein secretion is exosome release¹⁴², which is increased upon the expression of ATP13A2 via increased exosome biogenesis^{143,144}, RAB11 expression¹⁴⁵; and in a calcium-dependent manner upon thapsigargin treatment¹⁴⁶. α -synuclein spreading might also involve clathrin-mediated endocytosis¹⁴⁷, lymphocyte-activation gene 3 (LAG3)-mediated endocytosis¹⁴⁸ or lysosomal vesicles traveling through tunneling nanotubes¹⁴⁹. Importantly, protein spreading might occur in multiple neurodegenerative diseases because neurons are particularly vulnerable to protein propagation owing to their extensive anatomical connections¹⁵⁰. However, various issues remain unaddressed, including whether the spreading of Lewy body pathology is required for clinical symptoms, the relevance of using elevated fibril concentrations to induce spreading in various models and the heterogeneity of Lewy body pathology across PD cases that do not always follow the stereotypical caudo-rostral progression¹⁵¹. Thus, the role, timing and mechanisms of α -synuclein propagation remain to be further investigated in the context of cellular pathogenesis.

Glia and neuroinflammation.

The role of glia (oligodendrocytes, astrocytes and microglia) has been increasingly studied in the context of neurodegeneration in recent years. However, although α -synuclein accumulates in oligodendrocytes in MSA, whether oligodendrocyte dysfunction occurs in other synucleinopathies has not been well characterized. Similarly, astrocyte involvement in α -synuclein toxicity has not been clearly elucidated, although astrocytes can take up neuronally released α -synuclein via endocytosis, which leads to gene expression changes that are indicative of an inflammatory response¹⁵².

Microglial activation has been observed both in patients with PD¹⁵³ and those with MSA¹⁵⁴, which suggests that neuroinflammation might contribute to the pathogenesis of α -synuclein-mediated toxicity. Indeed, neuroinflammation has been observed in multiple animal models of α -synuclein toxicity^{155–158} and might be mediated by microglial expression of the major histocompatibility complex (MHC) II, a key regulator of the immune response, given that MHCII depletion reduces microglial activation and dopaminergic neurodegeneration in mouse models of α -synuclein toxicity¹⁵⁹. Increased α -synuclein expression also increases toll-like receptor (TLR)-4 immunoreactivity in mouse models of MSA¹⁵⁴.

Various mechanisms have been proposed through which α -synuclein might induce a neuroinflammatory response. Extracellular α -synuclein released from neurons has been found to be an endogenous agonist for TLR2, leading to microglial activation¹⁶⁰, whereas oligomeric α -synuclein has been proposed to directly bind the heterodimer TLR1/2 on the cell membrane to induce a proinflammatory response dependent on myeloid differentiation primary response gene 88 (MyD88) (ref. 161). α -synuclein has also been suggested to be a chemoattractant that promotes microglial migration¹⁶², and proinflammatory

responses to α -synuclein toxicity might be additionally mediated by the microRNA-155 (miR-155)¹⁶³. Finally, dopaminergic neurons in PD might be particularly susceptible to immunomodulation, because mice lacking cytokine IFN- β develop spontaneous neurodegeneration of dopaminergic neurons, motor and cognitive impairments and Lewy body pathology¹⁶⁴, and genetic polymorphisms in the locus of HLA-DR—a component of MHCII—have been linked to late-onset sporadic PD¹⁶⁵. Further studies on the role of neuroinflammation and microglial activation in α -synuclein toxicity will thus be important for understanding α -synuclein pathophysiology and might additionally contribute to the development of future therapeutics for synucleinopathies.

Interplay of α -synuclein with $a\beta$ and tau.

Lewy body pathology is observed in about half of patients with AD, and soluble α -synuclein levels are increased in AD-afflicted brains and correlated with cognitive decline³⁶, which suggests that α -synuclein might contribute to hippocampal and cholinergic neurodegeneration in AD. Early studies using doubly transgenic mouse models found that $a\beta$ enhanced α -synuclein fibrilization both *in vitro* and *in vivo*²², and that α -synuclein promoted $a\beta$ 1–38 aggregation upon coinubation *in vitro*²¹. By contrast, injection of α -synuclein fibrils into transgenic mouse models of AD failed to cross-seed $a\beta$ *in vivo*, and mice co-expressing α -synuclein A30P actually inhibited plaque formation in transgenic mutant amyloid precursor protein (APP) and presenilin 1 (PS1) mice¹⁹. These intriguing findings suggest that in contrast to α -synuclein's ability to cross-seed both itself and tau, α -synuclein suppresses $a\beta$ deposition and reduces plaque formation *in vivo*. Further studies will thus be crucial for examining whether α -synuclein directly interacts with $a\beta$ and whether preventing $a\beta$ aggregation increases the levels of toxic $a\beta$ oligomers and contributes to neuronal dysfunction, despite a reduction in plaque formation.

Interestingly, tau has previously been identified as a PD risk factor¹³. α -synuclein and tau cross-seed one another, and their coinubation leads to the fibrilization of both proteins^{20,23}. Misexpression of α -synuclein and tau in *Drosophila* leads to neuronal dysfunction and axonal transport defects¹⁶⁶, and α -synuclein oligomers potentially impair microtubule assembly¹⁰⁵. However, the precise role of the interplay between tau and α -synuclein in disease and the downstream cellular dysfunction that may occur remain to be further investigated.

Future questions in α -synuclein research

Multiple pathways and contributing factors have been investigated in the context of α -synuclein toxicity. However, several crucial questions remain unanswered in this field:

What are the precise mechanisms through which α -synuclein disrupts cellular pathways?

At the synapse, the pathological role of α -synuclein still remains controversial as to whether α -synuclein toxicity involves a loss of its physiological function at the synapse. Furthermore, the exact steps of synaptic-vesicle trafficking that are disrupted in disease, whether synaptic defects preferentially affect specific neuronal subpopulations and how pathogenic forms of α -synuclein interact with synaptic-vesicle machinery still remain

unclear. In addition, whether α -synuclein affects mitochondrial function directly by interacting with mitochondrial lipids and proteins or indirectly through other organelles is also unknown. Similarly, α -synuclein has been shown to disrupt multiple ER functions, including Golgi trafficking and calcium buffering, but the precise mechanisms through which α -synuclein interacts with ER proteins to induce these defects also remain unclear. Finally, as previously mentioned, few studies have examined the effect of α -synuclein toxicity on inter-organelle contacts or the live-cell dynamics of organelles. Thus, studies investigating α -synuclein's cellular localization, dynamics and interaction partners will be important for advancing our understanding of the basic cellular mechanisms through which α -synuclein disrupts organelle function.

Which cellular pathways are disrupted earliest in synucleinopathies?

This might depend on both the type of synucleinopathy and on genetic heterogeneity between patients, which could leave different pathways more susceptible to dysfunction. PD-linked mutations and risk factors cluster predominantly around endolysosomal proteins (LRRK2, ATP13A2 and GCase) and mitochondrial proteins (parkin, PINK1 and DJ-1), which suggests that α -synuclein might mediate the convergence between endolysosomal and mitochondrial pathway dysfunction in PD, and that these pathways might be disrupted early on in disease progression. Importantly, identifying which pathways are affected earliest in disease will be highly valuable for therapeutic development. For example, if decreased mitochondrial biogenesis due to decreased PGC-1 α activation is an early step in α -synuclein-induced toxicity, activators of PGC-1 α might be important for reducing cellular dysfunction. By contrast, if decreased mitochondrial biogenesis occurs as a compensatory response to inefficient lysosomal degradation, the activation of PGC-1 α could potentially exacerbate α -synuclein toxicity at later stages. Thus, future studies examining organelle dynamics and function in living cells over extended periods of time will be crucial to confirm the order of cellular pathway dysfunction in PD and other synucleinopathies.

Which factors contribute to α -synuclein accumulation?

Genetic forms of PD exemplify the crucial role of α -synuclein dosage on its toxicity, because both α -synuclein locus duplication and triplication lead to familial PD^{11,12}. In these cases, α -synuclein accumulation is a known starting cause of pathophysiology, and targeting α -synuclein directly or potential downstream pathways might be beneficial. By contrast, in sporadic forms of PD and other synucleinopathies, α -synuclein ultimately accumulates into Lewy bodies even without mutations or increased dosage levels of α -synuclein, which suggests that upstream factors, such as oxidation, nitration, decreased proteasomal and/or lysosomal function, increased dopamine adducts or interplay with $\alpha\beta$ and tau might contribute to α -synuclein accumulation. Furthermore cell-to-cell spreading involving neurons and/or glia might further contribute to the accumulation of α -synuclein in specific cellular subtypes, such as SNc dopaminergic neurons in PD or oligodendrocytes in MSA. Importantly, different factors might be more important in different synucleinopathies, or a combination of factors might be necessary to trigger initial α -synuclein accumulation. In these cases, targeting upstream factors that lead to α -synuclein accumulation would be most effective, and could even be preventive if targeted during prodromal stages before clinical onset. Finally, a subset of familial forms of PD linked to genes other than that encoding

α -synuclein also results in α -synuclein accumulation, which suggests that mutations in these genes might exacerbate the role of the upstream factors previously mentioned, or alternatively, might lead to α -synuclein accumulation through an independent pathway specific to that gene. Thus, understanding the nuances and the role that each factor has in different synucleinopathies and across patient populations will be crucial for informing our knowledge of α -synuclein toxicity in disease.

Therapeutically targeting α -synuclein in neurodegeneration

Various studies have targeted α -synuclein directly at various stages of its synthesis and action as a potential therapeutic intervention (Fig. 2). In addition, there are other therapeutic approaches currently in clinical trials that target contributing factors to α -synuclein toxicity, such as the selective vulnerability of A9 SNc dopaminergic neurons in PD using the calcium-channel blocker isradipine, which may also prove to be successful for treating synucleinopathies.

Reducing α -synuclein synthesis.

Given that increased α -synuclein expression causes familial PD, several studies have aimed to decrease its synthesis by using siRNA that targets α -synuclein mRNA. In mice, direct siRNA infusion decreases hippocampal and cortical α -synuclein levels for a week after infusion¹⁶⁷, whereas in mice expressing a human form of α -synuclein, injecting siRNA-containing exosomes decreases protein aggregation in the SNc¹⁶⁸. Given that antisense oligonucleotide (ASO)-mediated therapies are being tested in clinical trials currently as potential therapeutics for other neurodegenerative diseases, ASO targeting of α -synuclein may also be effective.

Increasing α -synuclein protein degradation.

Another mechanism for targeting α -synuclein involves increasing its lysosomal and/or autophagic degradation. Indeed, α -synuclein degradation is regulated by SIAH¹⁶⁹ and NEDD4 (ref. 170) ubiquitin ligases, S129 phosphorylation by polo-like kinase 2 (PLK2)¹⁷¹ and activation of lysosomal cysteine cathepsins¹⁷². Overexpression of the lysosomal transcription factor TFEB in rats expressing α -synuclein decreases α -synuclein oligomer levels and prevents lysosomal dysfunction decline and neurodegeneration¹⁰⁰. Passive immunization of mice overexpressing α -synuclein by using antibodies against α -synuclein also promote its lysosomal clearance¹⁷³ or target it into microglia, which rescues α -synuclein-induced neurodegeneration and behavioral deficits¹⁷⁴.

Another important therapeutic target that has emerged for α -synuclein degradation is GCase, because increased GCase levels enhance α -synuclein degradation in human neurons⁸⁰. Importantly expression of GCase in the central nervous system reduces α -synuclein aggregation in a presymptomatic mouse model of Gaucher's-related synucleinopathy mice; decreases soluble α -synuclein in mice expressing mutant human A53T α -synuclein¹⁷⁵; and reduces α -synuclein accumulation and dopaminergic neurodegeneration in several rodent models of α -synuclein toxicity^{176,177}. Recently, two noninhibitory GCase modulators (NCGC00188758 and NCGC607) were also found to increase GCase activity and decrease

α -synuclein accumulation and toxicity in human neurons derived from iPSCs^{107,178}. Furthermore, patients with Gaucher's disease who receive GCase enzyme replacement therapy (ERT) for more than 5 years have reduced oligomeric α -synuclein levels when compared with those who did not receive therapy¹⁷⁹, which further confirms the validity of increasing GCase activity as a therapeutic approach. Finally, increased expression of other lysosomal proteins, including LIMP2 (ref. 180) and ATP13A2 (refs. 181,182), also promote α -synuclein degradation in various models, presenting additional targets for the acceleration of α -synuclein degradation.

Reducing α -synuclein aggregation.

Given that α -synuclein oligomers and fibrils are implicated in α -synuclein toxicity, several strategies have been attempted to reduce their formation. The porphyrin phthalocyanine tetrasulfonate binds and stabilizes vesicle-associated α -synuclein, which thus delays its misfolding and aggregation¹⁸³. Passive immunization using a protofibril-selective antibody decreases soluble and membrane-bound α -synuclein protofibrils in the spinal cord and decreases motor dysfunction in mice expressing PD-associated mutant A30P α -synuclein¹⁸⁴. In addition, if native α -synuclein exists predominantly as a tetramer, compounds that stabilize α -synuclein in this conformation—as has been applied for transthyretin, which misfolds in the multisystem disorder transthyretin-related amyloidosis—might be effective at combating α -synuclein toxicity¹⁸⁵. Several clinical trials are currently using small molecules¹⁸⁶ to inhibit either α -synuclein aggregation (glycerol phenylbutyrate (University of Colorado, Denver); nilotinib (Georgetown University)) or α -synuclein oligomer formation (EGCG (University of Munich)).

Blocking α -synuclein propagation.

Because α -synuclein propagation may contribute to the spreading of α -synuclein toxicity, passive immunization studies to block spreading have also been performed. Antibodies against C-terminal truncated α -synuclein decrease its propagation *in vitro* and rescue motor and memory impairments in an α -synuclein mouse model¹⁸⁷, and monoclonal α -synuclein antibodies prevent propagation and uptake of α -synuclein and rescue dopaminergic neuron loss and motor deficits in mice injected with α -synuclein pffs¹⁸⁸. Importantly, understanding the role of propagation in disease will help to clarify whether these therapies will be successful for patients.

Active immunization.

Multiple studies have used active immunization to target α -synuclein. The first of these studies vaccinated human α -synuclein transgenic mice using human α -synuclein, which cleared α -synuclein aggregates, potentially via lysosomal pathways¹⁸⁹. Subsequent studies have treated different α -synuclein transgenic mice with various forms of human α -synuclein antigen, with similar reductions in aggregates, improved motor and memory functions and reduced dopaminergic degeneration and dopamine loss¹⁸⁶. Current PD and MSA clinical trials directly targeting α -synuclein involve active immunization with the vaccines PD01A and PD03A (AFFiRiS) for α -synuclein¹⁸⁶ or passive immunization with antibodies against α -synuclein¹⁹⁰, including PRX002 (Prothena) and BIIB054 (Biogen).

Targeted drug development

Previous clinical trials for PD have focused predominantly on improving general cellular pathways to slow disease progression, such as correcting mitochondrial dysfunction and oxidative damage with coenzyme Q10 (ref. 191). However, these studies have been unsuccessful at slowing disease progression, potentially because of the absence of defined therapeutic molecular pathways and targets, heterogeneity within patient populations and a lack of relevant biomarkers as clear readouts for drug efficacy. Consequently, future clinical studies with well-defined therapeutic targets backed by an improved understanding of the basic cellular mechanisms behind disease pathophysiology and the pathways affected early in disease will be crucial for improving clinical trial outcomes, both in PD and other synucleinopathies.

Therapeutically targeting α -synuclein via GCase is one example of a well-defined molecular target; multiple studies have now shown that GCase activation promotes α -synuclein degradation both *in vitro* and *in vivo*¹⁹². Moreover, because GCase is an enzyme with well-characterized substrates, drugs that target GCase can be examined early on during the clinical trial for their efficacy by measuring GCase enzyme activity levels in plasma and cerebrospinal fluid (CSF) to show effective target engagement, as well as α -synuclein plasma and CSF levels as clear readouts of α -synuclein degradation rates and potential biomarkers for disease risk and progression¹⁹³. Finally, further stratification of patient populations by well-characterized biomarkers, genetic screening and consistent clinical diagnostics before trial enrollment will also be important for producing a more homogenous patient population. Importantly, future work advancing our knowledge of α -synuclein toxicity as it relates to factors such as strain differences, propagation and interaction with other proteins such as $a\beta$ and tau may also influence future drug development and clinical trial design.

Targeting the immune system.

Finally, the role of neuroinflammation in α -synuclein toxicity has also received much attention recently, and multiple studies are now examining the effect of manipulating the immune system to reduce α -synuclein toxicity. Treatment with the hypertension drug Candesartan cilexetil inhibited TLR2 expression and reduced the proinflammatory response *in vitro* in microglia treated with oligomeric α -synuclein¹⁶¹. In rat models of α -synuclein toxicity, treatment with either the immunosuppressant FK506 or AZD1480, a JAK1/2 inhibitor of the JAK–STAT pathway important for microglial activation and cytokine expression, reduced dopaminergic neurodegeneration^{194,195}. In addition, treatment with potentially anti-inflammatory drugs, including hypoxanthine (a NF- κ B modulator) or lenalidomide (an NF- κ B signaling inhibitor) reduced motor-behavior defects and microgliosis in α -synuclein transgenic mice^{196,197}. Thus, immunomodulation might be an important regulator of α -synuclein toxicity and a potential therapeutic target in combination with direct targeting of α -synuclein.

Conclusions and future directions

Two decades ago, α -synuclein was identified as the main component of Lewy bodies¹ and genetically linked to familial PD⁴. Since then, numerous studies have implicated multiple dysfunctional pathways in its toxicity, as well as contributing factors, including its propagation, strain differences and glial activation. Importantly, these findings have identified various routes by which to therapeutically target α -synuclein, ranging from active and passive immunization to the upregulation of lysosomal machinery.

Several key goals still remain, including the establishment of a timeline of cellular pathway dysfunction during the progression of different synucleinopathies, further characterization of toxic and native α -synuclein species in control and disease-afflicted human brains, the identification of the role of α -synuclein propagation versus cell-autonomous factors and investigation of the role of glia and neuroinflammation. Finally, because α -synuclein is intimately connected with the fibrilization of both $a\beta$ and tau—key proteins in AD pathogenesis—understanding the interplay between these three proteins in the context of propagation and cellular toxicity will be crucial for advancing our understanding of AD and synucleinopathies, and potentially, for identifying novel therapeutics that are relevant to both fields.

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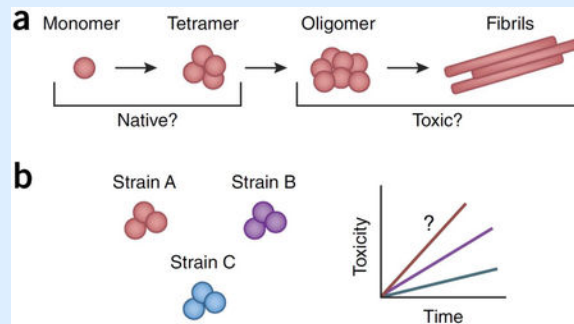
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Box 1**Understanding the many conformations of α -synuclein****Native conformations: monomer and tetramer.**

α -synuclein is able to transition between multiple different conformations, including monomers, tetramers, higher-level oligomers (soluble conformations), fibrils (highly ordered insoluble conformations characterized by β -sheet conformation) and aggregates shown in **a**. Early work demonstrated that α -synuclein natively exists as a monomer⁴⁰, and recent studies have used α -synuclein purified from mouse brain¹⁹⁸ and analysis of mammalian cells¹⁹⁹ to demonstrate a compact monomeric state for native α -synuclein, which helps to shield its non-amyloid- β component (NAC) region from spontaneous aggregation. In addition, α -synuclein has also been observed to exist as both metastable conformers and stable monomers²⁰⁰, as well as to form tetramers^{201,202} mediated by its KTKEGV repeats²⁰³. PD-linked α -synuclein mutations, including A53T and E46K, decrease its tetrameric and increase its monomeric conformation, which suggests that the unfolded monomer might be a source of α -synuclein toxicity¹⁸⁵. Thus, multiple forms of native α -synuclein might exist physiologically, depending on its cellular localization and membrane interactions.

Forming toxic conformations: oligomers and fibrils.

Multiple studies have examined the factors that promote α -synuclein's initial oligomerization. Polyunsaturated fatty acids increase α -synuclein oligomer levels, whereas saturated fatty acids decrease them²⁰⁴. In addition, a low amount of negatively charged lipids²⁰⁵, mildly acidic environments such as endosomes and lysosomes²⁰⁶, and lipid vesicles all promote α -synuclein oligomerization²⁰⁷. Upon formation, α -synuclein oligomers subsequently undergo conformational changes to become more stable and compact proteinase-K-resistant oligomers, which induce higher oxidative stress, before becoming fibrils²⁰⁸.

Several studies have now begun to investigate whether oligomers or downstream fibrils are the more toxic conformation. Some reports have suggested that oligomers are more toxic, because α -synuclein transgenic mice and PD- and DLB-afflicted patient brains showed increased levels of soluble, lipid-dependent α -synuclein oligomers when compared to controls²⁰⁴. α -synuclein PD-linked A53T and A30P mutations also accelerate oligomerization but not fibrilization²⁰⁹, and injection of α -synuclein variants

promoting oligomer rather than fibril formation into the rat brain causes more severe dopaminergic loss²¹⁰.

By contrast, recent work has suggested that α -synuclein fibrils might be 1,000-fold more toxic than their precursors²¹¹, and injection of different human α -synuclein assemblies into rat SNc demonstrated that fibrils rather than ribbons or oligomers induced the greatest amount of motor impairment, dopaminergic cell loss and synaptic impairment¹⁴⁰. Thus, further studying the role of different α -synuclein conformations, such as oligomers and fibrils, in disease will be helpful for understanding α -synuclein toxicity.

Differential strains.

Recent studies on α -synuclein have identified the existence of different strains, shown in **b** defined as conformational variants of α -synuclein—that exhibit distinct properties such as differences in structure and toxicity and ability to seed, propagate¹⁰⁸ and cross-seed tau fibrilization²⁰. These strain differences can occur both naturally or result from nuances in experimental preparation of higher-level α -synuclein conformations (i.e., oligomers and/or fibrils). Differences in α -synuclein strains have also been observed across different species (such as human and mouse); human α -synuclein but not mouse α -synuclein fibril inoculation into wild-type mice decreased Lewy body formation and was more effective in α -synuclein knockout mice as compared to wild-type mice, which suggests that efficient spreading might be attenuated when fibril and host monomers are from different species^{212,213}.

In addition, differences in α -synuclein strains also exist between synucleinopathies, such as PD and MSA. Interestingly, brain extracts from patients with MSA but not those with PD accelerated neurodegeneration when injected into transgenic mice, suggesting that MSA-derived strains of α -synuclein might be more toxic²¹⁴. Furthermore, brain extracts from different patients with MSA showed variable rates of α -synuclein transmission²¹⁵, which suggests the presence of patient-to-patient strain variability even within MSA. Importantly, α -synuclein strain differences among patients may contribute to patient variability such as age of onset and rate of disease progression.

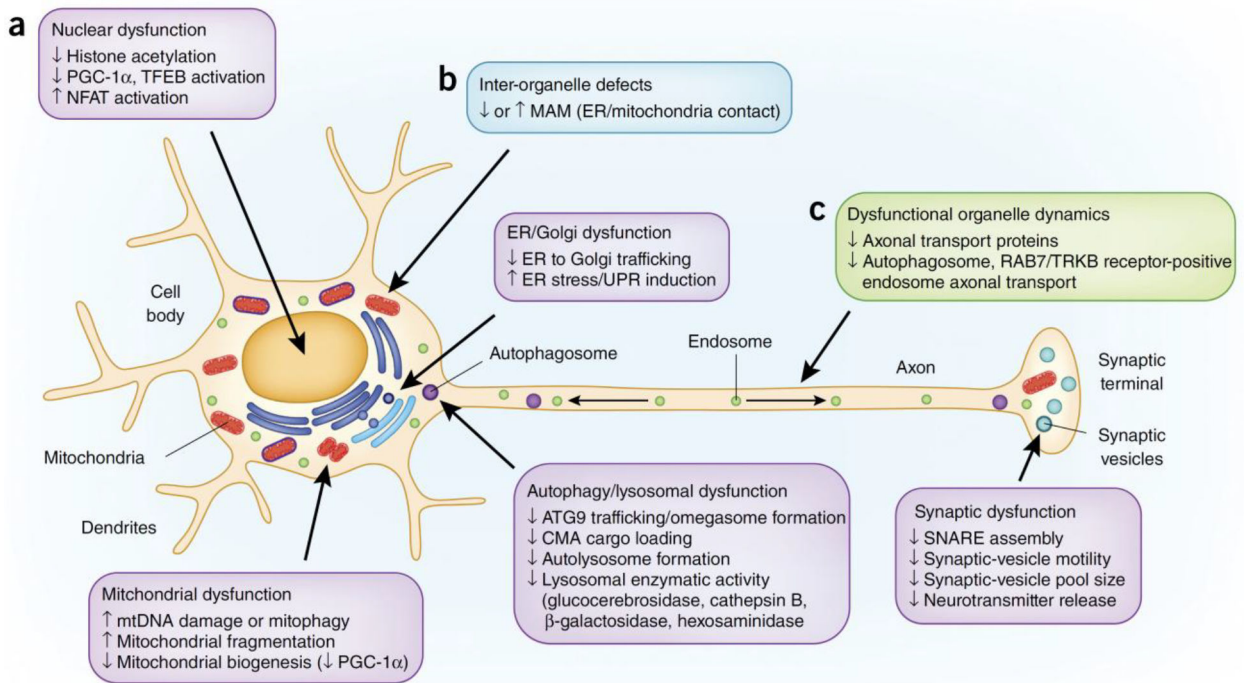


Figure 1. Pathways implicated in α -synuclein toxicity. (a–c) Organelle dysfunction (a, purple boxes), defects in inter-organelle contacts (b, blue box) and dysfunctional organelle dynamics (c, green box) have all been implicated in α -synuclein toxicity.

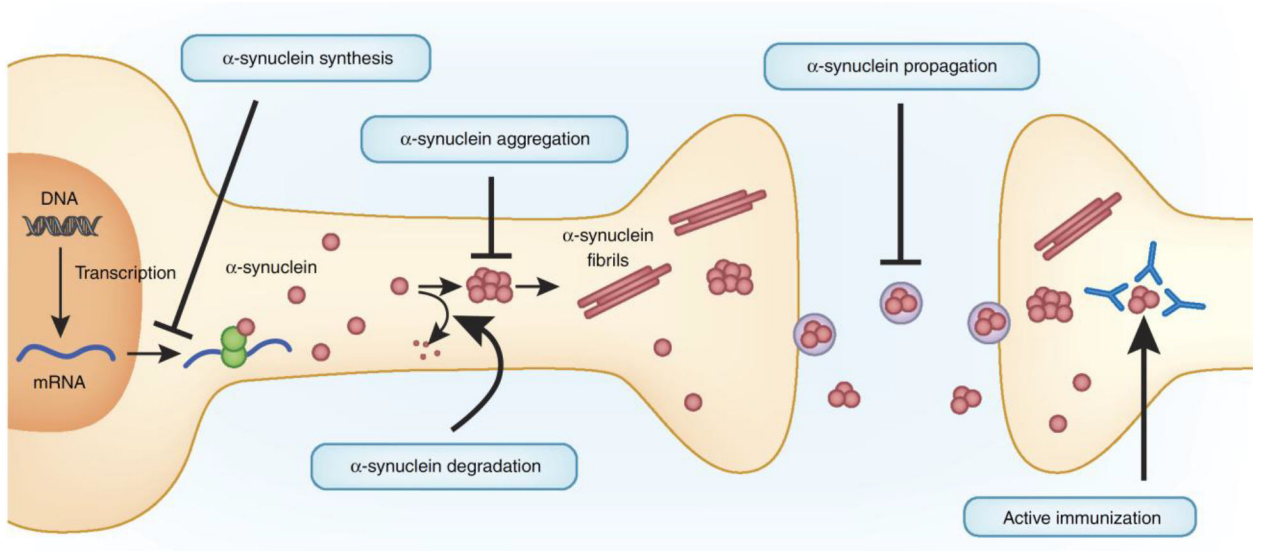


Figure 2.

Therapeutically targeting α -synuclein toxicity. Various pathways have been manipulated to decrease α -synuclein toxicity, largely in mouse models of α -synuclein toxicity. These include (i) reducing α -synuclein synthesis with siRNAs, (ii) increasing α -synuclein degradation, (iii) reducing α -synuclein aggregation, (iv) blocking α -synuclein propagation and (v) active immunization of α -synuclein. Drug development to increase lysosomal activity via glucocerebrosidase (GCase) to accelerate α -synuclein degradation, as well as clinical trials using both passive and active immunization against α -synuclein, are currently under way.

Table 1

Summary of diseases associated with α -synuclein toxicity

Disease	Genes associated	Symptoms	Pathology
Parkinson's disease (PD)	<ul style="list-style-type: none"> Autosomal dominant (<i>SNCA</i>⁴⁻¹⁰, <i>LRRK2</i>, <i>VPS35</i>, <i>EIF4G1</i>, <i>DNAJC13</i>, <i>CHCHD2</i>; <i>SNCA</i> duplication/triplication^{11,12}) Autosomal recessive (<i>PARK2</i>, <i>PINK1</i> and <i>DJ-1</i>) 	<ul style="list-style-type: none"> Parkinsonism (bradykinesia, muscular rigidity, resting tremors and postural instability)²⁴ Nonmotor symptoms (constipation, impaired olfaction and rapid-eye movement sleep behavior disorder (RBD)) Cognitive impairment 	<ul style="list-style-type: none"> SNC dopaminergic degeneration²⁴ Variable neuron loss in areas including locus coeruleus (LC), dorsal motor nucleus of the vagus (DMV) and the olfactory bulb^{1,23} α-synuclein Lewy body and neurite pathology in neurons¹
Parkinson's disease with dementia (PDD) or dementia with Lewy bodies (DLB)	N/A	<ul style="list-style-type: none"> Parkinsonism and dementia³⁴ In DLB versus PDD: fewer resting tremors, bilateral parkinsonism 	<ul style="list-style-type: none"> Cholinergic/SNC dopaminergic degeneration³⁴ α-synuclein Lewy body and neurite pathology in neurons¹⁷ β amyloid plaques and tau tangles
Multiple system atrophy (MSA)	<ul style="list-style-type: none"> Autosomal dominant (<i>SHC2</i> copy-number loss, <i>SNCA</i>) Autosomal recessive (<i>COQ2</i>) 	<ul style="list-style-type: none"> Parkinsonism, cerebellar ataxia, autonomic failure³³ Nonmotor symptoms (sexual dysfunction, urinary incontinence and RBD) 	<ul style="list-style-type: none"> SNC/olivopontocerebellar degeneration³³ α-synuclein pathology in oligodendrocytes¹⁶
Gaucher's disease (GD)	<ul style="list-style-type: none"> Autosomal recessive (<i>GBA1</i>) 	<ul style="list-style-type: none"> Type I adult-onset (thrombocytopenia, anemia, hepatosplenomegaly and bone pain)³⁷ Type II (infant)/III (juvenile) neuropathic form (seizures, cognitive impairment and oculomotor problems) 	<ul style="list-style-type: none"> α-synuclein Lewy body and neurite pathology in some patients³⁷
Additional lysosomal storage disorders (LSDs)	<ul style="list-style-type: none"> Sanfilippo syndrome (<i>SGSH</i>, <i>NAGLU</i>) Tay-Sachs and Sandhoff diseases (<i>HEXA/HEXB</i>) Hunter's syndrome (<i>IDS</i>) Niemann-Pick type C (<i>NPC1/2</i>) 	<ul style="list-style-type: none"> Multisystem disorder¹⁸ 	<ul style="list-style-type: none"> α-synuclein Lewy body and neurite pathology in some patients¹⁸
Neurodegeneration with brain iron accumulation (NBIA)	<ul style="list-style-type: none"> Autosomal recessive (<i>CLN9orf12</i>, <i>PLA2G6</i>, <i>ATP13A2/PARK9</i>) 	<ul style="list-style-type: none"> Variable symptoms that may include dystonia, muscle rigidity, spasticity and ataxia³⁹ 	<ul style="list-style-type: none"> Iron accumulation in the globus pallidus and SNC³⁹

Disease	Genes associated	Symptoms	Pathology
Alzheimer's disease (AD)	<ul style="list-style-type: none"> Autosomal dominant (<i>APOE</i>, <i>PS 1/2</i>) 	<ul style="list-style-type: none"> Progressive memory loss³⁵ Cognitive impairment 	<ul style="list-style-type: none"> α-synuclein Lewy body and neurite pathology in some patients Cortical and CA1 hippocampal degeneration³⁵ $A\beta$ amyloid plaques and tau tangles α-synuclein Lewy body and neurite pathology in some patients