Physiological Function of Alpha-Synuclein

Subjects: Neurosciences

Contributor: Tian-Sin Fan , Ruey-Meei Wu , Jamir Pitton Rissardo

Synucleinopathy underlies a wide spectrum of clinical syndromes, including Parkinson's disease (PD), Parkinson's disease dementia (PDD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), and pure autonomic failure (PAF). A common feature of these syndromes is alpha-synuclein (aS) aggregation and cellular inclusions. In synucleinopathies, the formation of the distinct αS species is determined by the nature of the self-assembly processes, which is influenced by many factors including the SNCA mutation or multiplication, epigenetic regulation, post-translational modification, micro-environments, etc. Both the oligomeric and fibrillar forms of αS are toxic to cells. The detrimental effects of αS continue to grow as αS fibrils start to form LBs, which can cause mitochondrial disassembly, mitophagy, mitochondrial depolarization, and synaptic dysfunction that result in progressive neurodegeneration.

Alpha-Synuclein Parkinson Disease Lewy body Neurodegeneration Biomarker Dementia SNCA

1. Alpha-Synuclein, Lewy Body, and Dementia

Synucleinopathy underlies a wide spectrum of clinical syndromes, including PD, PDD, dementia with Lewy bodies (DLB), multiple system atrophy (MSA), and pure autonomic failure (PAF). The first link of PD to αS was also the first conclusive demonstration of a genetic defect leading to PD, and thus has historical and conceptual value. In order to provide diagnostic accuracy and define patients likely to respond to disease-modifying therapy, a hierarchical classification has been proposed based on the underlying pathological protein deposition (αS), cellular inclusions (Lewy bodies or glial cytoplasmic inclusion, GCI), and clinical phenotypes (parkinsonism, dementia, or autonomic failure) [1]. The pathological hallmark of MSA is the presence of GCI in oligodendrocytes. In PAF, there is predominantly a peripheral deposition of Lewy bodies in autonomic ganglia and nerve fibers without evidence of central nervous system (CNS) dysfunction other than rapid eye movement sleep behavior disorder (REMSBD). Patients with PAF have an increased risk of developing PD, DLB, or MSA later in life [2], possibly indicating a pathophysiological disease continuum. REMSBD is a well-recognized prodrome of synucleinopathies [3], as well as a risk factor of developing cognitive impairment [4].

The Lewy body is a hallmark pathological feature in familial PD, sporadic PD, and other Lewy body diseases (LBD), including PDD and DLB [5][6][7]. They share αS aggregation and cellular inclusions of Lewy bodies as their key pathogenic events [8][9]. PDD and DLB are together known as Lewy body dementia, and the timing of dementia relative to the clinical features of parkinsonism is the major clinical distinction between PDD and DLB. PDD

describes dementia that occurs at least one year after the onset of well-established PD (the one-year rule) [10], whereas in DLB, dementia essentially precedes or co-occurs with parkinsonism and has core features of cognitive fluctuation and visual hallucination [11]. Although PDD and DLB share many overlapping clinical and pathological features, there are major differences. Histopathologically, limbic and neocortical involvement of Lewy pathology are both found in PDD and DLB. However, there is a higher burden of neocortical and limbic LBs, more prominent cortical atrophy, and a higher prevalence of coincident Alzheimer's disease (AD) pathology in DLB compared with PDD [12][13]. The propensity for LB propagation by seeding may differ between PDD and DLB as well [14]. On the other hand, at PDD's early stage, it shares a similar αS pathology with PD. Clinically, DLB does not begin with PD or PDD. DLB and PDD also differ in cognitive profiles. Memory and language impairments progress faster in DLB, whereas executive dysfunction progresses more quickly in PDD [15]. Controversy still exists as to whether PDD and DLB should be considered as separate disease entities, or as two ends of the LBD spectrum beginning at the Lewy pathology end with incidental Lewy body disease, through to PD, PDD, and DLB with AD at the amyloid pathology end. There is emerging agreement in clinical trials and research settings that PDD and DLB should be distinguished as two syndromes.

Another emerging concept connecting pathophysiology and cognitive function in neurodegenerative diseases is oscillopathies, which refer to conditions characterized by the abnormal synchronization of synaptic activity [16]. Accumulation of αS can alter synaptic structure and function, in turn impairing the physiological transmission through the cortico–basal ganglia–thalamic circuits, accounting for abnormalities in motor and cognitive function. Mitochondrial dysfunction is one of the putative mechanisms in many neurodegenerative disorders. The generation of neuronal oscillations highly relies on mitochondrial energy provision. Distinct patterns of brain oscillations may correlate with clinical symptoms and network impairment secondary to physiopathological changes [17].

2. Physiological Function and Potential Toxicity of Alpha-Synuclein

Alpha-synuclein (αS) is a 140-amino-acid protein localized in presynaptic nerve terminals [18]. It has three domains with distinct biochemical properties corresponding to the amino acid composition (**Figure 1**). The first 60 residues are known as the N-terminal domain; this region demonstrates α-helical propensity and an amphipathic membrane binding ability [19]. The non-amyloid β-component of plaque (NAC) domain comprises residues 61–95; this region is highly amyloidogenic and responsible for protofibril and fibril formation and aggregation [20]. The carboxyl-terminal (C-terminal) domain, composed of residues 96–140, is the segment where major phosphorylation and truncation occurs. The C-terminal domain of αS limits pathologic misfolding and aggregation due to its structural factors. The negatively charged C-terminal domain works as a self-chaperone to prevent αS fibrillation by interaction with the NAC region [21]. Loss of acidic C-terminal residues through truncation promotes fibril formation [22]. The complete physiological function of αS remains unknown, though it is well established that αS is involved in various neurophysiological processes, including synaptic vesicle recycling, neurotransmission, and synaptic plasticity [23][24][25][26].

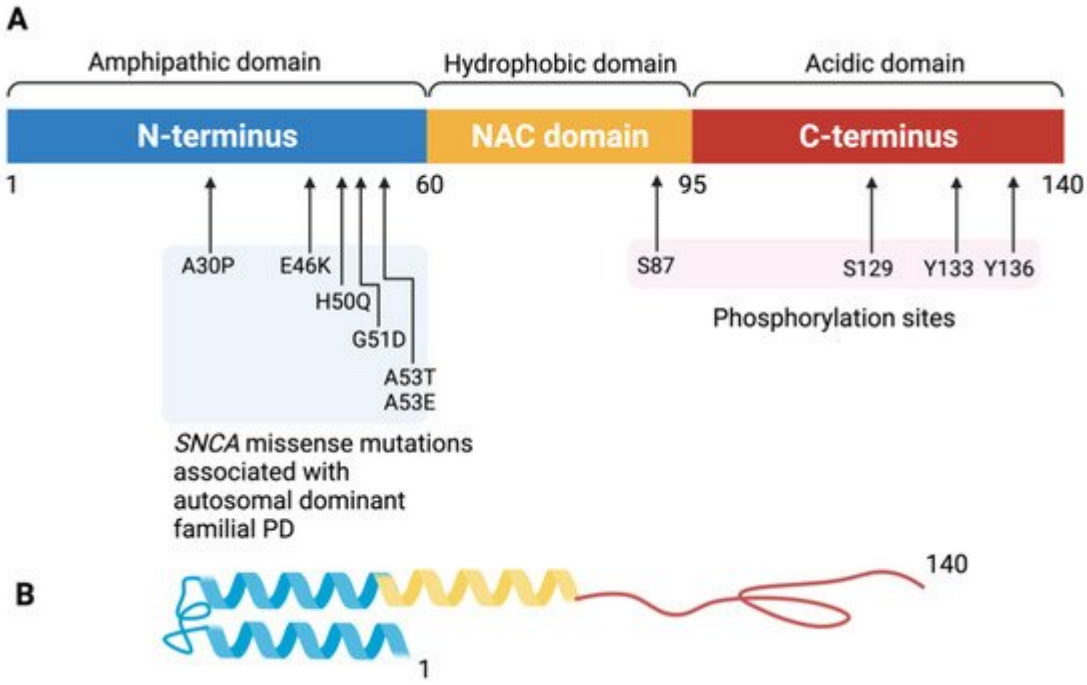

Figure 1. The structure of the alpha-synuclein monomer. (**A**) Schematic depiction of alpha-synuclein structure. The amino acid residues delimiting the N-terminus, NAC region, and C-terminus as well as those that are sites of known mutations are labeled. The 140-amino-acid protein can be divided into three distinct domains. The N-terminal amphipathic domain (in blue) contains the amino acid residues affected by the main alpha-synuclein gene mutations (A30P, E46K, H50Q, G51D, A53T, A53E) associated with autosomal dominant Parkinson disease. The N-terminal region has a helical folding propensity and is responsible for membrane binding. The hydrophobic non-amyloid β-component of plaque (NAC) domain (in yellow) is responsible for promoting aggregation. The C-terminal domain (in red) forms an acidic tail containing the main phosphorylation site at Ser129. The C-terminal domain modulates alpha-synuclein aggregation. (**B**) Tertiary structure of the α-synuclein monomer. Created with BioRender.com (accessed on 12 October 2021).

αS is normally a soluble protein, but it can aggregate to form insoluble fibrils which, in association with other molecules such as ubiquitin, neurofilament protein, alpha B crystallin, organelles, and lipid membranes, form Lewy bodies [27][28]. αS can exist in the neuron in a monomeric, oligomeric, and soluble protofibrillary state [29]. Monomeric αS is highly dynamic and can populate a large number of different conformational or assembly states [30][31]. In synucleinopathies, the formation of the distinct αS species is determined by the nature of the self-assembly processes, which is influenced by many factors including the alpha synuclein gene (HGNC approved symbol *SNCA*) mutation or multiplication, epigenetic regulation, post-translational modification, micro-environments, etc. [32][33]. The distinct forms of the αS protein stack aggregates in neurons, nerve fibers, or glial cells at different rates, and can lead to mixed fibrillar polymorphs (species) with different intermolecular interactions, surface characteristics, and pathological consequences [34][35][36]. However, the precise connection between αS cluster structure and toxicity remains a subject of intense and controversial discussion [34]. We will summarize the literature in the following paragraphs.

Both the oligomeric and fibrillar forms of αS are toxic to cells, but whether αS oligomers or fibrils are more toxic remains a subject of debate [34]. αS protofibrils disrupt cellular homeostasis and mediate neuronal death via intracellular targets. Secreted α-synuclein may exert deleterious effects on neighboring cells. Growing experimental evidence suggests that specific oligomeric species are the most cytotoxic forms of αS and play a key role in disease [37][38][39]. On the other hand, αS fibrils have also been reported to be toxic and their toxicity has been associated with membrane perturbation [40][41][42]. While oligomers are possibly implicated in the collapse of neuronal homeostasis, the fibrillar state(s) appears to be the most efficient at propagating itself both in vitro and in vivo. While αS oligomers possess toxic properties and are more robust than fibrils, there is no convincing evidence that they can spread in vivo rather than be formed as a collateral effect of the overall aggregation process [43]. In fact, there is no evidence that non-fibrillar oligomers can propagate in a manner similar to that of fibrils [34]. The αS fibrils can continue to aggregate in association with other proteins such as ubiquitin, neurofilament protein, and alpha B crystallin and form Lewy body-like inclusions [44][45]. The mechanistic relationship between oligomers and fibrils remains to be clarified, both in terms of oligomer assembly into fibrils and the potential dissolution of fibrils into oligomers [34].

αS clusters (oligomers and fibrils) can harm cells through various mechanisms, presumably by interacting with other biomolecules and organelles [46]. For example, it has been proposed that αS could interact with synaptic vesicles and synaptic proteins such as phospholipase D2 [47], various members of the family of RAB small GTPases [48], and SNARE complexes [35][49]. αS neurotoxicants can be classified as various channel inhibitors, receptor inhibitors, receptor agonists, synaptic vesicle inhibitors, and many more [32]. The toxicity of αS fibrils and oligomers is in part the consequence of changing the characteristics of lipid membranes. They affect, for example, membrane permeabilization and the formation of pore-like structures [50][51][52][53], lipid diffusion and packaging [54], synaptic vesicle fusion pore size [55], and membrane curvature [56]. The possible targets of αS include synaptic vesicles [57], endoplasmic reticulum (ER)–Golgi transport [58][59], mitochondria [60][61][62], and lysosomes and other proteolytic machinery [63][64][65]. The general principle is that multiple systems can be affected by αS clusters and, if they have a common attribute, they are likely to be lipid membranes [66].

The detrimental effects of αS continue to grow as αS fibrils start to form LBs. The exact mechanisms that promote the aggregation of αS into LBs and what role aggregation plays in pathogenesis remain to be clarified. A time-dependent shift in the morphology and localization of αS pathology from fibrils to cell body inclusions has been demonstrated. The initial aggregation of αS likely starts in presynaptic terminals and accumulates in axons. After reaching the neuronal cell body, αS aggregates recruit more αS monomers, undergo posttranslational modifications, and interact with other cellular components to form mature LBs. LB formation and maturation can cause mitochondrial disassembly, mitophagy, mitochondrial depolarization, and synaptic dysfunction that result in progressive neurodegeneration [44]. These findings also support the well-established concept that mitochondrial accumulation of αS is associated with impaired complex-I-dependent respiration, decreased mitochondrial membrane potential, and increased levels of reactive oxygen species [67][68].

Recent evidence supports a prion-like mechanism of αS aggregation and spread, whereby introduction of exogenous αS pre-formed fibrils causes endogenous αS to progressively adopt an insoluble, aggregated

conformation [69][70]. PD patient-derived αS aggregates can also be taken up by neurons and astrocytes and induce different endogenous responses in the two cell types, leading to neuronal death [71]. However, the exact mechanism of the spreading of αS fibrils remains a subject of intense discussion. Some possible pathways may include trans-synaptic transmission, direct membrane penetration, exocytosis and endocytosis, extracellular vesicles (EVs), and tunneling nanotubes [72][73][74][75][76][77].

To sum up, the neurotoxicity of αS aggregates and LB formation can lead to (1) the disintegration of synapses [78][79][80][81], (2) mitochondrial dysfunction, (3) membrane perturbation and dysfunction [82][83][84], (4) αS-induced neuroinflammation via microglial and astrocyte activation [85], and (5) prion-like propagation between neurons. It is also worth noting that the effects of the soluble (normal) form of αS have largely been overlooked, and thus it remains unclear whether the toxicity arises from the accumulation of abnormal αS or the depletion of the soluble (normal) αS.

References

1. Peter Jenner; Huw R. Morris; Trevor W. Robbins; Michel Goedert; John Hardy; Yoav Ben-Shlomo; Paul Bolam; David Burn; John V. Hindle; David Brooks; et al. Parkinson's Disease – the Debate on the Clinical Phenomenology, Aetiology, Pathology and Pathogenesis. *Journal of Parkinson's Disease* **2013**, *3*, 1-11, 10.3233/JPD-130175.
2. Elizabeth A. Coon; Jay N. Mandrekar; Sarah E. Berini; Eduardo E. Benarroch; Paola Sandroni; Phillip A. Low; Wolfgang Singer; Predicting phenoconversion in pure autonomic failure. *Neurology* **2020**, *95*, e889-e897, 10.1212/wnl.0000000000010002.
3. Bradley F. Boeve; Michael H. Silber; Tanis J. Ferman; John A. Lucas; Joseph E. Parisi; Association of REM sleep behavior disorder and neurodegenerative disease may reflect an underlying synucleinopathy. *Movement Disorders* **2001**, *16*, 622-630, 10.1002/mds.1120.
4. Ronald B Postuma; Alex Iranzo; Michele Hu; Birgit Högl; Bradley F Boeve; Raffaele Manni; Wolfgang H Oertel; Isabelle Arnulf; Luigi Ferini-Strambi; Monica Puligheddu; et al.Elena AntelmiValerie Cochen De CockDario ArnaldiBrit MollenhauerAleksandar VidenovicKarel ŠonkaKi-Young JungDieter KunzYves DauvilliersFederica ProviniSimon J LewisJitka BuskovaMilena PavlovaAnna HeidbrederJacques Y MontplaisirJoan SantamariaThomas R BarberAmbra StefaniErik K St.LouisMichele TerzaghiAnnette JanzenSmandra Leu-SemenescuGuiseppe PlazziFlavio NobiliFriederike Sixel-DoeringPetr DusekFrederik BesPietro CortelliKaylena Ehgoetz MartensJean-Francois GagnonCarles GaigMarco ZucconiClaudia TrenkwalderZiv Gan-OrChristine LoMichal RolinskiPhilipp MahlknechtEvi HolzknechtAngel R BoeveLuke N TeigenGianpaolo ToscanoGeert MayerSilvia MorbelliBenjamin DawsonAmelie Pelletier Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. *Brain* **2019**, *142*, 744-759, 10.1093/brain/awz030.

5. James E. Galvin; Kunihiro Uryu; Virginia M.-Y. Lee; John Q. Trojanowski; Axon pathology in Parkinson's disease and Lewy body dementia hippocampus contains alpha -, beta -, and gamma -synuclein. *Proceedings of the National Academy of Sciences* **1999**, *96*, 13450-13455, 10.1073/pnas.96.23.13450.
6. Maria Grazia Spillantini; Marie Luise Schmidt; Virginia M.-Y. Lee; John Q. Trojanowski; Ross Jakes; Michel Goedert; α-Synuclein in Lewy bodies. *Nature* **1997**, *388*, 839-840, 10.1038/42166.
7. Maria Grazia Spillantini; R. Anthony Crowther; Ross Jakes; Nigel J. Cairns; Peter L. Lantos; Michel Goedert; Filamentous α-synuclein inclusions link multiple system atrophy with Parkinson's disease and dementia with Lewy bodies. *Neuroscience Letters* **1998**, *251*, 205-208, 10.1016/s0304-3940(98)00504-7.
8. Katrin Beyer; Montserrat Domingo-Sàbat; Aurelio Ariza; Molecular Pathology of Lewy Body Diseases. *International Journal of Molecular Sciences* **2009**, *10*, 724-745, 10.3390/ijms10030724.
9. Kenji Kosaka; Latest concept of Lewy body disease. *Psychiatry and Clinical Neurosciences* **2014**, *68*, 391-394, 10.1111/pcn.12179.
10. Murat Emre; Dag Aarsland; Richard Brown; David Burn; Charles Duyckaerts; Yoshikino Mizuno; Gerald Anthony Broe; Jeffrey Cummings; Dennis W Dickson; Serge Gauthier; et al.Jennifer GoldmanChristopher GoetzAmos KorczynAndrew LeesRichard LevyIrene LitvanIan McKeithWarren OlanowWerner PoeweNiall QuinnChristina Sampaio MdEduardo TolosaBruno Dubois Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Movement Disorders* **2007**, *22*, 1689-1707, 10.1002/mds.21507.
11. Ian G. McKeith; Bradley F. Boeve; Dennis W. Dickson; Glenda Halliday; John-Paul Taylor; Daniel Weintraub; Dag Aarsland; James Galvin; Johannes Attems; Clive Ballard; et al.Ashley BaystonThomas G. BeachFrédéric BlancNicolaas BohnenLaura BonanniJose BrasPatrik BrundinDavid BurnAlice Chen-PlotkinJohn E. DudaOmar El-AgnafHoward FeldmanTanis J. FermanDominic FfytcheHiroshige FujishiroDouglas GalaskoJennifer G. GoldmanStephen N. GompertsNeill R. Graff-RadfordLawrence S. HonigAlex IranzoKejal KantarciDaniel KauferWalter KukullVirginia M.Y. LeeJames LeverenzSimon LewisCarol LippaAngela LundeMario MasellisEliezer MasliahPamela McLeanBrit MollenhauerThomas J. MontineEmilio MorenoEtsuro MoriMelissa MurrayJohn O'BrienSotoshi OrimoRonald B. PostumaShankar RamaswamyOwen RossDavid P. SalmonAndrew SingletonAngela TaylorAlan ThomasPietro TiraboschiJon ToledoJohn Q. TrojanowskiDebby TsuangZuzana WalkerMasahito YamadaKenji Kosaka Diagnosis and management of dementia with Lewy bodies. *Neurology* **2017**, *89*, 88-100, 10.1212/wnl.0000000000004058.
12. Yaroslau Compta; Laura Parkkinen; Sean S. O'Sullivan; Jana Vandrovcova; Janice L. Holton; Catherine Collins; Tammaryn Lashley; Constantinos Kallis; David R. Williams; Rohan de Silva; et

al.Andrew J. LeesTamas Revesz Lewy- and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important?. *Brain* **2011**, *134*, 1493-1505, 10.1093/brain/awr031.

13. Nicolaas I. Bohnen; Daniel I. Kaufer; Larry S. Ivanco; Brian Lopresti; Robert A. Koeppe; James G. Davis; Chester A. Mathis; Robert Y. Moore; Steven DeKosky; Cortical Cholinergic Function Is More Severely Affected in Parkinsonian Dementia Than in Alzheimer Disease. *Archives of Neurology* **2003**, *60*, 1745-1748, 10.1001/archneur.60.12.1745.
14. María Graciela Cersosimo; Propagation of alpha-synuclein pathology from the olfactory bulb: possible role in the pathogenesis of dementia with Lewy bodies. *Cell and Tissue Research* **2017**, *373*, 233-243, 10.1007/s00441-017-2733-6.
15. Denis S. Smirnov; Douglas Galasko; Steven D. Edland; J. Vincent Filoteo; Lawrence A. Hansen; David P. Salmon; Cognitive decline profiles differ in Parkinson disease dementia and dementia with Lewy bodies. *Neurology* **2020**, *94*, e2076-e2087, 10.1212/wnl.0000000000009434.
16. Tommaso Schirinzi; Marco Canevelli; Antonio Suppa; Matteo Bologna; Luca Marsili; The continuum between neurodegeneration, brain plasticity, and movement: a critical appraisal. *Reviews in the Neurosciences* **2020**, *31*, 723-742, 10.1515/revneuro-2020-0011.
17. Felix Chan; Nichola Z. Lax; Ceri H. Davies; Doug Turnbull; Mark O. Cunningham; Neuronal oscillations: A physiological correlate for targeting mitochondrial dysfunction in neurodegenerative diseases?. *Neuropharmacology* **2016**, *102*, 48-58, 10.1016/j.neuropharm.2015.10.033.
18. Luc Maroteaux; J T Campanelli; R H Scheller; Synuclein: a neuron-specific protein localized to the nucleus and presynaptic nerve terminal. *The Journal of Neuroscience* **1988**, *8*, 2804-2815, 10.1523/jneurosci.08-08-02804.1988.
19. Tim Bartels; Logan S. Ahlstrom; Avigdor Leftin; Frits Kamp; Christian Haass; Michael F. Brown; Klaus Beyer; The N-Terminus of the Intrinsically Disordered Protein α-Synuclein Triggers Membrane Binding and Helix Folding. *Biophysical Journal* **2010**, *99*, 2116-2124, 10.1016/j.bpj.2010.06.035.
20. Jose A. Rodriguez; Magdalena I. Ivanova; Michael Sawaya; Duilio Cascio; Francis E. Reyes; Dan Shi; Smriti Sangwan; Elizabeth L. Guenther; Lisa M. Johnson; Meng Zhang; et al.Lin JiangMark A. ArbingBrent NannengaJohan HattneJulian WhiteleggeAaron S. BrewsterMarc MesserschmidtSébastien BoutetNicholas K. SauterTamir GonenDavid S. Eisenberg Structure of the toxic core of α-synuclein from invisible crystals. *Nature* **2015**, *525*, 486-490, 10.1038/nature15368.
21. José M. Souza; Benoit I. Giasson; Virginia M.-Y. Lee; Harry Ischiropoulos; Chaperone-like activity of synucleins.. *FEBS Letters* **2000**, *474*, 116-119, 10.1016/s0014-5793(00)01563-5.
22. Zachary A. Sorrentino; Benoit I. Giasson; The emerging role of α-synuclein truncation in aggregation and disease. *Journal of Biological Chemistry* **2020**, *295*, 10224-10244, 10.1074/jbc.re

v120.011743.

23. Jacqueline Burré; Manu Sharma; Thomas C. Südhof; Definition of a Molecular Pathway Mediating -Synuclein Neurotoxicity. *The Journal of Neuroscience* **2015**, *35*, 5221-5232, 10.1523/jneurosci.4650-14.2015.
24. Ken Nakamura; Venu Nemani; Farnaz Azarbal; Gaia Skibinski; Jon M. Levy; Kiyoshi Egami; Larissa Munishkina; Jue Zhang; Brooke Gardner; Junko Wakabayashi; et al.Hiromi SesakiYifan ChengSteven FinkbeinerRobert L. NussbaumEliezer MasliahRobert H. Edwards Direct Membrane Association Drives Mitochondrial Fission by the Parkinson Disease-associated Protein α-Synuclein. *Journal of Biological Chemistry* **2011**, *286*, 20710-20726, 10.1074/jbc.m110.213538.
25. Jessika Bridi; Frank Hirth; Mechanisms of α-Synuclein Induced Synaptopathy in Parkinson's Disease. *Frontiers in Neuroscience* **2018**, *12*, 80, 10.3389/fnins.2018.00080.
26. Jacqueline Burré; The Synaptic Function of α-Synuclein. *Journal of Parkinson's Disease* **2015**, *5*, 699-713, 10.3233/JPD-150642.
27. Koichi Wakabayashi; Kunikazu Tanji; Fumiaki Mori; Hitoshi Takahashi; The Lewy body in Parkinson's disease: Molecules implicated in the formation and degradation of α-synuclein aggregates. *Neuropathology* **2007**, *27*, 494-506, 10.1111/j.1440-1789.2007.00803.x.
28. Sarah H. Shahmoradian; Amanda J. Lewis; Christel Genoud; Jürgen Hench; Tim E. Moors; Paula Navarro; Daniel Castaño-Díez; Gabriel Schweighauser; Alexandra Graff-Meyer; Kenneth N. Goldie; et al.Rosmarie SütterlinEvelien HuismanAngela IngrassiaYvonne De GierAnnemieke J. M. RozemullerJing WangAnne De PaepeJohannes ErnyAndreas StaempfliJoerg HoernschemeyerFrederik GroßerüschkampDaniel NiediekerSamir F. El-MashtolyMarialuisa QuadriWilfred F. J. Van IjckenVincenzo BonifatiKlaus GerwertBernd BohrmannStephan FrankMarkus BritschgiHenning StahlbergWilma D. J. Van De BergMatthias E. Lauer Lewy pathology in Parkinson’s disease consists of crowded organelles and lipid membranes. *Nature Neuroscience* **2019**, *22*, 1099-1109, 10.1038/s41593-019-0423-2.
29. Ulf Dettmer; Andrew J. Newman; Frank Soldner; Eric S. Luth; Nora C. Kim; Victoria von Saucken; John Sanderson; Rudolf Jaenisch; Tim Bartels; Dennis Selkoe; et al. Parkinson-causing α-synuclein missense mutations shift native tetramers to monomers as a mechanism for disease initiation. *Nature Communications* **2015**, *6*, 7314, 10.1038/ncomms8314.
30. A. C. M. Ferreon; Yann Gambin; Edward Lemke; A. A. Deniz; Interplay of -synuclein binding and conformational switching probed by single-molecule fluorescence. *Proceedings of the National Academy of Sciences* **2009**, *106*, 5645-5650, 10.1073/pnas.0809232106.
31. Agya K. Frimpong; Rinat Abzalimov; Vladimir N. Uversky; Igor A. Kaltashov; Characterization of intrinsically disordered proteins with electrospray ionization mass spectrometry: Conformational heterogeneity of α-synuclein. *Proteins: Structure, Function, and Bioinformatics* **2009**, *78*, 714-722, 10.1002/prot.22604.

32. Dharmin Rokad; Shivani Ghaisas; Dilshan Harischandra; Huajun Jin; Vellareddy Anantharam; Arthi Kanthasamy; Anumantha G. Kanthasamy; Role of neurotoxicants and traumatic brain injury in α-synuclein protein misfolding and aggregation. *Brain Research Bulletin* **2016**, *133*, 60-70, 10.1016/j.brainresbull.2016.12.003.

33. Subhrangshu Guhathakurta; Eugene Bok; Baggio A. Evangelista; Yoon-Seong Kim; Deregulation of α-synuclein in Parkinson's disease: Insight from epigenetic structure and transcriptional regulation of SNCA. *Progress in Neurobiology* **2017**, *154*, 21-36, 10.1016/j.pneurobio.2017.04.004.

34. Parvez Alam; Luc Bousset; Ronald Melki; Daniel E. Otzen; α-synuclein oligomers and fibrils: a spectrum of species, a spectrum of toxicities. *Journal of Neurochemistry* **2019**, *150*, 522-534, 10.1111/jnc.14808.

35. N. Cremades; S.W. Chen; C.M. Dobson; Structural Characteristics of α-Synuclein Oligomers. *Cellular Nutrient Utilization and Cancer* **2017**, *329*, 79-143, 10.1016/bs.ircmb.2016.08.010.

36. Wouter Peelaerts; Luc Bousset; Anke Van der Perren; Anastasiya Moskalyuk; Rocco Pulizzi; Michele Giugliano; Chris Van Den Haute; Ronald Melki; Veerle Baekelandt; α-Synuclein strains cause distinct synucleinopathies after local and systemic administration. *Nature* **2015**, *522*, 340-344, 10.1038/nature14547.

37. Serene W. Chen; Srdja Drakulic; Emma Deas; Myriam Ouberai; Francesco A. Aprile; Rocío Arranz; Samuel Ness; Cintia Roodveldt; Tim Guilliams; Erwin J. De-Genst; et al.David KlenermanNicholas W. WoodTuomas P.J. KnowlesCarlos AlfonsoGermán RivasAndrey Y. AbramovJosé María ValpuestaChristopher M. DobsonNunilo Cremades Structural characterization of toxic oligomers that are kinetically trapped during α-synuclein fibril formation. *Proceedings of the National Academy of Sciences* **2015**, *112*, E1994-E2003, 10.1073/pnas.1421204112.

38. Nunilo Cremades; Samuel I.A. Cohen; Emma Deas; Andrey Y. Abramov; Allen Y. Chen; Angel Orte; Massimo Sandal; Richard W. Clarke; Paul Dunne; Francesco A. Aprile; et al.Carlos W. BertonciniNicholas W. WoodTuomas P.J. KnowlesChristopher M. DobsonDavid Klenerman Direct Observation of the Interconversion of Normal and Toxic Forms of α-Synuclein. *Cell* **2012**, *149*, 1048-1059, 10.1016/j.cell.2012.03.037.

39. Giuliana Fusco; Serene W. Chen; Philip T. F. Williamson; Roberta Cascella; Michele Perni; James A. Jarvis; Cristina Cecchi; Michele Vendruscolo; Fabrizio Chiti; Nunilo Cremades; et al.Liming YingChristopher M. DobsonAlfonso De Simone Structural basis of membrane disruption and cellular toxicity by α-synuclein oligomers. *Science* **2017**, *358*, 1440-1443, 10.1126/science.aan6160.

40. Julia Gath; Luc Bousset; Birgit Habenstein; Ronald Melki; Anja Böckmann; Beat H. Meier; Unlike Twins: An NMR Comparison of Two α-Synuclein Polymorphs Featuring Different Toxicity. *PLOS*

ONE **2014**, *9*, e90659, 10.1371/journal.pone.0090659.

41. Elodie Monsellier; Luc Bousset; Ronald Melki; α-Synuclein and huntingtin exon 1 amyloid fibrils bind laterally to the cellular membrane. *Scientific Reports* **2016**, *6*, srep19180, 10.1038/srep19180.
42. Laura Pieri; Karine Madiona; Luc Bousset; Ronald Melki; Fibrillar α-Synuclein and Huntingtin Exon 1 Assemblies Are Toxic to the Cells. *Biophysical Journal* **2012**, *102*, 2894-2905, 10.1016/j.bpj.2012.04.050.
43. Wojciech Paslawski; Maria Andreasen; Søren Bang Nielsen; Nikolai Lorenzen; Karen Thomsen; Jørn Døvling Kaspersen; Jan Skov Pedersen; Daniel E. Otzen; High Stability and Cooperative Unfolding of α-Synuclein Oligomers. *Biochemistry* **2014**, *53*, 6252-6263, 10.1021/bi5007833.
44. Anne-Laure Mahul-Mellier; Johannes Burtscher; Niran Maharjan; Laura Weerens; Marie Croisier; Fabien Kuttler; Marion Leleu; Graham W. Knott; Hilal A. Lashuel; The process of Lewy body formation, rather than simply α-synuclein fibrillization, is one of the major drivers of neurodegeneration. *Proceedings of the National Academy of Sciences* **2020**, *117*, 4971-4982, 10.1073/pnas.1913904117.
45. Sydney Weber Boutros; Jacob Raber; Vivek K. Unni; Effects of Alpha-Synuclein Targeted Antisense Oligonucleotides on Lewy Body-Like Pathology and Behavioral Disturbances Induced by Injections of Pre-Formed Fibrils in the Mouse Motor Cortex. *Journal of Parkinson's Disease* **2021**, *11*, 1091-1115, 10.3233/JPD-212566.
46. Luis D. Bernal-Conde; Rodrigo Ramos-Acevedo; Mario A. Reyes-Hernández; Andrea J. Balbuena-Olvera; Ishbelt D. Morales-Moreno; Rubén Argüero-Sánchez; Birgitt Schuele; Magdalena Guerra-Crespo; Alpha-Synuclein Physiology and Pathology: A Perspective on Cellular Structures and Organelles. *Frontiers in Neuroscience* **2020**, *13*, 1399, 10.3389/fnins.2019.01399.
47. Jacqueline E. Payton; Richard J. Perrin; Wendy S. Woods; Julia M. George; Structural Determinants of PLD2 Inhibition by α-Synuclein. *Journal of Molecular Biology* **2004**, *337*, 1001-1009, 10.1016/j.jmb.2004.02.014.
48. E. Dalfó; I. Ferrer; α-Synuclein binding to rab3a in multiple system atrophy. *Neuroscience Letters* **2005**, *380*, 170-175, 10.1016/j.neulet.2005.01.034.
49. Jacqueline Burré; Manu Sharma; Theodoros Tsetsenis; Vladimir Buchman; Mark R. Etherton; Thomas C. Südhof; α-Synuclein Promotes SNARE-Complex Assembly in Vivo and in Vitro. *Science* **2010**, *329*, 1663-1667, 10.1126/science.1195227.
50. Min Zhu; Jie Li; Anthony L. Fink; The Association of α-Synuclein with Membranes Affects Bilayer Structure, Stability, and Fibril Formation. *Journal of Biological Chemistry* **2003**, *278*, 40186-40197, 10.1074/jbc.m305326200.

51. Michael J. Volles; Jr. Peter T. Lansbury; Vesicle Permeabilization by Protofibrillar α-Synuclein Is Sensitive to Parkinson's Disease-Linked Mutations and Occurs by a Pore-like Mechanism. *Biochemistry* **2002**, *41*, 4595-4602, 10.1021/bi0121353.
52. Rakez Kayed; Yuri Sokolov; Brian Edmonds; Theresa M. McIntire; Saskia C. Milton; James E. Hall; Charles G. Glabe; Permeabilization of Lipid Bilayers Is a Common Conformation-dependent Activity of Soluble Amyloid Oligomers in Protein Misfolding Diseases. *Journal of Biological Chemistry* **2004**, *279*, 46363-46366, 10.1074/jbc.c400260200.
53. Cristina Cecchi; Massimo Stefani; The amyloid-cell membrane system. The interplay between the biophysical features of oligomers/fibrils and cell membrane defines amyloid toxicity. *Biophysical Chemistry* **2013**, *182*, 30-43, 10.1016/j.bpc.2013.06.003.
54. Aditya Iyer; Nathalie Schilderink; Mireille M.A. E. Claessens; Vinod Subramaniam; Membrane-Bound Alpha Synuclein Clusters Induce Impaired Lipid Diffusion and Increased Lipid Packing. *Biophysical Journal* **2016**, *111*, 2440-2449, 10.1016/j.bpj.2016.10.016.
55. Todd Logan; Jacob Bendor; Chantal Toupin; Kurt Thorn; Robert H. Edwards; α-Synuclein promotes dilation of the exocytotic fusion pore. *Nature Neuroscience* **2017**, *20*, 681-689, 10.1038/nn.4529.
56. Pieter E. S. Smith; Jeffrey Brender; Ayyalusamy Ramamoorthy; Induction of Negative Curvature as a Mechanism of Cell Toxicity by Amyloidogenic Peptides: The Case of Islet Amyloid Polypeptide. *Journal of the American Chemical Society* **2009**, *131*, 4470-4478, 10.1021/ja809002a.
57. Lindsey G. Soll; Julia N. Eisen; Karina J. Vargas; Audrey T. Medeiros; Katherine M. Hammar; Jennifer R. Morgan; α-Synuclein-112 Impairs Synaptic Vesicle Recycling Consistent With Its Enhanced Membrane Binding Properties. *Frontiers in Cell and Developmental Biology* **2020**, *8*, 405, 10.3389/fcell.2020.00405.
58. Antony A. Cooper; Aaron D. Gitler; Anil Cashikar; Cole M. Haynes; Kathryn J. Hill; Bhupinder Bhullar; Kangning Liu; Kexiang Xu; Katherine E. Strathearn; Fang Liu; et al.Songsong CaoKim A. CaldwellGuy A. CaldwellGerald MarsischkyRichard D. KolodnerJoshua LaBaerJean-Christophe RochetNancy M. BoniniSusan Lindquist α-Synuclein Blocks ER-Golgi Traffic and Rab1 Rescues Neuron Loss in Parkinson's Models. *Science* **2006**, *313*, 324-328, 10.1126/science.1129462.
59. Nirmal Gosavi; He-Jin Lee; Jun Sung Lee; Smita Patel; Seung-Jae Lee; Golgi Fragmentation Occurs in the Cells with Prefibrillar α-Synuclein Aggregates and Precedes the Formation of Fibrillar Inclusion. *Journal of Biological Chemistry* **2002**, *277*, 48984-48992, 10.1074/jbc.m208194200.
60. Latha Devi; Vijayendran Raghavendran; Badanavalu M. Prabhu; Narayan G. Avadhani; Hindupur K. Anandatheerthavarada; Mitochondrial Import and Accumulation of α-Synuclein Impair Complex

I in Human Dopaminergic Neuronal Cultures and Parkinson Disease Brain. *Journal of Biological Chemistry* **2008**, *283*, 9089-9100, 10.1074/jbc.m710012200.

61. Ken Nakamura; α-Synuclein and Mitochondria: Partners in Crime?. *Neurotherapeutics* **2013**, *10*, 391-399, 10.1007/s13311-013-0182-9.
62. Ge Gao; Zhipeng Wang; Lingling Lu; Chunli Duan; Xiaomin Wang; Hui Yang; Morphological analysis of mitochondria for evaluating the toxicity of α-synuclein in transgenic mice and isolated preparations by atomic force microscopy. *Biomedicine & Pharmacotherapy* **2017**, *96*, 1380-1388, 10.1016/j.biopha.2017.11.057.
63. Leonidas Stefanis; Kristin E. Larsen; Hardy J. Rideout; David Sulzer; Lloyd A. Greene; Expression of A53T Mutant But Not Wild-Type α-Synuclein in PC12 Cells Induces Alterations of the Ubiquitin-Dependent Degradation System, Loss of Dopamine Release, and Autophagic Cell Death. *The Journal of Neuroscience* **2001**, *21*, 9549-9560, 10.1523/jneurosci.21-24-09549.2001.
64. Ana Maria Cuervo; Leonidas Stefanis; Ross Fredenburg; Peter T. Lansbury; David Sulzer; Impaired Degradation of Mutant α-Synuclein by Chaperone-Mediated Autophagy. *Science* **2004**, *305*, 1292-1295, 10.1126/science.1101738.
65. Maria Xilouri; Oystein Rod Brekk; Leonidas Stefanis; Alpha-synuclein and Protein Degradation Systems: a Reciprocal Relationship. *Molecular Neurobiology* **2012**, *47*, 537-551, 10.1007/s12035-012-8341-2.
66. Mark R Cookson; α-Synuclein and neuronal cell death. *Molecular Neurodegeneration* **2009**, *4*, 9-9, 10.1186/1750-1326-4-9.
67. Emily Rocha; Briana De Miranda; Laurie H. Sanders; Alpha-synuclein: Pathology, mitochondrial dysfunction and neuroinflammation in Parkinson's disease. *Neurobiology of Disease* **2018**, *109*, 249-257, 10.1016/j.nbd.2017.04.004.
68. Stephen Mullin; Anthony Schapira; α-Synuclein and Mitochondrial Dysfunction in Parkinson's Disease. *Molecular Neurobiology* **2013**, *47*, 587-597, 10.1007/s12035-013-8394-x.
69. Valerie R. Osterberg; Kateri Spinelli; Leah J. Weston; Kelvin Luk; Randall L. Woltjer; Vivek K. Unni; Progressive Aggregation of Alpha-Synuclein and Selective Degeneration of Lewy Inclusion-Bearing Neurons in a Mouse Model of Parkinsonism. *Cell Reports* **2015**, *10*, 1252-1260, 10.1016/j.celrep.2015.01.060.
70. Laura A. Volpicelli-Daley; Kelvin Luk; Tapan Patel; Selcuk A. Tanik; Dawn M. Riddle; Anna Stieber; David Meaney; John Q. Trojanowski; Virginia M.-Y. Lee; Exogenous α-Synuclein Fibrils Induce Lewy Body Pathology Leading to Synaptic Dysfunction and Neuron Death. *Neuron* **2011**, *72*, 57-71, 10.1016/j.neuron.2011.08.033.
71. Fabio Cavaliere; Loic Cerf; Benjamin Dehay; Paula Ramos-Gonzalez; Francesca De Giorgi; Mathieu Bourdenx; Alban Bessede; Jose A. Obeso; Carlos Matute; François Ichas; et al.Erwan

Bezard In vitro α-synuclein neurotoxicity and spreading among neurons and astrocytes using Lewy body extracts from Parkinson disease brains. *Neurobiology of Disease* **2017**, *103*, 101-112, 10.1016/j.nbd.2017.04.011.

72. Christopher Mezias; Nolwen L. Rey; Patrik Brundin; Ashish Raj; Neural connectivity predicts spreading of alpha-synuclein pathology in fibril-injected mouse models: Involvement of retrograde and anterograde axonal propagation. *Neurobiology of Disease* **2019**, *134*, 104623-104623, 10.1016/j.nbd.2019.104623.
73. Baraa Hijaz; Laura A. Volpicelli-Daley; Initiation and propagation of α-synuclein aggregation in the nervous system. *Molecular Neurodegeneration* **2020**, *15*, 1-12, 10.1186/s13024-020-00368-6.
74. Ariadna Recasens; Benjamin Dehay; Jordi Bové; Iria Carballo-Carbajal; Sandra Dovero; Ana Pérez-Villalba; Pierre-Olivier Fernagut; Javier Blesa; Annabelle Parent; Celine Perier; et al.Isabel FariñasJosé A. ObesoErwan BezardMiquel Vila Lewy body extracts from Parkinson disease brains trigger α-synuclein pathology and neurodegeneration in mice and monkeys. *Annals of Neurology* **2013**, *75*, 351-362, 10.1002/ana.24066.
75. Jason Howitt; Andrew Francis Hill; Exosomes in the Pathology of Neurodegenerative Diseases. *Journal of Biological Chemistry* **2016**, *291*, 26589-26597, 10.1074/jbc.r116.757955.
76. Karine Gousset; Edwin Schiff; Christelle Langevin; Zrinka Marijanovic; Anna Caputo; Duncan T. Browman; Nicolas Chenouard; Fabrice de Chaumont; Angelo De Martino; Jost Enninga; et al.Jean-Christophe Olivo-MarinDaniela N MannelChiara Zurzolo Prions hijack tunnelling nanotubes for intercellular spread. *Nature* **2009**, *11*, 328-336, 10.1038/ncb1841.
77. He-Jin Lee; Smita Patel; Seung-Jae Lee; Intravesicular Localization and Exocytosis of -Synuclein and its Aggregates. *The Journal of Neuroscience* **2005**, *25*, 6016-6024, 10.1523/jneurosci.0692-05.2005.
78. Veronica Ghiglieri; Valeria Calabrese; Paolo Calabresi; Alpha-Synuclein: From Early Synaptic Dysfunction to Neurodegeneration. *Frontiers in Neurology* **2018**, *9*, 295, 10.3389/fneur.2018.00295.
79. Hilal A. Lashuel; Cassia R. Overk; Abid Oueslati; Eliezer Masliah; The many faces of α-synuclein: from structure and toxicity to therapeutic target. *Nature Reviews Neuroscience* **2012**, *14*, 38-48, 10.1038/nrn3406.
80. Cristina Román-Vendrell; Audrey T. Medeiros; John B. Sanderson; Haiyang Jiang; Tim Bartels; Jennifer R. Morgan; Effects of Excess Brain-Derived Human α-Synuclein on Synaptic Vesicle Trafficking. *Frontiers in Neuroscience* **2021**, *15*, 73, 10.3389/fnins.2021.639414.
81. Qihui Wu; Hajime Takano; Dawn M. Riddle; John Q. Trojanowski; Douglas A. Coulter; Virginia M.-Y. Lee; α-Synuclein (αSyn) Preformed Fibrils Induce Endogenous αSyn Aggregation, Compromise

Synaptic Activity and Enhance Synapse Loss in Cultured Excitatory Hippocampal Neurons. *The Journal of Neuroscience* **2019**, *39*, 5080-5094, 10.1523/jneurosci.0060-19.2019.

82. Roberta Cascella; Serene W. Chen; Alessandra Bigi; José D. Camino; Catherine K. Xu; Christopher M. Dobson; Fabrizio Chiti; Nunilo Cremades; Cristina Cecchi; The release of toxic oligomers from α-synuclein fibrils induces dysfunction in neuronal cells. *Nature Communications* **2021**, *12*, 1-16, 10.1038/s41467-021-21937-3.
83. Natalia P. Alza; Pablo A. Iglesias González; Melisa A. Conde; Romina M. Uranga; Gabriela A. Salvador; Lipids at the Crossroad of α-Synuclein Function and Dysfunction: Biological and Pathological Implications. *Frontiers in Cellular Neuroscience* **2019**, *13*, 175, 10.3389/fncel.2019.00175.
84. Emma I. O'Leary; Jennifer C. Lee; Interplay between α-synuclein amyloid formation and membrane structure. *Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics* **2018**, *1867*, 483-491, 10.1016/j.bbapap.2018.09.012.
85. Géraldine Gelders; Veerle Baekelandt; Anke Van Der Perren; Linking Neuroinflammation and Neurodegeneration in Parkinson’s Disease. *Journal of Immunology Research* **2018**, *2018*, 1-12, 10.1155/2018/4784268.