Interaction between pathogenic proteins in neurodegenerative disorders

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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 engaging 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 ‘proteopathies’ [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 intracytoplasmic 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 fibrillar 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

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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-fibrillar, 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 bio-active 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 protec 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 tetramers 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 by αSyn oligomers, the toxicity of which has been demonstrated in vitro [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 [44–50], 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-
isms 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—Ab 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 Ab but not total amyloid plaque burden correlates with neuronal loss and astrocitic 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 Ab 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 Ab and tau [69–71]. There is an interaction between tau and Ab 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 Ab toxicity via the regulator of calcineurin gene RCAN1 and GSK-3β, producing a sequential mechanism for Ab and tau pathology [295]. The senile plaque, where Ab 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 with both Ab and tau [79]. There are also well-documented data indicating that Ab and tau meet at the synapse, in about 25% of synaptosomes preserved from cryopreserved material, phospho (p)-tau and Ab 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, Ab formation is the critical step in driving AD pathogenesis, implying the aggregation of Ab 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 Ab.

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 impairing 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 to 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 [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 ligands (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 GTFase 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 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 claims 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 phenomenon may result from direct cross-seeding of tau by aggregated Aβ [125, 126], indirect pathways such as Aβ-induced tau hyperphosphorylation, 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 neural 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(1) 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 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-occurrence of both proteins, as an increase in p-tau is one of the key features in the brains of all tautopathies 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 anti-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 signaling 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 activities 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 exposure may also induce 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-3 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 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 isofoms 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 TDP than tau [213], and Aβ is known to initiate hyperphosphorylation of tau [71]. Cortical Aβ load is associated with Aβ plaque burden in a subset of PD patients [214]. Aβ peptides enhance Aβ accumulation and neuronal deficits in a tg mouse model [215], and Aβ-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 with 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, Aβ and tau, have also been shown to interact with p25 [219]. p25 was found in LBs in PD and DLB, but does not co-localize with the inclusions in tauopathies [220]. Expression of p25 and Aβ in a rat oligodendroglial cell line resulted in disruption of the microtubule cytoskeleton, formation of Aβ oligomers and apoptosis [221]. p25 promotes the oligomerization of Aβ and accelerates inclusion formation leading to oligodendroglial death [222]. p25 is probably being an early event for the formation of GCIs in MSA.

Interactions between Aβ, Aβ and tau may be a molecular mechanism in the overlapping pathology of AD and PD/LBD [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).

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, Aβ-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], with the reliability of Lewy pathology staging in sporadic PD has been a matter of discussion [233–236]. The concept that Aβ 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 Aβ-positive LBs in some cells [237–239]. These data imply for a host-to-graft propagation of Aβ, and a neuron-to-neuron (interneuron) transmission or transsynaptic spread of Aβ appears a likely interpretation for the propagation of the disease. Similar accumulation of Aβ 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 Aβ 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 Aβ can recruit endogenous Aβ in the recipient cells, act as a permissive template and promote misfolding in small aggregates [241]. Some of the uptake of Aβ 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 Aβ [34, 239]. These suggestions are supported by the observation that neural grafts placed into tg mice expressing human Aβ take up the human protein and form Aβ-positive aggregates [227, 241, 243].

Most recent studies demonstrated that preformed fibrils generated from full-length and truncated recombinant Aβ enter primary hippocampal neurons, probably by adsorptive-mediated endocytosis, and promote recruitment of soluble endogenous Aβ into insoluble PD-like LBs and LNs. Remarkably, endogenous Aβ was sufficient for formation of these aggregates, and overexpression of wild-type or mutant Aβ was not required. Accumulation of pathologic Aβ 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 Aβ inducing misfolding of Aβ 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 Aβ appear to be possible [227, 241, 243].

Fig. 4 Morphologic interrelations of synucleinopathies, tauopathies and amyloidopathies. NFTs: neurofibrillary tangles; PSP: progressive supra-nuclear palsy; CBD: corticobasal degeneration; PDD: Parkinson disease dementia; DLB: dementia with Lewy bodies; AD: Alzheimer disease; LBs: Lewy bodies.
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 fibril formation [1, 34, 124, 226–256]. 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) and other pathological conformers that 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 proteinaceous 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

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

| Inoculum                              | Host                                      | Propagation effect                                                                 |
|----------------------------------------|-------------------------------------------|------------------------------------------------------------------------------------|
| Amyloid-β                               | APP transgenic mice (intracerebral injection) | Amyloid-β deposition at injection site and in adjacent brain structures [84, 223, 224] |
| Tau                                     | 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)                      | Neuronal cells                             | Endocytic uptake of αSyn aggregates [227]                                           |
| Aggregate-producing neuronal cell cultures | Primary hippocampal neurons               | Adsorptive-mediated endocytosis promoting soluble αSyn into insoluble PD-like LBs and LNs [35] |
| Introduction of αSyn aggregates by preformed fibrils generated from truncated recombinant human wild-type αSyn | Mouse neuronal progenitor cells grafted into mouse brains | Interneuronal transmission of human αSyn [227]                                           |
| Transgenic mice overexpressing human αSyn | Foetal stem cells grafted into the brains of patients with Parkinson disease | Interneuronal transmission of Lewy inclusions [223, 228, 229] |
| 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                          | 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.
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 transynaptic 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 Atz17 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 corresponding 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 SOD1 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 between 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 unreliable [8, 206]. 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], whytau, 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 proteinaceous 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 objec-
tives for therapeutic interference [246]. Inhibition of early αSyn
aggregation events would consequently prevent αSyn oligomer-
related toxicity [279], which would fit also for other proteinopa-
thies and related NDDs thereby improving diagnostic and therapeutic
possibilities.

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Conflict of interest statement

The author confirms that there are no conflicts of interest.

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