Alzheimer Disease Review Series *J. Cell. Mol. Med. Vol 16, No 6, 2012 pp. 1166-1183*

Guest Editor: B.O. Popescu

Interaction between pathogenic proteins in neurodegenerative disorders

Kurt A. Jellinger *

Institute of Clinical Neurobiology, Vienna, Austria

Received: October 19, 2011; Accepted: December 5, 2011

Abstract

The misfolding and progressive aggregation of specific proteins in selective regions of the nervous system is a seminal occurrence in many neurodegenerative disorders, and the interaction between pathological/toxic proteins to cause neurodegeneration is a hot topic of current neuroscience research. Despite clinical, genetic and experimental differences, increasing evidence indicates considerable overlap between synucleinopathies, tauopathies and other protein-misfolding diseases. Inclusions, often characteristic hallmarks of these disorders, suggest interactions of pathological proteins enganging common downstream pathways. Novel findings that have shifted our understanding in the role of pathologic proteins in the pathogenesis of Alzheimer, Parkinson, Huntington and prion diseases, have confirmed correlations/overlaps between these and other neurodegenerative disorders. Emerging evidence, in addition to synergistic effects of tau protein, amyloid-β, α-synuclein and other pathologic proteins, suggests that prion-like induction and spreading, involving secreted proteins, are major pathogenic mechanisms in various neurodegenerative diseases, depending on genetic backgrounds and environmental factors. The elucidation of the basic molecular mechanisms underlying the interaction and spreading of pathogenic proteins, suggesting a dualism or triad of neurodegeneration in protein-misfolding disorders, is a major challenge for modern neuroscience, to provide a deeper insight into their pathogenesis as a basis of effective diagnosis and treatment.

Keywords: neurodegeneration • protein misfolding • oligomers • interaction • aggregation • spreading • pathogenic factors

Introduction

Neurodegenerative disorders (NDDs) such as Alzheimer disease (AD), Parkinson disease (PD), frontotemporal lobar degeneration (FTLD), Huntington disease (HD), prion and motoneuron diseases are being realized to have common cellular and molecular mechanisms including protein aggregation and inclusion body formation in selected areas of the nervous system. Therefore, these disorders are summarized as 'proteinopathies' [1–5], and are also called 'neurodegenerative conformational diseases' [6], 'protein aggregation diseases' [281], 'protein misfolding disorders' [182], or 'neurodegenerative foldopathies' [282]. The size, shape, location, and protein composition of the aggregates are characteristic features of the diseases. Although the different localizations of hallmark protein aggregates [extracellular amyloid-β (Aβ) deposits and intracellular hyperphosphorylated tau (p-tau) in AD, α-synuclein (αSyn) containing cytoplasmic Lewy bodies (LBs) and neurites (LNs) in PD, αSyn containing glial cytoplasmic inclusions (GCI) in multiple system atrophy (MSA), intranuclear huntingtin inclusions in HD, TDP-43 intrancytoplasmic and intranuclear inclusions in AD and FTLD] may suggest that each protein strikes a single cellular domain, recent studies indicate the possibility of common pathogenesis with overlap between the different disorders [2, 4, 7–13]. The deposits consist of insoluble fibrillary aggregates containing misfolded protein with β-sheet formation. The most probable explanation is that these inclusions and aggregates represent an end stage of a molecular or 'molecular misreading' [283] multistep cascade of complicated events that might result from an imbalance between protein synthesis, aggregation and clearance possibly

*Correspondence to: Kurt A. JELLINGER,
Institute of Clinical Neurobiology, Vienna, Austria.
Tel./Fax: +43 1 5266534
E-mail: kurt.jellinger@univie.ac.at

doi: 10.1111/j.1582-4934.2011.01507.x

because of the decline of cellular protein quality processes [14, 15] or 'molecular misreading' [283]. It appears reasonable that an earlier stage may be more directly tied up to the—hitherto unknown—pathogenesis of the disorders than the inclusions themselves, which may or may not represent diagnostic hallmarks or signposts. It has been suggested that the translocation of proteins to the mitochondrial membrane may play an important role in triggering or perpetuating neurodegeneration (ND) causing mitochondrial destruction [16, 17]. In many of these disorders, ND is likely to initiate at the synaptic site, where discrete protein aggregates, known as oligomers, impair neuronal transmission and functioning [18, 19, 92, 284].

Oligomers are usually diffusible, non-fibrillary, small-order aggregates, whereas larger polymers, in the form of amyloid fibrils, comprise the inclusion bodies and extracellular deposits that characterize these disorders and are now believed to represent a pathway for sequestration of more toxic oligomers [20]. Different types of Aβ oligomers are associated with various degrees of toxicity; they may differ in their underlying structure and may follow different assembly pathways [21]. The high contents of lipid rafts of the neuronal plasma membrane renders these cells particularly vulnerable to the cytotoxic attack of amyloid proteins and represents one of the reasons for the high vulnerability of the CNS to misfolded proteins [285]. Recent studies indicate that the presence of Aβ seeds, and not the age of the host is critical for the initiation of Aβ aggregation in the brain [22]. Small intermediates along the pathway from oligomer to fibril have also been reported to form 'pore-like' structures that might themselves disrupt ionic homeostasis and influence synaptic dysfunction, while large insoluble deposits might function as reservoirs of the bioactive oligomers that can lead to synaptic and mitochondrial dysfunction, neuronal apoptosis and cell death [23–25]. This, among others, is probably because of iron-related oxidative damage mediated by αSyn oligomerization *via* oxidative stress during the development of PD pathology [26–28]. On the other hand, brain-permeable small-molecule inhibition of heat shock protein Hsp90 has been shown to prevent αSyn oligomer formation and protect against αSyn-induced toxicity [29]. αSyn has recently been shown to occur physiologically as helically folded tetrameres that resist aggregation. It has been hypothesized that αSyn tetrameres undergo destabilization before aggregate formation [286]. Aβ promotes αSyn aggregation *in vivo* [215] and both might directly interact [8] to form hybrid channel-like structures [25]. Misfolding and subsequent aggregation of αSyn play a central role in the pathogenesis of synucleinopathies [30, 31]. The levels of soluble αSyn oligomeric species are increased by phosphorylation at Ser129 [32]. Elevated levels of soluble αSyn oligomers have been detected in postmortem brain extracts from patients with dementia with Lewy bodies (DLB), which were significantly higher than in AD and controls [33]. Evidence further suggests that protein propagation might contribute not only to the spreading and progression of the disease, but also to ND. Recent studies suggest that such protein spreading might occur in AD, PD, FTLD and other NDDs [1, 23, 34, 35]. Seeding induced by αSyn oligomers, the toxicity of which has been demonstrated *in vivo* [36], can induce intracellular αSyn aggregation, providing evidence for spreading of αSyn pathology [37, 38] similar to that of prions [34] and seeding of normal tau by pathological tau conformers drives pathogenesis of Alzheimer-like tangles [56], but the exact molecular pathways of transmissible proteins are not yet fully understood [39].

Amyloid-β causes downstream loss of dendrites and synapses, and functional disruption of neuronal networks [40, 41]. It induces the neurodegenerative triad of spine loss, dendritic changes and neuritic dystrophies through calcineurin activation [42], oxidative stress, mitochondrial dysfunction, impaired synaptic transmission, disruption of membrane integrity and impaired axonal transport [43], whereas soluble tau species rather than aggregated ones induce ND [44]. Cellular prion protein (PrPc) is a high-affinity receptor for Aβ oligomers mediating their toxicity on synaptic plasticity [45–50], but it mediates neurotoxic signalling of β-sheet-rich conformers independent of prion replication [248]. Co-transfection of tau gene in cortical neurons with a proteasome activity reporter (GFP-CL1) resulted in down-regulation of the proteasome system, suggesting a possible mechanism that contributes to intracellular PrPC accumulation, indicating a possible crosstalk between tau and prion proteins in the pathogenesis of tau-induced ND [287]. Likewise, tau-inhibiting tubulin oligomerization induced by prion protein points to a possible molecular link between NDDs and transmissible spongiform encephalopathies [288]. A case with a rare PRNP mutation (Q160X) resulting in the production of truncated PrP suggests that PRNP mutations that result in a truncation of PrP lead to a prolonged clinical course consistent with AD-like pathology [289].

Tau phosphorylation proceeds to tau aggregation that is favoured by kinases like glycogen synthase kinase-3β (GSK-3β) [51], while inhibition of GSK-3β activity prevented not only tau phosphorylation but also tau aggregation in the hippocampus [52]. It is unclear whether tau accumulation or its conformational changes are related to tau-induced ND [53]. Recent studies showed that caspase activation, observed in a tg mouse model overexpressing GSK-3β [54], precedes tangle formation [55]. Seeding of normal tau by pathological tau conformers further drives pathogenesis of neurofibrillary tangles (NFT) [56].

TDP-43 proteinopathies are distinct from most other NDDs because they are due to protein misfolding without amyloidosis, while TDP-43 inclusions show abnormal phosphorylation, ubiquitination and C-terminal fragments [57]. However, TDP-43 is present in AD, other NDDs and normal ageing, suggesting that TDP-43 proteinopathies can be considered in two classes—primary and secondary [58]. The presence of TDP-43 changes in AD and Down syndrome may be a secondary phenomenon, relating more to aging than to AD itself, but it may be integral to the pathology of AD and to some extent determine its clinical phenotype [290]. TDP-43 and fused in sarcoma, both DNA-/RNA-binding proteins, show genetic interaction in amyotrophic lateral sclerosis (ALS) and FTLD [59, 60]. The molecular mechanisms of TDP-43-mediated ND have been critically reviewed recently [291].

However, the mechanism by which oligomers trigger ND still remains elusive, and it is unclear, whether there is a common underlying pathogenic mechanism inducing both ND and fibrillary protein aggregates that are typical for different disease processes (double or triple amyloidosis) or if they represent a common final pathology leading to ND. The aim of this article is to review the molecular mecha-

nisms and interactions between the various pathological proteins in NDDs.

The proteopathic basis of AD

The brains in patients with AD, in addition to neuron and synapse loss, are characterized by two hallmark lesions—Aβ containing plaques and NFT, which are composed of hyperphosphorylated forms of microtubulus-associated tau protein [61, 62] (Fig. 1). Progression of NFT pathology throughout the brain strongly correlates with disease progression [63], while brain oligomeric Aβ but not total amyloid plaque burden correlates with neuronal loss and astrocytic inflammatory response in APP/tau tg mice [64] and in humans with the APP (E693Δ) mutation [292, 293]. Loss of synapses is one of the earliest events that has been associated with functional impairment [65, 66]. Although both Aβ and tau have been extensively studied with regard to their separate modes of toxicity [67], suggesting that both proteins exhibit synergistic effects on mitochondrial function finally leading to ND [68], more recently new light has been shed on their possible interactions and synergistic effects in AD, linking Aβ and tau [69–71]. There is an interaction between tau and Aβ mediated by increased activity of GSK-3β, a major kinase that hyperphosphorylates tau to produce pathological forms of tau [72–75], which may represent an interesting link between the two pathogenic hallmarks of these disorders [74, 76–78]. In addition, there may be a participation of the protein 14-3-3 in the oligomerization and aggregation of tau [294]. Hyperphosphorylation of tau may be a consequence of Aβ toxicity via the regulator of calcineurin gene RCAN1 and GSK-3β, producing a sequential mechanism for Aβ and tau pathology [295].

The senile plaque, where Aβ deposits and tau-positive processes meet, is probably one important site of interactions: the cytoplasmic domain of amyloid precursor protein (APP), phosphorylated on threonine 668, could be the intermate as it appears to be associated both with tau and Aβ [79]. There are also well-documented data incidating that Aβ and tau meet at the synapse, as in about 25% of synaptosomes preserved from cryopreserved material, phospho (p)-tau and Aβ were co-localized [80]. Recent studies established a common, direct and synergistic toxicity of pathologic APP and tau products in synaptic mitochondria contributing to synaptic deterioration in AD [296], which is associated with reduction of the postsynaptic scaffold protein PSD-95 in both tg mice and AD [297].

According to the amyloid cascade hypothesis, Aβ formation is the critical step in driving AD pathogenesis, implying the aggregation of Aβ as critical, early trigger in the chain of events that leads to tauopathy, neuronal dysfunction and dementia [81] (Fig. 2). Support for this concept stems from the identification of pathogenic mutations in

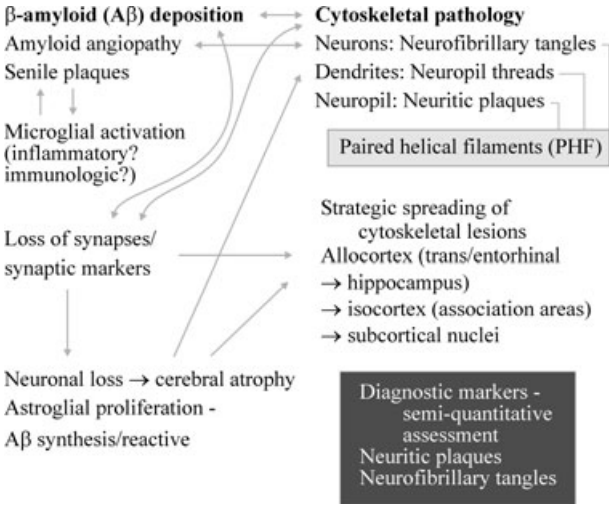

Fig. 1 Neuropathology of Alzheimer disease and morphological markers.

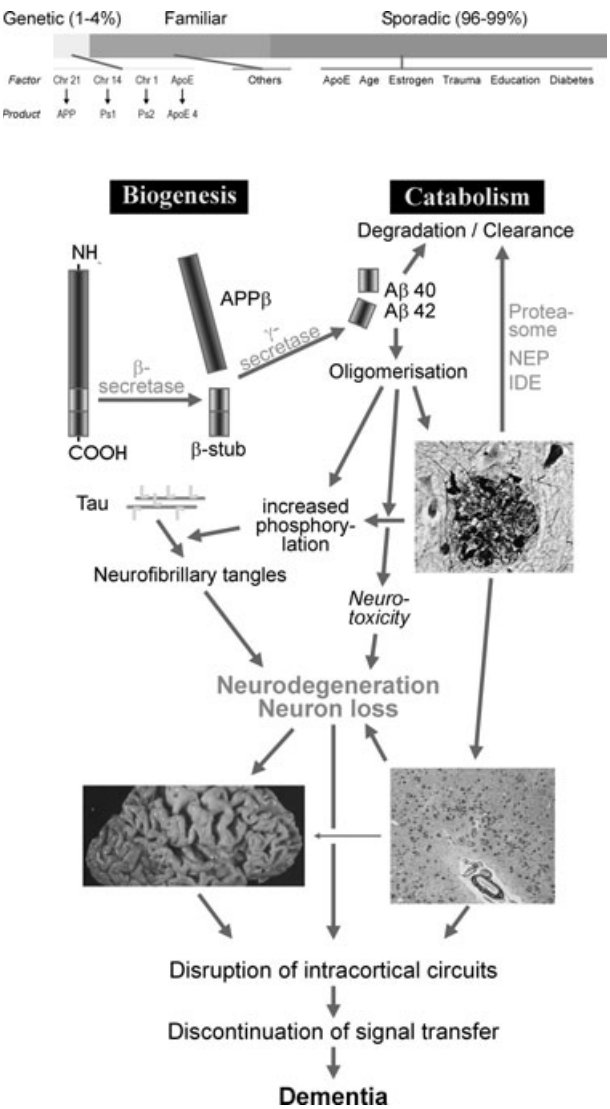

Fig. 2 Pathogenesis of Alzheimer disease (major factors).

patients with familial AD linked to Aβ formation and a higher frequency of AD in people with trisomy 21, who carry an additional APP allele [82]. All firmly established genetic risk factors for AD promote the buildup of Aβ, either by increasing its production, promoting its aggregation or impending its elimination [83]. While oral, intravenous, intraocular and intranasal inoculation yielded no detectable introduction of cerebral β-amyloidosis in APP23 tg mice, intracerebral transmission through Aβ-contaminated steel wires [84] and intraperitoneal inoculation with Aβ-rich extracts after prolonged incubation times did [85]. Soluble Aβ seeds also mediated β-amyloidosis in the brain [86] and may be induced in βAPP tg rats that are relatively refractory of spontaneous original Aβ deposits [87], whereas peripheral reduction of Aβ may reduce brain Aβ [88]. Previous studies of Aβ induction have used short incubation periods to dissociate seeded Aβ induction from endogenous Aβ deposition of the host, showing that Aβ deposition, actuated in one brain area, eventually spreads throughout the brain (for a review, see [22]). Recent longitudinal imaging studies indicate that cerebral Aβ deposition precedes clinical AD by a decade or more [89]. How Aβ aggregates impair neuronal function remains uncertain, but evidence is growing that oligomeric forms of the protein, which can range in size from dimers to dodecamers or larger [90–93], are more deleterious to brain function than are histologically obvious Aβ lesions such as senile plaques and cerebral amyloid angiopathy (CAA). On the other hand, according to recent data, at least some of the Aβ toxicity appears to be tau-dependent [70, 94].

Although Aβ and tau exert toxicity through separate mechanisms [95], evidence from both *in vitro* and *in vivo* models suggest that there are three possible models of interaction between the two: (1) Aβ drives tau pathology, supported by induction of tau hyperphosphorylation by Aβ formation in APP tg mice [96], induction of neuronal tau hyperphosphorylation by Aβ oligomers [97] or Aβ-derived diffusible ligants (ADDL) [97], and, together with neuritic degeneration, by soluble Aβ-protein dimers isolated from Alzheimer cortex [93] or by Aβ-rich brain extracts [98]. Tau hyperphosphorylation leads to tau dissociation from microtubules and increased accumulations in some dendritic compartments [99]. Together with NFT formation, it seems to be linked to abnormal mitochondrial distribution in neurons [298], whereas abnormal interactions between the GTPase dynamic-related protein 1 (Drp1), acting in the outer mitochondrial membrane, and Aβ have recently been identified in AD brains [299]. Furthermore, aggravation of NFT pathology is induced by intracranial injection of synthetic Aβ into mutant tau tg mice [100]. Aβ exacerbates neuronal dysfunction caused by human tau expression in a *Drosophila* model of AD [101], whereas inhibition of GSK-3 ameliorates Aβ pathology in this model [102]. The pathogenic effects of Aβ-42 were also significantly suppressed when Aβ-42 is expressed in a *Drosophila* tau null line, demonstrating an interaction between the two proteins [102]. Overall, the *Drosophila* models of tauopathy in which both tau and APP are co-expressed can provide valuable insights into the cellular pathways mediating the interaction between these two proteins [103]. Amyloid precursor protein tg mice develop abundant Aβ accumulation as well as tau pathology similar to that observed in AD [104], but none of the APP models fully recapitulate AD cellular and behavioral pathology [300, 301]. In an AD mouse model, Aβ accelerates the spatiotemporal progress of tau pathology, particularly in the perforant pathway, whereas tau pathology did not have the same effect on Aβ pathology [105]. In APP/PS1K1 mice, transient intraneuronal Aβ rather than extracellular plaque pathology correlates with neuron loss in the frontal cortex [302]. Glucocorticoids increased Aβ and tau pathology in another mouse model of AD [106].

On the other hand, a single-dose intraventricular injection of an Aβ antibody in 4-month-old mice cleared intraneuronal Aβ pathology and reduced early cognitive deficits [107], and inhibition of GSK-3β attenuated Aβ-induced tau phosphorylation *in vitro* and can reduce tau pathology *in vivo* [52, 108]. Other data suggest induction of NFT formation by amyloidogenic peptides rather than specifically by Aβ [109]. While the 3xTg AD mouse model, based on early intraneuronal accumulation of Aβ played an important role in supporting the 'intraneuronal Aβ hypothesis' [107], recent evidence claimes that these mice early and age-dependently accumulate APP instead of Aβ within neurons [110, 111], thus challenging this hypothesis. The intracellular domain of APP alters gene expression and induces neuron-specific apoptosis [112, 113]. It should be recognized, however, that the 3xTG-AD mouse model demonstrates AD-like pathology but with some key differences to human AD, suggesting divergent pathogenic mechanisms [114]. In the human brain APP rather than Aβ is detected intracellularly when using specific antibodies [303]. (2) Synergistic effects of Aβ and tau by impairment of mitochondrial respiration in triple tg mice that display both Aβ and tau pathologies [115]. This indicates the convergence of Aβ and tau on mitochondrial deterioration and establishes a molecular link in AD pathology *in vivo* [116, 117].

(3) Tau mediates Aβ toxicity, supported by the observation that $tau^{-/-}$ neurons are protected from Aβ-induced cell death in cell culture [94, 99, 118]. Tau reduction also prevents Aβ-induced defects in axonal transport of mitochondria and other cargoes [119], which may link the 'tau hypothesis' to other ones, the axonal transport impairment hypothesis, according to which tau induces failure of axonal transport [120, 121], and the 'oxidative stress hypothesis', which suggests that mitochondria are functionally impaired, resulting in the production of reactive oxidative species [122]. Astrocytes have been shown to be important mediators of Aβ-induced neurotoxicity and tau hyperphosphorylation in primary cultures [54]. Soluble oligomeric forms of Aβ stimulate Aβ production *via* astrogliosis in the rat brain [123].

Although knowledge about the roles of tau and its interactions with Aβ is increasing (see [1, 124]), many questions about the scaffolding partners for tau in its interaction with Aβ are still unanswered. While this phenomen may result from direct cross-seeding of tau by aggregated Aβ [125, 126], indirect pathways such as Aβ-induced tau phophorylation, inflammation and/or disruption of proteostasis [70, 77, 127] have not been excluded.

While structural and functional changes in tau mutant mice neurons are not linked to the presence of NFTs, or co-occur independent of mature NFTs [128], the incidence of plaques and tangles correlates positively in human AD, but a consistent anatomical relationship between these lesions is not apparent [61]. Cross-sectional analysis of postmortem human brain reveals a characteristic progression of Aβ plaques and a highly stereotypical appearance of NFTs [129]. Aβ

plaques develop first in the neocortex, followed by the allocortex and then the subcortex, and the progression of their appearances often corresponds to functionally and anatomically coupled brain regions [130–133]. Neurofibrillary tau pathology first arises in the locus ceruleus (LC) and entorhinal brain regions [134–137]. The pattern that emerges from these studies implies neuronal transport and synaptic exchange mechanisms in the spread of AD lesions within the brain [120, 136]. Several studies indicating that tau pathology of AD begins in the brainstem [137–139], and the recent demonstration of tau-positive pretangle material or early NFT stages without the presence of Aβ plaques in the LC before the involvement of the entorhinal region of the cortex in young individuals [137, 140] may indicate that not only reclassification of currently existing neuropathological staging NFT categories for AD could be necessary but also a rethinking of the amyloid cascade hypothesis that might not be valid for sporadic AD cases [129]. According to these authors, sporadic AD could be the result of two separate factors: first, a tauopathy, possibly beginning in young age and, second, negative influences of Aβ after a given threshold is crossed. As shown in animal models, Aβ might be capable of exacerbating the underlying tauopathy so that it develops into clinical AD [100, 104], but, currently, too little is known about the pace with which the pathologic process in human brain develops. A novel antibody capture assay for paraffin-embedded tissue detected wide-ranging Aβ and paired helical filament tau in cognitively normal older adults [141], and other recent findings indicate that Aβ-associated brain volume loss occurs only in the presence of p-tau (in cerebrospinal fluid or CSF) in humans at risk for dementia [142].

As we gain a deeper understanding of the different cellular functions of tau, the focus shifts from the axon, where tau has a principal role as microtubule-associated protein, to the dendrite, where it mediates Aβ toxicity [70]. On the other hand, according to several data, tau aggregates may be a consequence rather than a cause of ND [55, 143]. Therefore, the effects promoted by Aβ and tau should be analysed more specifically to identify the mechanisms that underly Aβ and tau toxicity and/or neuroprotection to find appropriate therapeutic targets [144].

Protein interactions in PD

Intracytoplasmic proteinaceous inclusions, primarily composed of tau and/or αSyn, are predominant pathological features of AD and PD, respectively [145]. However, the co-existence of these and other pathological proteinaceous aggregates like Aβ has been identified in many NDDs [146–148]. Proteomic analysis of cortical LBs revealed 296 proteins [149], while in brainstem LBs 90 proteins were identified, differing from Pick bodies and suggesting a complex formation process [150]. A recent proteomic study of the LC of PD brains revealed a total of 2495(!) proteins of which 87 were different from controls. The majority of these proteins are known to be involved in processes that have been implicated in the pathogenesis of PD previously, including mitochondrial dysfunction, oxidative stress, protein misfolding, cytoskeleton dysregulation, alterations in autophagy, and inflammation. Several individual proteins were identified that have hitherto not been associated with PD, such as regucalcin, which plays a role in maintaining intracellular calcium homeostasis, and isoform 1 of kinectin, which is involved in transport of cellular components along microtubules. These findings indicate that the proteome of PD-LC and non-neurological controls provide data that are relevant to the pathogenesis of PD, reflecting both known and potentially novel pathogenetic pathways [151]. Mitochondrial dysfunction significantly contributes to PD pathology; however, to what extent it contributes to the pathogenesis of sporadic PD remains to be elucidated [304].

The co-occurrence of both αSyn and tau or other pathologic proteins highlights the interface between them [7, 11, 152, 153]. They may be co-aggregated in the same brain or even in the same region or in the same cell in human brains [147, 154–156] and tg mice [157]. Recent data suggest that αSyn secretion might be triggered by the toxic properties of overexpressed αSyn and that tau specifically enhances αSyn secretion. The synergistic effect between αSyn and tau may be relevant for many NDDs that show co-occurence of both proteins, as an increase in p-tau is one of the key features in the brains of all tauopathies and has been shown to reduce binding of tau to microtubules [158].

Whereas αSyn can spontaneously polymerize into amyloidogenic fibrils, *in vitro*, tau polymerization requires an inducing agent [159]. Dopamine facilitates αSyn oligomerization and promotes formation and secretion of non-fibrillary αSyn oligomers [305, 306], and the chaperone Hsc70 affects the cellular propagation of αSyn aggregates and their spread throughout the CNS in PD [307]. Cellular models, various transgenic and other experimental PD models provided novel insights into the role of αSyn in the hyperphosphorylation of tau protein observed in disease [159–167]. These data suggest that oxidatively modified αSyn is degraded by the proteasome and plays an pro-aggregatory role for tau [166], and that αSyn is an *in vivo* regulator of tau protein phosphorylation at Ser(262). Toxic interactions with αSyn may lead to hyperphosphorylation of tau and eventually to the deposition of both proteins in the disease [168]. Oxidatively modified αSyn degraded by the proteasome further promotes the recruitment of tau to protein inclusions in oligodendroglial cells in synucleinopathies [166] E46K human αSyn tg mice develop Lewy-like and tau pathology associated with age-dependent motor impairments, and studies on the ability of E46K αSyn to induce tau inclusions in cellular models suggest both direct and indirect mechanisms of protein aggregation being possibly involved in the formation of tau inclusions observed in PD, supporting the notion that αSyn is involved in the pathogenesis of human diseases [169]. On the other hand, tau enhances αSyn aggregation and toxicity and disrupts αSyn inclusion formation in cellular models [156].

Recent postmortem studies showed increased accumulation of tau protein phosphorylated at Ser 262 and 396/404 in the striata of PD patients and in the A53T αSyn mutant mouse model of PD [162, 170]. This is related to increased activity of GSK-3β [75, 161, 164], a major kinase that hyperphosphorylates tau to produce pathologic forms of tau [50, 74]. This is stimulated by αSyn that associates with the actin cytoskeleton [171] and by GSK-3β [172]. On the other hand, αSyn is a substrate for GSK-3 and GSK-3 inhibition protects against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and other Parkinsonian toxins [308]. Dopamine D1 receptor activation induces tau

phosphorylation *via* cyclin-dependent kinase 5 (cdk5) and GSK-3β signalling pathways [173]. Expression of both GSK-3β and microtubule-associated protein/microtubule affinity-regulating kinase 2 inhibited the formation of αSyn-induced tau aggregation [159]. Reduced 19S and 20S proteasomal subunit activites in PD striata suggest that they account for the abnormal disposal of αSyn and p-tau. The small decrease in proteasomal activity in PD striata is consistent with other studies that showed no significant changes of these proteins in PD striata but lower activity in substantia nigra (SN) [174]. In an MPTP model and in MPP^+ cellular models, αSyn has been shown to induce GSK-3β-catalysed tau phosphorylation [175–177]. Parkinson disease-associated risk factors such as environmental toxins and αSyn mutations promote tau phosphorylation at Ser 262, causing microtubule instability, which leads to neuronal degeneration [165]. Rotenon exposure may also induce αSyn and Aβ aggregation, as well as increased hyperphosphorylation of tau, while high concentrations of the pesticide lead to cell death before protein aggregation [167].

Hyperphosphorylation of tau by αSyn in the MPTP model of parkinsonism has been observed [175]. Tau in MPTP models and in human postmortem PD striata is hyperphosphorylated at the same sites (Ser 202, 262 and 396/404) as in AD [170], whereas phosphorylation of soluble tau differs in AD and Pick disease brains [178]. Tauopathy in PD striata is restricted to dopaminergic neurons, whereas degeneration in the inferior frontal cortex, associated with increased tau deposition because of diminished proteasomal activity in the absence of oxidative stress and pGSK-3β activity is not associated with tauopathy [170]. In the αSyn overexpressing mouse model of PD tauopathy, along with microtubule destabilization, exists primarily in the brainstem and striatum, the two brain regions known to express high levels of αSyn and undergo the highest levels of degeneration in human PD. Thus, tauopathy in PD may have a restricted pattern of distribution [163], which differs from its generalized affection in AD. Whether there are differences in the three- and four-repeat tau pathology between these disorders is not yet fully understood and needs further investigation, as has recently been performed for both AD and four-repeat tauopathies using new methods [179].

There is strong interaction between αSyn, tau and Aβ, particularly in their oligomeric forms, which might synergistically promote their mutual aggregation and *vice versa* [30, 168, 180]. Cross-seeding between dissimilar proteins that share β-sheet structures has been described, for example, of Aβ and αSyn [25], tau and αSyn [181] and prion protein and Aβ [182]. *In vivo* interactions between αSyn and tau are supported by genetic studies that link the *MAPT* gene, which encodes tau, with increased risk of sporadic PD [183–186], and in familial PD [155], fibrillation of αSyn and tau is caused by the A53T mutation [181]. A family with early onset dementia showed widespread appearance of LBs and NFTs, but no amyloid deposits [187]. There is recent evidence that prions trigger hyperphosphorylation of tau in genetic, sporadic and transmitted forms of prion diseases in the absence of amyloid plaques [11].

Neurofibrillary tau pathology is modulated by genetic variations of αSyn [188]. Tau phosphorylation is found in synapse-enriched fractions of frontal cortex in PD and AD [189] and in brainstems of αSyn mice [190]. Direct links between αSyn and tau are supported by the accumulation of both proteins within synaptic terminals in AD brains and APP Swedish mutant mice [19, 189], the co-localization of both proteins in both NFTs and LBs, especially in neuronal populations vulnerable for both aggregates [154, 191–193], in the olfactory bulb in AD with amygdaloid LBs [191] and in neuronal and glial cytoplasmic inclusions in MSA [194, 195]. Between 15% and 60% of AD brains show numerous αSyn lesions in the amygdala, even in the absence of subcortical LBs [196, 197]. Alzheimer disease with amygdala LBs is considered to be a distinct form of α-synucleinopathy [198] in which tau and αSyn pathology are co-localized [191]. In AD patients with clinical extrapyramidal symptoms, between 50% and 88% of the patients showed extensive αSyn pathology co-localized with p-tau in SN, tau and less αSyn pathology in brainstem significantly increasing with higher neuritic Braak stages [199–201]. Co-occurrence of abnormal deposition of tau, αSyn and TDP-43 in AD, DLB and other NDDs [146, 202, 203], highlight the interface between these and other misfolded proteins.

In conclusion, genetic, pathologic and biochemical evidence support a role for tau in the pathogenesis of PD [168], and concurrence of tau, αSyn and TDP-43 pathology in brains of AD and LB diseases provide a better understanding of the pathogenic pathways in these disorders [146]. It has been suggested that the process of LB formation is triggered, at least in part, by Alzheimer pathology [147, 204], while the interaction between αSyn and tau in MSA awaits further elucidation [195, 205]. Recent data suggest that PD and AD could be linked by progressive accumulation of p-tau, activated GSK-3β and αSyn [162, 170, 206], while activation of caspase and caspase-cleft Δtau may represent a common way of abnormal intracellular accumulation of both tau and αSyn, promoted by Aβ deposition, and unifying the pathology of AD and LB diseases [8, 207, 208] (Fig. 3). Emerging evidence suggests that secreted proteins such as Aβ and cytosolic proteins such as tau and αSyn, are spreading by cell-to-cell transmission, thus unifying the pathogenesis of many NDDs [34, 209], but is is not fully understood whether they are the result of similar protein aggregation and misfolding mechanisms.

Combined determination of αSyn, tau and Aβ concentrations in CSF show differential patterns in these disorders [210]; in particular, tau/αSyn ratios can contribute to the discrimination of PD [211], while different soluble isoforms of APP and other CSF biomarkers

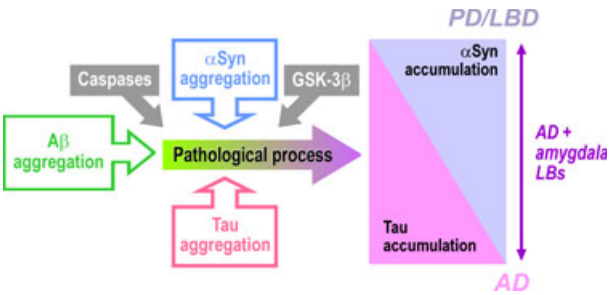

Fig. 3 Hypothetic diagram unifying pathologic processes in Alzheimer and Lewy body diseases. PD: Parkinson disease; LBD: Lewy body disease; LBs: Lewy bodies; AD: Alzheimer disease.

may differentiate between AD and LB diseases [212]. Other studies have suggested that Aβ is more likely to promote the deposition of αSyn than tau [213], and Aβ is known to inititate hyperphosporylation of tau [71]. Cortical αSyn load is associated with Aβ plaque burden in a subset of PD patients [214]. Aβ peptides enhance αSyn accumulation and neuronal deficits in a tg mouse model [215], and αSyn-induced synapse damage is enhanced by Aβ-42 [216]. Both can be linked by separate mechanisms driven by a common upstream component [217]. Recent studies showed that Aβ-42 tightly binds to tubulin polymerization-promoting protein (TPPP/p25) and causes aberrant protein aggregations inhibiting the physiologically relevant TPPP/p25-derived microtubule assembly.

TPPP/p25 expression enhances cellular sensitivity to dopamine toxicity [218], and the interaction of TPPP/p25 and Aβ can produce pathologic aggregates in AD and LB diseases [219], although other proteins, for example, αSyn and tau, have also been shown to interact with p25 [219]. p25α was found in LBs in PD and DLB, but does not co-localize with the inclusions in tauopathies [220]. Expression of p25α and αSyn in a rat oligodendroglial cell line resulted in disruption of the microtubule cytoskeleton, formation of αSyn oligomers and apoptosis [221]. p25α promotes the oligomerization of αSyn and accelerates inclusion formation leading to oligodendroglial death [222], p25α probably being an early event for the formation of GCIs in MSA.

Interactions between Aβ, αSyn and tau may be a molecular mechanism in the overlapping pathology of AD and PD/DLB [8, 208], probably generated by the same stimulus with the outcome possibly having an inverse relationship depending on genetic background or environmental factors. These lesions represent a collision of two or more processes, but it is unclear whether there is a common underlying final pathology leading to neuronal degeneration (see [9]) (Fig. 4).

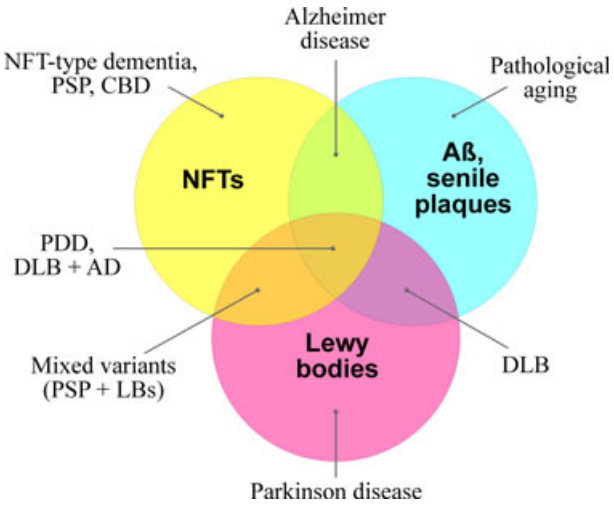

Fig. 4 Morphologic interrelations of synucleinopathies, tauopathies and amyloidopathies. NFTs: neurofibrillary tangles; PSP: progressive supranuclear palsy; CBD: corticobasal degeneration; PDD: Parkinson disease dementia; DLB: dementia with Lewy bodies; AD: Alzheimer disease; LBs: Lewy bodies.

Induction and spread of protein aggregates in NDDs

Mounting evidence implicates that templated corruption of disease-specific proteins and the propagation of proteins may be a unifying mechanism of disease progression and, thus, has important implications for understanding the onset and progression of various NDDs (Table 1). In PD, αSyn-rich lesions that characterize LB pathology, first arise in the lower brainstem and in the anterior olfactory nucleus and olfactory bulb; they subsequently appear in a predictable sequence in mesencephalic and neocortical regions [230–232], although the reliability of Lewy pathology staging in sporadic PD has been a matter of discussion [233–236]. The concept that αSyn lesions ramify within the CNS by a seeding-like process is supported by the observation that foetal dopaminergic transplants in the striatum of a subset of PD patients surviving more than 5 years may develop αSyn-positive LBs in some cells [237–239]. These data imply for a host-to-graft propagation of αSyn, and a neuron-to-neuron (interneuron) transmission or transsynaptic spread of αSyn appears a likely interpretation for the propagation of the disease. Similar accumulation of αSyn occurs in stem cells transplanted into transgenic mice [34]. It has been suggested that LBs develop in transplanted dopaminergic neurons in a fashion similar to that in the host SN [240], but it could not be determined whether the LB-like inclusions were formed by the spread of αSyn fibrils, or whether some other toxic effect of the neighbouring diseased neurons introduced these inclusions [35]. Moreover, the effects of LBs in the grafted neurons are unclear, as LB pathology in neurons does not necessarily mean their functional impairment. Secreted αSyn can recruit endogenous αSyn in the recipient cells, act as a permissive template and promote misfolding in small aggregates [241]. Some of the upake of αSyn from the extracellular space appears to occur *via* endocytosis, although additional mechanisms might also contribute [241, 242]. It is probable to trigger the formation of large LB-like aggregates in cultured cells, when artificial methods, bypassing physiologic uptake mechanisms, are used to promote the entry of misfolded αSyn [34, 239]. These suggestions are supported by the observation that neural grafts placed into tg mice expressing human αSyn take up the human protein and form Syn-positive aggregates [227, 241, 243].

Most recent studies demonstrated that preformed fibrils generated from full-length and truncated recombinant αSyn enter primary hippocampal neurons, probably by adsorptive-mediated endocytosis, and promote recruitment of soluble endogenous αSyn into insoluble PD-like LBs and LNs. Remarkably, endogenous αSyn was sufficient for formation of these aggregates, and overexpression of wild-type or mutant αSyn was not required. Accumulation of pathologic αSyn led to selective decrease in synaptic proteins, impairment of neuronal excitability and connectivity and, eventually, neuron death [35].

In vivo approaches in cell culture could not discriminate between a 'prion-like' corruptive templating mechanism—host-derived—translocated αSyn inducing misfolding of αSyn generated in the graft, *versus* a simple translocation of aggregated synuclein from the host to the graft, as in cell culture all the mechanisms needed for prion-like behaviour of misfolded αSyn appear to be possible [227, 241, 243].

Table 1 Evidence for spreading of non-prion protein aggregates in the central nervous system (modified from [34])

Inoculum	Host	Propagation effect
Amyloid-β		
Brain homogenates from Alzheimer disease or APP transgenic mice	APP transgenic mice (intracerebral injection)	Amyloid-β deposition at injection site and in adjacent brain structures [84, 223, 224]
Tau		
Tau fibrils	Cultured neuronal cells	Endocytic uptake of exogenous tau fibrils and induction of cytoplasmic endogenous tau proteins. Cell-to-cell transmission of tau taken up by cultured cells [225, 226]
Brain extracts from tau transgenic mice	Transgenic mice expressing human wild-type tau (intracerebral injection)	Spreading of tau from site of injection to other brain structures [194]
α-Synuclein (αSyn)		
Aggregate-producing neuronal cell cultures	Neuronal cells	Endocytic uptake of αSyn aggregates [227]
Introduction of αSyn aggregates by preformed fibrils generated from truncated recombinant human wild-type αSyn	Primary hippocampal neurons	Adsorptive-mediated endocytosis promoting soluble αSyn into insoluble PD-like LBs and LNs [35]
Transgenic mice overexpressing human αSyn	Mouse neuronal progenitor cells grafted into mouse brains	Interneuronal transmission of human αSyn [227]
Brains of patients with Parkinson disease	Foetal stem cells grafted into the brains of patients with Parkinson disease	Interneuronal transmission of Lewy inclusions [223, 228, 229]
PolyQ proteins		
In vitro-generated polyQ peptide fibres	Mammalian cells in culture	Internalization of fibres with subsequent recruitment of soluble endogenous polyQ proteins and aggregate formation [228]

APP: amyloid precursor protein; PD: Parkinson disease; polyQ: polyglutamine; LBs: Lewy bodies; LNs: Lewy neurites.

These and other data suggest that αSyn pathology could be induced in cells and may spread by a 'prion-like' mechanism involving the transmission of conformationally altered αSyn [244–247]. Recent studies indicated that cellular prion (PrP/C) mediates neurotoxic signalling of β-sheet-rich conformers independent of prion replication [248]. Although the mechanism of spread remains uncertain, there is evidence that prions can be conveyed between neurons by transsynaptic transport [244]. Prion toxicity may be exerted by neither PrPc nor PrPSc but *via* a toxic intermediate, the generation of which requires conversation to take place and is therefore dependent on local availability of PrPc [249]. Transmissible prion disease can be induced by PrP structures different from that of authentic PrPSc suggesting a new mechanism designated as "deformed templating" postulates that a change in the PrP folding pattern from the one present in rPrP fibrils to an alternative specific for PrP(Sc) can occur [309]. The propagation of αSyn lesions by cell-to-cell passage has been demonstrated, as has the induction of proteinaceous lesions associated with other NDDs [262], such as aggregates of superoxide dismutase 1 (SOD1) in ALS [250, 251], aggregates of polyamine [228], which typify HD and spinocerebellar ataxias, or cytosolic aggregates of TDP-43 [252], which are present in ALS and FTLD with TDP-43-positive inclusions (FTLD-TDP) [253]. The capability of passing between living cells is not limited to prions and those cited before; it was also shown for aggregates of truncated tau, consisting of the microtubule-binding region and a fluorescent protein tag that can leave and enter cells in culture and promote the aggregates and fibrillization of normal tau within them [1, 34, 124, 226, 254–256]. It should be emphasized, however, that with the recognition that tau, αSyn, Aβ, TDP-43 and other pathological conformers are transmissible, there is no evidence that they are infectious. Hence, it appears important to distinguish between cell-to-cell transmission from brain-to-brain transmission (αSyn, tau, Aβ, TDP-43). Therefore, it seems important to make a clear distinction between transmissible, non-infectious disease proteins (active in NDDS) and prions, which, by definition, are poteinaceous infectious particles, as the evidence that AD, PD, DLB, FTLD, HD and ALS are infectious is not supported by many studies that clearly demonstrated this for iatrogenic Creutzfeldt-Jakob disease [257, 258]; see also reference [1]. Amyloid transformers can spread from cell to cell in the brains of affected individuals, thereby spreading the specific neurodegenerative phenotypes distinctive to the protein being converted to amyloid. This transmittability mandates re-evaluation of emerging neuronal graft and stem cell

therapies [310]. Accumulation of cellular proteins within dystrophic neurites in amyloid plaques in AD brain could support the hypothesis that PrPc accumulation in dystrophic neurites reflects a response to impairments in cellular degradation, endocytosis, or transport mechanisms associated with AD rather than a non-specific cross-reactivity between PrPc and aggregated Abeta or tau [311]. On the other hand, the identification of molecules able to mimic or recapitulate antiamyloidogenic and antioxidative functions of PrPc may provide a new avenue for the battle against the devastating ND in AD [259]. A profound molecular cross talk between misfolded proteins in animal models of AD and prion disease may have important implications for understanding the origin and progression of these disorders [312]. Although the exact involvement in the pathophysiology of prion disorders and NDDs and a possible overlap between both disease categories have to be further investigated, the interaction between prion protein and toxic Aβ assemblies can be therapeutically targeted at multiple sites [260].

The recent demonstration of tau-positive pretangle material in the LC before involvement of the transentorhinal region of the cerebral cortex in young individuals [137, 140] suggests a progression of tau pathology *via* neuron-to-neuron transmission and transsynaptic transport of tau protein aggregates [136], and seeding of neuronal tau by pathological tau conformers drives pathogenesis of Alzheimer-like tangles [56]. The induction and spread of both Aβ and tau aggregates in experimental animals is well documented (see mutant P201S tau), as found in frontotemporal dementia with parkinsonism (FTDP-17); it is capable of spreading through the cortex of an Alz17 tg mouse expressing the human wild-type protein and induce an NFT-like pathology that consists of human tau in brain areas distant from the injection site [255]. These and other data raise the possibility that neurodegenerative pathologies could spread within the brain *via* a mechanism analogous to prion-like self-propagation *via* dissemination by cells, although alternative mechanisms, such as disruption of basic cellular proteostasis by exogenous aggregates, cannot be excluded [261]. However, the means by which templated conversion occurs, remain poorly understood [34, 244, 246, 262]. *In vitro*, aggregates of pathogenic proteins can all be taken up by endocytosis and induce the misfolding of the coresponding intracellular proteins, while cytoplasmic protein aggregates can translocate from one cell to another [7, 100, 117, 170, 175, 231, 245]. It appears well documented that αSyn and S0D1 are secreted into the cell medium [34, 244, 263]. Furthermore, tau and αSyn are present in blood and CSF in both monomeric and oligomeric forms, suggesting release of these normally intracellular proteins *in vivo* [211, 263–265]. The intercellular transfer of cytosolic protein aggregates may also occur through nanotubes, exosomes or microvesicles [244]. Like other pathogenic proteins, Aβ can be taken up, modified and secreted by cells *in vitro* [118, 266], and—together with tau—it is also present in the CSF [267–269]. At the current state of knowledge, the exact involvement in the pathophysiology of prion disease and the NDDs is not fully understood and deserves further investigation to elucidate the possible overlaps between these disorders. Most recent cell culture studies showed that embryonic stem cell neurons can modulate the activity of a network of host neurons [270].

Conclusions

Synergies between Aβ, tau and αSyn have been recently described, suggesting that they accelerate ND and cognitive decline [272]. Interaction beween these proteins may be a molecular mechanism in the overlapping pathology of LB disease and AD, possibly representing a complex continuum, characterized by variable amounts of pathologic proteins, and Aβ is suggested to promote accumulation of both αSyn and tau. The procession from Aβ to neurite pathology in the cerebral cortex of AD and DLB may be unifiable [8, 208]. DLB-3xtg-AD mice exhibit accelerated formation of αSyn and LB-like inclusions in the cortex, and enhanced increase of p-tau deposits immunoreactive for antibody AT8 in the hippocampus and neocortex provide further evidence that tau, αSyn and Aβ interact *in vivo* to promote accumulation of each other and accelerate cognitive dysfunction, although accumulation of αSyn alone can significantly disrupt cognition [271, 272]. Polymorphic tau and Aβ-tau aggregates may be due to sequences which are prone to variable turn locations along the tau repeats, suggesting that synergistic interactions between repeats in tau protein and Aβ may be responsible for accelerated aggregation *via* polymorphic states [126]. These changes and common inflammatory mechanisms in these disorders [273] could be generated by the same stimulus, with the outcome possibly having an inverse relationship depending on genetic backgrounds and environmental factors. Although recent data documented co-localization of αSyn and tau in LBs [191], of Aβ and p-tau in synaptosomes [80], synaptic terminals [19] and in triple transgenic mice [115], why tau, Aβ and αSyn pathologies are so intimately associated remains one of the major questions of the pathogenesis of ND in selected/vulnerable brain regions that are typical for different disease processes (double or triple amyloidoses). It has been suggested that these pathologies represent a common final pathway leading to or preventing neuronal damage [9, 157, 206].

The induction and proliferation of poteinaceous aggregates by corruptive templating appears to be a common feature of multiple, clinically diverse disorders, although many questions remain to be answered [274]. The basic molecular mechanisms (presumed regional differences in proteasomal, caspase and GSK-3β activities, oxidative stress in the presence of αSyn deposition, etc.) need further elucidation, and the molecular basis of the synergistic effects of αSyn, p-tau, Aβ and other pathologic proteins, suggesting a dualism or triad of ND, are a major challenge for modern neuroscience [275]. In humans, Aβ deposition begins decades prior to the onset of cognitive decline and, therefore, has been considered an early and predictive indicator of AD [89]. *In vivo*, the appearance of soluble Aβ seeds may precede the appreciable Aβ deposition in plaques and blood vessels. As potent Aβ seeds, like prions [276], appear to be relatively small [86], soluble Aβ forms could serve as biomarkers in body fluids, and an effective disease-modifying therapy should be initiated prophylactically, before the disease has inflicted irreversible damage to the brain. The early appearance of pathological aggregates in the peripheral nervous system and their relatively systematic spread within the brain [277, 278] in synucleinopathies, and other neurodegenerative proteinopathies [5] suggests that seeds travelling

between cells from one region to another might be profitable objectives for therapeutic interference [246]. Inhibition of early αSyn aggregation events would consequently prevent αSyn oligomer-related toxicity [279], which would fit also for other proteinopathies [1]. Furthermore, the cell-to-cell transfer and the induction of pathogenic protein aggregates in cellular grafts [224, 243, 246] emphasize the needs to protect grafted cells form host-induced protein templating [1]. The hypothetical risk of transmission of non-prion proteopathies—like that of prion diseases [84, 280, 313]—suggests a need for more research into the epidemiology of such disorders as well as analysis of tissue and organ donations to minimize the risk for transmission of such diseases. An extended multidisciplinary research of the molecular and cell biology of protein aggregation is needed to improve our insight into the molecular pathogenesis of proteinopathies and related NDDs thereby improving diagnostic and therapeutic possibilities.

Acknowledgements

The authors thank Mr. E. Mitter-Ferstl, Ph.D., for secretarial and computer work. The study was partially supported by the Society for the Support of Research in Experimental Neurology, Vienna, Austria.
Financial interest disclosures: None.

Conflict of interest statement

The author confirms that there are no conflicts of interest.

References

1. **Jucker M, Walker LC.** Pathogenic protein seeding in Alzheimer's disease and other neurodegenerative disorders. *Ann Neurol.* 2011; 70: 532–40.
2. **Golde TE, Miller VM.** Proteinopathy-induced neuronal senescence: a hypothesis for brain failure in Alzheimer's and other neurodegenerative diseases. *Alzheimers Res Ther.* 2009; 1: 5.
3. **Forman MS, Trojanowski JQ, Lee VM.** TDP-43: a novel neurodegenerative proteinopathy. *Curr Opin Neurobiol.* 2007; 17: 548–55.
4. **McMillan PJ, Leverenz JB.** From model system to clinical medicine: pathophysiologic links of common proteinopathies. *Alzheimers Res Ther.* 2010; 2: 26.
5. **Wakabayashi K, Mori F, Tanji K, *et al.*** Involvement of the peripheral nervous system in synucleinopathies, tauopathies and other neurodegenerative proteinopathies of the brain. *Acta Neuropathol.* 2010; 120: 1–12.
6. **Kong XC, Bao XQ, Liu GT.** [Neurodegenerative conformational disease and heat shock proteins]. *Yao Xue Xue Bao.* 2010; 45: 1333–8.
7. **Galpern WR, Lang AE.** Interface between tauopathies and synucleinopathies: a tale of two proteins. *Ann Neurol.* 2006; 59: 449–58.
8. **Mandal PK, Pettegrew JW, Masliah E, *et al.*** Interaction between Abeta peptide and alpha synuclein: molecular mechanisms in overlapping pathology of Alzheimer's and Parkinson's in dementia with Lewy body disease. *Neurochem Res.* 2006; 31: 1153–62.
9. **Jellinger KA.** Basic mechanisms of neurodegeneration: a critical update. *J Cell Mol Med.* 2010; 14: 457–87.
10. **Kovacs GG, Botond G, Budka H.** Protein coding of neurodegenerative dementias: the neuropathological basis of biomarker diagnostics. *Acta Neuropathol.* 2010; 119: 389–408.
11. **Reiniger L, Lukic A, Linehan J, *et al.*** Tau, prions and Abeta: the triad of neurodegeneration. *Acta Neuropathol.* 2011; 121: 5–20.
12. **Dickson DW.** Introduction. In: Weller RO, editor. Neurodegeneration: The Molecular Pathology of Dementia and Movement Disorders. Oxford: Wiley-Blackwell: 2011. p. 3–5.
13. **Jellinger KA.** Interaction between a-synuclein and other proteins in neurodegenerative disorders. *Sci World J.* 2011; 11: 1893–907.
14. **Powers ET, Morimoto RI, Dillin A, *et al.*** Biological and chemical approaches to diseases of proteostasis deficiency. *Annu Rev Biochem.* 2009; 78: 959–91.
15. **Naiki H, Nagai Y.** Molecular pathogenesis of protein misfolding diseases: pathological molecular environments *versus* quality control systems against misfolded proteins. *J Biochem.* 2009; 146: 751–6.
16. **Filosto M, Scarpelli M, Cotelli MS, *et al.*** The role of mitochondria in neurodegenerative diseases. *J Neurol.* 2011; 258: 1763–74.
17. **Schon EA, Przedborski S, Crews L.** Mitochondria: the next (neurode)generation. *Neuron.* 2011; 70: 1033–53.
18. **Schulz-Schaeffer WJ.** The synaptic pathology of alpha-synuclein aggregation in dementia with Lewy bodies, Parkinson's disease and Parkinson's disease dementia. *Acta Neuropathol.* 2010; 120: 131–43.
19. **Takahashi RH, Capetillo-Zarate E, Lin MT, *et al.*** Co-occurrence of Alzheimer's disease abeta-amyloid and tau pathologies at synapses. *Neurobiol Aging* 2010; 31: 1145–52.
20. **Lansbury PT, Lashuel HA.** A century-old debate on protein aggregation and neurodegeneration enters the clinic. *Nature* 2006; 443: 774–9.
21. **Glabe CG.** Structural classification of toxic amyloid oligomers. *J Biol Chem.* 2008; 283: 29639–43.
22. **Hamaguchi T, Eisele YS, Varvel NH, *et al.*** The presence of Abeta seeds, and not age *per se*, is critical to the initiation of Abeta deposition in the brain. *Acta Neuropathol.* 2011; in press: doi: 10.1007/s00401-011-0912-1.
23. **Gadad BS, Britton GB, Rao KS.** Targeting oligomers in neurodegenerative disorders: lessons from alpha-synuclein, tau, and amyloid-beta peptide. *J Alzheimers Dis.* 2011; 24: 223–32.
24. **Patterson KR, Remmers C, Fu Y, *et al.*** Characterization of prefibrillar Tau oligomers *in vitro* and in Alzheimer disease. *J Biol Chem.* 2011; 286: 23063–76.
25. **Tsigelny IF, Crews L, Desplats P, *et al.*** Mechanisms of hybrid oligomer formation in the pathogenesis of combined Alzheimer's and Parkinson's diseases. *PLoS ONE* 2008; 3: e3135.
26. **Olivares D, Huang X, Branden L, *et al.*** Physiological and pathological role of alpha-synuclein in Parkinson's disease through iron mediated oxidative stress; the role of a putative iron-responsive element. *Int J Mol Sci.* 2009; 10: 1226–60.
27. **Kostka M, Hogen T, Danzer KM, *et al.*** Single particle characterization of iron-induced

pore-forming alpha-synuclein oligomers. *J Biol Chem.* 2008; 283: 10992–1003.
28. **Levin J, Högen T, Hillmer AS, *et al.*** Generation of ferric iron links oxidative stress to alpha-synuclein oligomer formation. *J Parkinson Dis.* 2011; 1: 205–16.
29. **Putcha P, Danzer KM, Kranich LR, *et al.*** Brain-permeable small-molecule inhibitors of Hsp90 prevent alpha-synuclein oligomer formation and rescue alpha-synuclein-induced toxicity. *J Pharmacol Exp Ther.* 2010; 332: 849–57.
30. **Uversky VN.** Neuropathology, biochemistry, and biophysics of alpha-synuclein aggregation. *J Neurochem.* 2007; 103: 17–37.
31. **Spillantini MG.** Introduction to alpha-synucleinopathies. In: Dickson DW, Weller RO, editors. *Neurodegeneration: The Molecular Pathology of Dementia and Movement Disorders*, 2nd ed. Oxford: Blackwell Publishing Ltd.; 2011. p. 191–3.
32. **Chen L, Periquet M, Wang X, *et al.*** Tyrosine and serine phosphorylation of alpha-synuclein have opposing effects on neurotoxicity and soluble oligomer formation. *J Clin Invest.* 2009; 119: 3257–65.
33. **Paleologou KE, Kragh CL, Mann DM, *et al.*** Detection of elevated levels of soluble alpha-synuclein oligomers in post-mortem brain extracts from patients with dementia with Lewy bodies. *Brain* 2009; 132: 1093–101.
34. **Lee SJ, Desplats P, Sigurdson C, *et al.*** Cell-to-cell transmission of non-prion protein aggregates. *Nat Rev Neurol.* 2010; 6: 702–6.
35. **Volpicelli-Daley LA, Luk KC, Patel TP, *et al.*** Exogenous alpha-synuclein fibrils induce Lewy body pathology leading to synaptic dysfunction and neuron death. *Neuron* 2011; 72: 57–71.
36. **Winner B, Jappelli R, Maji SK, *et al.*** *In vivo* demonstration that alpha-synuclein oligomers are toxic. *Proc Natl Acad Sci USA* 2011; 108: 4194–9.
37. **Danzer KM, Krebs SK, Wolff M, *et al.*** Seeding induced by alpha-synuclein oligomers provides evidence for spreading of alpha-synuclein pathology. *J Neurochem.* 2009; 111: 192–203.
38. **Steiner JA, Angot E, Brundin P.** A deadly spread: cellular mechanisms of alpha-synuclein transfer. *Cell Death Differ.* 2011; 18: 1425–33.
39. **Hilker R, Brotchie JM, Chapman J.** Pros and cons of a prion-like pathogenesis in Parkinson's disease. *BMC Neurol.* 2011; 11: 74.
40. **Spires-Jones TL, Meyer-Luehmann M, Osetek JD, *et al.*** Impaired spine stability underlies plaque-related spine loss in an Alzheimer's disease mouse model. *Am J Pathol.* 2007; 171: 1304–11.
41. **Kuchibhotla KV, Goldman ST, Lattarulo CR, *et al.*** Abeta plaques lead to aberrant regulation of calcium homeostasis *in vivo* resulting in structural and functional disruption of neuronal networks. *Neuron* 2008; 59: 214–25.
42. **Wu HY, Hudry E, Hashimoto T, *et al.*** Amyloid beta induces the morphological neurodegenerative triad of spine loss, dendritic simplification, and neuritic dystrophies through calcineurin activation. *J Neurosci.* 2010; 30: 2636–49.
43. **Crouch PJ, Harding SM, White AR, *et al.*** Mechanisms of Abeta mediated neurodegeneration in Alzheimer's disease. *Int J Biochem Cell Biol.* 2008; 40: 181–98.
44. **Fox LM, William CM, Adamowicz DH, *et al.*** Soluble tau species, not neurofibrillary aggregates, disrupt neural system integration in a tau transgenic model. *J Neuropathol Exp Neurol.* 2011; 70: 588–95.
45. **Nygaard HB, Strittmatter SM.** Cellular prion protein mediates the toxicity of beta-amyloid oligomers: implications for Alzheimer disease. *Arch Neurol.* 2009; 66: 1325–8.
46. **Chen S, Yadav SP, Surewicz WK.** Interaction between human prion protein and amyloid-beta (Abeta) oligomers: role of N-terminal residues. *J Biol Chem.* 2010; 285: 26377–83.
47. **Zou WQ, Xiao X, Yuan J, *et al.*** Amyloid-beta42 interacts mainly with insoluble prion protein in the Alzheimer brain. *J Biol Chem.* 2011; 286: 15095–105.
48. **Forloni G, Balducci C.** Beta-amyloid oligomers and prion protein: fatal attraction? *Prion* 2011; 5: 10–5.
49. **Gunther EC, Strittmatter SM.** Beta-amyloid oligomers and cellular prion protein in Alzheimer's disease. *J Mol Med.* 2010; 88: 331–8.
50. **Lauren J, Gimbel DA, Nygaard HB, *et al.*** Cellular prion protein mediates impairment of synaptic plasticity by amyloid-beta oligomers. *Nature* 2009; 457: 1128–32.
51. **Hanger DP, Noble W.** Functional implications of glycogen synthase kinase-3-mediated tau phosphorylation. *Int J Alzheimers Dis.* 2011; 2011: 352805.
52. **Engel T, Goni-Oliver P, Lucas JJ, *et al.*** Chronic lithium administration to FTDP-17 tau and GSK-3beta overexpressing mice prevents tau hyperphosphorylation and neurofibrillary tangle formation, but pre-formed neurofibrillary tangles do not revert. *J Neurochem.* 2006; 99: 1445–55.
53. **Alonso AC, Li B, Grundke-Iqbal I, *et al.*** Mechanism of tau-induced neurodegeneration in Alzheimer disease and related tauopathies. *Curr Alzheimer Res.* 2008; 5: 375–84.
54. **Lucas JJ, Hernandez F, Gomez-Ramos P, *et al.*** Decreased nuclear beta-catenin, tau hyperphosphorylation and neurodegeneration in GSK-3beta conditional transgenic mice. *EMBO J.* 2001; 20: 27–39.
55. **de Calignon A, Fox LM, Pitstick R, *et al.*** Caspase activation precedes and leads to tangles. *Nature* 2010; 464: 1201–4.
56. **Guo JL, Lee VM.** Seeding of normal tau by pathological tau conformers drives pathogenesis of Alzheimer-like tangles. *J Biol Chem.* 2011; 286: 15317–31.
57. **Kwong LK, Uryu K, Trojanowski JQ, *et al.*** TDP-43 proteinopathies: neurodegenerative protein misfolding diseases without amyloidosis. *Neurosignals* 2008; 16: 41–51.
58. **Wilson AC, Dugger BN, Dickson DW, *et al.*** TDP-43 in aging and Alzheimer's disease – a review. *Int J Clin Exp Pathol.* 2011; 4: 147–55.
59. **Mackenzie IR, Rademakers R, Neumann M.** TDP-43 and FUS in amyotrophic lateral sclerosis and frontotemporal dementia. *Lancet Neurol.* 2010; 9: 995–1007.
60. **Lanson NA Jr, Maltare A, King H, *et al.*** A *Drosophila* model of FUS-related neurodegeneration reveals genetic interaction between FUS and TDP-43. *Hum Mol Genet.* 2011; 20: 2510–23.
61. **Serrano-Pozo A, Frosch MP, Masliah E, *et al.*** Neuropathological alterations in Alzheimer disease. *Cold Spring Harb Perspect Med.* 2011; 1: a006189.
62. **Querfurth HW, LaFerla FM.** Alzheimer's disease. *N Engl J Med.* 2010; 362: 329–44.
63. **Braak H, Braak E.** Staging of Alzheimer's disease-related neurofibrillary changes. *Neurobiol Aging* 1995; 16: 271–8.
64. **DaRocha-Souto B, Scotton TC, Coma M, *et al.*** Brain oligomeric beta-amyloid but not total amyloid plaque burden correlates with neuronal loss and astrocyte inflammatory response in amyloid precursor protein/tau transgenic mice. *J Neuropathol Exp Neurol.* 2011; 70: 360–76.
65. **Selkoe DJ.** Alzheimer's disease is a synaptic failure. *Science* 2002; 298: 789–91.
66. **Scheff SW, Price DA, Schmitt FA, *et al.*** Synaptic loss in the inferior temporal gyrus in mild cognitive impairment and Alzheimer's disease. *J Alzheimers Dis.* 2011; 24: 547–57.
67. **Hardy J.** The relationship between amyloid and tau. *J Mol Neurosci.* 2003; 20: 203–6.

68. **Rhein V, Eckert A.** Effects of Alzheimer's amyloid-beta and tau protein on mitochondrial function – role of glucose metabolism and insulin signalling. *Arch Physiol Biochem.* 2007; 113: 131–41.
69. **Gotz J, Lim YA, Ke YD, *et al.*** Dissecting toxicity of tau and beta-amyloid. *Neurodegener Dis.* 2010; 7: 10–2.
70. **Ittner LM, Gotz J.** Amyloid-beta and tau – a toxic pas de deux in Alzheimer's disease. *Nat Rev Neurosci.* 2011; 12: 65–72.
71. **Huang HC, Jiang ZF.** Accumulated amyloid-beta peptide and hyperphosphorylated tau protein: relationship and links in Alzheimer's disease. *J Alzheimers Dis.* 2009; 16: 15–27.
72. **Ferrer I, Barrachina M, Puig B.** Glycogen synthase kinase-3 is associated with neuronal and glial hyperphosphorylated tau deposits in Alzheimer's disease, Pick's disease, progressive supranuclear palsy and corticobasal degeneration. *Acta Neuropathol.* 2002; 104: 583–91.
73. **Ferrer I, Gomez-Isla T, Puig B, *et al.*** Current advances on different kinases involved in tau phosphorylation, and implications in Alzheimer's disease and tauopathies. *Curr Alzheimer Res.* 2005; 2: 3–18.
74. **Baum L, Seger R, Woodgett JR, *et al.*** Overexpressed tau protein in cultured cells is phosphorylated without formation of PHF: implication of phosphoprotein phosphatase involvement. *Brain Res Mol Brain Res.* 1995; 34: 1–17.
75. **Leroy A, Landrieu I, Huvent I, *et al.*** Spectroscopic studies of GSK3β phosphorylation of the neuronal tau protein and its interaction with the N-terminal domain of apolipoprotein E. *J Biol Chem.* 2010; 285: 33435–44.
76. **Hooper C, Killick R, Lovestone S.** The GSK3 hypothesis of Alzheimer's disease. *J Neurochem.* 2008; 104: 1433–9.
77. **Hernandez F, Gomez de Barreda E, Fuster-Matanzo A, *et al.*** GSK3: a possible link between beta amyloid peptide and tau protein. *Exp Neurol.* 2010; 223: 322–5.
78. **Proctor CJ, Gray DA.** GSK3 and p53 – is there a link in Alzheimer's disease? *Mol Neurodegener.* 2010; 5: 7.
79. **Shin RW, Ogino K, Shimabuku A, *et al.*** Amyloid precursor protein cytoplasmic domain with phospho-Thr668 accumulates in Alzheimer's disease and its transgenic models: a role to mediate interaction of Abeta and tau. *Acta Neuropathol.* 2007; 113: 627–36.
80. **Fein JA, Sokolow S, Miller CA, *et al.*** Co-localization of amyloid beta and tau pathology in Alzheimer's disease synaptosomes. *Am J Pathol.* 2008; 172: 1683–92.
81. **Hardy J, Selkoe DJ.** The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* 2002; 297: 353–6.
82. **Bertram L, Tanzi RE.** The genetic epidemiology of neurodegenerative disease. *J Clin Invest.* 2005; 115: 1449–57.
83. **Castellano JM, Kim J, Stewart FR, *et al.*** Human apoE isoforms differentially regulate brain amyloid-beta peptide clearance. *Sci Transl Med.* 2011; 3: 89ra57.
84. **Eisele YS, Bolmont T, Heikenwalder M, *et al.*** Induction of cerebral beta-amyloidosis: intracerebral *versus* systemic Abeta inoculation. *Proc Natl Acad Sci USA.* 2009; 106: 12926–31.
85. **Eisele YS, Obermuller U, Heilbronner G, *et al.*** Peripherally applied Abeta-containing inoculates induce cerebral beta-amyloidosis. *Science* 2010; 330: 980–2.
86. **Langer F, Eisele YS, Fritschi SK, *et al.*** Soluble Aβ seeds are potent inducers of cerebral β-amyloid deposition. *J Neurosci.* 2011; 31: 14488–95.
87. **Rosen RF, Fritz JJ, Dooyema J, *et al.*** Exogenous seeding of cerebral beta-amyloid deposition in betaAPP-transgenic rats. *J Neurochem.* 2011; in press: doi: 10.1111/j.1471-4159.2011.07551.x.
88. **Sutcliffe EL, Bunting KL, He YQ, *et al.*** Chromatin-associated protein kinase C-theta regulates an inducible gene expression program and microRNAs in human T lymphocytes. *Mol Cell.* 2011; 41: 704–19.
89. **Holtzman DM, Morris JC, Goate AM.** Alzheimer's disease: the challenge of the second century. *Sci Transl Med.* 2011; 3: 77sr1.
90. **Lesne S, Koh MT, Kotilinek L, *et al.*** A specific amyloid-beta protein assembly in the brain impairs memory. *Nature* 2006; 440: 352–7.
91. **Lambert MP, Barlow AK, Chromy BA, *et al.*** Diffusible, nonfibrillar ligands derived from Abeta1–42 are potent central nervous system neurotoxins. *Proc Natl Acad Sci USA.* 1998; 95: 6448–53.
92. **Shankar GM, Li S, Mehta TH, *et al.*** Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. *Nat Med.* 2008; 14: 837–42.
93. **Jin M, Shepardson N, Yang T, *et al.*** Soluble amyloid beta-protein dimers isolated from Alzheimer cortex directly induce tau hyperphosphorylation and neuritic degeneration. *Proc Natl Acad Sci USA.* 2011; 108: 5819–24.
94. **Roberson ED, Scearce-Levie K, Palop JJ, *et al.*** Reducing endogenous tau ameliorates amyloid beta-induced deficits in an Alzheimer's disease mouse model. *Science.* 2007; 316: 750–4.
95. **Small DH, Mok SS, Bornstein JC.** Alzheimer's disease and Abeta toxicity: from top to bottom. *Nat Rev Neurosci.* 2001; 2: 595–8.
96. **Gotz J, Streffer JR, David D, *et al.*** Transgenic animal models of Alzheimer's disease and related disorders: histopathology, behavior and therapy. *Mol Psychiatry.* 2004; 9: 664–83.
97. **De Felice FG, Wu D, Lambert MP, *et al.*** Alzheimer's disease-type neuronal tau hyperphosphorylation induced by Abeta oligomers. *Neurobiol Aging.* 2008; 29: 1334–47.
98. **Bolmont T, Clavaguera F, Meyer-Luehmann M, *et al.*** Induction of tau pathology by intracerebral infusion of amyloid-beta-containing brain extract and by amyloid-beta deposition in APP x Tau transgenic mice. *Am J Pathol.* 2007; 171: 2012–20.
99. **Ittner LM, Ke YD, Delerue F, *et al.*** Dendritic function of tau mediates amyloid-beta toxicity in Alzheimer's disease mouse models. *Cell.* 2010; 142: 387–97.
100. **Gotz J, Chen F, van Dorpe J, *et al.*** Formation of neurofibrillary tangles in P301l tau transgenic mice induced by Abeta 42 fibrils. *Science.* 2001; 293: 1491–5.
101. **Folwell J, Cowan CM, Ubhi KK, *et al.*** Abeta exacerbates the neuronal dysfunction caused by human tau expression in a *Drosophila* model of Alzheimer's disease. *Exp Neurol.* 2010; 223: 401–9.
102. **Sofola O, Kerr F, Rogers I, *et al.*** Inhibition of GSK-3 ameliorates Abeta pathology in an adult-onset *Drosophila* model of Alzheimer's disease. *PLoS Genet.* 2010; 6: e1001087. doi: 10.1371/journal.pgen.1001087.
103. **Cowan CM, Sealey MA, Quraishe S, *et al.*** Modelling tauopathies in *Drosophila*: insights from the fruit fly. *Int J Alzheimers Dis.* 2011; in press.
104. **Oddo S, Caccamo A, Shepherd JD, *et al.*** Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. *Neuron.* 2003; 39: 409–21.
105. **Hurtado DE, Molina-Porcel L, Iba M, *et al.*** Aβ accelerates the spatiotemporal progression of tau pathology and augments tau amyloidosis in an Alzheimer mouse model. *Am J Pathol.* 2010; 177: 1977–88.

106. **Green KN, Billings LM, Roozendaal B, *et al.*** Glucocorticoids increase amyloid-beta and tau pathology in a mouse model of Alzheimer's disease. *J Neurosci.* 2006; 26: 9047–56.
107. **Billings LM, Oddo S, Green KN, *et al.*** Intraneuronal Abeta causes the onset of early Alzheimer's disease-related cognitive deficits in transgenic mice. *Neuron* 2005; 45: 675–88.
108. **Gong EJ, Park HR, Kim ME, *et al.*** Morin attenuates tau hyperphosphorylation by inhibiting GSK3beta. *Neurobiol Dis.* 2011; 44, 223–30.
109. **Coomaraswamy J, Kilger E, Wolfing H, *et al.*** Modeling familial Danish dementia in mice supports the concept of the amyloid hypothesis of Alzheimer's disease. *Proc Natl Acad Sci USA.* 2010; 107: 7969–74.
110. **Winton MJ, Lee EB, Sun E, *et al.*** Intraneuronal APP, not free Abeta peptides in 3xTg-AD mice: implications for tau *versus* Abeta-mediated Alzheimer neurodegeneration. *J Neurosci.* 2011; 31: 7691–9.
111. **Wirths O, Dins A, Bayer TA.** AbetaPP accumulation and/or intraneuronal Abeta accumulation? The 3xTg-AD mouse model revisited. *J Alzheimers Dis.* 2011 in press: doi: 10.3233/JAD-2011-111529.
112. **Nakayama K, Ohkawara T, Hiratochi M, *et al.*** The intracellular domain of amyloid precursor protein induces neuron-specific apoptosis. *Neurosci Lett.* 2008; 444: 127–31.
113. **Ohkawara T, Nagase H, Koh CS, *et al.*** The amyloid precursor protein intracellular domain alters gene expression and induces neuron-specific apoptosis. *Gene.* 2011; 475: 1–9.
114. **Hunter JM, Bowers WJ, Maarouf CL, *et al.*** Biochemical and morphological characterization of the AbetaPP/PS/Tau TRIPLE transgenic mouse model and its relevance to sporadic Alzheimer's disease. *J Alzheimers Dis.* 2011; 27: 361–76.
115. **Rhein V, Song X, Wiesner A, *et al.*** Amyloid-beta and tau synergistically impair the oxidative phosphorylation system in triple transgenic Alzheimer's disease mice. *Proc Natl Acad Sci USA* 2009; 106: 20057–62.
116. **Eckert A, Schmitt K, Gotz J.** Mitochondrial dysfunction – the beginning of the end in Alzheimer's disease? Separate and synergistic modes of tau and amyloid-beta toxicity. *Alzheimers Res Ther.* 2011; 3: 15.
117. **Eckert A, Schulz KL, Rhein V, *et al.*** Convergence of amyloid-beta and tau pathologies on mitochondria *in vivo*. *Mol Neurobiol.* 2010; 41: 107–14.
118. **Rajendran L, Honsho M, Zahn TR, *et al.*** Alzheimer's disease beta-amyloid peptides are released in association with exosomes. *Proc Natl Acad Sci USA* 2006; 103: 11172–7.
119. **Vossel KA, Zhang K, Brodbeck J, *et al.*** Tau reduction prevents Abeta-induced defects in axonal transport. *Science* 2010; 330: 198.
120. **Saper CB, Wainer BH, German DC.** Axonal and transneuronal transport in the transmission of neurological disease: potential role in system degenerations, including Alzheimer's disease. *Neuroscience* 1987; 23: 389–98.
121. **Stamer K, Vogel R, Thies E, *et al.*** Tau blocks traffic of organelles, neurofilaments, and APP vesicles in neurons and enhances oxidative stress. *J Cell Biol.* 2002; 156: 1051–63.
122. **Pappolla MA, Omar RA, Kim KS, *et al.*** Immunohistochemical evidence of oxidative [corrected] stress in Alzheimer's disease. *Am J Pathol.* 1992; 140: 621–8.
123. **Perez JL, Carrero I, Gonzalo P, *et al.*** Soluble oligomeric forms of beta-amyloid (Abeta) peptide stimulate Abeta production *via* astrogliosis in the rat brain. *Exp Neurol.* 2010; 223: 410–21.
124. **Novak P, Prcina M, Kontsekova E.** Tauons and prions: infamous cousins? *J Alzheimers Dis.* 2011; 26: 413–30.
125. **Guo JP, Arai T, Miklossy J, *et al.*** Abeta and tau form soluble complexes that may promote self aggregation of both into the insoluble forms observed in Alzheimer's disease. *Proc Natl Acad Sci USA* 2006; 103: 1953–8.
126. **Miller Y, Ma B, Nussinov R.** Synergistic interactions between repeats in tau protein and Abeta amyloids may be responsible for accelerated aggregation *via* polymorphic states. *Biochemistry* 2011; 50: 5172–81.
127. **Yoshiyama Y, Higuchi M, Zhang B, *et al.*** Synapse loss and microglial activation precede tangles in a P301S tauopathy mouse model. *Neuron* 2007; 53: 337–51.
128. **Rocher AB, Crimins JL, Amatrudo JM, *et al.*** Structural and functional changes in tau mutant mice neurons are not linked to the presence of NFTs. *Exp Neurol.* 2010; 223: 385–93.
129. **Braak H, Thal DR, Ghebremedhin E, *et al.*** Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. *J Neuropathol Exp Neurol.* 2011; 70: 960–9.
130. **Thal DR, Rub U, Orantes M, *et al.*** Phases of Abeta-deposition in the human brain and its relevance for the development of AD. *Neurology* 2002; 58: 1791–800.
131. **Thal DR, Capetillo-Zarate E, Del Tredici K, *et al.*** The development of amyloid beta protein deposits in the aged brain. *Sci Aging Knowledge Environ.* 2006; 2006: re1.
132. **Buckner RL, Snyder AZ, Shannon BJ, *et al.*** Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. *J Neurosci.* 2005; 25: 7709–17.
133. **Walker LC, Jucker M.** Amyloid by default. *Nat Neurosci.* 2011; 14: 669–70.
134. **Braak H, Braak E.** Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol.* 1991; 82: 239–59.
135. **Alafuzoff I, Arzberger T, Al-Sarraj S, *et al.*** Staging of neurofibrillary pathology in Alzheimer's disease: a study of the BrainNet Europe Consortium. *Brain Pathol.* 2008; 18: 484–96.
136. **Braak H, Del Tredici K.** Alzheimer's pathogenesis: is there neuron-to-neuron propagation? *Acta Neuropathol.* 2011; 121: 589–95.
137. **Braak H, Del Tredici K.** The pathological process underlying Alzheimer's disease in individuals under thirty. *Acta Neuropathol.* 2011; 121: 171–81.
138. **Simic G, Stanic G, Mladinov M, *et al.*** Does Alzheimer's disease begin in the brainstem? *Neuropathol Appl Neurobiol.* 2009; 35: 532–54.
139. **Grinberg LT, Rub U, Ferretti RE, *et al.*** The dorsal raphe nucleus shows phospho-tau neurofibrillary changes before the transentorhinal region in Alzheimer's disease. A precocious onset?. *Neuropathol Appl Neurobiol.* 2009; 35: 406–16.
140. **Elobeid A, Soininen H, Alafuzoff I.** Hyperphosphorylated tau in young and middle-aged subjects. *Acta Neuropathol.* 2011; in press: doi: 10.1007/s00401-011-0897-9.
141. **Postupna N, Rose SE, Bird TD, *et al.*** Novel antibody capture assay for paraffin-embedded tissue detects wide-ranging amyloid beta and paired helical filament-tau accumulation in cognitively normal older adults. *Brain Pathol.* 2011; in press: doi: 10.1111/j.1750-3639.2011.00542.x.
142. **Desikan RS, McEvoy LK, Thompson WK, *et al.*** Amyloid-beta associated volume loss occurs only in the presence of phospho-tau. *Ann Neurol.* 2011; 70: 657–61.

143. **Avila J.** Alzheimer disease: caspases first. *Nat Rev Neurol.* 2010; 6: 587–8.
144. **Iqbal K, Grundke-Iqbal I.** Opportunities and challenges in developing Alzheimer disease therapeutics. *Acta Neuropathol.* 2011; 122: 543–9.
145. **Irvine GB, El-Agnaf OM, Shankar GM, *et al.*** Protein aggregation in the brain: the molecular basis for Alzheimer's and Parkinson's diseases. *Mol Med.* 2008; 14: 451–64.
146. **Higashi S, Iseki E, Yamamoto R, *et al.*** Concurrence of TDP-43, tau and alpha-synuclein pathology in brains of Alzheimer's disease and dementia with Lewy bodies. *Brain Res.* 2007; 1184: 284–94.
147. **Iseki E, Togo T, Suzuki K, *et al.*** Dementia with Lewy bodies from the perspective of tauopathy. *Acta Neuropathol.* 2003; 105: 265–70.
148. **Miklossy J, Steele JC, Yu S, *et al.*** Enduring involvement of tau, beta-amyloid, alpha-synuclein, ubiquitin and TDP-43 pathology in the amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam (ALS/PDC). *Acta Neuropathol.* 2008; in press: 116: 625–37.
149. **Leverenz JB, Umar I, Wang Q, *et al.*** Proteomic identification of novel proteins in cortical Lewy bodies. *Brain Pathol.* 2007; 17: 139–45.
150. **Burns SA, Moran CR, Pingerelli PL, *et al.*** Redefining the Lewy body: evidence of distinct protein composition and nonrandon assembly process (abstr.). *Mov Disord.* 2008; 23(Suppl 1): S22.
151. **van Dijk KD, Berendse HW, Drukarch B, *et al.*** The proteome of the locus ceruleus in Parkinson's disease: relevance to pathogenesis. *Brain Pathol.* 2011; in press: doi: 10.1111/j.1750-3639.2011.00540.x.
152. **Goris A, Williams-Gray CH, Clark GR, *et al.*** Tau and alpha-synuclein in susceptibility to, and dementia in, Parkinson's disease. *Ann Neurol.* 2007; 62: 145–53.
153. **Strobel G.** The spectrum series: grappling with the overlap between Alzheimer's and Parkinson's diseases. 9th International Conference on Alzheimer's and Parkinson's Diseases, 11–15 March 2009, Prague, Czech Republic. *J Alzheimers Dis.* 2009; 18: 625–40.
154. **Arai Y, Yamazaki M, Mori O, *et al.*** Alpha-synuclein-positive structures in cases with sporadic Alzheimer's disease: morphology and its relationship to tau aggregation. *Brain Res.* 2001; 888: 287–96.
155. **Duda JE, Giasson BI, Mabon ME, *et al.*** Concurrence of alpha-synuclein and tau brain pathology in the Contursi kindred. *Acta Neuropathol.* 2002; 104: 7–11.
156. **Badiola N, de Oliveira RM, Herrera F, *et al.*** Tau enhances alpha-synuclein aggregation and toxicity in cellular models of synucleinopathy. *PLoS ONE* 2011; 6: e26609.
157. **Maries E, Dass B, Collier TJ, *et al.*** The role of alpha-synuclein in Parkinson's disease: insights from animal models. *Nat Rev Neurosci.* 2003; 4: 727–38.
158. **Badiola N, Suarez-Calvet M, Lleo A.** Tau phosphorylation and aggregation as a therapeutic target in tauopathies. *CNS Neurol Disord Drug Targets.* 2010; 9: 727–40.
159. **Waxman EA, Giasson BI.** Induction of intracellular tau aggregation is promoted by alpha-synuclein seeds and provides novel insights into the hyperphosphorylation of tau. *J Neurosci.* 2011; 31: 7604–18.
160. **Nonaka T, Watanabe ST, Iwatsubo T, *et al.*** Seeded aggregation and toxicity of {alpha}-synuclein and tau: cellular models of neurodegenerative diseases. *J Biol Chem.* 2010; 285: 34885–98.
161. **Duka T, Duka V, Joyce JN, *et al.*** Alpha-synuclein contributes to GSK-3beta-catalyzed tau phosphorylation in Parkinson's disease models. *FASEB J.* 2009; 23: 2820–30.
162. **Wills J, Credle J, Haggerty T, *et al.*** Tauopathic changes in the striatum of A53T alpha-synuclein mutant mouse model of Parkinson's disease. *PLoS ONE* 2011; 6: e17953.
163. **Kaul T, Credle J, Haggerty T, *et al.*** Region-specific tauopathy and synucleinopathy in brain of the alpha-synuclein overexpressing mouse model of Parkinson's disease. *BMC Neurosci.* 2011; 12: 79.
164. **Haggerty T, Credle J, Rodriguez O, *et al.*** Hyperphosphorylated tau in an alpha-synuclein-overexpressing transgenic model of Parkinson's disease. *Eur J Neurosci.* 2011; 33: 1598–610.
165. **Qureshi HY, Paudel HK.** Parkinsonian neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and α-synuclein mutations promote tau protein phosphorylation at Ser262 and destabilize microtubule cytoskeleton *in vitro*. *J Biol Chem.* 2011; 286: 5055–68.
166. **Riedel M, Goldbaum O, Richter-Landsberg C.** Alpha-synuclein promotes the recruitment of tau to protein inclusions in oligodendroglial cells: effects of oxidative and proteolytic stress. *J Mol Neurosci.* 2009; 39: 226–34.
167. **Chaves RS, Melo TQ, Martins SA, *et al.*** Protein aggregation containing beta-amyloid, alpha-synuclein and hyperphosphorylated tau in cultured cells of hippocampus, substantia nigra and locus coeruleus after rotenone exposure. *BMC Neurosci.* 2010; 11: 144.
168. **Lei P, Ayton S, Finkelstein DI, *et al.*** Tau protein: relevance to Parkinson's disease. *Int J Biochem Cell Biol.* 2010; 42: 1775–8.
169. **Emmer KL, Waxman EA, Covy JP, *et al.*** E46K human {alpha}-synuclein transgenic mice develop Lewy-like and tau pathology associated with age-dependent detrimental motor impairments. *J Biol Chem.* 2011; 286: 35104–8.
170. **Wills J, Jones J, Haggerty T, *et al.*** Elevated tauopathy and alpha-synuclein pathology in postmortem Parkinson's disease brains with and without dementia. *Exp Neurol.* 2010; 225: 210–8.
171. **Esposito A, Dohm CP, Kermer P, *et al.*** Alpha-synuclein and its disease-related mutants interact differentially with the microtubule protein tau and associate with the actin cytoskeleton. *Neurobiol Dis.* 2007; 26: 521–31.
172. **Kawakami F, Suzuki M, Shimada N, *et al.*** Stimulatory effect of alpha-synuclein on the tau-phosphorylation by GSK-3beta. *FEBS J.* 2011; 278: 4895–904.
173. **Lebel M, Patenaude C, Allyson J, *et al.*** Dopamine D1 receptor activation induces tau phosphorylation *via* cdk5 and GSK3 signaling pathways. *Neuropharmacology* 2009; 57: 392–402.
174. **McNaught KS, Belizaire R, Jenner P, *et al.*** Selective loss of 20S proteasome alpha-subunits in the substantia nigra pars compacta in Parkinson's disease. *Neurosci Lett.* 2002; 326: 155–8.
175. **Duka T, Rusnak M, Drolet RE, *et al.*** Alpha-synuclein induces hyperphosphorylation of tau in the MPTP model of parkinsonism. *FASEB J.* 2006; 20: 2302–12.
176. **Duka T, Sidhu A.** The neurotoxin, MPP+, induces hyperphosphorylation of tau, in the presence of alpha-synuclein, in SH-SY5Y neuroblastoma cells. *Neurotox Res.* 2006; 10: 1–10.
177. **Kozikowski AP, Gaisina IN, Petukhov PA, *et al.*** Highly potent and specific GSK-3beta inhibitors that block tau phosphorylation and decrease alpha-synuclein protein expression in a cellular model of Parkinson's disease. *Chem Med Chem.* 2006; 1: 256–66.
178. **van Eersel J, Bi M, Ke YD, *et al.*** Phosphorylation of soluble tau differs in Pick's disease and Alzheimer's disease brains. *J Neural Transm.* 2009; 116: 1243–51.

179. **Uchihara T, Hara M, Nakamura A, *et al.*** Tangle evolution differentiated by three- and four-repeat tau. Double immunofluorolabeling study with two monoclonal antibodies. *Histochem Cell Biol.* 2011; in press: doi: 10.1007/s00418-011-0891-2.
180. **Giasson BI, Forman MS, Higuchi M, *et al.*** Initiation and synergistic fibrillization of tau and alpha-synuclein. *Science.* 2003; 300: 636–40.
181. **Kotzbauer PT, Giasson BI, Kravitz AV, *et al.*** Fibrillization of alpha-synuclein and tau in familial Parkinson's disease caused by the A53T alpha-synuclein mutation. *Exp Neurol.* 2004; 187: 279–88.
182. **Morales R, Estrada LD, Diaz-Espinoza R, *et al.*** Molecular cross talk between misfolded proteins in animal models of Alzheimer's and prion diseases. *J Neurosci.* 2010; 30: 4528–35.
183. **Seto-Salvia N, Clarimon J, Pagonabarraga J, *et al.*** Dementia risk in Parkinson disease: disentangling the role of MAPT haplotypes. *Arch Neurol.* 2011; 68: 359–64.
184. **Simon-Sanchez J, Schulte C, Bras JM, *et al.*** Genome-wide association study reveals genetic risk underlying Parkinson's disease. *Nat Genet.* 2009; 41: 1308–12.
185. **Williams-Gray CH, Evans JR, Goris A, *et al.*** The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. *Brain* 2009; 132: 2958–69.
186. **Wray S, Lewis PA.** A tangled web – tau and sporadic Parkinson's disease. *Front Psychiatry* 2010; 1: 150.
187. **Clarimon J, Molina-Porcel L, Gomez-Isla T, *et al.*** Early-onset familial Lewy body dementia with extensive tauopathy: a clinical, genetic, and neuropathological study. *J Neuropathol Exp Neurol.* 2009; 68: 73–82.
188. **Peuralinna T, Oinas M, Polvikoski T, *et al.*** Neurofibrillary tau pathology modulated by genetic variation of alpha-synuclein. *Ann Neurol.* 2008; 64: 348–52.
189. **Muntane G, Dalfo E, Martinez A, *et al.*** Phosphorylation of tau and alpha-synuclein in synaptic-enriched fractions of the frontal cortex in Alzheimer's disease, and in Parkinson's disease and related alpha-synucleinopathies. *Neuroscience* 2008; 152: 913–23.
190. **Frasier M, Walzer M, McCarthy L, *et al.*** Tau phosphorylation increases in symptomatic mice overexpressing A30P alpha-synuclein. *Exp Neurol.* 2005; 192: 274–87.
191. **Fujishiro H, Tsuboi Y, Lin WL, *et al.*** Co-localization of tau and alpha-synuclein in the olfactory bulb in Alzheimer's disease with amygdala Lewy bodies. *Acta Neuropathol.* 2008; 116: 17–24.
192. **Shao CY, Crary JF, Rao C, *et al.*** Atypical protein kinase C in neurodegenerative disease II: PKCiota/lambda in tauopathies and alpha-synucleinopathies. *J Neuropathol Exp Neurol.* 2006; 65: 327–35.
193. **Ishizawa T, Mattila P, Davies P, *et al.*** Colocalization of tau and alpha-synuclein epitopes in Lewy bodies. *J Neuropathol Exp Neurol.* 2003; 62: 389–97.
194. **Piao YS, Hayashi S, Hasegawa M, *et al.*** Co-localization of alpha-synuclein and phosphorylated tau in neuronal and glial cytoplasmic inclusions in a patient with multiple system atrophy of long duration. *Acta Neuropathol.* 2001; 101: 285–93.
195. **Nagaishi M, Yokoo H, Nakazato Y.** Tau-positive glial cytoplasmic granules in multiple system atrophy. *Neuropathology* 2011; 31: 299–305.
196. **Dickson DW.** Alpha-synuclein and the Lewy body disorders. *Curr Opin Neurol.* 2001; 14: 423–32.
197. **Trembath Y, Rosenberg C, Ervin JF, *et al.*** Lewy body pathology is a frequent co-pathology in familial Alzheimer's disease. *Acta Neuropathol.* 2003; 105: 484–8.
198. **Uchikado H, Lin WL, DeLucia MW, *et al.*** Alzheimer disease with amygdala Lewy bodies: a distinct form of alpha-synucleinopathy. *J Neuropathol Exp Neurol.* 2006; 65: 685–97.
199. **Attems J, Quass M, Jellinger KA.** Tau and alpha-synuclein brainstem pathology in Alzheimer disease: relation with extrapyramidal signs. *Acta Neuropathol.* 2007; 113: 53–62.
200. **Burns JM, Galvin JE, Roe CM, *et al.*** The pathology of the substantia nigra in Alzheimer disease with extrapyramidal signs. *Neurology* 2005; 64: 1397–403.
201. **Liu Y, Stern Y, Chun MR, *et al.*** Pathological correlates of extrapyramidal signs in Alzheimer's disease. *Ann Neurol.* 1997; 41: 368–74.
202. **Nakashima-Yasuda H, Uryu K, Robinson J, *et al.*** Co-morbidity of TDP-43 proteinopathy in Lewy body related diseases. *Acta Neuropathol.* 2007; 114: 221–9.
203. **Arai T, Mackenzie IR, Hasegawa M, *et al.*** Phosphorylated TDP-43 in Alzheimer's disease and dementia with Lewy bodies. *Acta Neuropathol.* 2009; 117: 125–36.
204. **Saito Y, Ruberu NN, Sawabe M, *et al.*** Lewy body-related alpha-synucleinopathy in aging. *J Neuropathol Exp Neurol.* 2004; 63: 742–9.
205. **Jellinger K.** Unusual tau in MSA. *Neuropathology.* 2011; in press: doi: 10.1111/j.440-789.2011.01246.x.
206. **Jellinger KA.** Interaction between alpha-synuclein and tau in Parkinson's disease. Comment on Wills ,*et al.*: Elevated tauopathy and alpha-synuclein pathology in postmortem Parkinson's disease brains with and without dementia. Exp Neurol 2010; 225: 210–218.
207. **Lee VM, Giasson BI, Trojanowski JQ.** More than just two peas in a pod: common amyloidogenic properties of tau and alpha-synuclein in neurodegenerative diseases. *Trends Neurosci.* 2004; 27: 129–34.
208. **Obi K, Akiyama H, Kondo H, *et al.*** Relationship of phosphorylated alpha-synuclein and tau accumulation to Abeta deposition in the cerebral cortex of dementia with Lewy bodies. *Exp Neurol.* 2008; 210: 409–20.
209. **Lee SJ, Lim HS, Masliah E, *et al.*** Protein aggregate spreading in neurodegenerative diseases: problems and perspectives. *Neurosci Res.* 2011; 70: 339–48.
210. **Mollenhauer B, Locascio JJ, Schulz-Schaeffer W, *et al.*** Alpha-synuclein and tau concentrations in cerebrospinal fluid of patients presenting with parkinsonism: a cohort study. *Lancet Neurol.* 2011; 10: 230–40.
211. **Parnetti L, Chiasserini D, Bellomo G, *et al.*** Cerebrospinal fluid tau/alpha-synuclein ratio in Parkinson's disease and degenerative dementias. *Mov Disord.* 2011; 26: 1428–35.
212. **Mulugeta E, Londos E, Hansson O, *et al.*** Cerebrospinal fluid levels of sAPPalpha and sAPPbeta in Lewy body and Alzheimer's disease: clinical and neurochemical correlates. *Int J Alzheimers Dis.* 2011; 2011: 495025.
213. **Pletnikova O, West N, Lee MK, *et al.*** Abeta deposition is associated with enhanced cortical alpha-synuclein lesions in Lewy body diseases. *Neurobiol Aging* 2005; 26: 1183–92.
214. **Lashley T, Holton JL, Gray E, *et al.*** Cortical alpha-synuclein load is associated with amyloid-beta plaque burden in a subset of Parkinson's disease patients. *Acta Neuropathol.* 2008; 115: 417–25.
215. **Masliah E, Rockenstein E, Veinbergs I, *et al.*** Beta-amyloid peptides enhance alpha-synuclein accumulation and neuronal deficits in a transgenic mouse model linking Alzheimer's disease and Parkinson's disease. *Proc Natl Acad Sci USA.* 2001; 98: 12245–50.

216. **Bate C, Gentleman S, Williams A.** Alpha-synuclein induced synapse damage is enhanced by amyloid-beta1-42. *Mol Neurodegener.* 2010; 5: 55.
217. **Small SA, Duff K.** Linking Abeta and tau in late-onset Al.zheimer's disease: a dual pathway hypothesis. *Neuron* 2008; 60: 534–42.
218. **Fjorback AW, Sundbye S, Dachsel JC, *et al.*** P25alpha/TPPP expression increases plasma membrane presentation of the dopamine transporter and enhances cellular sensitivity to dopamine toxicity. *FEBS J.* 2011; 278: 493–505.
219. **Olah J, Vincze O, Virok D, *et al.*** Interactions of pathological hallmark proteins: tubulin polymerization promoting protein/p25, β-amyloid and α-synuclein. *J Biol Chem.* 2011; 286: 34088–100.
220. **Kovacs GG, Laszlo L, Kovacs J, *et al.*** Natively unfolded tubulin polymerization promoting protein TPPP/p25 is a common marker of alpha-synucleinopathies. *Neurobiol Dis.* 2004; 17: 155–62.
221. **Kragh CL, Lund LB, Febbraro F, *et al.*** α-synuclein aggregation and ser-129 phosphorylation-dependent cell death in oligodendroglial cells. *J Biol Chem.* 2009; 284: 10211–22.
222. **Hasegawa T, Baba T, Kobayashi M, *et al.*** Role of TPPP/p25 on alpha-synuclein-mediated oligodendroglial degeneration and the protective effect of SIRT2 inhibition in a cellular model of multiple system atrophy. *Neurochem Int.* 2010; 57: 857–66.
223. **Luk KC, Song C, O'Brien P, *et al.*** Exogenous alpha-synuclein fibrils seed the formation of Lewy body-like intracellular inclusions in cultured cells. *Proc Natl Acad Sci USA* 2009; 106: 20051–6.
224. **Meyer-Luehmann M, Coomaraswamy J, Bolmont T, *et al.*** Exogenous induction of cerebral beta-amyloidogenesis is governed by agent and host. *Science* 2006; 313: 1781–4.
225. **Lee HJ, Patel S, Lee SJ.** Intravesicular localization and exocytosis of alpha-synuclein and its aggregates. *J Neurosci.* 2005; 25: 6016–24.
226. **Clavaguera F, Bolmont T, Crowther RA, *et al.*** Transmission and spreading of tauopathy in transgenic mouse brain. *Nat Cell Biol.* 2009; 11: 909–13.
227. **Desplats P, Lee HJ, Bae EJ, *et al.*** Inclusion formation and neuronal cell death through neuron-to-neuron transmission of alpha-synuclein. *Proc Natl Acad Sci USA* 2009; 106: 13010–5.
228. **Ren PH, Lauckner JE, Kachirskaia I, *et al.*** Cytoplasmic penetration and persistent infection of mammalian cells by polyglutamine aggregates. *Nat Cell Biol.* 2009; 11: 219–25.
229. **Mendez I, Vinuela A, Astradsson A, *et al.*** Dopamine neurons implanted into people with Parkinson's disease survive without pathology for 14 years. *Nat Med.* 2008; 14: 507–9.
230. **Braak H, Del Tredici K, Rub U, *et al.*** Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003; 24: 197–211.
231. **Braak H, Del Tredici K.** Neuroanatomy and pathology of sporadic Parkinson's disease. *Adv Anat Embryol Cell Biol.* 2009; 201: 1–119.
232. **Braak H, Del Tredici K.** [Pathophysiology of sporadic Parkinson's disease]. *Fortschr Neurol Psychiatr.* 2010; 78: S2–4.
233. **Parkkinen L, Pirttila T, Alafuzoff I.** Applicability of current staging/categorization of alpha-synuclein pathology and their clinical relevance. *Acta Neuropathol.* 2008; 115: 399–407.
234. **Kalaitzakis ME, Graeber MB, Gentleman SM, *et al.*** Controversies over the staging of alpha-synuclein pathology in Parkinson's disease. *Acta Neuropathol.* 2008; 116: 125–8.
235. **Jellinger KA.** A critical evaluation of current staging of alpha-synuclein pathology in Lewy body disorders. *Biochim Biophys Acta* 2009; 1792: 730–40.
236. **Dickson DW, Uchikado H, Fujishiro H, *et al.*** Evidence in favor of Braak staging of Parkinson's disease. *Mov Disord.* 2010; 25: S78–82.
237. **Kordower JH, Chu Y, Hauser RA, *et al.*** Transplanted dopaminergic neurons develop PD pathologic changes: a second case report. *Mov Disord.* 2008; 23: 2303–6.
238. **Li JY, Englund E, Holton JL, *et al.*** Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation. *Nat Med.* 2008; 14: 501–3.
239. **Brundin P, Li JY, Holton JL, *et al.*** Research in motion: the enigma of Parkinson's disease pathology spread. *Nat Rev Neurosci.* 2008; 9: 741–5.
240. **Li JY, Englund E, Widner H, *et al.*** Characterization of Lewy body pathology in 12- and 16-year-old intrastriatal mesencephalic grafts surviving in a patient with Parkinson's disease. *Mov Disord.* 2010; 25: 1091–6.
241. **Hansen C, Angot E, Bergstrom AL, *et al.*** Alpha-synuclein propagates from mouse brain to grafted dopaminergic neurons and seeds aggregation in cultured human cells. *J Clin Invest.* 2011; 121: 715–25.
242. **Lee HJ, Suk JE, Bae EJ, *et al.*** Assembly-dependent endocytosis and clearance of extracellular alpha-synuclein. *Int J Biochem Cell Biol.* 2008; 40: 1835–49.
243. **Kordower JH, Dodiya HB, Kordower AM, *et al.*** Transfer of host-derived alpha synuclein to grafted dopaminergic neurons in rat. *Neurobiol Dis.* 2011; 43: 552–7.
244. **Aguzzi A, Rajendran L.** The transcellular spread of cytosolic amyloids, prions, and prionoids. *Neuron* 2009; 64: 783–90.
245. **Angot E, Steiner JA, Hansen C, *et al.*** Are synucleinopathies prion-like disorders? *Lancet Neurol.* 2010; 9: 1128–38.
246. **Brundin P, Melki R, Kopito R.** Prion-like transmission of protein aggregates in neurodegenerative diseases. *Nat Rev Mol Cell Biol.* 2010; 11: 301–7.
247. **Goedert M, Clavaguera F, Tolnay M.** The propagation of prion-like protein inclusions in neurodegenerative diseases. *Trends Neurosci.* 2010; 33: 317–25.
248. **Resenberger UK, Harmeier A, Woerner AC, *et al.*** The cellular prion protein mediates neurotoxic signalling of beta-sheet-rich conformers independent of prion replication. *EMBO J.* 2011; 30: 2057–70.
249. **Sandberg MK, Al-Doujaily H, Sharps B, *et al.*** Prion propagation and toxicity *in vivo* occur in two distinct mechanistic phases. *Nature* 2011; 470: 540–2.
250. **Chia R, Tattum MH, Jones S, *et al.*** Superoxide dismutase 1 and tgSOD1 mouse spinal cord seed fibrils, suggesting a propagative cell death mechanism in amyotrophic lateral sclerosis. *PLoS ONE.* 2010; 5: e10627.
251. **Munch C, O'Brien J, Bertolotti A.** Prion-like propagation of mutant superoxide dismutase-1 misfolding in neuronal cells. *Proc Natl Acad Sci USA* 2011; 108: 3548–53.
252. **Furukawa Y, Kaneko K, Watanabe S, *et al.*** A seeding reaction recapitulates intracellular formation of Sarkosyl-insoluble transactivation response element (TAR) DNA-binding protein-43 inclusions. *J Biol Chem.* 2011; 286: 18664–72.
253. **Mackenzie IR, Neumann M, Baborie A, *et al.*** A harmonized classification system for FTLD-TDP pathology. *Acta Neuropathol.* 2011; 122: 111–3.
254. **Novak M.** Truncated tau protein as a new marker for Alzheimer's disease. *Acta Virol.* 1994; 38: 173–89.
255. **Frost B, Jacks RL, Diamond MI.** Propagation of tau misfolding from the outside to the inside of a cell. *J Biol Chem.* 2009; 284: 12845–52.

256. **Frost B, Ollesch J, Wille H, *et al.*** Conformational diversity of wild-type tau fibrils specified by templated conformation change. *J Biol Chem.* 2009; 284: 3546–51.
257. **Brown P, Brandel JP, Preece M, *et al.*** Iatrogenic Creutzfeldt-Jakob disease: the waning of an era. *Neurology.* 2006; 67: 389–93.
258. **Brown P.** Transmissible spongiform encephalopathy in the 21st century: neuroscience for the clinical neurologist. *Neurology.* 2008; 70: 713–22.
259. **Watt NT, Hooper NM.** Prion protein in Alzheimer's disease – Editorial. *Future Neurol* 2007; 2: 587–90.
260. **Freir DB, Nicoll AJ, Klyubin I, *et al.*** Interaction between prion protein and toxic amyloid beta assemblies can be therapeutically targeted at multiple sites. *Nat Commun.* 2011; 2: 336.
261. **Balch WE, Morimoto RI, Dillin A, *et al.*** Adapting proteostasis for disease intervention. *Science* 2008; 319: 916–9.
262. **Frost B, Diamond MI.** Prion-like mechanisms in neurodegenerative diseases. *Nat Rev Neurosci.* 2010; 11: 155–9.
263. **Urushitani M, Sik A, Sakurai T, *et al.*** Chromogranin-mediated secretion of mutant superoxide dismutase proteins linked to amyotrophic lateral sclerosis. *Nat Neurosci.* 2006; 9: 108–18.
264. **Hu WT, Chen-Plotkin A, Arnold SE, *et al.*** Biomarker discovery for Alzheimer's disease, frontotemporal lobar degeneration, and Parkinson's disease. *Acta Neuropathol.* 2010; 120: 385–99.
265. **Mollenhauer B, Bibl M, Esselmann H, *et al.*** Tauopathies and synucleinopathies: do cerebrospinal fluid beta-amyloid peptides reflect disease-specific pathogenesis? *J Neural Transm.* 2007; 114: 919–27.
266. **Hu X, Crick SL, Bu G, *et al.*** Amyloid seeds formed by cellular uptake, concentration, and aggregation of the amyloid-beta peptide. *Proc Natl Acad Sci USA* 2009; 106: 20324–9.
267. **Sierks MR, Chatterjee G, McGraw C, *et al.*** CSF levels of oligomeric alpha-synuclein and beta-amyloid as biomarkers for neurodegenerative disease. *Integr Biol.* 2011, 3: 1188–96.
268. **Bibl M, Mollenhauer B, Esselmann H, *et al.*** CSF amyloid-beta-peptides in Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia. *Brain* 2006; 129: 1177–87.
269. **Aerts MB, Esselink RA, Claassen JA, *et al.*** CSF Tau, Abeta42, and MHPG differentiate dementia with Lewy bodies from Alzheimer's disease. *J Alzheimers Dis.* 2011; 27: 377–84.
270. **Weick JP, Liu Y, Zhang SC.** Human embryonic stem cell-derived neurons adopt and regulate the activity of an established neural network. *Proc Natl Acad Sci USA.* 2011; 108: 20189–94. doi: http://dx.doi.org/10.1073/pnas.1108487108.
271. **Tomiyama T, Matsuyama S, Iso H, *et al.*** A mouse model of amyloid beta oligomers: their contribution to synaptic alteration, abnormal tau phosphorylation, glial activation, and neuronal loss *in vivo. J Neurosci.* 2010; 30: 4845–56.
272. **Clinton LK, Blurton-Jones M, Myczek K, *et al.*** Synergistic interactions between Abeta, tau, and alpha-synuclein: acceleration of neuropathology and cognitive decline. *J Neurosci.* 2010; 30: 7281–9.
273. **Mrak RE, Griffin WS.** Common inflammatory mechanisms in Lewy body disease and Alzheimer disease. *J Neuropathol Exp Neurol.* 2007; 66: 683–6.
274. **Haass C.** Initiation and propagation of neurodegeneration. *Nat Med.* 2010; 16: 1201–4.
275. **Kanehisa M, Limviphuvadh V, Tanabe M.** Knowledge-based analysis of protein interaction networks in neurodegenerative diseases. In: Alzate O., editor. *Neuroproteomics.* Boca Raton, FL: CRC Press; 2010. p. 147–62.
276. **Silveira JR, Raymond GJ, Hughson AG, *et al.*** The most infectious prion protein particles. *Nature* 2005; 437: 257–61.
277. **Bloch A, Probst A, Bissig H, *et al.*** Alpha-synuclein pathology of the spinal and peripheral autonomic nervous system in neurologically unimpaired elderly subjects. *Neuropathol Appl Neurobiol.* 2006; 32: 284–95.
278. **Braak H, de Vos RA, Bohl J, *et al.*** Gastric alpha-synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology. *Neurosci Lett.* 2006; 396: 67–72.
279. **Danzer KM, Haasen D, Karow AR, *et al.*** Different species of alpha-synuclein oligomers induce calcium influx and seeding. *J Neurosci.* 2007; 27: 9220–32.
280. **Prusiner SB.** *Prion Biology and Diseases*, 2nd ed. Cold Spring Harbor: Cold Spring Harbor Laboratory, 2004.
281. **Aguzzi A, O'Connor T.** Protein aggregation diseases: pathogenicity and therapeutic perspectives. *Nat Rev Drug Discov.* 2010; 9: 237–48.
282. **Zilka N, Kontsekova E, Novak M.** Chaperone-like antibodies targeting misfolded tau protein: new vistas in the immunotherapy of neurodegenerative foldopathies. *J Alzheimers Dis.* 2008; 15: 169–79.
283. **Dennissen FJ, Kholod N, Steinbusch HW, *et al.*** Misframed proteins and neurodegeneration: a novel view on Alzheimer's and Parkinson's diseases. *Neurodegener Dis.* 2010; 7: 76–9.
284. **Selkoe DJ.** Soluble oligomers of the amyloid beta-protein impair synaptic plasticity and behavior. *Behav Brain Res.* 2008; 192: 106–13.
285. **Malchiodi-Albedi F, Paradisi S, Matteucci A, *et al.*** Amyloid oligomer neurotoxicity, calcium dysregulation, and lipid rafts. *Int J Alzheimers Dis.* 2011; 2011: 906964.
286. **Bartels T, Choi JG, Selkoe DJ.** alpha-Synuclein occurs physiologically as a helically folded tetramer that resists aggregation. *Nature.* 2011; 477: 107–10.
287. **Canu N, Filesi I, Pristera A, *et al.*** Altered Intracellular Distribution of PrPC and Impairment of Proteasome Activity in Tau Overexpressing Cortical Neurons. *J Alzheimers Dis.* 2011; 27: 603–13.
288. **Osiecka KM, Nieznanska H, Skowronek KJ, *et al.*** Tau inhibits tubulin oligomerization induced by prion protein. *Biochim Biophys Acta.* 2011; 1813: 1845–53.
289. **Jayadev S, Nochlin D, Poorkaj P, *et al.*** Familial prion disease with Alzheimer disease-like tau pathology and clinical phenotype. *Ann Neurol.* 2011; 69: 712–20.
290. **Davidson YS, Raby S, Foulds PG, *et al.*** TDP-43 pathological changes in early onset familial and sporadic Alzheimer's disease, late onset Alzheimer's disease and Down's Syndrome: association with age, hippocampal sclerosis and clinical phenotype. *Acta Neuropathol.* 2011; 122: 703–13.
291. **Lee EB, Lee VM, Trojanowski JQ.** Gains or losses: molecular mechanisms of TDP43-mediated neurodegeneration. *Nat Rev Neurosci.* 2011; 13: 38–50.
292. **Tomiyama T, Matsuyama S, Iso H, *et al.*** A mouse model of amyloid beta oligomers: their contribution to synaptic alteration, abnormal tau phosphorylation, glial activation, and neuronal loss *in vivo. J Neurosci.* 2010; 30: 4845–56.
293. **Umeda T, Tomiyama T, Sakama N, *et al.*** Intraneuronal amyloid beta oligomers cause cell death via endoplasmic reticulum stress, endosomal/lysosomal leakage, and mitochondrial dysfunction *in vivo. J Neurosci Res.* 2011; 89: 1031–42.
294. **Sluchanko NN, Gusev NB.** Probable participation of 14-3-3 in tau protein oligomerization and aggregation. *J Alzheimers Dis.* 2011; 27: 467–76.

295. **Lloret A, Badia MC, Giraldo E, *et al.*** Amyloid-beta toxicity and tau hyperphosphorylation are linked via RCAN1 in Alzheimer's disease. *J Alzheimers Dis.* 2011; 27: 701–9.
296. **Amadoro G, Corsetti V, Atlante A, *et al.*** Interaction between NH(2)-tau fragment and Aβ in Alzheimer's disease mitochondria contributes to the synaptic deterioration. *Neurobiol Aging.* 2011; in press: doi: http://dx.doi.org/10.1016/j.neurobiolaging.2011.08.001.
297. **Shao CY, Mirra SS, Sait HB, *et al.*** Postsynaptic degeneration as revealed by PSD-95 reduction occurs after advanced Abeta and tau pathology in transgenic mouse models of Alzheimer's disease. *Acta Neuropathol.* 2011; 122: 285–92.
298. **Kopeikina KJ, Carlson GA, Pitstick R, *et al.*** Tau accumulation causes mitochondrial distribution deficits in neurons in a mouse model of tauopathy and in human Alzheimer's disease brain. *Am J Pathol.* 2011; 179: 2071–82.
299. **Karbowski M, Neutzner A, Youle RJ.** The mitochondrial E3 ubiquitin ligase MARCH5 is required for Drp1 dependent mitochondrial division. *J Cell Biol.* 2007; 178: 71–84.
300. **Duyckaerts C, Potier MC, Delatour B.** Alzheimer disease models and human neuropathology: similarities and differences. *Acta Neuropathol.* 2008; 115: 5–38.
301. **Kokjohn TA, Roher AE.** Amyloid precursor protein transgenic mouse models and Alzheimer's disease: understanding the paradigms, limitations, and contributions. *Alzheimers Dement.* 2009; 5: 340–7.
302. **Christensen DZ, Bayer TA, Wirths O.** Intracellular Ass triggers neuron loss in the cholinergic system of the APP/PS1KI mouse model of Alzheimer's disease. *Neurobiol Aging.* 2010; 31: 1153–63.
303. **Aho L, Pikkarainen M, Hiltunen M, *et al.*** Immunohistochemical visualization of amyloid-beta protein precursor and amyloid-beta in extra- and intracellular compartments in the human brain. *J Alzheimers Dis.* 2010; 20: 1015–28.
304. **Nakamura K, Nemani VM, Azarbal F, *et al.*** Direct membrane association drives mitochondrial fission by the Parkinson disease-associated protein alpha-synuclein. *J Biol Chem.* 2011; 286: 20710–26.
305. **Yamakawa K, Izumi Y, Takeuchi H, *et al.*** Dopamine facilitates alpha-synuclein oligomerization in human neuroblastoma SH-SY5Y cells. *Biochem Biophys Res Commun.* 2010; 391: 129–34.
306. **Lee HJ, Baek SM, Ho DH, *et al.*** Dopamine promotes formation and secretion of non-fibrillar alpha-synuclein oligomers. *Exp Mol Med.* 2011; 43: 216–22.
307. **Pemberton S, Madiona K, Pieri L, *et al.*** Hsc70 protein interaction with soluble and fibrillar alpha-synuclein. *J Biol Chem.* 2011; 286: 34690–9.
308. **Lei P, Ayton S, Bush AI, Adlard PA.** GSK-3 in neurodegenerative diseases. *Int J Alzheimers Dis.* 2011; 2011: 189246.
309. **Makarava N, Kovacs GG, Savtchenko R, *et al.*** Genesis of mammalian prions: From non-infectious amyloid fibrils to a transmissible prion disease. *PLoS Pathog.* 2011; 7: e1002419.
310. **Cushman M, Johnson BS, King OD, *et al.*** Prion-like disorders: blurring the divide between transmissibility and infectivity. *J Cell Sci.* 2010; 123: 1191–201.
311. **Takahashi RH, Tobiume M, Sato Y, *et al.*** Accumulation of cellular prion protein within dystrophic neurites of amyloid plaques in the Alzheimer's disease brain. *Neuropathology.* 2011; 31: 208–14.
312. **Moreno-Gonzalez I, Soto C.** Misfolded protein aggregates: mechanisms, structures and potential for disease transmission. *Semin Cell Dev Biol.* 2011; 22: 482–7.
313. **Riek R.** Cell biology: infectious Alzheimer's disease? *Nature.* 2006; 444: 429–31.