World Journal of Neurology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5316/wjn.v4.i4.23

World J Neurol 2014 December 28; 4(4): 23-35
ISSN 2218-6212 (online)

REVIEW

Protein seeding in Alzheimer's disease and Parkinson's disease: Similarities and differences

Tarek Ibrahim, JoAnne McLaurin

Tarek Ibrahim, JoAnne McLaurin, Sunnybrook Research Institute and Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto M4N 3M5, Canada
Author contributions: Ibrahim T and McLaurin J contributed to this paper.
Supported by In part by CIHR MOP#102467 (McLaurin J); Cryptic Rite Charitable Foundation (McLaurin J)
Conflict-of-interest: The authors declare no conflict of interest with this publication.

Correspondence to: JoAnne McLaurin, PhD, Sunnybrook Research Institute and Department of Laboratory Medicine and Pathobiology, University of Toronto, 2075 Bayview Avenue, Rm S113, Toronto M4N 3M5, Canada. jmclaurin@sri.utoronto.ca
Telephone: +1-416-4806100-2270
Fax: +1-416-4805737
Received: September 30, 2014
Peer-review started: October 1, 2014
First decision: October 28, 2014
Revised: November 21, 2014
Accepted: December 3, 2014
Article in press: December 10, 2014
Published online: December 28, 2014

Abstract

Neurodegenerative pathology can be seeded by introduction of misfolded proteins and peptides into the nervous system. Models of Alzheimer's disease (AD) and Parkinson's disease (PD) have both demonstrated susceptibility to this seeding mechanism, emphasizing the role of misfolded conformations of disease-specific proteins and peptides in disease progression. Thinking of the amyloidogenic amyloid-beta peptide (Aβ) and alpha-synuclein (α-syn), of AD and PD, respectively, as prionoids requires a comparison of these molecules and the mechanisms underlying the progression of disease. Aβ and α-syn, despite their size differences, are both natively unstructured and misfold into β-structured conformers. Additionally, several studies implicate the significant role of membrane interactions, such as those with lipid rafts in the plasma membrane, in mediating protein aggregation and transfer of Aβ and α-syn between cells that may be common to both AD and PD. Examination of inter-neuronal transfer of proteins/peptides provides evidence into the core mechanism of neuropathological propagation. Specifically, uptake of aggregates likely occurs by the endocytic pathway, possibly in response to their formation of membrane pores *via* a mechanism shared with pore-forming toxins. Failure of cellular clearance machinery to degrade misfolded proteins favours their release into the extracellular space, where they can be taken up by directly connected, nearby neurons. Although similarities between AD and PD are frequent and include mechanistically similar transfer processes, what differentiates these diseases, in terms of temporal and spatial patterns of propagation, may be in part due to the differing kinetics of protein misfolding. Several examples of animal models demonstrating seeding and propagation by exogenous treatment with Aβ and α-syn highlight the importance of both the environment in which these seeds are formed as well as the environment into which the seeds are propagated. Although these studies suggest potent seeding effects by both Aβ and α-syn, they emphasize the need for future studies to thoroughly characterize "seeds" as well as analyze changes in the nervous system in response to exogenous insults.

Key words: Alzheimer's disease; Parkinson's disease;

Prionoid; Seeding; Propagation; Protein misfolding

Core tip: The disease-specific proteins of Alzheimer's and Parkinson's disease show many similarities as prion-like seeds in the brain. In addition to sharing structural features as misfolded proteins, the interactions and mechanisms that underlie the propagation of these proteins may also be shared, hijacking natural cellular responses in ways not unlike those of pore-forming toxins. Differences in temporal and spatial patterns of disease progression stems from the existence of conformational variants. Misfolded proteins that can be generated *in vitro*, can seed widespread pathology in non-transgenic animal models and question our understanding of disease progression in neurodegenerative diseases.

Ibrahim T, McLaurin J. Protein seeding in Alzheimer's disease and Parkinson's disease: Similarities and differences. *World J Neurol* 2014; 4(4): 23-35 Available from: URL: http://www.wjgnet.com/2218-6212/full/v4/i4/23.htm DOI: http://dx.doi.org/10.5316/wjn.v4.i4.23

INTRODUCTION

The purpose of this review is to examine patterns that are present in the progression of Alzheimer's disease (AD) and Parkinson's disease (PD), with a focus on identifying parallel mechanisms that underlie disease as well as differences that characterize each disease classified as neurodegenerative diseases, both exhibit neuronal loss/dysfunction in various regions of the central nervous system (CNS). Observations made from analyses of tissue from patients as well as animal models continue to provide evidence that the pathological route taken by both AD and PD is related to their disease-specific proteins. The amyloidogenic proteins, amyloid beta peptide (Aβ) in AD and alpha-synuclein (α-syn) in PD[1], have recently been shown to propagate throughout cerebral networks as misfolded seeds. This has likened the spread of pathology to that of prion diseases, which exhibit templating[2], a process where misfolded proteins can induce endogenous protein to misfold.

AD and PD are the two most prevalent neurodegenerative diseases worldwide. Neither race nor gender is spared by either disease and cures for both have remained elusive. By 2010, 35.6 million people were living with AD, a number that is expected to double in the following two decades. PD has a worldwide prevalence estimated at 7 million patients.

AD is the most common cause of dementia and is characterized by a progressive loss of cognitive function, most noticeably in the form of memory loss. This can be followed by further dysfunction in language, visuospatial and executive systems. Hallmarks of AD include the presence of Aβ-containing amyloid (senile) plaques in the extracellular milieu of the CNS and surrounding blood vessels as well as neurofibrillary tangles (NFT) produced by intracellular aggregation of the microtubule associated protein Tau. PD is the most common cause of movement disorders and exhibits clinical symptoms that can be divided into two groups: the more apparent motor symptoms such as resting tremors, bradykinesia and loss of postural reflexes; and the non-motor symptoms such as olfactory dysfunction, sleep disturbances and depression[3]. The pathology is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) of the midbrain and decreased levels of dopamine in regions of the striatum where SNpc neurons project. PD is also characterized by formation of α-syn-containing intracellular inclusions known as Lewy bodies and Lewy neurites[4]. The detection of a combination of amyloid plaques, neurofibrillary tangles and Lewy bodies in patients, signifying overlapping pathology of AD and PD, have led to the classification of the conditions Dementia with Lewy Bodies and Parkinson's Disease Dementia; Dementia with Lewy Bodies patients demonstrate clinical dementia within 1 year of being diagnosed with PD while PD Dementia patients exhibit dementia at later stages of PD[5]. Both AD and PD are chronic illnesses in which clinical symptoms may manifest many years after pathology has commenced. In AD, the accumulation of Aβ protein in the brain primarily occurs before the appearance of the first clinical symptom[6,7]. Lewy bodies of PD also typically appear before the appearance of a classic motor symptom[8,9]. Despite linkage of both diseases to mutations in certain genes, the majority of cases are sporadic in nature.

AMYLOIDOGENIC PROTEINS

Protein folding is a fragile event that requires specific environmental conditions. Subcellular processes exist to regulate and to ensure the folding and stabilization of newly generated proteins into native conformations. Maintenance of pH, temperature and osmolarity as well as ensuring appropriate post-translational modifications of folded proteins ensure the stability required to perform the intended function. Disruption of these processes enhances the rate at which proteins adopt alternate secondary and tertiary structures, which in turn may favor the production of misfolded conformers. It is now thought that subpopulations of misfolded proteins can act as pro-aggregatory seeds that initiate a cascade of pathology in susceptible neuronal populations and may represent the catastrophic event from which many neurodegenerative pathologies progress[10]. Misfolded structures accumulate leading to their deposition into insoluble lesions that spread throughout the central nervous system over time. These lesions can appear both intracellularly and extracellularly and are implicated in the development of neurodegenerative disease states. Diseases such as AD, PD and Amyotrophic lateral sclerosis are characterized by the presence of these deposits which are thought to spread in a prion-like manner[11].

In AD and PD, supramolecular structures, amyloid

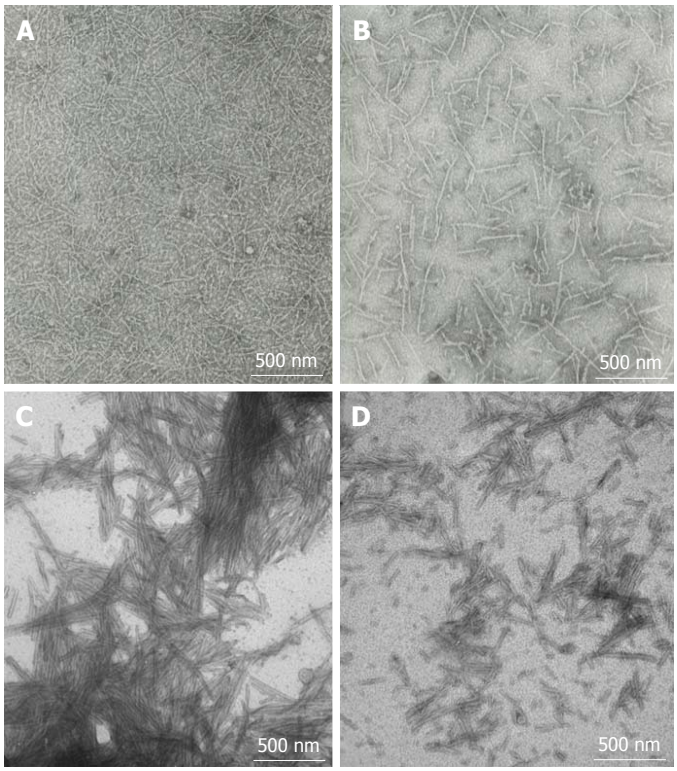

Figure 1 Fibrillar amyloid-beta peptide and alpha-synuclein. A and B: Amyloid-beta (10 mg/mL) was aggregated at room temperature for 72 h with shaking; C and D: α-synuclein (2 mg/mL) was aggregated by incubation at 37 ℃ for 144 h with shaking. Aggregation leads to formation of fibrils with varying structures. Fibrils were negatively stained with 2% phosphotungstic acid and their formation was confirmed using Transmission Electron Microscopy at 75 kV. Images display 40000 × magnification.

fibrils, are formed through the accumulation of subunits rich in β-pleated sheet secondary structure (Figure 1). The disease-specific proteins, Aβ[12] and α-syn[13] have been shown to adopt secondary structures that allow for the formation of the cross β-structure characteristic of amyloid[1]. The monomeric proteins undergo a nucleation-dependent mechanism of aggregation to form oligomers, protofibrils and other intermediate structures. Oligomers formed on the amyloid aggregation pathway will eventually reach a fibrillar state while off-pathway aggregates typically reach equilibrium and terminate aggregation in a prefibrillar state. Physicochemical properties such as hydrophobicity, secondary structure propensities, charge and aromatic interactions underlie the propensity of these proteins and peptide fragments to aggregate[14]. For both Aβ and α-syn monomers, stabilization of a partially folded pre-molten globule-like state, either by lowering of pH or increase in temperature[15,16], is believed to be the critical first step in the formation of the fibrils[17]. Fibrils are metastable structures that, once formed, may represent lower energy states than the native protein structure. The stability is strengthened by dehydration of misfolded species, a process promoted by binding of ligands that render the protein less solvent-accessible[18]. Surfaces that promote clustering of Aβ and α-syn, then, likely promote fibrillization. Several events promote protein misfolding and must be actively countered.

Aβ ranges in length from 36-43 amino acid residues and is formed by the cleavage of the single transmembrane protein amyloid precursor protein (APP). The actions of two proteolytic events, the enzyme beta (β) secretase and the complex gamma secretase, generate $A\beta_{40/42}$. These sequential cleavage events are localized to lipid bilayers where APP and the proteases are present; the plasma membrane as well as the membranes of golgi apparatus and endoplasmic reticulum have been shown to generate Aβ peptides[19-21]. As $A\beta_{42}$ is more hydrophobic and, as such, more fibrillogenic[22] than $A\beta_{40}$, processes that lead to higher ratios of $A\beta_{42}$:$A\beta_{40}$ promote the development of amyloid. Mutations in several genes encoding proteins involved in the production of Aβ, including APP, PS1 and PS2, promote this pathological ratio and are linked to familial, early-onset AD. Aβ fibrils cluster to form the extracellular cerebral amyloid plaques that are observed in AD[23].

α-Syn differs from Aβ in that it is a full length protein and is significantly larger (14 KDa *vs* 4 KDa for Aβ). It consists of 140 amino acid residues and is localized to the presynaptic terminals of neurons in most brain regions[24]. Missense mutations in the α-syn gene, *SNCA*, (A53T, A30P and E46K) are linked to autosomal dominantly-inherited early-onset PD[25-27]. Furthermore, overexpression of α-syn by multiplication of *SNCA*, showed accelerated formation of Lewy-like structures in SHSY-5Y neuroblastoma cells, of which fibrillar α-syn is the main component[28]. *In vivo* mouse models of α-syn overexpression have been developed. Mice

primarily display an increase in Lewy body formation in neuronal populations that are dictated by the nature of the transgene incorporation[29]. Models with higher levels of α-syn overexpression may also display dopaminergic cell loss in the SNpc and motor deficits associated with this loss[29]. Models of transgenic mice expressing human α-syn with the A53T mutation display α-syn aggregation and inclusion formation; however, these mice do not show any degeneration in dopaminergic populations in the SNpc[30]. Although the native functional role of α-syn is currently unknown, many studies have pointed to the involvement of α-syn in synaptic transmission by regulating neurotransmitter release[31]. Involvement in synaptic transmission has also been suggested for Aβ where it may be involved in feedback regulation of neuronal activity and modulation of glutamatergic and cholinergic inputs[32,33].

In addition to Aβ and α-syn, aggregation of tau protein is implicated in neurodegeneration seen in AD and other tauopathies. Hyperphosphorylation of tau leads to formation of intracellular insoluble neurofibrillary tangles, the presence of which correlates with the clinical manifestation of dementia in AD[6]. The colocalization of α-syn inclusions and tau neurofibrillary tangles in some neurodegenerative diseases may be due to a common mechanism. *In vivo* studies have suggested seeding of both proteopathic species occurs by specific strains of fibrillar α-syn[34]. Mouse models have also shown acceleration of neurofibrillary tangles formation by injections of fibrillar Aβ[35] and overexpression of mutant APP[36,37]. Interestingly, prior studies have also established an interaction between α-syn and Aβ. Both Aβ and α-syn have been shown to seed each other's aggregation *in vitro*[38] and a stretch of hydrophobic amino acid residues (61-95) found in the central portion of α-syn has been termed the non-Aβ component of AD amyloid (NAC) after discovery in Aβ plaques[39]. Both are thought to be natively unstructured and flexible monomers with brief but residual secondary structure[40-42]. Aβ has a central hydrophobic region (17-21) that permits strong intermolecular interactions between monomers and provides the peptides with an enhanced propensity to aggregate[40]. α-Syn contains the central hydrophobic NAC region, which forms intermolecular interactions[43]. Despite a lack of homology in amino acid sequence, several amyloidogenic proteins and peptide fragments are thought to share common structural features as oligomers[44]. This commonality is supported by the inhibition of amyloid formation of many peptides/proteins by a single compound. Inositol stereoisomers such as *scyllo*-inositol have been shown to stabilize non-toxic forms of $A\beta_{42}$[45,46] while also attenuating Aβ[47] and α-syn[48] mediated toxicity *in vitro*. Polyphenols have also been shown to inhibit fibrillogenesis through aromatic interactions[14] that prevent conversion of large oligomer into fibrils or further elongation of pre-existing fibrils[14]. Many additional classes of inhibitors have been shown to promote oligomeric forms of both Aβ and α-syn that do not effect cell viability[49].

HISTOLOGICAL SPREAD

Histological studies of tissue from AD and PD patients have identified patterns of pathology that can be classified by a staging scheme[6,8]. Despite notable inter-individual variation at early stages of AD, a three stage scheme was established following the consistent spread of amyloid deposition from basal isocortical areas to the hippocampal formation[6]. Also developed was a six stage scheme that correlates the preclinical and clinical progression of dementia with the increasing presence of NFTs[6]. Current AD diagnoses take measures of amyloid load into account along with NFT spread and the extent of dementia symptoms exhibited. These measures are compared to reference ratios that are predicted by age to diagnose individuals as having a high, intermediate or low likelihood of AD[7]. For PD, Braak *et al*[8] developed a six stage scheme for disease progression starting with the presence of intraneuronal inclusions in the dorsal (X) motor nucleus and proceeding upward through the midbrain culminating in the cortex. There is no standard diagnostic test for PD, with diagnoses typically relying on a combination of neurological examination to confirm α-syn pathology and SNpc dopaminergic neuron loss along with examination of motor symptoms. Currently there is intensive research on identifying accurate biomarkers for early detection of AD and PD[3,4,50-52].

Both AD and PD pathology follows a pattern of progression that is spatiotemporally regulated with pathological spread into interconnected regions. As pathological hallmarks of AD and PD increase within the brain, patterns of spread for each disease rarely differ in origin and direction, especially in familial forms of disease. This has lent credence to the recent hypothesis that Aβ and α-syn pathology spreads by transfer of aggregates to interconnected regions. Newly taken up aggregates, whether oligomeric or fibrillar, can then induce templating of endogenous peptide/protein and lead to elevated levels of pathological conformers that alter cellular homeostasis. This is in line with the proposal that Aβ and α-syn should be termed "prionoids"[53,54]; amyloids that exhibit prion-like transmission from cell-to-cell but have not yet proven transmissible between individuals and are not tractable by microbiological techniques[54].

MOLECULAR INTERACTIONS

The lipid bilayer of the plasma membrane exhibits dynamic features that are responsible for interaction with the extracellular environment. The composition of the plasma membrane is heterogeneous and is known to contain specialized domains that play a significant role in neuropathological mechanisms due to protein-lipid interactions. Protein-lipid interactions can modulate aggregation by recruiting proteins to increase local

concentration, favoring conversion into a partially-folded state (aggregation prone) and by modulation of the depth that the protein/peptide penetrates the membrane affecting nucleation propensity. Anionic charges on surface head-groups first attract these peptides and act as conformational catalysts for amyloidogenic fibrillization. Polyunsaturated fatty acids concomitantly enhance interactions by increasing membrane fluidity, favoring association and insertion of peptides/proteins such as Aβ/α-syn[55] into the transmembrane. Initially, Aβ[46] and α-syn[56,57] were shown to interact with phosphatidylinositols, aiding in the binding to the membrane and enhancing aggregation[57]. More recent studies highlighted the importance of lipid rafts in the aggregation pathway, specialized micro-domains that are rich in cholesterol and sphingolipids such as gangliosides[58]. Gangliosides-Aβ interaction drives aggregation into toxic oligomers[59] by promotion of α-helical secondary structure that eventually converts to β-sheets[60]. The ganglioside GM1, the most abundant ganglioside in lipid rafts, is enriched in neuronal membranes, and compared to other gangliosides, demonstrated the greatest seeding of Aβ oligomers[60]. Seeding was potentiated by clustering of the lipid moiety, which was further stabilized by increasing cholesterol concentrations in the membrane[61,62]. Surprisingly, the more recent literature argues for the protective role of sterols through inhibition of Aβ fibrillization and toxicity[63,64] (reviewed by Bucciantini)[65]. As cholesterol decreases membrane fluidity, it likely hinders insertion and nucleation of Aβ and α-syn at the surface[65]; although these effects are not sufficient to counter GM1 interactions[66]. α-Syn interacts with GM1, which promotes conversion into an oligomeric α-helix rich structure, but in contrast to Aβ, prevents α-syn from aggregation into fibrils[67]. GM1 is also involved in endocytotic internalization of monomeric α-syn into microglial cells similar to previously described internalization of bacterial toxins[68]. Together, it is apparent that membranes play an important role in the misfolding of amyloidogenic proteins.

CELL TO CELL TRANSFER

Consistent evidence of spread of AD and PD pathology to interconnected regions of the CNS suggested cell-to-cell transfer of disease-related proteins. The presence of Aβ and α-syn in extracellular fluids supports the existence of mechanisms that release protein/peptides extracellularly. *In vivo* dialysis of human CNS revealed the presence of Aβ in the CSF[69]. Furthermore, Aβ is present in blood plasma[70] and recent studies suggest that pathological forms of Aβ ($Aβ_{42}$) in the CSF have predictive value as biomarkers[51]. α-Syn monomers are also detected in extracellular biological fluids like the cerebrospinal fluid[71] and blood plasma and oligomeric forms show elevated levels in the fluids of PD patients[50]. Careful understanding of the mechanisms that underlie how or why cells react to pathological forms of Aβ and α-syn may explain this spread and identify methods to limit it.

In vitro studies have shown that small amounts of Aβ can be transported outside cells *via* fusion of peptide containing multivesicular bodies (MVBs) with the plasma membrane followed by the release of Aβ-carrying exosomes[72]. More recent evidence showed that soluble oligomeric forms of Aβ undergo cell-to-cell transfer between directly connected rat primary neurons and human SHSY-5Y cells in donor-acceptor co-culture models[73]. Transfer failed when cells didn't form direct connections, identifying the importance of connectivity and supporting observations that prion-like transfer *in vivo* occurs between interconnected neuronal networks[74-76]. Although differing oligomeric Aβ isoforms ($Aβ_{40}$/$Aβ_{11-42}$/$Aβ_{42}$/$Aβ_{3(pE)-40}$), including amino-terminally truncated pyroglutamylated Aβ (pE-Aβ) were transferred between cells, the more cytotoxic $Aβ_{42}$ was transferred to a greater extent[77]. This transfer appeared to be an early response to stress in degradation and clearance pathways and occurred more robustly with increased accumulation of non-degradable forms of the peptide[77]. Interestingly, protofibrillar/fibrillar forms of Aβ were more easily degraded and cleared by the lysosomal machinery and thus undergo less transfer than oligomeric forms[77]. Earlier studies also showed that the majority of internalized Aβ was found in compartments that compose the endocytic pathway, specifically late endosomes and lysosomes, and that uptake is dependent on endocytosis[19]. Despite these results, there remains many questions in regard to the mechanisms that underlie Aβ transfer and release into the extracellular milieu.

More progress has been accomplished in elucidating mechanisms of α-syn transfer between neurons. Several studies have shown that exocytotic/endocytotic mechanisms[78-80] as well as exosomes[81,82] are used by cells to externalize and internalize α-syn. Lee *et al*[80] showed that despite α-syn generally being localized within the cytosol, small amounts of α-syn are constitutively released extracellularly, in both native and pathological forms. Exocytosis of α-syn is *via* a non-classical vesicular transport system independent of the endoplasmic reticulum and Golgi apparatus. Prior to release, α-syn was detected in the lumen of intracellular large core dense vesicles where the intravesicular α-syn fraction was more aggregation-prone than the cytosolic fraction[80]. Another study by Desplats *et al*[79] demonstrated α-syn transfer between co-cultured neuronal populations in the absence of membrane leakage, although, transfer was more robust in the presence of neuronal degeneration. Furthermore, α-syn uptake was mitigated in dominant negative mutant acceptor cells that cannot form endocytotic vesicles[79]. Co-localization of internalized α-syn with endosomal markers was detected *in vitro*[79] and *in vivo*[78] and provided support for the reliance of cells on endocytosis for uptake of extracellular α-syn. Vesicular export of α-syn was further studied *in vitro* and demonstrated that, similar to Aβ, exosomes were responsible for the release of a portion

of the α-syn detected extracellularly[82,83]. Exosomes were found to be contain oligomeric α-syn both bound to the outer membrane and within lumenal fractions. Exosomes containing α-syn were more readily taken up by cells than lipid-free α-syn oligomers[83]. Additionally, induction of lysosomal dysfunction, using lysosomal inhibitors, potentiated the release of exosomes associated α-syn oligomers[81,83] while enhancement of autophagy diminished α-syn release[83]. Cellular conditions that lead to accumulation of α-syn, particularly pathological forms, favors extracellular release. Conversely, packaging in vesicles may explain how misfolded proteins enter naïve cells undetected.

Since the discovery of Lewy bodies in long-term fetal nigral tissue grafted into the striatum of PD patients[84-86], studies have subsequently shown α-syn transfer in rat models of PD. Angot *et al*[78] injected a viral vector into the SNpc of Sprague-Dawley rats to overexpress human α-syn in local neurons. Three weeks post-transfection, dopaminergic neurons were grafted intrastriatally and showed uptake of human α-syn one week later. Uptake was more robust in rats sacrificed at later time points (2 and 4 wk post-graft)[78]. The study also demonstrated, *in vivo*, the presence of human α-syn in endosomal compartments as well as core regions of cytoplasmic inclusions[78], supporting previous *in vitro* results that exogenous α-syn recruits endogenous protein to aggregate[87]. It has become apparent that trans-synaptic interneuronal transfer of Aβ and α-syn occurs in various conformations and structures. This identifies a relatively similar mechanism by which amyloidogenic proteins may propagate through the nervous system in AD and PD. Further investigation into whether this process is exclusive to pathological states, as in, whether this transfer is a cellular response to aberrant structures, is important for the development of therapeutic strategies targeting amyloid transfer.

MECHANISM OF TRANSFER

Transfer of proteins between cells is common however the mechanism that underlies transfer of pathologic species is not fully elucidated. Notably, certain forms of both Aβ and α-syn have been identified as stressors of the lysosomal degradation pathway. Emerging data implicate this stress in the extracellular release of aggregates. Lysosomal stress by Aβ is not fully understood but recent observations that oligomeric Aβ accumulated in lysosomes[88-90], induced abnormal lysosomal morphology and increased the size of the lysosomes suggests a similar mechanism as that reported for α-syn[77,91]. Internalized α-syn was shown to induce lysosomal rupture and it was suggested that this rupture is a mechanism that contributes to the release of α-syn[91]. Small fractions of these proteins in the cell may be diverted from the lysosomal degradation pathway to MVBs and exosomes for transport out of the cell. This diversion is likely a cellular attempt to rid itself of potentially toxic accumulations and is supported by the highly cytotoxic fractions of α-syn and Aβ located within exosomes[83]. Recent reports have shown that exosomes contain only 1.5% of the released α-syn[14] and as such, it is not the primary route for α-syn release from cells. These results point to the hijacking of toxin-induced cellular responses as a method for the further spread of amyloidogenic toxic species *via* a mechanism similar to the pore-forming toxins released by the bacterium *Staphylococcus aureus* (*S. aureus*)[92] and *Bacillus anthracis*[93]. *S. aureus* releases α-hemolysin to form heptameric pores in the membrane, and cellular survival depends on internalization of these pores. Once internalized, non-degraded fractions are sorted into MVBs to be released as exosomes, toxin-carrying exosomes[92]. Anthrax toxin is an AB toxin that relies on its two components, lethal factor and protective antigen, to infiltrate cells and compromise their function[93]. Protective antigen and lethal factor interact at plasma membranes, are endocytosed and interact with the limiting and intraluminal membranes of endosomes, delivering lethal factor to the cytosol and lumen of intraluminal vesicles. This loading partially allows lethal factor to be released within exosomes to deliver the toxin to nearby cells where it enters and rapidly attacks its targets. These mechanisms are analogous to aggregated forms of Aβ and α-syn interacting with plasma membranes, entering cells, and being loaded into exosomes for extracellular release.

Furthermore, pores formed by amyloidogenic proteins are similar in structure to the β-barrels formed by pore-forming toxins[94]. Antibodies that recognize the structure of Aβ and α-syn annular protofibrils also bind heptameric β-barrels of α-hemolysin, indicating that Aβ and α-syn protofibrils share a conformational state with this pore-forming toxin[95]. Formation of these small pores by bacterial toxins elicits endocytosis in an attempt by the cell to maintain survival. Endocytosed toxins are targeted for autophagy but as these pores are resistant to degradation, cells then exocytose vesicles as a protection method. Removal of these membrane interactions is intended to restore homeostasis and prevent cytotoxicity. Studies of Aβ transfer suggest that propagation is not secondary to cytotoxicity and instead occurs as an early response to failure of the cell's clearance machinery[77]. Endocytosis of membrane disrupting agents, mainly those that form small (approximately 2 nm in diameter) pores, occurs on the scale of hours to remove the pores from the surface[96]. The similarity by which many non-endogenous interactions manipulate a cell's natural response systems suggests that the propagation of amyloidogenic proteins is aided by lipid membrane interactions that enhance association with the endocytic pathway (Figure 2).

ANIMAL MODELS

Propagation of amyloid proteins, as measured by the presence of amyloid plaques and Lewy bodies and Lewy

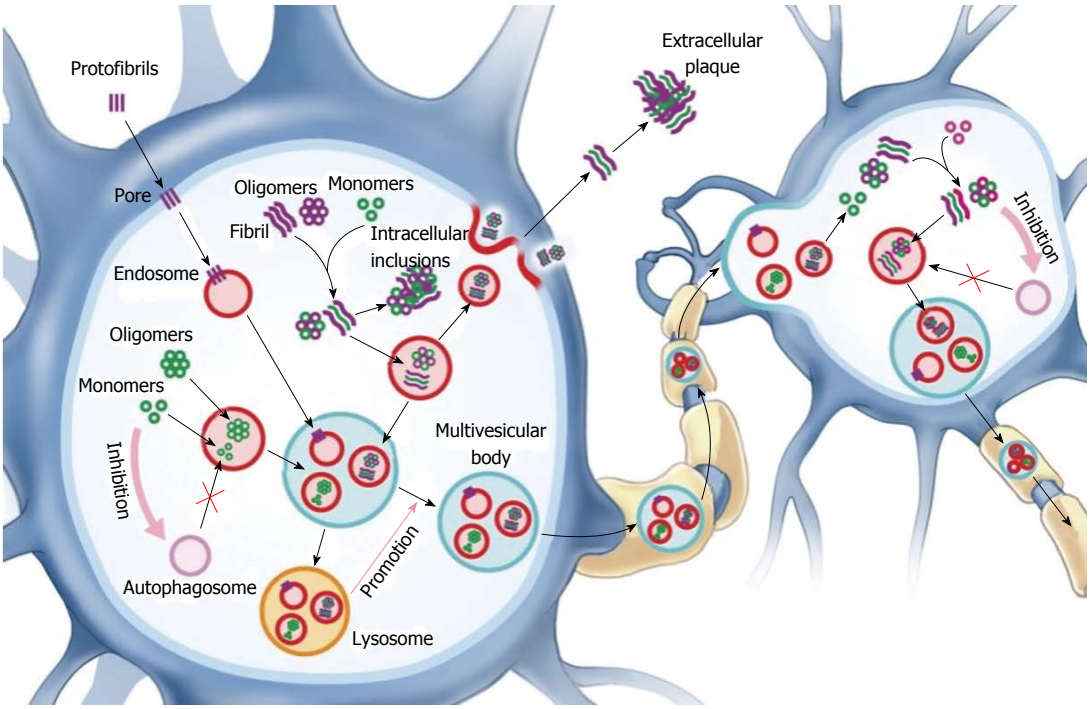

Figure 2 Several mechanisms are proposed to underlie the extracellular release of amyloidogenic proteins from neurons. Lysosomal dysfunction due to uptake and accumulation of proteopathic species that are not degraded promotes the release of misfolded species by exosomes and exocytosis. Uptake by nearby neurons likely occurs *via* an endocytic mechanism and allows proteopathic species (oligomers and fibrils) to seed the templating of endogenous protein into a misfolded conformation. Pore formation by insertion of protofibrillar amyloid-beta and alpha-synuclein prompts a cellular response to undergo endocytosis and degradation. Inhibition of autophagosome formation may contribute to amyloid deposition as well as transfer of amyloidogenic species.

Table 1 Seeding of Alzheimer's disease and Parkinson's disease-like pathology in mice

	AD	PD
Misfolded peptide/protein	Aβ peptide τ protein	α-syn protein
Pathological deposits	Intracellular (neurofibrillary tangles) Extracellular (amyloid plaques)	Intracellular (lewy bodies/lewy neurites)
Exogenous seeding of brain homogenates		
Transgenic mouse models	Human AD brain extracts into APP23[98,103,105], P21[102] and HuAPPwt[101] Rodent APP brain extracts into APP23[98,100,103], APP-PS1[98]	No reports Rodent α-syn brain extracts into M83[75,106]
Non-transgenic mice	Human AD brain extracts into Fischer 344 rats-no seeding[102]; into mice-no seeding[97] Rodent APP brain extracts into C57BL/6 J-no seeding[98]	Human Dementia with Lewy Bodies brain extracts into C57BL/6 J mice[76]
Exogenous seeding of synthetic peptides/protein		
Transgenic mouse models	Aβ40 and AβS26C into APP23[100] Aβ40/42 into APP23-no seeding[98]	Mouse α-Syn Fibrils into M83[75] Human α-Syn Fibrils into M83 and M47[108,109]
Non-transgenic mice	No reports	Mouse α-Syn Fibrils into C57BL/6 J[74,76,107,108] Human α-Syn Fibrils into C57BL/6 J[76,107,108]

Aβ: Amyloid-beta; τ: Tau; α-Syn: Alpha-synuclein; AD: Alzheimer's disease; APP: Amyloid precursor protein; PD: Parkinson's disease.

neurites, follows a stereotypical pattern[6,8] in AD and PD patients. To explain this, it is hypothesized that Aβ and α-syn transfer through neuronal networks and seed the misfolding of endogenous protein in naïve cells. Several experimental paradigms support this hypothesis, particularly, seeding and propagation of pathology in animals treated with exogenous misfolded protein (Table 1). Prion-like seeding of Aβ was demonstrated by injection of AD brain homogenates into APP-overexpressing mice leading to senile plaque formation near the injection site, 5 mo post-injection[97]. Although this provided the first evidence of Aβ seeding *in vivo*, it did not provide unequivocal evidence that Aβ was responsible for the seeding of pathology. Contamination of homogenate tissue with other seeding agents such as gangliosides and/or other molecules implicated in amyloid

aggregation may have accelerated the aggregation kinetics of endogenous Aβ. Meyer and colleagues, demonstrated the necessity for Aβ peptide after immunodepletion of Aβ from the injected extracts, protein denaturation, or Aβ immunization of APP23 mice attenuated seeding activity in the injected hosts[98]. Use of extracts from different AD mouse models, APP23 mice carrying the Swedish mutation and APP-PS1 mice carrying the Swedish and PS-1 L166P mutations, leads to differing seeding patterns in the hippocampus; APP23 extracts promote formation of primarily diffuse and filamentous lesions while APP-PS1 extracts promote formation of compact, punctate lesions[98]. Synthetic or cell-culture derived Aβ failed to demonstrate seeding altogether. The failure of synthetic Aβ aggregates generated in an *in vitro* environment to seed was attributed to Aβ peptide polymorphism and the possibility of differing strains of Aβ exhibiting different seeding potential[98]. Langer *et al*[99] characterized these proteopathic species and revealed that both fibrillar proteinase K-resistant and lower order soluble, proteinase K sensitive Aβ species from the same AD brain extract show seeding activity *in vivo*. Since different forms of Aβ found in AD brain extracts show more robust induction of pathology compared to synthetic Aβ fractions, it was proposed that endogenous Aβ species contain a structural feature capable of templating endogenous Aβ that is not generated in synthetic Aβ oligomers/protofibrils *in vitro*. Additionally, the soluble and insoluble fractions of brain extracts differ in the distribution pattern and morphology of aggregates formed within the brain; this is hypothesized to be due to differing propagation/transfer of both species *in vivo*. Stöhr *et al*[100] was able to show that fibrillized synthetic $A\beta_{40}$ and $(A\beta S26C)_2$, a mutant $A\beta_{40}$ peptide that forms covalent dimers and aggregates into neurotoxic fibrils, induced amyloid plaques that propagated throughout the brain from a single ipsilateral injection. Albeit, it was noted that synthetic fibrils were less potent than both AD brain lysates and Aβ purified from these extracts. Purified Aβ reduced seeding time by 40% and was attributed to 10-fold higher levels of pure Aβ than those in extracts, which suggested that the effect was concentration-dependent. Nonetheless, purification of Aβ from *in vivo* homogenates and recapitulation of results generated by injection of total homogenates demonstrated that Aβ alone was sufficient to generate seeding *in vivo*. More importantly, seeding by synthetic fibrils indicates that cofactors of aggregation found *in vivo* are not critical for induction of proteopathic conformations.

More recently, induction of Aβ aggregation in mouse[101] and rat[102] models that express human APP, but never develop AD pathology, was shown after injection of brain extracts from advanced AD patients. Despite never developing pathology during normal aging, the rat model (APP21-transgenic line) expresses a human *APP* gene carrying the Swedish and Indiana mutations and represents a model of AD-susceptibility. HuAPPwt mice, express the wildtype human *APP* gene, demonstrated that susceptibility to templating was not dependent on the presence of pathological mutations in Aβ. These results also suggest that murine APP retains resistance to templating, strengthening the importance of identifying conformational variants of amyloid (strains) for future propagation studies. Evidence for the existence of conformational variants of misfolded Aβ was demonstrated when brain extracts from AD patients carrying different mutations (Arctic *vs* Swedish) or with sporadic AD displayed different patterns of pathology in inoculated APP23 mice[103]. Extracts from all AD cases led to similar deposition of parenchymal Aβ plaques but differences were detected in cerebrovascular deposition. Patterns of Aβ deposition that surround blood vessels and spread into the parenchyma in mice inoculated with Arctic mutation-containing extracts; contrastingly, extracts from sporadic and Swedish mutation-carrying cases displayed a thin, compact layer of Aβ surrounding vessels, with the exception of a sporadic case displaying a combination of phenotypes[103]. These differences were maintained when homogenates from mice that had developed pathology post-inoculation were injected into younger mice, demonstrating serial transmission of seeding that was dependent on the properties of the seeds[103]. Interestingly, transgenic mice overexpressing the Arctic and Swedish mutations show the spreading cerebral amyloid angiopathy phenotype as compared to mice carrying only the Swedish mutation, which show thin, compact layers of Aβ perivascularly[104]. This suggests that the Arctic mutation promotes a dominant phenotype of cerebral amyloid angiopathy. Fritschi *et al*[105] further supported the existence of Aβ variants when it was shown that Aβ seeds derived from soluble AD brain extracts, but not Aβ CSF fractions, led to Aβ plaque deposition in APP transgenic mice. Despite Aβ levels being significantly higher in the CSF, they failed to seed pathology and this was attributed to their processing; CSF Aβ was not N-terminally truncated like Aβ peptides found in the soluble brain extract[105].

Propagation studies investigating prion-like behavior of α-syn have also demonstrated seeding properties. Mougenot *et al*[106] injected M83 mice (mouse model of PD expressing α-syn with the *A53T* mutation) with brain homogenates from older M83 mice that developed intracellular α-syn inclusions and showed that this inoculation accelerated the appearance of synuclein pathology while shortening lifespan. Luk *et al*[75] showed that young M83 mice inoculated with both lysates of aged M83 mice and synthetic α-syn fibrils developed accelerated pathology, further demonstrating that seeding of pathology was solely dependent on α-syn *in vivo*. Unilateral injections into the neocortex and striatum led to formation of inclusions containing phosphorylated endogenous α-syn in regions directly and indirectly connected to the injection sites such as the frontal cortex, thalamus, hypothalamus, substantia nigra pars compacta, locus coeruleus, cerebellar nuclei, and the spinal cord. The pathology was bilateral and phosphorylation of

α-syn at serine 129 (pSer129) was used as an indicator of pathological fibrillar α-syn. Hyperphosphorylated α-syn-containing inclusions were detected in the SNpc and were accompanied by diminished tyrosine hydroxylase staining. These observations suggested that misfolded wildtype α-syn underwent interneuronal transfer, seeded the formation of intracellular inclusions by recruiting endogenous α-syn, and initiated neuronal degeneration in dopaminergic neurons. It was also demonstrated that induction and propagation of PD-like pathology occurs in wildtype mice[74]. Pathology, as measured by inclusion formation and dopaminergic neurodegeneration, was detected as early as 30 d post-injection and was progressive becoming more severe at 90 d in both transgenic and wildtype mice[74,75]. Masuda-Suzukake *et al*[76] used human synthetic α-syn fibrils and insoluble fractions of α-syn from patients with Dementia with Lewy Bodies for injection into SNpc of wild type mice. Pathology was detected in regions connected to the injection site, starting at 90 d post-injection and showing maximal severity at 15 mo. Injection of fibrils into the SNpc led to intracellular inclusions appearing in the striatum, amygdala, stria terminalis and dentate gyrus[76]. Masuda *et al*[76] suggests that the detection of pathology in hippocampal regions, unlike mice injected into the neocortex and striatum, which do not display pathology in the hippocampus, are likely dependent on the injection site. Masuda-Suzukake *et al*[107] confirmed the importance of the injection site in determining regional transfer of pathology by injecting wildtype mice in three different regions and showing differential spread of pathology. Within one month of inoculation, α-synuclein spread from the substantia nigra to the amygdala and stria terminalis; from the striatum to the amygdala, substantia nigra and throughout the cortex; and from the entorhinal cortex to the dentate gyrus and CA3 regions of the hippocampus, the fimbria and the septal nucleus[107]. Other differences, such as rate of inclusion formation and degeneration of SNpc neurons may be linked to fibril length. Luk *et al*[75] used fibrils fragmented by sonication whereas Masuda and colleagues initially used full-length fibrils. Masuda-Suzukake *et al*[107] used fragmented fibrils in later experiments and see pathology as early as 1 mo post-injection. Shorter fragments may increase the surface area available for interaction with the cell leading to accelerated seeding process. Interestingly, in both studies, wildtype mice presented with very similar pathological distribution regardless of whether disease brain lysates or synthetic fibrils were used. This suggests that, in contrast to Aβ, α-syn fibrils displayed limited conformational heterogeneity since *in vitro* conditions are sufficient to create seeds with equivalent potency to those generated *in vivo*. Interestingly, a study by Sacino *et al*[108] questions the propagation of pathology in wildtype mice by injection of wildtype α-syn preformed fibrils. Initially, it was shown that injecting human α-syn preformed-fibrils in M83 mice hippocampi led to widespread inclusion formation throughout the CNS, including the hippocampus, striatum and cortex, three regions that typically do not develop pathology in M83 mice. However, detection of pathological α-syn in white matter tracts was absent conflicting with previous observations[74-76]. Furthermore, injection of both human and mouse α-syn fibrils into non-transgenic mice led to limited inclusion formation that was restricted to the injection sites. Inoculations were bilateral into the hippocampi and cortices of 2 mo old mice and detection of pathology at increasing time points post-injection showed decreasing immunoreactivity of pathological α-syn specific antibodies. The study attributes previously seen widespread staining to cross-reactivity of phospho-specific antibodies targeting phosphorylated α-syn (pSer129) with phosphorylated neurofilament-L (pSer473 NFL)[108]. More recently, Sacino and colleagues injected soluble (Δ71-82) and fibrillar human α-syn into M20 mice (overexpressing Human wildtype α-syn) that do not typically develop Parkinson-like pathology, as measured by presence appearance of Lewy bodies, in their lifespan[109]. By 4 mo post-injection, inoculated mice developed α-syn pathology at the injection site, the hippocampus, as well as the cortex, striatum, midbrain, and brainstem[109]. Induction of Lewy body formation using soluble species that do not fibrillize, implicates mechanisms other than templating in the disturbance of protein homeostasis. Furthermore, results suggest that overexpression of WT α-syn compromises resistance to templating and transmission since similar inoculations into non-transgenic mice failed to show spread to other regions[108]. As such, replication of studies between laboratories will be necessary to distinguish pathological seeding with α-syn.

The variability in results reported by different groups attempting to induce propagation of pathology by exogenously added seeds indicates that the mechanisms of propagation are likely complex. Sacino *et al*[108] suggests that conformational variations are a major factor explaining some of the inconsistencies seen in literature. Additionally, Sacino *et al*[108] suggests that seeding/transfer of α-syn possibly occurs as a result of the neurotoxic effects of the injected aggregates as well as the disruption of normal proteostatic mechanisms[108], neuroimmune activation and/or injury response[109]. Guo *et al*[110] reinforce the need for biochemical identification of conformational variants of amyloidogenic peptides and proteins, such as seen with Aβ[111] and α-syn[112,113]. Future studies should not only thoroughly characterize/profile the species prior to injection, but should extensively analyze changes that occur *in vivo* as a result of amyloidogenic seeds.

AD and PD exhibit many similarities in mechanisms potentially linked to their etiology. As it stands, strong evidence supports amyloidogenic structures seeding native peptides/proteins to pathologically misfold, facilitating the progression of disease. The neurotoxic effects of various aggregate subpopulations have not been characterized sufficiently to understand whether the mechanisms underlying toxicity contributes to the propagation of

pathology during disease progression. As well, oligomers, protofibrils and fibrils have been shown to display overlapping functions, such as membrane disruption, despite differences in structure. Different members of the aggregation pathway may share extensive β-sheet structure, but understanding molecular variations in the tertiary and quaternary structures may help in the understanding of their structure-function relationships and how this relationship progresses during aggregation.

REFERENCES

1 **Conway KA**, Lee SJ, Rochet JC, Ding TT, Williamson RE, Lansbury PT. Acceleration of oligomerization, not fibrillization, is a shared property of both alpha-synuclein mutations linked to early-onset Parkinson's disease: implications for pathogenesis and therapy. *Proc Natl Acad Sci USA* 2000; **97**: 571-576 [PMID: 10639120]

2 **Hardy J**, Revesz T. The spread of neurodegenerative disease. *N Engl J Med* 2012; **366**: 2126-2128 [PMID: 22646635 DOI: 10.1056/NEJMcibr1202401]

3 **Waragai M**, Sekiyama K, Fujita M, Tokuda T, Hashimoto M. Biomarkers for the diagnosis and management of Parkinson's disease. *Expert Opin Med Diagn* 2013; **7**: 71-83 [PMID: 23530844 DOI: 10.1517/17530059.2013.733694]

4 **Cookson MR**. alpha-Synuclein and neuronal cell death. *Mol Neurodegener* 2009; **4**: 9 [PMID: 19193223]

5 **Irwin DJ**, Lee VM, Trojanowski JQ. Parkinson's disease dementia: convergence of α-synuclein, tau and amyloid-β pathologies. *Nat Rev Neurosci* 2013; **14**: 626-636 [PMID: 23900411 DOI: 10.1038/nrn3549]

6 **Braak H**, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol* 1991; **82**: 239-259 [PMID: 1759558 DOI: 10.1007/BF00308809]

7 **Serrano-Pozo A**, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. *Cold Spring Harb Perspect Med* 2011; **1**: a006189 [PMID: 22229116 DOI: 10.1101/cshperspect.a006189]

8 **Braak H**, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003; **24**: 197-211 [PMID: 12498954 DOI: 10.1016/S0197-4580(02)00065-9]

9 **Halliday GM**, McCann H. The progression of pathology in Parkinson's disease. *Ann N Y Acad Sci* 2010; **1184**: 188-195 [PMID: 20146698 DOI: 10.1111/j.1749-6632.2009.05118.x]

10 **Aguzzi A**. Neurodegeneration: Alzheimer's disease under strain. *Nature* 2014; **512**: 32-34 [PMID: 25100477 DOI: 10.1038/512032a]

11 **Jucker M**, Walker LC. Self-propagation of pathogenic protein aggregates in neurodegenerative diseases. *Nature* 2013; **501**: 45-51 [PMID: 24005412 DOI: 10.1038/nature12481]

12 **Lührs T**, Ritter C, Adrian M, Riek-Loher D, Bohrmann B, Döbeli H, Schubert D, Riek R. 3D structure of Alzheimer's amyloid-beta(1-42) fibrils. *Proc Natl Acad Sci USA* 2005; **102**: 17342-17347 [PMID: 16293696 DOI: 10.1073/pnas.0506723102]

13 **Vilar M**, Chou HT, Lührs T, Maji SK, Riek-Loher D, Verel R, Manning G, Stahlberg H, Riek R. The fold of alpha-synuclein fibrils. *Proc Natl Acad Sci USA* 2008; **105**: 8637-8642 [PMID: 18550842 DOI: 10.1073/pnas.0712179105]

14 **Porat Y**, Abramowitz A, Gazit E. Inhibition of amyloid fibril formation by polyphenols: structural similarity and aromatic interactions as a common inhibition mechanism. *Chem Biol Drug Des* 2006; **67**: 27-37 [PMID: 16492146 DOI: 10.1111/j.1747-0285.2005.00318.x]

15 **Su Y**, Chang PT. Acidic pH promotes the formation of toxic fibrils from beta-amyloid peptide. *Brain Res* 2001; **893**: 287-291 [PMID: 11223020 DOI: 10.1016/S0006-8993(00)03322-9]

16 **Uversky VN**, Li J, Fink AL. Evidence for a partially folded intermediate in alpha-synuclein fibril formation. *J Biol Chem* 2001; **276**: 10737-10744 [PMID: 11152691 DOI: 10.1074/jbc.M010907200]

17 **Uversky VN**, Fink AL. Conformational constraints for amyloid fibrillation: the importance of being unfolded. *Biochim Biophys Acta* 2004; **1698**: 131-153 [PMID: 15134647 DOI: 10.1016/j.bbapap.2003.12.008]

18 **Silva JL**, Vieira TC, Gomes MP, Bom AP, Lima LM, Freitas MS, Ishimaru D, Cordeiro Y, Foguel D. Ligand binding and hydration in protein misfolding: insights from studies of prion and p53 tumor suppressor proteins. *Acc Chem Res* 2010; **43**: 271-279 [PMID: 19817406 DOI: 10.1021/ar900179t]

19 **Chafekar SM**, Baas F, Scheper W. Oligomer-specific Abeta toxicity in cell models is mediated by selective uptake. *Biochim Biophys Acta* 2008; **1782**: 523-531 [PMID: 18602001 DOI: 10.1016/j.bbadis.2008.06.003]

20 **Koo EH**, Squazzo SL. Evidence that production and release of amyloid beta-protein involves the endocytic pathway. *J Biol Chem* 1994; **269**: 17386-17389 [PMID: 8021238]

21 **Nunan J**, Small DH. Regulation of APP cleavage by alpha-, beta- and gamma-secretases. *FEBS Lett* 2000; **483**: 6-10 [PMID: 11033346 DOI: 10.1016/S0014-5793(00)02076-7]

22 **Jarrett JT**, Berger EP, Lansbury PT. The carboxy terminus of the beta amyloid protein is critical for the seeding of amyloid formation: implications for the pathogenesis of Alzheimer's disease. *Biochemistry* 1993; **32**: 4693-4697 [PMID: 8490014 DOI: 10.1021/bi00069a001]

23 **Hardy J**. Amyloid, the presenilins and Alzheimer's disease. *Trends Neurosci* 1997; **20**: 154-159 [PMID: 9106355 DOI: 10.1016/S0166-2236(96)01030-2]

24 **Iwai A**, Masliah E, Yoshimoto M, Ge N, Flanagan L, de Silva HA, Kittel A, Saitoh T. The precursor protein of non-A beta component of Alzheimer's disease amyloid is a presynaptic protein of the central nervous system. *Neuron* 1995; **14**: 467-475 [PMID: 7857654 DOI: 10.1016/0896-6273(95)90302-X]

25 **Krüger R**, Kuhn W, Müller T, Woitalla D, Graeber M, Kösel S, Przuntek H, Epplen JT, Schöls L, Riess O. Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease. *Nat Genet* 1998; **18**: 106-108 [PMID: 9462735 DOI: 10.1038/ng0298-106]

26 **Polymeropoulos MH**, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, Pike B, Root H, Rubenstein J, Boyer R, Stenroos ES, Chandrasekharappa S, Athanassiadou A, Papapetropoulos T, Johnson WG, Lazzarini AM, Duvoisin RC, Di Iorio G, Golbe LI, Nussbaum RL. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science* 1997; **276**: 2045-2047 [PMID: 9197268 DOI: 10.1126/science.276.5321.2045]

27 **Zarranz JJ**, Alegre J, Gómez-Esteban JC, Lezcano E, Ros R, Ampuero I, Vidal L, Hoenicka J, Rodriguez O, Atarés B, Llorens V, Gomez Tortosa E, del Ser T, Muñoz DG, de Yebenes JG. The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. *Ann Neurol* 2004; **55**: 164-173 [PMID: 14755719 DOI: 10.1002/ana.10795]

28 **Singleton AB**, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, Hulihan M, Peuralinna T, Dutra A, Nussbaum R, Lincoln S, Crawley A, Hanson M, Maraganore D, Adler C, Cookson MR, Muenter M, Baptista M, Miller D, Blancato J, Hardy J, Gwinn-Hardy K. alpha-Synuclein locus triplication causes Parkinson's disease. *Science* 2003; **302**: 841 [PMID: 14593171 DOI: 10.1126/science.1090278]

29 **Magen I**, Chesselet MF. Genetic mouse models of Parkinson's disease The state of the art. *Prog Brain Res* 2010; **184**: 53-87 [PMID: 20887870 DOI: 10.1016/S0079-6123(10)84004-X]

30 **Lee MK**, Stirling W, Xu Y, Xu X, Qui D, Mandir AS, Dawson TM, Copeland NG, Jenkins NA, Price DL. Human alpha-synuclein-harboring familial Parkinson's disease-linked Ala-53 --> Thr mutation causes neurodegenerative disease with alpha-synuclein aggregation in transgenic mice. *Proc Natl Acad Sci USA* 2002; **99**: 8968-8973 [PMID: 12084935 DOI: 10.1073/pnas.132197599]

31 **Marques O**, Outeiro TF. Alpha-synuclein: from secretion to

dysfunction and death. *Cell Death Dis* 2012; **3**: e350 [PMID: 22825468 DOI: 10.1038/cddis.2012.94]
32 **Kamenetz F**, Tomita T, Hsieh H, Seabrook G, Borchelt D, Iwatsubo T, Sisodia S, Malinow R. APP processing and synaptic function. *Neuron* 2003; **37**: 925-937 [PMID: 12670422 DOI: 10.1016/S0896-6273(03)00124-7]
33 **Turner PR**, O'Connor K, Tate WP, Abraham WC. Roles of amyloid precursor protein and its fragments in regulating neural activity, plasticity and memory. *Prog Neurobiol* 2003; **70**: 1-32 [PMID: 12927332 DOI: 10.1016/S0301-0082(03)00089-3]
34 **Guo JL**, Covell DJ, Daniels JP, Iba M, Stieber A, Zhang B, Riddle DM, Kwong LK, Xu Y, Trojanowski JQ, Lee VM. Distinct α-synuclein strains differentially promote tau inclusions in neurons. *Cell* 2013; **154**: 103-117 [PMID: 23827677 DOI: 10.1016/j.cell.2013.05.057]
35 **Götz J**, Chen F, van Dorpe J, Nitsch RM. Formation of neurofibrillary tangles in P3011 tau transgenic mice induced by Abeta 42 fibrils. *Science* 2001; **293**: 1491-1495 [PMID: 11520988 DOI: 10.1126/science.1062097]
36 **Hurtado DE**, Molina-Porcel L, Iba M, Aboagye AK, Paul SM, Trojanowski JQ, Lee VM. A{beta} accelerates the spatiotemporal progression of tau pathology and augments tau amyloidosis in an Alzheimer mouse model. *Am J Pathol* 2010; **177**: 1977-1988 [PMID: 20802182]
37 **Lewis J**, Dickson DW, Lin WL, Chisholm L, Corral A, Jones G, Yen SH, Sahara N, Skipper L, Yager D, Eckman C, Hardy J, Hutton M, McGowan E. Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP. *Science* 2001; **293**: 1487-1491 [PMID: 11520987 DOI: 10.1126/science.1058189]
38 **Ono K**, Takahashi R, Ikeda T, Yamada M. Cross-seeding effects of amyloid β-protein and α-synuclein. *J Neurochem* 2012; **122**: 883-890 [PMID: 22734715 DOI: 10.1111/j.1471-4159.2012.07847.x]
39 **Uéda K**, Fukushima H, Masliah E, Xia Y, Iwai A, Yoshimoto M, Otero DA, Kondo J, Ihara Y, Saitoh T. Molecular cloning of cDNA encoding an unrecognized component of amyloid in Alzheimer disease. *Proc Natl Acad Sci USA* 1993; **90**: 11282-11286 [PMID: 8248242]
40 **Sgourakis NG**, Yan Y, McCallum SA, Wang C, Garcia AE. The Alzheimer's peptides Abeta40 and 42 adopt distinct conformations in water: a combined MD / NMR study. *J Mol Biol* 2007; **368**: 1448-1457 [PMID: 17397862 DOI: 10.1016/j.jmb.2007.02.093]
41 **Ullman O**, Fisher CK, Stultz CM. Explaining the structural plasticity of α-synuclein. *J Am Chem Soc* 2011; **133**: 19536-19546 [PMID: 22029383 DOI: 10.1021/ja208657z]
42 **Zhang S**, Casey N, Lee JP. Residual structure in the Alzheimer's disease peptide: probing the origin of a central hydrophobic cluster. *Fold Des* 1998; **3**: 413-422 [PMID: 9806943 DOI: 10.1016/S1359-0278(98)00054-6]
43 **Giasson BI**, Murray IV, Trojanowski JQ, Lee VM. A hydrophobic stretch of 12 amino acid residues in the middle of alpha-synuclein is essential for filament assembly. *J Biol Chem* 2001; **276**: 2380-2386 [PMID: 11060312 DOI: 10.1074/jbc.M008919200]
44 **Kayed R**, Head E, Thompson JL, McIntire TM, Milton SC, Cotman CW, Glabe CG. Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis. *Science* 2003; **300**: 486-489 [PMID: 12702875 DOI: 10.1126/science.1079469]
45 **Dasilva KA**, Shaw JE, McLaurin J. Amyloid-beta fibrillogenesis: structural insight and therapeutic intervention. *Exp Neurol* 2010; **223**: 311-321 [PMID: 19744483 DOI: 10.1016/j.expneurol.2009.08.032]
46 **McLaurin J**, Franklin T, Chakrabartty A, Fraser PE. Phosphatidylinositol and inositol involvement in Alzheimer amyloid-beta fibril growth and arrest. *J Mol Biol* 1998; **278**: 183-194 [PMID: 9571042 DOI: 10.1006/jmbi.1998.1677]
47 **McLaurin J**, Golomb R, Jurewicz A, Antel JP, Fraser PE. Inositol stereoisomers stabilize an oligomeric aggregate of Alzheimer amyloid beta peptide and inhibit abeta -induced toxicity. *J Biol Chem* 2000; **275**: 18495-18502 [PMID: 10764800 DOI: 10.1074/jbc.M906994199]
48 **Vekrellis K**, Xilouri M, Emmanouilidou E, Stefanis L. Inducible over-expression of wild type alpha-synuclein in human neuronal cells leads to caspase-dependent non-apoptotic death. *J Neurochem* 2009; **109**: 1348-1362 [PMID: 19476547 DOI: 10.1111/j.1471-4159.2009.06054.x]
49 **Masuda M**, Suzuki N, Taniguchi S, Oikawa T, Nonaka T, Iwatsubo T, Hisanaga S, Goedert M, Hasegawa M. Small molecule inhibitors of alpha-synuclein filament assembly. *Biochemistry* 2006; **45**: 6085-6094 [PMID: 16681381 DOI: 10.1021/bi0600749]
50 **El-Agnaf OM**, Salem SA, Paleologou KE, Curran MD, Gibson MJ, Court JA, Schlossmacher MG, Allsop D. Detection of oligomeric forms of alpha-synuclein protein in human plasma as a potential biomarker for Parkinson's disease. *FASEB J* 2006; **20**: 419-425 [PMID: 16507759 DOI: 10.1096/fj.03-1449com]
51 **Shaw LM**, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, Blennow K, Soares H, Simon A, Lewczuk P, Dean R, Siemers E, Potter W, Lee VM, Trojanowski JQ. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. *Ann Neurol* 2009; **65**: 403-413 [PMID: 19296504 DOI: 10.1002/ana.21610]
52 **Sierks MR**, Chatterjee G, McGraw C, Kasturirangan S, Schulz P, Prasad S. CSF levels of oligomeric alpha-synuclein and beta-amyloid as biomarkers for neurodegenerative disease. *Integr Biol* (Camb) 2011; **3**: 1188-1196 [PMID: 22076255 DOI: 10.1039/c1ib00018g]
53 **Aguzzi A**. Cell biology: Beyond the prion principle. *Nature* 2009; **459**: 924-925 [PMID: 19536253 DOI: 10.1038/459924a]
54 **Aguzzi A**, Rajendran L. The transcellular spread of cytosolic amyloids, prions, and prionoids. *Neuron* 2009; **64**: 783-790 [PMID: 20064386 DOI: 10.1016/j.neuron.2009.12.016]
55 **Hellstrand E**, Grey M, Ainalem ML, Ankner J, Forsyth VT, Fragneto G, Haertlein M, Dauvergne MT, Nilsson H, Brundin P, Linse S, Nylander T, Sparr E. Adsorption of α-synuclein to supported lipid bilayers: positioning and role of electrostatics. *ACS Chem Neurosci* 2013; **4**: 1339-1351 [PMID: 23823878 DOI: 10.1021/cn400066t]
56 **Narayanan V**, Scarlata S. Membrane binding and self-association of alpha-synucleins. *Biochemistry* 2001; **40**: 9927-9934 [PMID: 11502187 DOI: 10.1021/bi002952n]
57 **Necula M**, Chirita CN, Kuret J. Rapid anionic micelle-mediated alpha-synuclein fibrillization in vitro. *J Biol Chem* 2003; **278**: 46674-46680 [PMID: 14506232 DOI: 10.1074/jbc.M308231200]
58 **London E**, Brown DA. Insolubility of lipids in triton X-100: physical origin and relationship to sphingolipid/cholesterol membrane domains (rafts). *Biochim Biophys Acta* 2000; **1508**: 182-195 [PMID: 11090825 DOI: 10.1016/S0304-4157(00)00007-1]
59 **Yanagisawa K**, Odaka A, Suzuki N, Ihara Y. GM1 ganglioside-bound amyloid beta-protein (A beta): a possible form of preamyloid in Alzheimer's disease. *Nat Med* 1995; **1**: 1062-1066 [PMID: 7489364 DOI: 10.1038/nm1095-1062]
60 **Kakio A**, Nishimoto S, Yanagisawa K, Kozutsumi Y, Matsuzaki K. Interactions of amyloid beta-protein with various gangliosides in raft-like membranes: importance of GM1 ganglioside-bound form as an endogenous seed for Alzheimer amyloid. *Biochemistry* 2002; **41**: 7385-7390 [PMID: 12044171 DOI: 10.1021/bi0255874]
61 **Mori K**, Mahmood MI, Neya S, Matsuzaki K, Hoshino T. Formation of GM1 ganglioside clusters on the lipid membrane containing sphingomyeline and cholesterol. *J Phys Chem B* 2012; **116**: 5111-5121 [PMID: 22494278 DOI: 10.1021/

jp207881k]
62 **Yip CM**, Elton EA, Darabie AA, Morrison MR, McLaurin J. Cholesterol, a modulator of membrane-associated Abeta-fibrillogenesis and neurotoxicity. *J Mol Biol* 2001; **311**: 723-734 [PMID: 11518526 DOI: 10.1006/jmbi.2001.4881]
63 **Micelli S**, Meleleo D, Picciarelli V, Gallucci E. Effect of sterols on beta-amyloid peptide (AbetaP 1-40) channel formation and their properties in planar lipid membranes. *Biophys J* 2004; **86**: 2231-2237 [PMID: 15041662 DOI: 10.1016/S0006-3495(04)74281-2]
64 **Qiu L**, Buie C, Reay A, Vaughn MW, Cheng KH. Molecular dynamics simulations reveal the protective role of cholesterol in β-amyloid protein-induced membrane disruptions in neuronal membrane mimics. *J Phys Chem B* 2011; **115**: 9795-9812 [PMID: 21740063 DOI: 10.1021/jp2012842]
65 **Bucciantini M**, Rigacci S, Stefani M. Amyloid aggregation: Role of biological membranes and the aggregate-membrane system. *J Phys Chem Lett* 2014; **5**: 517-527 [DOI: 10.1021/jz4024354]
66 **Evangelisti E**, Cecchi C, Cascella R, Sgromo C, Becatti M, Dobson CM, Chiti F, Stefani M. Membrane lipid composition and its physicochemical properties define cell vulnerability to aberrant protein oligomers. *J Cell Sci* 2012; **125**: 2416-2427 [PMID: 22344258 DOI: 10.1242/jcs.098434]
67 **Martinez Z**, Zhu M, Han S, Fink AL. GM1 specifically interacts with alpha-synuclein and inhibits fibrillation. *Biochemistry* 2007; **46**: 1868-1877 [PMID: 17253773 DOI: 10.1021/bi061749a]
68 **Park JY**, Kim KS, Lee SB, Ryu JS, Chung KC, Choo YK, Jou I, Kim J, Park SM. On the mechanism of internalization of alpha-synuclein into microglia: roles of ganglioside GM1 and lipid raft. *J Neurochem* 2009; **110**: 400-411 [PMID: 19457104 DOI: 10.1111/j.1471-4159.2009.06150.x]
69 **Bateman RJ**, Munsell LY, Morris JC, Swarm R, Yarasheski KE, Holtzman DM. Human amyloid-beta synthesis and clearance rates as measured in cerebrospinal fluid in vivo. *Nat Med* 2006; **12**: 856-861 [PMID: 16799555 DOI: 10.1038/nm1438]
70 **Poduslo JF**, Curran GL, Wengenack TM, Malester B, Duff K. Permeability of proteins at the blood-brain barrier in the normal adult mouse and double transgenic mouse model of Alzheimer's disease. *Neurobiol Dis* 2001; **8**: 555-567 [PMID: 11493021 DOI: 10.1006/nbdi.2001.0402]
71 **Borghi R**, Marchese R, Negro A, Marinelli L, Forloni G, Zaccheo D, Abbruzzese G, Tabaton M. Full length alpha-synuclein is present in cerebrospinal fluid from Parkinson's disease and normal subjects. *Neurosci Lett* 2000; **287**: 65-67 [PMID: 10841992 DOI: 10.1016/S0304-3940(00)01153-8]
72 **Rajendran L**, Honsho M, Zahn TR, Keller P, Geiger KD, Verkade P, Simons K. Alzheimer's disease beta-amyloid peptides are released in association with exosomes. *Proc Natl Acad Sci USA* 2006; **103**: 11172-11177 [PMID: 16837572 DOI: 10.1073/pnas.0603838103]
73 **Nath S**, Agholme L, Kurudenkandy FR, Granseth B, Marcusson J, Hallbeck M. Spreading of neurodegenerative pathology via neuron-to-neuron transmission of β-amyloid. *J Neurosci* 2012; **32**: 8767-8777 [PMID: 22745479 DOI: 10.1523/JNEUROSCI.0615-12.2012]
74 **Luk KC**, Kehm V, Carroll J, Zhang B, O'Brien P, Trojanowski JQ, Lee VM. Pathological α-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice. *Science* 2012; **338**: 949-953 [PMID: 23161999 DOI: 10.1126/science.1227157]
75 **Luk KC**, Kehm VM, Zhang B, O'Brien P, Trojanowski JQ, Lee VM. Intracerebral inoculation of pathological α-synuclein initiates a rapidly progressive neurodegenerative α-synucleinopathy in mice. *J Exp Med* 2012; **209**: 975-986 [PMID: 22508839 DOI: 10.1084/jem.20112457]
76 **Masuda-Suzukake M**, Nonaka T, Hosokawa M, Oikawa T, Arai T, Akiyama H, Mann DM, Hasegawa M. Prion-like spreading of pathological α-synuclein in brain. *Brain* 2013; **136**: 1128-1138 [PMID: 23466394 DOI: 10.1093/brain/awt037]
77 **Domert J**, Rao SB, Agholme L, Brorsson AC, Marcusson J, Hallbeck M, Nath S. Spreading of amyloid-β peptides via neuritic cell-to-cell transfer is dependent on insufficient cellular clearance. *Neurobiol Dis* 2014; **65**: 82-92 [PMID: 24412310 DOI: 10.1016/j.nbd.2013.12.019]
78 **Angot E**, Steiner JA, Lema Tomé CM, Ekström P, Mattsson B, Björklund A, Brundin P. Alpha-synuclein cell-to-cell transfer and seeding in grafted dopaminergic neurons in vivo. *PLoS One* 2012; **7**: e39465 [PMID: 22737239 DOI: 10.1371/journal.pone.0039465]
79 **Desplats P**, Lee HJ, Bae EJ, Patrick C, Rockenstein E, Crews L, Spencer B, Masliah E, Lee SJ. Inclusion formation and neuronal cell death through neuron-to-neuron transmission of alpha-synuclein. *Proc Natl Acad Sci USA* 2009; **106**: 13010-13015 [PMID: 19651612 DOI: 10.1073/pnas.0903691106]
80 **Lee HJ**, Patel S, Lee SJ. Intravesicular localization and exocytosis of alpha-synuclein and its aggregates. *J Neurosci* 2005; **25**: 6016-6024 [PMID: 15976091 DOI: 10.1523/JNEUROSCI.0692-05.2005]
81 **Alvarez-Erviti L**, Seow Y, Schapira AH, Gardiner C, Sargent IL, Wood MJ, Cooper JM. Lysosomal dysfunction increases exosome-mediated alpha-synuclein release and transmission. *Neurobiol Dis* 2011; **42**: 360-367 [PMID: 21303699 DOI: 10.1016/j.nbd.2011.01.029]
82 **Emmanouilidou E**, Melachroinou K, Roumeliotis T, Garbis SD, Ntzouni M, Margaritis LH, Stefanis L, Vekrellis K. Cell-produced alpha-synuclein is secreted in a calcium-dependent manner by exosomes and impacts neuronal survival. *J Neurosci* 2010; **30**: 6838-6851 [PMID: 20484626 DOI: 10.1523/JNEUROSCI.5699-09.2010]
83 **Danzer KM**, Kranich LR, Ruf WP, Cagsal-Getkin O, Winslow AR, Zhu L, Vanderburg CR, McLean PJ. Exosomal cell-to-cell transmission of alpha synuclein oligomers. *Mol Neurodegener* 2012; **7**: 42 [PMID: 22920859 DOI: 10.1186/1750-1326-7-42]
84 **Kordower JH**, Brundin P. Lewy body pathology in long-term fetal nigral transplants: is Parkinson's disease transmitted from one neural system to another? *Neuropsychopharmacology* 2009; **34**: 254 [PMID: 19079079 DOI: 10.1038/npp.2008.161]
85 **Kordower JH**, Chu Y, Hauser RA, Freeman TB, Olanow CW. Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. *Nat Med* 2008; **14**: 504-506 [PMID: 18391962 DOI: 10.1038/nm1747]
86 **Li JY**, Englund E, Holton JL, Soulet D, Hagell P, Lees AJ, Lashley T, Quinn NP, Rehncrona S, Björklund A, Widner H, Revesz T, Lindvall O, Brundin P. Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation. *Nat Med* 2008; **14**: 501-503 [PMID: 18391963 DOI: 10.1038/nm1746]
87 **Volpicelli-Daley LA**, Luk KC, Patel TP, Tanik SA, Riddle DM, Stieber A, Meaney DF, Trojanowski JQ, Lee VM. Exogenous α-synuclein fibrils induce Lewy body pathology leading to synaptic dysfunction and neuron death. *Neuron* 2011; **72**: 57-71 [PMID: 21982369 DOI: 10.1016/j.neuron.2011.08.033]
88 **Agholme L**, Hallbeck M, Benedikz E, Marcusson J, Kågedal K. Amyloid-β secretion, generation, and lysosomal sequestration in response to proteasome inhibition: involvement of autophagy. *J Alzheimers Dis* 2012; **31**: 343-358 [PMID: 22555375]
89 **Lai AY**, McLaurin J. Inhibition of amyloid-beta peptide aggregation rescues the autophagic deficits in the TgCRND8 mouse model of Alzheimer disease. *Biochim Biophys Acta* 2012; **1822**: 1629-1637 [PMID: 22800931 DOI: 10.1016/j.bbadis.2012.07.003]
90 **Zheng H**, Koo EH. Biology and pathophysiology of the amyloid precursor protein. *Mol Neurodegener* 2011; **6**: 27 [PMID: 21527012 DOI: 10.1186/1750-1326-6-27]
91 **Freeman D**, Cedillos R, Choyke S, Lukic Z, McGuire K,

Marvin S, Burrage AM, Sudholt S, Rana A, O'Connor C, Wiethoff CM, Campbell EM. Alpha-synuclein induces lysosomal rupture and cathepsin dependent reactive oxygen species following endocytosis. *PLoS One* 2013; **8**: e62143 [PMID: 23634225 DOI: 10.1371/journal.pone.0062143]

92 **Husmann M**, Beckmann E, Boller K, Kloft N, Tenzer S, Bobkiewicz W, Neukirch C, Bayley H, Bhakdi S. Elimination of a bacterial pore-forming toxin by sequential endocytosis and exocytosis. *FEBS Lett* 2009; **583**: 337-344 [PMID: 19101547 DOI: 10.1016/j.febslet.2008.12.028]

93 **Abrami L**, Brandi L, Moayeri M, Brown MJ, Krantz BA, Leppla SH, van der Goot FG. Hijacking multivesicular bodies enables long-term and exosome-mediated long-distance action of anthrax toxin. *Cell Rep* 2013; **5**: 986-996 [PMID: 24239351 DOI: 10.1016/j.celrep.2013.10.019]

94 **Lashuel HA**, Petre BM, Wall J, Simon M, Nowak RJ, Walz T, Lansbury PT. Alpha-synuclein, especially the Parkinson's disease-associated mutants, forms pore-like annular and tubular protofibrils. *J Mol Biol* 2002; **322**: 1089-1102 [PMID: 12367530 DOI: 10.1016/S0022-2836(02)00735-0]

95 **Kayed R**, Pensalfini A, Margol L, Sokolov Y, Sarsoza F, Head E, Hall J, Glabe C. Annular protofibrils are a structurally and functionally distinct type of amyloid oligomer. *J Biol Chem* 2009; **284**: 4230-4237 [PMID: 19098006 DOI: 10.1074/jbc.M808591200]

96 **Bischofberger M**, Gonzalez MR, van der Goot FG. Membrane injury by pore-forming proteins. *Curr Opin Cell Biol* 2009; **21**: 589-595 [PMID: 19442503 DOI: 10.1016/j.ceb.2009.04.003]

97 **Kane MD**, Lipinski WJ, Callahan MJ, Bian F, Durham RA, Schwarz RD, Roher AE, Walker LC. Evidence for seeding of beta -amyloid by intracerebral infusion of Alzheimer brain extracts in beta -amyloid precursor protein-transgenic mice. *J Neurosci* 2000; **20**: 3606-3611 [PMID: 10804202]

98 **Meyer-Luehmann M**, Coomaraswamy J, Bolmont T, Kaeser S, Schaefer C, Kilger E, Neuenschwander A, Abramowski D, Frey P, Jaton AL, Vigouret JM, Paganetti P, Walsh DM, Mathews PM, Ghiso J, Staufenbiel M, Walker LC, Jucker M. Exogenous induction of cerebral beta-amyloidogenesis is governed by agent and host. *Science* 2006; **313**: 1781-1784 [PMID: 16990547 DOI: 10.1126/science.1131864]

99 **Langer F**, Eisele YS, Fritschi SK, Staufenbiel M, Walker LC, Jucker M. Soluble Aβ seeds are potent inducers of cerebral β-amyloid deposition. *J Neurosci* 2011; **31**: 14488-14495 [PMID: 21994365 DOI: 10.1523/JNEUROSCI.3088-11.2011]

100 **Stöhr J**, Watts JC, Mensinger ZL, Oehler A, Grillo SK, DeArmond SJ, Prusiner SB, Giles K. Purified and synthetic Alzheimer's amyloid beta (Aβ) prions. *Proc Natl Acad Sci USA* 2012; **109**: 11025-11030 [PMID: 22711819 DOI: 10.1073/pnas.1206555109]

101 **Morales R**, Duran-Aniotz C, Castilla J, Estrada LD, Soto C. De novo induction of amyloid-β deposition in vivo. *Mol Psychiatry* 2012; **17**: 1347-1353 [PMID: 21968933 DOI: 10.1038/mp.2011.120]

102 **Rosen RF**, Fritz JJ, Dooyema J, Cintron AF, Hamaguchi T, Lah JJ, LeVine H, Jucker M, Walker LC. Exogenous seeding of cerebral β-amyloid deposition in βAPP-transgenic rats. *J Neurochem* 2012; **120**: 660-666 [PMID: 22017494 DOI: 10.1111/j.1471-4159.2011.07551.x]

103 **Watts JC**, Condello C, Stöhr J, Oehler A, Lee J, DeArmond SJ, Lannfelt L, Ingelsson M, Giles K, Prusiner SB. Serial propagation of distinct strains of Aβ prions from Alzheimer's disease patients. *Proc Natl Acad Sci USA* 2014; **111**: 10323-10328 [PMID: 24982139 DOI: 10.1073/pnas.1408900111]

104 **Knobloch M**, Konietzko U, Krebs DC, Nitsch RM. Intracellular Abeta and cognitive deficits precede beta-amyloid deposition in transgenic arcAbeta mice. *Neurobiol Aging* 2007; **28**: 1297-1306 [PMID: 16876915 DOI: 10.1016/j.neurobiolaging.2006.06.019]

105 **Fritschi SK**, Langer F, Kaeser SA, Maia LF, Portelius E, Pinotsi D, Kaminski CF, Winkler DT, Maetzler W, Keyvani K, Spitzer P, Wiltfang J, Kaminski Schierle GS, Zetterberg H, Staufenbiel M, Jucker M. Highly potent soluble amyloid-β seeds in human Alzheimer brain but not cerebrospinal fluid. *Brain* 2014; **137**: 2909-2915 [PMID: 25212850 DOI: 10.1093/brain/awu255]

106 **Mougenot AL**, Nicot S, Bencsik A, Morignat E, Verchère J, Lakhdar L, Legastelois S, Baron T. Prion-like acceleration of a synucleinopathy in a transgenic mouse model. *Neurobiol Aging* 2012; **33**: 2225-2228 [PMID: 21813214 DOI: 10.1016/j.neurobiolaging.2011.06.022]

107 **Masuda-Suzukake M**, Nonaka T, Hosokawa M, Kubo M, Shimozawa A, Akiyama H, Hasegawa M. Pathological alpha-synuclein propagates through neural networks. *Acta Neuropathol Commun* 2014; **2**: 88 [PMID: 25095794 DOI: 10.1186/PREACCEPT-1296467154135944]

108 **Sacino AN**, Brooks M, Thomas MA, McKinney AB, McGarvey NH, Rutherford NJ, Ceballos-Diaz C, Robertson J, Golde TE, Giasson BI. Amyloidogenic α-synuclein seeds do not invariably induce rapid, widespread pathology in mice. *Acta Neuropathol* 2014; **127**: 645-665 [PMID: 24659240 DOI: 10.1007/s00401-014-1268-0]

109 **Sacino AN**, Brooks M, McKinney AB, Thomas MA, Shaw G, Golde TE, Giasson BI. Brain injection of α-synuclein induces multiple proteinopathies, gliosis, and a neuronal injury marker. *J Neurosci* 2014; **34**: 12368-12378 [PMID: 25209277 DOI: 10.1523/JNEUROSCI.2102-14.2014]

110 **Guo JL**, Lee VM. Cell-to-cell transmission of pathogenic proteins in neurodegenerative diseases. *Nat Med* 2014; **20**: 130-138 [PMID: 24504409 DOI: 10.1038/nm.3457]

111 **Petkova AT**, Leapman RD, Guo Z, Yau WM, Mattson MP, Tycko R. Self-propagating, molecular-level polymorphism in Alzheimer's beta-amyloid fibrils. *Science* 2005; **307**: 262-265 [PMID: 15653506 DOI: 10.1126/science.1105850]

112 **Bousset L**, Pieri L, Ruiz-Arlandis G, Gath J, Jensen PH, Habenstein B, Madiona K, Olieric V, Böckmann A, Meier BH, Melki R. Structural and functional characterization of two alpha-synuclein strains. *Nat Commun* 2013; **4**: 2575 [PMID: 24108358 DOI: 10.1038/ncomms3575]

113 **Cremades N**, Cohen SI, Deas E, Abramov AY, Chen AY, Orte A, Sandal M, Clarke RW, Dunne P, Aprile FA, Bertoncini CW, Wood NW, Knowles TP, Dobson CM, Klenerman D. Direct observation of the interconversion of normal and toxic forms of α-synuclein. *Cell* 2012; **149**: 1048-1059 [PMID: 22632969 DOI: 10.1016/j.cell.2012.03.03]

P- Reviewer: Juan DS, Riva N **S- Editor**: Song XX
L- Editor: A **E- Editor**: Liu SQ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com