What is the Link Between Protein Aggregation and Interneuronal Lesion Propagation in Neurodegenerative Disease?

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1. Introduction

During the past 10-15 years it has become clear that most major neurodegenerative diseases (Alzheimer’s disease, Parkinson’s disease, ALS, tauopathies, prion diseases and trinucleotide repeat diseases – henceforth to be referred to collectively as AANDs) share cellular and systemic features that suggest a common underlying mechanism of pathogenesis. At the cellular level, our understanding of the common aspects of AAND pathogenesis can be most simply summarized in terms of the downstream consequences of uncontrollable protein oligomerization and aggregation in postmitotic cells. The aggregated proteins block or disrupt normal proteosomal turnover and autophagy and become abnormally modified over time, generating toxicity via multiple pathways (mitochondrial damage, increased intracellular Ca++, caspase activation etc.) eventually leading to neurodegeneration and neuron death. This hypothesis is consistent with a key genetic similarity between these diseases – e.g. that familial forms are typically caused by autosomal dominant mutations that favor aggregation (in the case of asyn, tau, PrP and SOD1) or formation (in the case of APP and CAG repeat sequences) of disease-specific, aggregation-prone proteins. These similarities have suggested to many that a single central defect (i.e. the failure of normal protein folding) lies at the heart of most or all of the diseases listed above, and has led to them being categorized be some as “protein misfolding diseases”.

While the importance of aggregate formation (and its attendant cellular dysfunctions) in each of these diseases is well established and has been intensively studied, our understanding of the intercellular and systemic aspects of these diseases is less detailed. That said, enough has been learned about their roles in neuronal biology and pathobiology and in the neuropathogenesis of AANDs to generate a general consensus that AAND development is 1) not cell autonomous and 2) that AANDs have another common hallmark—the progressive involvement of synaptically connected regions of the CNS over time in disease-specific patterns. Furthermore, it has become clear that important synergistic interactions between specific aggregation-prone proteins (tau and asyn (83), PrP and APP/Abeta (134), PrP and tau (216), PrP and asyn (95) may occur at both at the cellular and interneuronal level that affect the pathogenesis of specific AANDs. However, while neurofibrillary lesions develop according to characteristic, disease-specific sequences between highly interconnected regions of the brain in some AANDs (e.g. AD, tauopathies...
and LBD), the mechanisms by which the tendency toward aggregate formation is propagated between neurons as the disease progresses remains unclear, as does the degree to which such mechanisms contribute to disease pathogenesis as a whole. Similarly, there is still a gap between what we now know about the normal (mostly as monomer) and toxic (mostly as oligomers and aggregates) functions of each of these proteins at the cellular level. We know a good deal about the factors that favor AAND oligomerization, but very little about how oligomerization actually occurs in human disease. In particular, we have no real idea how these factors might 1) interact synergistically to drive cytotoxicity and degeneration and 2) are related to the mechanisms by which interneuronal toxicity is propagated between neurons in different parts of the brain. This review will attempt to integrate relatively recent findings about the interactions between the 3 most widely studied of these proteins (i.e. tau, alpha synuclein and the prion protein) both with each other and with cellular mechanisms associated with unconventional protein secretion into a framework that will account for common pathogenic features of these diseases and suggest future avenues of inquiry. For the sake of clarity, the discussion will be focused on asyn, tau and PrP and their interactions with APP/Abeta, and will omit a detailed consideration of other diseases that may have similar pathogenetic features (e.g ALS, Huntington’s disease) and associated aggregation-prone proteins (SOD1, polyglutamine expansions, TDP-43, FUS), except when these become relevant to the discussion of general mechanisms. It will be guided by the example of PrP misprocessing and prion diseases, where the key link between intracellular protein aggregation, interneuronal transfer and the spread of neurofibrillary lesions through the brain has already been definitively established and which provides hints as to where to look for similar links in other AANDs.

Overview of common neuropathological and genetic aspects of AAND pathogenesis at the cellular and systemic levels

The predominant focus of basic research over the past 2 decades into the pathogenesis of all of the major AANDs has been on 1) the mechanisms responsible for protein aggregate formation and 2) the nature of cytotoxic changes that accompany and result from the aggregation of each of the proteins being discussed. As a consequence, aggregation-associated events and downstream consequences of aggregation such as the failure of protein turnover mechanisms in long-lived postmitotic cells such as neurons are among the best-characterized cytopathological features of neurodegenerative diseases. This work has generated a broad consensus that aggregation causes the failure of normal protein turnover mechanisms and the consequent development of abnormal toxic routes of protein disposal are central pathogenic events of the degenerative diseases that afflict the human central nervous system as it ages. Common toxic elements downstream of protein aggregation in AANDs include: 1) aggregation associated damage to protein turnover mechanisms, 2) mitochondrial dysfunction and or maldistribution leading to apoptosis-associated changes due to low ATP, generation of oxidative stress and abnormal Ca++ fluxes and 3) aggregate-mediated sequestration of normal proteins resulting in a loss of the normal function associated with sequestered proteins.

The classic example of a neuropathogenesis pattern suggestive of lesion spread in AANDs (outside of prion diseases) is provided by Alzheimer’s Disease (AD). Ever since the seminal studies of Heiko and Eva Braak (27), it has been apparent that the neurofibrillary degenerative changes of AD develop in a characteristic sequence that closely follows the clinical progression of symptoms (11, 203). The earliest changes occur in specific limbic
regions concerned with olfaction, spatial localization and episodic memory formation and consolidation (transentorhinal, entorhinal, pyriform cortices), functions that are typically compromised in the earliest clinical (and even preclinical) phases of AD. This is followed by the progressive involvement of limbic and paralimbic centers including the hippocampus, adjacent allocortical regions of the medial temporal lobe (e.g. subiculum), the insula and anterior cingulate cortex. Again, these neuropathological changes match the development of AD symptoms quite closely, with changes in emotional processing and short term memory becoming evident by the time AD can be recognized as such in the clinic, together with the onset of cognitive changes. The most prominently affected limbic centers are strongly interconnected with one another synaptically as well as functionally (203), as would be necessary for lesion propagation via transsynaptic toxicity transfer. The areas affected in this “limbic stage” of mild AD make up only a small proportion of the brain by volume (24), but make and receive major inputs to and from large neocortical regions that become involved in later (isocortical) stages of AD, which could account for the sudden expansion of AD neurofibrillary lesions at the onset of Braak Stage 5 (24, 202). Although some regions of the brain (e.g. the primary sensory and motor cortices) are almost never involved significantly in AD despite being strongly interconnected with highly vulnerable limbic centers, it seems likely that this is due to cell specific or even connectivity-specific factors (8) that may delineate individual AANDs from one another (63, 59, 109, 116).

The progressive involvement of synaptically interconnected brain regions seen in AD is mirrored in non-AD tauopathies such as frontotemporal dementia (FTD), Pick’s Disease (PiD) progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) and involve some of the same parts of the brain (prefrontal/frontal cortex temporal cortex, insula) although the areas of initial involvement are different from AD and from each other (9, 10, 11, 63). Similarly, Parkinson’s Disease (PD) and PD-associated dementing syndromes such as Lewy Body Disease (LBD) share a common set of vulnerable loci (dopaminergic neurons in the substantia nigra, brainstem autonomic nuclei, olfactory bulb and neocortical loci) but vary significantly in the initial nidus of vulnerability and the degree of involvement of other parts of the brain (48, recently reviewed in 3, 50, 59). Also, the progression of Lewy Body containing lesions in LBD and PD differs significantly from that seen in AD in that it is not tightly linked to overall clinical or neuropathological severity (28). Overall, significant overlap between the areas vulnerable to synucleinopathies with those involved in early stages of AD (nucleus of Meynert, olfactory bulb, various isocortical loci) and in non-AD tauopathies (basal ganglia, isocortex). Familial prion diseases (familial fatal insomnia, Creutzfeld Jacob disease (CJD), Gerstmann-Schenker-Straussler syndrome) show a similar pattern (lesion evolution via a subset of synaptically connected areas from characteristic initiation loci) with a common set of vulnerable loci (thalamus, neocortex, ANS, cerebellum) that partly overlaps those of the other ANDDs (illustrated in Figure 1).

Another distinctive feature of AANDs as a group is the manifestation of each syndrome in both sporadic and familial forms, with exonic or intronic mutations in a specific aggregation-prone protein being sufficient to generate a (usually) dominant allele capable of replicating all aspects of the (usually more common) sporadic disease with high penetrance (197). Perhaps the most interesting aspects of this pattern are a) the degree of similarity between sporadic and familial disease forms, and b) the greater tendency of sporadic, but not familial, disease forms to show asymmetrical development, especially in non AD tauopathies (59, 143). These emphasize the importance of both selective vulnerability and synaptic connectivity as common factors in these diseases, and is consistent with the
intriguing relationship between acquired, sporadic and familial forms of prion diseases such as Creutzfeld-Jacob disease (CJD), where the point of origin is clearly different in each case, but common aspects of vulnerability and synaptic connectivity are sufficient to generate a common clinical presentation (CJD), despite the presence of characteristic differences in lesion form (175). A similar relationship may hold between certain non-AD tauopathies and clinically identical diseases (both called FTDP or FTDP-17) involving loss of function changes in RNA-binding proteins (TDP-43, progranin) involved in the localization and translation of cytoskeletal proteins (hnRNPs), including tau and neurofilament proteins (147). Here, TDP-43 and or progranin may be activating downstream elements of a common

Fig. 1. Schematic illustrating the relationship between the characteristically vulnerable regions in AD, (green) nonAD tauopathies (pink), familial prion diseases (yellow) and synucleinopathies (blue). Regions typically involved in multiple AAND disease classes are shown in overlapping areas. Individual syndromes from all of these diseases eventually involve polymodal (associative) isocortical areas and thus cause dementia, even though severe cognitive changes may be absent or develop very late in other members of each group (e.g. Parkinson’s Disease, fatal familial insomnia). Vulnerable areas in familial and sporadic forms of each AAND are identical, with familial syndromes beginning earlier and progressing faster than sporadic ones. Characteristic areas of vulnerability for frontotemporal syndromes (FTDP-U) that involve TDP-43 and FUS rather than tau aggregates and acquired forms of prion disease (vCJD, kuru) are virtually identical to non AD tauopathies (pink) and familial prion diseases (yellow), respectively, possibly owing to the presence of “prion like” motifs in these proteins (53). ANS: autonomic nervous sytem, MFB: medial forebrain bundle/nucleus of Meynert, GP: globus pallidus
mislocalization of proteins important in the maintenance of neuronal polarity from the axon to the soma and dendrites via a failure of hnRNmediated mRNA localization. This possibility is particularly intriguing since a) hnRN interactions with the 3' UTR of the mRNA encoding tau have been shown to be responsible for both tau localization to the axon (12, 146) and the generation of neuronal polarity (147) and b) the neuropathology of AD and non-AD tauopathies suggests that polarity loss plays a role in tauopathy pathogenesis (107, 1741). Overall, the common neuropathological and genetic features of AANDs involving tau, asyn and PrP are largely consistent with the existence of a common lesion propagation mechanism (or several closely related mechanisms) that involves direct interneuronal transfer of a toxic factor between adjacent and transsynaptic neurons.

Linking aggregation to lesion spreading – The case of the prion protein

The prototypic (and most extreme) example of an aggregation-prone protein that propagates its misfolded state at the protein, cellular and even organismal level is of course the prion protein (PrP), the misfolding of which mediates a class of mostly rare neurological degenerative diseases (transmissible spongiform encephalopathies) of humans and other mammals, the best known of which are CJD, scrapie, and kuru. Due to the pioneering work of Tikva Alper, Carlton Gadjusek and (particularly and most recently) Stanley Prusiner and co-workers over the past 50 years, and after rigorous verification by often highly skeptical investigators, there is now a general consensus that the so called “Prion hypothesis” proposed by Prusiner 30 years ago has correctly predicted key peculiarities of prion disease transmission such as the effect of PrP knockouts (31) and thus correctly describes the pathogenesis of these diseases (reviewed in 3, 49, 175). The Prion Hypothesis states that individual molecules of a single, widely expressed protein (the prion protein, or PrP) becomes misfolded and misprocessed in a manner that makes it adopt a neurotoxic conformation (PrP\textsubscript{Sc}), but more importantly, permits it to transmit this conformation on to other prion proteins in the normal (PrP\textsubscript{C}) conformation. The peculiar and controversial history of prion biology thus provides us with a highly verified example of how the misprocessing of an aggregation-prone protein into a toxic form can result in the interneuronal propagation of a protein with self regenerating, neurotoxic characteristics, and thus effect the spreading of neurofibrillary lesions to adjacent, presynaptic or postsynaptic neurons. The likely relevance of PrP misprocessing mechanisms to the pathogenesis of tauopathies, synucleinopathies, and other AANDs is further underscored by recent demonstrations that immensely subtle differences in PrP misprocessing and PrP\textsubscript{Sc} structure appear to mediate the distinctive clinical and neuropathological manifestations of the various prion diseases (18, 40, 49, 168). In addition, recent studies of the normal cellular functions of PrP\textsubscript{C} suggest that it is involved in the function of the actin-rich subcortical cytoskeleton and its interactions with microtubules, cellular membrane trafficking, cell adhesion and signal transduction in a variety of cell types (reviewed in 3, 53). In neurons, PrP\textsubscript{C} appears to play a critical (if subtle) role in synaptic plasticity and most interestingly, in the propagation of HIV infection in the CNS (149, 180). The similarities in the cellular function, localization and misprocessing of PrP, APP/Abeta, asyn and tau identify likely points of interaction between these proteins, and synergy in their misprocessing, which are discussed further below.
Table 1. Comparison of the pathobiological characteristics of 4 aggregation-prone proteins responsible for most aggregation-associated neurodegenerative diseases (AANDs) in humans. The table summarizes aspects of disease-associated misprocessing of 4 aggregation-prone proteins (amyloid precursor protein/beta amyloid (APP/Abeta) tau, alpha synuclein (asyn) and prion (PrP)) discussed in the text that are relevant to both aggregate formation and lesion propagation in major human neurodegenerative diseases (Alzheimer’s Disease (AD), Down’s Syndrome (DS), Pick’s Disease (PiD), progressive supernuclear palsy (PSP), corticobasal degeneration (CBD), Parkinson’s disease (PD), Lewy Body disease (LBD), Creutzfeld-Jakob disease (CJD), Gerstmann Straussler Schenker disease (GSS), fatal familial insomnia (FFI), kuru and variant CJD (vCJD). *publication in review (185)

| Etiology | APP/Abeta (AD, DS) | tau (PD, PSP, CBD) | Asyn (PD, LBD) | PrP (CJD, GSS, FFI, kuru, vCJD) |
|----------|-------------------|--------------------|----------------|-------------------------------|
| Sporadic | Most (80%)        | Varies             | Most (95%)     | Probably most (CJD)           |
| Dominant | APP (1%)          | tau (exonic, isoform splicing) | Asyn LRRK2 | PrP               |
| Recessive |                   |                    | DJ1, Pink1, Parkin |                  |

| Risk Factors | APP expression (DS) | Asyn expression (H1 haplotype) | diverse loci in mitochondria | PrP129 |
|--------------|---------------------|-------------------------------|-------------------------------|--------|
| Genetic      |                     | tau expression (H1 haplotype) | diverse loci in mitochondria | PrP129 |
| Environmental | TBI, axotomy        | TBI, axotomy                  | ROS-generating toxins         | PrP129 |

| Neuropathology | Neuronal vulnerability factors | Asyn expression | dopaminergic | PrP expression |
|----------------|--------------------------------|----------------|-------------|---------------|
|                | plasticity                    | tau expression | High ROS    | Cerebellum     |
|                | large size                    | NF expression  | varies with mutation | kuru, vCJD    |
|                | glutamatergic                 | neurofil threads |               |               |
|                |                                | dystrophic neurites |               |               |
|                |                                | dystrophic neurites |               |               |
|                |                                | dystrophic neurites |               |               |
|                |                                | dystrophic neurites |               |               |
|                | Connectivity-based pathogenesis | yes            | yes          | yes           |

| Propagation | Clinical | no | no | yes | yes |
|-------------|----------|----|----|-----|-----|
| Interneuronal transfer (human protein) | secretion | in situ culture | in situ culture | culture | culture |
| | secretion mechanism | exosome | exosome expression | exosome expression | exosome | exosome |
| | uptake | culture | culture | culture | in situ | in situ |
| | transmission | in situ (IP injection) | in situ | in situ | in situ | in situ |
| | transmitted toxicity | in situ culture | in situ culture | culture | culture |

| Synergy | Clinical | PD, LBD | PD, LBD | AD, tauopathy | Unclear |
|---------|----------|---------|---------|---------------|---------|
| Neurpathology | PD, LBD (tau) | Asyn Abeta | tau, Abeta | tau, Abeta |

| Protein interaction | Asyn, PrP tau (binding) | Asyn (coaggregation) | tau (coaggregation) | Asyn, PrP |
|---------------------|-------------------------|----------------------|---------------------|-----------|
| | APP (binding) | Asyn (coaggregation) | tau (coaggregation) | Asyn, Abeta |
| | tau | Asyn | Abeta | tau |
2. Common structural/functional features of AAND proteins favoring aggregation and intercellular transfer

General molecular and cellular considerations

The abnormal and irreversible oligomerization and/or aggregation of specific proteins (e.g. tau, asyn, PrP) is the central common feature in AAND cytopathogenesis and by itself accounts for many of the other common cellular features of these diseases (a good review of the subject can be found in 196). Familial AANDs are typically induced by intronic, autosomal dominant mutations that either directly favor aggregation (tau, asyn, PrP), favor events that lead to generation of the aggregation-prone form of the protein (e.g. cleavage, abnormal association with other proteins, abnormal glycosylation or phosphorylation), or both (tau, PrP) (3, 50, 202). Exceptions to the autosomal dominant pattern include recessive mutations responsible for loss of function effects in protein turnover pathways (e.g. parkin 126). These genetics suggest that AAND pathology is due to a gain of function leading to aggregate formation and downstream toxicity involving the poisoning or overloading of proteasomal or autophagy-based protein turnover. A common structural feature among these proteins relevant to their tendency to aggregate is the co-existence in each one of a “core” domain which can form beta sheet interactions plus at least one other domain that inhibits this tendency, resulting in a balance between a normal conformation (rich in alpha helix or “random coil”) conformation and an abnormal beta sheet-rich conformation that favors aggregation (50, 5, 156). Key common features in the cellular functions of tau, asyn and PrP include interaction with both chaperone proteins and with signal transduction elements, which might be expected of proteins capable of both aggregation and transcellular movement, respectively. Moreover, all three proteins are frequently associated with cellular membranes under normal conditions, especially in synapses (29, 71, 76, 148, 212, 213, 233) where they interact with APP (an integral membrane protein) and/or Abeta (93, 171), and are substrates for lipid raft-associated Srk family tyrosine kinases (e.g. fyn - 95, 137, 188, syk - 136 and abl - 37). In particular, the luminal localization of each protein in endosomes and/or trafficking vesicles associated with unconventional secretion (35, 78, 140, 142), reviewed in 215), and the interactions (in some cases copolymerization) that can occur between them (83, 134, 171, 216, 217) make endosomal pathways a highly plausible candidate site that might mediate the synergistic misprocessing of these proteins. An endosome-mediated common misprocessing pathway is also consistent with the availability of templating polyanionic ligands such as membrane-associated proteoglycans favoring further aggregation and toxicity (51, 52, 91, 106, 111), and the ready diversion of endocytosed proteins to unconventional secretion pathways (68, 70, 733, 102, 116, 124, 140, 175, 215).

Tau, asyn and PrP are all “switch” proteins that alternate between 2 states based on regulated charge/charge modifications. Under normal circumstances, asyn, tau and PrP function as soluble monomers that interact extensively with other proteins in the both in the cytosol and in association with cellular membranes. Soluble PrPC and asyn contain alpha helical and random coil domains, and take up a predominantly random coil conformation in aqueous solution (186, 219, 231). In cells, tau normally extends along microtubules, where it stabilizes them by preventing classic dynamic instability via binding to them at multiple sites in its aggregation prone-microtubule binding domain (MTBR) (33). Tau:MT binding is itself dynamic (186), and tau interacts with fyn kinase, actin and protein chaperones via loci
that overlap the MTBR when not bound to MTs (95, 107, 189). Monomeric asyn exists in both membrane-associated and cytosolic loci, and like tau, can bind to both actin and tubulin (4). As with tau, disease-causing mutations in asyn cause it to preferentially bind to membrane-associated proteins (69). Both membrane and MT-associated asyn have been found to aggregate (4, 139), in some cases forming clusters of microvesicles (195). PrP possesses an aggregation-prone domain (octopeptide repeat) that appears to be oligomerized reversibly during endocytosis. Unlike tau, it also possesses a separate N terminal MT-binding domain (231). All three proteins possess-aggregation-prone domains via which they aggregate resulting in a significant increase in beta sheet structure (156, 187, 231). Deletion analyses of all three proteins show that the removal or inactivation of non-aggregating domains (the N terminus of PrP, the tau N and C termini, the asyn C terminus) may tip this balance toward aggregate formation (1, 38, 112, 226). Post-translational regulation of each protein via phosphorylation may also do this (5, 41, 42, 80), either because it blocks the binding of the aggregation-prone domain to its normal cellular ligand, thereby permitting self assembly (156), or by favoring conversion of soluble oligomer to insoluble higher-order aggregates (187). Familial disease mutations may mimic these changes (13, 66, 80) as well. Overall, while tau, asyn and PrP are capable of aggregate formation and normally interact with both MTs and membrane associated components, the details of how oligomer formation and membrane association is related to normal function vary considerably. A key common feature relevant to the appearance of gain-of-function properties leading to interneuronal propagation in AANDs is the existence of self-binding/assembly capable and assembly-inhibiting domains in each protein that are normally balanced in favor of monomeric functions. This can thus act as a “switch” between normal and abnormal processing pathways which may be mutated to favor oligomer formation in familial AANDs, or alternatively, be “flipped” by derangement of regulatory elements (e.g. kinase/phosphatase and protease activities) that induce these posttranslational processing events in sporadic AAND pathogenesis.

Protein misprocessing in AANDs becomes irreversible and opens processing pathways associated with cellular membranes. A key feature of almost all AANDs involving tau, asyn and PrP is that they can occur as both familial and sporadic syndromes, which suggests that a common AAND pathogenesis mechanism must involve self-regenerating alteration in cellular function that is largely irreversible. Initial stages of oligomerization (e.g. dimerization) are most likely insufficient to do this, since all 3 proteins are normally found in a variety of reversible folding states, including low level oligomers, and are ligands for membrane-associated signal transduction kinases that reversibly oligomerize downstream elements (205). However, the binding of these proteins to templating ligands is likely to create higher-order oligomers that could become subject to irreversible structural changes such as proteolytic cleavage (90, 226, 234) and covalent crosslinking (62, 118, 161, 192). The nature of ligands shown to be capable of doing this currently includes 1) the proteins themselves, in the case of PrP\(\text{Sc}\) (175) and mutant asyn (227), 2) polyanions such as heparan sulfate proteoglycans (HSPGs) (106, 225) or RNA (57, 119) and 3) other aggregation-prone proteins (83, 93, 95, 216). Other effectively irreversible changes in the cellular environment may be produced by downstream toxic effects of the initial aggregates, such as protease activation (7, 169), possibly aided by ionophore formation (39, 84, 133), or the recruitment of monomers into existing toxic aggregates via sequestration (6, 120). Endocytosed proteins that bind to the membrane via charge-charge interactions will undergo an acidification of
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their environment that may favor templating interactions and oligomer formation (67). Hyperphosphorylation, cleavage and aggregation of wild type tau isoforms can be induced simply by increasing the concentration of protein that is not MT-associated and thus vulnerable to misfolding (reviewed by 13, 203), causing the release of tau to the cytosol. This kind of release likely accompanies Abeta or axotomy-induced MT loss (32, 101), and thus could account for some of the dependence of tau misprocessing on Abeta generation and traumatic head injury in AD (151, 178).

While aggregate formation is a central event in the misprocessing of aggregation-prone proteins that drive AAND pathogenesis, it remains unclear how it is connected to the diversion of these proteins into the unconventional secretion pathways that might account for the interneuronal transmission of neurofibrillary lesions that appears to occur in these diseases. One possibly relevant property common to tau, asyn and PrP is their tendency to associate with membranes (29, 40, 53, 67, 173, 230, 233) and bind to membrane associated molecules such as HS PGs and fatty acids (44, 222, 225, 232). HS PG binding favors oligomer and fibril formation (52, 91, 120, 225) and may facilitate interactions with APP, which also interacts with HS PGs in cholesterol rich microdomains (lipid rafts 64, 193). Such interactions seem to be favored in AAND pathogenesis, since APP, tau and asyn colocalize with HS PGs in AAND neuropathological lesions (51, 59, 109 197). HS PGs may facilitate interactions between asyn and tau (both localized to elements on the inside of the membrane) and PrPC, which is typically found on the exterior surface attached via a GPI anchor (163, 232) and may themselves mediate transcellular protein movement, as has been suggested by studies of morphogen movement during Drosophila development (166), possibly by trapping interacting proteins in the extracellular space (232). Raft-associated interactions appear to be important in disease-associated misprocessing of tau, asyn and PrP mediated via fyn (131, 138, 188, 221), in aggregation (195, 230) and in disruption of signal transduction pathways in CNS dendrites (108, 117). Lipid association also drives oligomer and filament formation of Abeta, tau and PrP (44, 208, 221). In a very recent study by Binder and colleagues (170), a mAb specific for tau oligomer identified the presence of arachidonic acid as one of the requirements for early oligomer formation in cell culture. Similarly, the presence of membrane anchors and raft localization motifs plays an essential role in the development of characteristic lesion morphology of PrP-mediated disease (40); the removal of the GPI anchor has been shown to produce novel syndromes in transgenic models (43), while the removal of all of the multiple raft localization motifs on PrP blocks lesion formation and propagation entirely (16, reviewed in 209).

The relationship between asyn misprocessing and membrane localization in AANDs may be more complex than that of PrP and tau, since some, but not all disease-inducing mutations block raft-asyn association (75). Like PrP and tau, asyn is localized to lipid raft microdomains in presynaptic terminals, where it accumulates in dystrophic neurites associated with Parkinson’s Disease and Lewy body dementia (81). Similarly, asyn fibrillization is favored by interactions with unsaturated fatty acids (173) but unlike tau, this is inhibited by saturated fatty acids (233). A particularly intriguing recent finding by Fang et. al. demonstrated a direct link between oligomerization and unconventional secretion in a study showing that higher-order oligomerization can drive exosome-mediated secretion of a wide variety of oligomerized proteins (70). This is particularly interesting given that tau, asyn and PrP are all substrates for fyn and related raft-associated srk tyrosine kinases (136, 138, 188), and that such interactions are associated with AAND pathogenesis (19, 110) and have potentially...
self-regenerative features (i.e. by activating both the tyrosine kinase and its substrate 179). Such activation can result in fyn-mediated endocytosis via the caveolar pathway (204) or direct release of microvesicles to the extracellular space mediated via the SH4 domain of fyn (or other srk kinases) (34, 210). Regulation of endocytosis and exocytosis in neuronal growth cones by srk family kinases regulates endothelial apical endocytosis (77) and has been described in the marine snail Aplysia (223) suggesting that this is an evolutionarily conserved role for fyn-like Srk family kinases in diverse tissues. Developmental programs requiring high levels of localized membrane addition (e.g. neurite outgrowth) are dependent on the local presence of both srk family kinases and aggregation-prone proteins such as tau (20, 21) asyn (17) or Abeta (172) and are often abnormally reactivated in AANDs (26, 108, 174).

3. Cytopathological features linking aggregation and secretion in AANDDs

We have discussed the generation of abnormal tau, asyn and PrP oligomers as the most likely proximate cause of neurodegeneration in AANDs and proposed a common set of membrane-associated ligands for these proteins (e.g. HSPGs, signal transduction pathway kinases, fatty acids) which might mediate common aspects of their misprocessing, including their oligomerization, cellular colocalization and diversion into unconventional secretion pathways. Several features peculiar to neuronal AAND pathobiology that seem particularly likely to be important are discussed below.

Misprocessing of APP to Abeta 1-42 in early endosomes

So far, this discussion has focused the discussion on tau, asyn and PrP as aggregation-prone proteins immediately responsible for downstream neurotoxicity, and has ignored the contribution of aberrant APP misprocessing to Abeta in AAND pathogenesis, despite its well established importance in the pathogenesis of AD in particular (32, 94). However, it has now generally regarded as established that APP misprocessing to Abeta is the initiating event in the pathological cascade leading to AD, even if much of the proximate cytotoxicity driving neurodegeneration is mediated by tau (87, 125, 177, 180). The high cholesterol environment of rafts appears to be necessary for AAND associated misprocessing both in cell culture and in in situ AD models (64, 120, 198, 208). Furthermore, Abeta production and toxicity appears to play an important role in AANDs involving asyn and PrP as well as tau (48, 58, 134, 164, 198). Most important for the present analysis is the major site of Abeta production from APP – the early endosome. Endosomal production of Abeta 1-42 RNAi experiments have shown that APP endocytosis requires the raft marker flotillin2 in neurons, and furthermore, that misprocessing of wild type APP to Abeta 1-42 is blocked by inhibition of endocytosis (191), as is the secretion of Abeta to the extracellular space (46). APP is recruited to rafts by the raft-associated tyrosine kinase fyn (155), where its interactions with tau, asyn and PrP may play a role in both oligomerization and raft patching (163) leading to secretion of these proteins via either endocytosis and eventually exosome-mediated release (68, 70, 73, 176, 185), or microvesicle shedding (145, 163). This similarity should result in extensive opportunities for co-oligomerization between tau, asyn and possibly PrP in endosomal processing, resulting in diversion of oligomerized proteins to the exosome pathway – schematized in Figure 3.

AAND-associated proteins interact with APP in lipid rafts and may affect A beta production. There is some reason to believe that tau may influence APP misprocessing to
Abeta in association with endosomes, since tau binds to and may modulate the activity of presenilin 1, an intrinsic membrane protein which serves as the gamma secretase responsible for completing the cleavage of APP to Abeta (207), and is the site of most mutations responsible for autosomal dominant familial AD. Similarly, PrPc is normally endocytosed via a raft specific, flotillin2/clathrin dependent pathway (204), and it has been suggested that the conversion of PrPc to PrPsc, like APP cleavage to Abeta, occurs during endosome formation. There is indeed some evidence that PrP conversion to misfolded PrPsc forms can increase the misprocessing of APP by increasing the activity of the so-called beta secretase, which cleaves APP to a extracellularly released fragment and a “C99” transmembrane domain (14). Asyn interactions with APP have also been shown to greatly increase the level of Abeta secretion from PC12 cells (121). Conversely, the observation that Abeta activates the srk family kinase Abl resulting in tau phosphorylation at sites crucial to disease-associated tau aggregation (34), is also consistent with the possibility that Abeta-induced tau misprocessing may occur in the context of endosome formation.

AAND-associated protein misprocessing may favor exosomal secretion by damaging autophagy-mediated protein turnover mechanisms. It has long been suspected that alterations in protein turnover mechanisms play a significant role in the cytopathogenesis of AANDs. Under normal conditions, much of the proteolytic turnover of small cytosolic proteins such as tau, asyn and very likely PrP as well is accomplished via the ubiquitin/proteosome pathway (88, 181, 218). The aggregation of these proteins blocks this pathway, apparently due to the steric limitations of the proteosome, resulting in the ubiquitination of tau and Asyn aggregates typically seen in AANDs (158, 220). This provokes the upregulation of the macroautophagy (or simply autophagy) pathway, producing endosomal and lysosomal hypertrophy (35, 36, 165, 167) presumably due to the diversion of proteosome-mediated turnover of AAND associated proteins to the autophagy pathway. It is now becoming clear that aberrant autophagy pathway function is a general phenomenon in AANDs, and increasingly appears that autophagy pathway insufficiency rather than overactivity is the key cytopathological factor (105, 220), reviewed in (153). Since autophagy can function to remove cytosolic debris from cells via lysosomes as well as recycle cytosolic components, this may provide a secretion route for aggregated or misprocessed proteins in AANDs, especially if lysosome-mediated proteolysis is compromised (see Figure 2). Specific inhibition of autophagy combined with tau overexpression results in tau aggregate formation even in cultured neuronal cells, with tau aggregates (104) and toxic cleavage fragments (129) accumulating in lysosomal compartments. Blockade of normal retrograde axonal transport of lysosomes in AD (23) or by specific mutation (178) appears to inhibit autolysosome function indirectly by preventing amphisome-lysosome fusion in the soma, which may favor secretion by diverting incompletely degraded cytoskeletal material into exosomal secretion pathways (Figure 2). Such secretion has been described as “exophagy” in yeast (2). It is quite possible that this kind of diversion into exosomal secretion pathways may apply generally in AANDs, as autophagy disruption also occurs to a significant extent in association with asyn, Abeta, and PrPsc-positive lesions in AANDs (154, 164). Moreover, the tendency of AAND associated proteins to disrupt retrograde transport of autophagosomes (229) could very well promote exosomal secretion of these proteins from ectopic locations in the distal axons, providing a mechanism for the long distance lesion propagation seen in AD (203) and other AANDs (9-11) - see further discussion below).
Fig. 2. Overview of possible secretion routes for AAND-associated proteins based on current literature. Unconventional secretion has now been demonstrated for tau, asyn, PrP and Abeta in various model systems.
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This schematic illustrates how an aggregation-prone cytosolic protein with alternative membrane-associated ligands (in this case tau and fyn, respectively) might become aberrantly included in one of several possible vesicle trafficking pathways leading to unconventional release if it is released from its normal cytosolic ligand (microtubules) due to disease-associated conditions, which include hyperphosphorylation and microtubule loss, and which can be mimicked by overexpression (142). While tau is shown in this figure, the exosomal secretion pathways for Asyn, A beta, and PrP appear to be similar, especially since misprocessing of each of these proteins favors membrane-associated misprocessing (1) in association with the activation of autophagy (2) combined with disruption of downstream autophagic mechanisms that are necessary for the complete degradation of proteins in the autophagosome (3). While the secretion mechanism that has been identified for any of these proteins is nominally the “classic” exosomal pathway, marked by the presence of exosome-enriched proteins (e.g. Alix), it is likely that exosome secretion occurs via a number of closely related pathways that are associated to a greater or lesser degree with macroautophagy and lysosome-mediated protein turnover. Some of these pathways are indistinguishable from (or even included in) the “classical” exosome pathway (which does not involve lysosomal processing) and can be identified only via the identification of autophagosomal marker proteins (e.g cleaved LC3 (LC3II), cytoskeletal/mitochondrial proteins (COX, tubulins) and/or lysosomal markers (LAMP2, cathepsins) copurified with exosomal/MVB markers and the AAND-associated protein in question. Involvement of autophagy-associated mechanisms to form a hybrid “exophagy” pathway (2) is particularly likely if misprocessing is associated with aggregate-induced impairment of autophagy, as occurs in AANDs. Secretion pathways are elaborated from Abrahamsen et. al. (2) and Nickel (163). (1) microvesicle shedding– this pathway is driven by srk kinase activity and oligomer-mediated “patching”, but does not involve endocytosis, (2) endosome recycling pathway, (3) classic exosome pathway, (4) non-exosomal autophagosome dumping (commonly seen with tau overexpression models), (5-6) “exophagy” pathways either without autophagolysosomal formation.

Unconventional secretion may be linked to axonal transport and neuronal polarity defects caused by AAND-associated protein misprocessing. Another attractive area to look for common links between AAND associated aggregation and secretion of tau, PrP, asyn and APP is that of axonal transport and axonal identity. Each of these proteins is normally axonally localized (22, 127, 150), and the misprocessing of each protein has been shown to disrupt axoplasmic transport in AANDs and AAND models, (157, 162, 199, 200, reviewed in 183), while disruption of dynein/dynactin mediated “patching”, but does not involve endocytosis, (2) endosome recycling pathway, (3) classic exosome pathway, (4) non-exosomal autophagosome dumping (commonly seen with tau overexpression models), (5-6) “exophagy” pathways either without autophagolysosomal formation.

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The reported nature of the disruptions of axonal transport has most often involved the obstruction of axonal transport and accompanied by neurodegeneration via what may be effectively an axotomy syndrome related to synapse loss and growth factor deprivation (157, 195) However, the more interesting possibility, at least with respect to lesion propagation, is that misprocessed tau, asyn or PrP could be itself aberrantly transported along the axon in ways that could account for disease-specific features of AANDs. There is a great deal of circumstantial and correlative evidence in favor of a major role for axonal...
transport of vesicle-associated pathogens within the CNS, which closely resembles the movement of infectious prions within the brain (3, 53, 215). Interneuronal movement of HIV has recently been shown to involve PrP<sup>C</sup> mediation (181) and the binding of a raft-localizing domain that also mediates Abeta and PrP<sup>Sc</sup> localization to rafts (149), lending direct support to the operation of this mechanism in AANDs. The transfer of PrP<sup>Sc</sup> from the gut to the CNS in diseases such as kuru and vCJD involves passage through lymphatic tissues where intercellular movement of both proteins and viral particles occurs via exosomes (215) the unconventional secretion pathway common to asyn, Abeta, PrP and tau (68, 73, 176, 185). Each of these proteins is associated with axonally transported vesicles (71, 76, 123, 127, 140, 141, 150, 230), sometimes in colocalization with (71) or functionally linked with one another (134) in synapses. Moreover, exosome release of PrP has recently been tied to synaptic function with specific neurotransmitters (135), illustrating one mechanism by which specific anterograde and or retrograde pathways might be targeted. The possible operation of common a “prion like” propagation of vesicle-associated misprocessed protein in AAND pathogenesis is further strengthened by the demonstrations that Abeta toxicity can be propagated from the peritoneal cavity to the CNS in a manner similar to ingested prions (65), and that vesicle-associated tau can be dendritically transported and secreted in an in situ tauopathy model (123, 141). Finally, numerous studies of LBD, AD and CJD pathology in human patients and/or disease models have now documented the selective colocalization of axonally transported tau and asyn in dystrophic neurites associated with neurofibrillary lesions (neuritic plaques) produced by APP and/or PrP based amyloids (81, 82, 109) suggesting that synergistic interactions associated with vesicle formation (presumably during endocytosis or endosomal processing) may play a role in the lesion overlap and risk synergy so often seen in AAND neuropathology and epidemiology.

Is polarity loss connected to the misprocessing and secretion of tau and other AAND-associated proteins?

Another aspect of axonal function that is of particular relevance to tauopathies and AD, but may well be involved in any or all of the AANDs under discussion, is the selective effect of tau misprocessing on axonal identity, process outgrowth and synaptic connectivity in AD and non-AD tauopathies. Tau is normally axonally localized in neurons (22) and plays a well-established role in axonal outgrowth (20, 34, 60, 235, reviewed in 91) and in the generation of axonal identity in at least some CNS neuron types (21, 34). Much of this developmental activity of tau involves interactions with the plasma membrane and signal transduction elements rather than MTs (20, 115, 235), and appears to be partly recapitulated in AD and tauopathy pathogenesis with the outgrowth of axonlike processes (neuropil threads). Another aspect of AD pathogenesis that reflects developmental tau function is the loss of neuronal polarity seen in the neuropathology of AD and non-AD tauopathies, which is manifested in a) the progressive movement of tau from the axons to the somatodendritic compartment with the development of neurofibrillary pathology (15, 89) and b) the origination of many tau-positive neuropil threads from the dendrites of neurons in AD (107, 174).

The link between AAND neuropathology and polarity loss accounts for important neuropathological and etiological peculiarities of AD, including: a) the mislocalization and trapping of signal transduction elements essential to the establishment of axonal identity and neuronal polarity, such as CRMP-2 (159, 228) and PAR1/MARK kinase (21), and b) the greatly increased risk (up to 19 fold) that traumatic brain injury (TBI) and chronic injury
caused by multiple concussions (CTE) poses for the development of neurodegenerative disease, AD in particular (152). Torsion and stretching injury to the brain resulting in occult axotomy of long tracts in the CNS is a major pathological feature in CTE (212), and can occur very close to the soma of the axotomized neuron without killing it (194). Such injury results in the accumulation of axonally transported asyn, APP, PrP and in some cases tau at the proximal axon stump of injured neurons that are reminiscent of axonal swellings containing these proteins in AANDs (15, 162, 212).

Studies in lower vertebrate (98, 99, 101) and mammalian (45, 144, 182) systems have consistently suggested that polarity loss induced by proximal axotomy could be a mechanism capable of linking axonal injury and the development of AAND-like neuropathology. Proximal axotomy induces ectopic axonlike sprouting (98, 182), the aberrant phosphorylation and missorting of cytoskeletal proteins (99, 100) and thus reproduces key aspects of AD neuritic pathology (26, 107, 174). Missorting of axonal elements such as tau can produce AD-like loss of function degenerative changes in the axon such as synapse loss (54) as well as somatodendritic hyperphosphorylated tau accumulation, which it does even at low levels of overexpression in murine transgenics (30, 86). Interestingly, tau induced neuropathology in tauopathy models produces a number of toxic changes in the dendrites that might shed light on the link between tau misprocessing and interneuronal tau transfer. Tau expression in models causes progressive dendritic degeneration (101) and has specific effects on dendritic MT number (103) and function (61) that resemble both AD pathology (27, 151) and the effects of proximal axotomy (72, 182, 200, 101). A recent result of particular interest in this context is the recent demonstration by Ittner and co-workers (117) that ectopically localized dendritic tau mediates Abeta toxicity in a transgenic mouse tauopathy model. This finding highlights the possibility that Abeta-mediated tau misprocessing might be initiated by the aberrant juxtaposition of (normally axonal) tau with membrane-associated signal transduction partners that are present in dendrites, causing abnormalities in tau processing that lead to aggregation and eventually secretion, possibly via interactions with synaptic Abeta (71, 135). The dependence of neuronal polarization and axonal outgrowth on normal interactions between tau and localized membrane-associated tyrosine kinases (20, 21, 55) and the sensitivity of dendritic integrity to disruption of dendritic signal transduction pathways by mislocalized PrP (115) suggests that the relocalization of key proteins in AANDs might be a generally applicable mechanism in the misprocessing of AAND proteins by which normal cellular functions and interactions are replaced by abnormal ones by missorting events associated with damage to axonal transport and identity mechanisms.

4. Summary and conclusions

The aggregation of the AAND-associated proteins tau, asyn, PrP and APP/Abeta appears to be triggered by one or more post-translational events (cleavage/phosphorylation/glycosylation) that redistribute charges so as to change the predominant secondary structure from an unfolded/alpha helical pattern to a beta pleated sheet pattern. This change is associated with and driven by familial disease mutations, and may also be favored by the interaction with hydrophobic elements in cellular membranes and/or the binding of perimembranous polyanions (e.g. HSPGs), raising the interesting (and heretofore largely ignored) possibility that aggregate formation in AANDs may depend at least in part on interactions with cellular membranes. The relationship between membrane associated misprocessing and the cytopathogenesis of AANDs is summarized in Figure 3.
Fig. 3. Summary of common cellular misprocessing pathways linking aggregation and interneuronal transfer of AAND-associated proteins

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Hypothetical scheme by which the initial misfolding of AAND-associated proteins (tau asyn, PrP and Abeta) produces intracellular aggregates and other typical AAND cytopathological features in combination with the propagation of this pathology to adjacent, presynaptic and postsynaptic neurons. AAND cytopathology is produced via a combination of pathological gain of function and loss of function toxicity pathways as indicated. Recent evidence for a common membrane associated misprocessing route that causes the diversion of endocytosed proteins into abnormal vesicle trafficking pathways is highlighted, as it links oligomerization with interneuronal transfer and offers multiple opportunities for the colocalization and synergistic interaction (e.g. co-oligomerization) between AANDs at the cellular level necessary to explain the clinical and neuropathological evidence for synergy between AANDs. The classical cytosolic route for aggregate formation is also shown. Novel relationships suggested by recent studies (peach - see text for discussion) that account for key common and/or specific AAND features and could be fruitful foci of future research include links between a) axonal damage, protein mislocation due to polarity loss, and aberrant toxic interactions with dendritic signalling pathways and b) membrane-associated oligomerization and aggregate formation are shown as well, as c) the possible link between damage to axonal transport (failure of normal autophagosome/lysosome colocalization) and unconventional secretion.

Current evidence indicates that initial protein misprocessing in AANDs becomes irreversible due to cleavage and/or crosslinking events that are favored by and occur during the oligomerization/aggregation process and that novel emergent pathological interactions due to polymerization eventually become dominant in the affected neuron, leading both to the dysfunction and death of the aggregate-containing neuron and the spreading of the aggregation tendency to other neurons, where the degenerative cycle is repeated. The retrograde and/or anterograde transfer of membrane associated, oligomerized, toxic protein to other neurons involves axonal propagation of endosome-derived vesicles via transport mechanisms that may have been altered by aggregate-mediated toxicity. Lesion spreading occurs either 1) via a toxic consequence of aberrant neuronal function, such as the loss of transneuronal trophic factor transmission or the increased generation of toxic byproducts of degeneration, or 2) via the actual transfer of misprocessed proteins from one neuron to another. Evidence supporting the latter possibility (that lesion spread occurs via actual protein transfer in AANDs) has accumulated recently, as specific secretion, uptake, transfer and interneuronal toxicity transfer has now been observed for each of these proteins (47, 57, 73, 74, 75, 85, 123, 124, 128, 135, 140 - summarized in Table 1) and a common unconventional secretion pathway (i.e. exosome-mediated secretion) has been identified for PrP and Abeta (73, 176) and (quite recently) asyn and tau (68, 185). A hypothetical common misprocessing pathway for these proteins in AANDs is schematized in Figure 3.

The focus of this discussion has been on the shared characteristics of tau, asyn, PrP and Abeta that could allow each to a) associate with signal transduction elements in membrane raft domains and b) interact and oligomerize in association with elements capable of driving endocytosis (HSPGs, each other, possibly RNA, possibly via acidification driven charge-charge interactions) under circumstances which allow entry to exosomal secretion pathways, possibly via modifications induced in protein turnover mechanisms (autophagy) by aggregate toxicity. In particular, I have focused on whether this hypothesis is consistent with the now voluminous evidence that AANDs involving tau, asyn, PrP and APP misprocessing overlap one another in their etiology and pathogenesis, and whether and how well this hypothesized common link between aggregation and lesion propagation accounts for the
peculiarities of a specific protein–disease pair (tau and AD). While the necessarily general nature of this analysis precludes the accurate identification of emergent common mechanisms of AAND pathogenesis in any detail, it is hoped that it can provide a framework that may help guide further investigation in this rapidly changing field.

5. References

[1] Abrahamsen H and H Stenmark (2011) Protein Secretion: Unconventional Exit by Exophagy Current Biology, 20: R4-8
[3] Aguzzi A, Sigurdson C, Heikenwaelder M. Molecular mechanisms of prion pathogenesis. Ann Rev Pathol 2008; 3: 11–40.
[4] Alim M.A., Q.L. Ma, K. Takeda, T. Aizawa, M. Matsubara, M. Nakamura, A. Asada, T. Saito, H. Kaji, M. Yoshii, S. Hisanaga and K. Ueda, Demonstration of a role for alpha-synuclein as a functional microtubule-associated protein, J. Alzheimer’s Dis. 2004; 6:435–442.
[5] Alonso AC, Zaidi T, Novak, M, Grundke-Iqbal I, Iqbal K. Hyperphosphorylation induces self-assembly of tau into tangles of paired helical filaments and straight filaments Proc Natl Acad Sci USA 2001; 98: 6923–6928.
[6] Alonso, AD, Grundke-Iqbal I, Barra HS, Iqbal K. Abnormal phosphorylation of tau and the mechanism of Alzheimer neurofibrillary degeneration: sequestration of microtubule associated proteins 1 and 2 and the disassembly of microtubules. Proc Nat Acad Sci USA 1997; 94: 298-303.
[7] Amadoro G, Serafino AL, Barbato C, Ciotti MT, Sacco A, Calissano P, Canu N. Role of N-terminal tau domain integrity on the survival of cerebellar granule neurons. Cell Death Differ 2004; 11: 217–230.
[8] Arendt T. Disturbance of neuronal plasticity is a critical pathogenetic event in Alzheimer’s disease Reversible paired helical filament-like phosphorylation of tau is an adaptive process associated with neuronal plasticity in hibernating animals. Int. J. Devl Neuroscience 2001; 19: 231–245
[9] Armstrong RA, Cairns NJ, Lantos PL. Clustering of Pick bodies in Pick’s disease. Neurosci Lett 1998;242:81–4.
[10] Armstrong RA, Cairns NJ, Lantos PL. Dementia with Lewy bodies: clustering of Lewy bodies in human patients. Neurosci Lett 1997;224:41–4.
[11] Armstrong RA, Cairns NJ, Lantos PL. . What does the study of spatial patterns tell us about the pathogenesis of neurodegenerative disorders? Neuropathology 2001; 21: 1–12.
[12] Aronov S, Aranda G, Behar L, Ginzberg I. 2001. Axonal tau mRNA localization coincides with tau protein in living neuronal cells and depends on axonal targeting signal. J. Neurosci. 21: 6577-6587.
[13] Avila J. Tau phosphorylation and aggregation in Alzheimer's disease pathology. FEBS Lett 2006; 580:2922-2927.
[14] Baier M, Apelt J, Riemer C, Gültner S, Schwarz A, Bamme T, Burwinkel M, Schliebs R. 2008 Prion infection of mice transgenic for human APPSwe: increased accumulation of cortical formic acid extractable Ab(1-42) and rapid scrapie disease development. Int J Dev Neurosci. 26(7):821-4.

www.intechopen.com
What is the Link Between Protein Aggregation and Interneuronal Lesion Propagation in Neurodegenerative Disease?

[15] Bancher C., Brunner C., Lassman H, Budka H, Jellinger K, Wiche G, Seitelberger F, Grundke-Iqbal I, Iqbal K, Wisniewski HM. Accumulation of abnormally phosphorylated tau precedes the formation of neurofibrillary tangles in Alzheimer’s disease. Brain Res 2109; 477: 90–99.

[16] Baron GS, Caughey B. Effect of glycosylphosphatidylinositol anchordependent and -independent prion protein association with model raft membranes on conversion to the protease-resistant isoform. J Biol Chem 2003;278:15983–92.

[17] Beggs HE, Soriano P, Maness PF (1994) NCAM-dependent neurite outgrowth is inhibited in neurons from Fyn-minus mice. J Cell Biol 127, 825-833.

[18] Bessen RA, Kocisko DA, Raymond GJ, Nandan S, Lansbury PT, Caughey B (1995) Non-genetic propagation of strain-specific properties of scrapie prion protein. Nature 375:698–700.

[19] Bhaskar K, Hobbs GA, Yen SH, Lee G: Tyrosine phosphorylation of tau accompanies disease progression in transgenic mouse models of tauopathy. Neuropathol Appl Neurobiol; 2010; 36(6):462-77

[20] Biernat J, Mandelkow EM. The development of cell processes induced by tau protein requires phosphorylation of Serine 262 and 356 in the repeat domain and is inhibited by phosphorylation in the proline-rich domains. Mol Biol Cell 1999; 10:727-740.

[21] Biernat J. et al. Protein kinase MARK/PAR-1 is required for neurite outgrowth and establishment of neuronal polarity. Mol Biol Cell 2002; 13: 4013–4028.

[22] Binder LI, Frankfurter A, Rebhun LI. The distribution of tau polypeptides in the mammalian central nervous system. J Cell Biol 1985; 101:1371–1378.

[23] Boland BA, Kumar A, Lee F-M, Platt J, Wegiel J, Yu WH, Nixon, RA. Autophagy induction and autophagosome clearance in neurons: relationship to autophagic pathology in Alzheimer's disease. J Neurosci 2008; 28: 6926–6937.

[24] Braak H, Alafuzoff I, Arzberger T, Kretzschmar H, Del Tredici K, Staging of Alzheimer disease neurofibrillary pathology using paraffin sections and immunocytochemistry, Acta Neuropath 112, 2006, pp.389-404

[25] Braak E, Braak H, Mandelkow EM. A sequence of cytoskeleton changes related to the formation of neurofibrillary tangles and neuropil threads. Acta Neuropath 1994; 87: 554-567.

[26] Braak H, Braak E. Neuropil threads occur in dendrites of tangle-bearing nerve cells. Neuropathol Appl Neurobiol 1988; 14:39-44.

[27] Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. Acta Neuropath 1991; 82: 239-259.

[28] Braak, H., Ghebremedhin, E., Rueb, U., Bratzke, H. and K. del Tradici Stages in the development of Parkinson's disease-related pathology Cell Tissue Res. 2005; 318: 121–134.

[29] Brandt, R., Léger, J., and Lee, G. Interaction of tau with the neural plasma membrane mediated by tau's amino-terminal projection domain. J. Cell Biol. 1995; 131:1327-1340.

[30] Brion JP, Tremp G, Octave JN. Transgenic expression of the shortest human tau affects its compartmentalization and its phosphorylation as in the pretangle stage of Alzheimer's disease. Am J Pathol. 1999; 54: 255-270.

[31] Büeler HR, Aguzzi A, Sailer A, Greiner RA, Autenried P, Aguet M, Weissmann C. Mice devoid of PrP are resistant to scrapie. Cell 73: 1339–1347, 1993.

[32] Busciglio J, Lorenzo A, Yeh J, Yankner BA. Amyloid fibrils induce tau phosphorylation and loss of microtubule binding. Neuron 1995; 14: 879–888.
[33] Butner KA, Kirschner, MW. Tau protein binds to microtubules through a flexible array of distributed weak sites. *J Cell Biol* 1991; 122:717–730.

[34] Caceres A, Kosik KS. Inhibition of neurite polarity by tau antisense oligonucleotides in primary cerebellar neurons. *Nature* 1990; 343: 461–463.

[35] Cataldo AM, Barnett JL, Berman SA, Li J, Quarless S, Bursztajn S, Lippa C, Nixon RA. Gene expression and cellular content of cathepsin D in Alzheimer's disease brain: evidence for early up-regulation of the endosomal-lysosomal system. *Neuron* 1995; 14: 671-680.

[36] Cataldo AM, Petanceska S, Terio NB, Peterhoff CM, Durham R, Mercken M, Mehta PD, Buxbaum J, Haroutunian V, Nixon RA. Abeta localization in abnormal endosomes: association with earliest Abeta elevations in AD and Down syndrome. *Neurobiol Aging* 2004;25:1353–1272.

[37] Cancino, G.I., et al., c-Abl tyrosine kinase modulates tau pathology and Cdk5 phosphorylation in AD transgenic mice. *Neurobiol.Aging* 2009; 32: 1249-1351.

[38] Caughey B, Raymond GJ, Ernst D, Race RE (1991) N-terminal truncation of the scrapie-associated form of PrP by lysosomal protease(s): implications regarding the site of conversion of PrP to the protease-resistant state. *J Virol* 65: 6597–6603.

[39] Caughey, B. and P. Lansbury Protofibrils, Pores, Fibrils, and Neurodegeneration: Separating the Responsible Protein Aggregates from The Innocent Bystanders. *Annu. Rev. Neurosci.* 2003. 26:267–98

[40] Caughey B, Baron GS. 2006. Prions and their partners in crime. *Nature* 443:803–10

[41] Chang E, Kim S, Schafer KN, Kuret J: Pseudophosphorylation of tau protein directly modulates its aggregation kinetics. *Biochim Biophys Acta*; 2011;1814(2): 388-95.

[42] Chen L. and M.B. Feany, Alpha-synuclein phosphorylation controls neurotoxicity and inclusion formation in a *Drosophila* model of Parkinson disease, *Nat. Neurosci.* 8 (2005), pp. 657–663.

[43] Chesebro B, Race B, Meade-White K, LaCasse R, Race R, et al. (2010) Fatal Transmissible Amyloid Encephalopathy: A New Type of Prion Disease Associated with Lack of Prion Protein Membrane Anchoring. *PLoS Pathog* 6(3): e1000800.

[44] Chirita CN, Necula M, Kuret J. Anionic micelles and vesicles induce tau fibrillization in vitro. *J Biol Chem* 2003; 278:25644-50.

[45] Cho EY, So KF. Characterization of the sprouting response of axon-like processes from retinal ganglion cells after axotomy in adult hamsters: a model using intravitreal implantation of a peripheral nerve. *J Neurocytol* 1992; 21: 589–603.

[46] Cirrito, J. R., Kang, J. E., Lee, J., Stewart, et. al. Endocytosis is required for synaptic activity-dependent release of amyloid-beta in vivo. *Neuron* 2008; 58, 42-51.

[47] Clavaguera F, Bolmont T, Crowther RA, Abramowski D, Frank S, Probst A, Fraser G, Stalder AK, Beibel M, Staufenbiel M, Jucker M, Goedert M, Tolnay M. Transmission and spreading of tauopathy in transgenic mouse brain. *Nat Cell Biol* 2009; 11: 909-913.

[48] Clinton LK, Blurton-Jones M, Myczek K, Trojanowski JQ, LaFerla FM. Synergistic Interactions between Abeta, tau, and alpha-synuclein: acceleration of neuropathology and cognitive decline. *J Neurosci.* 2010; 30(21): 7281-9.

[49] Collinge, J and AR Clarke A General Model of Prion Strains and Their Pathogenicity *Science* 2007; 318, 930-936.

[50] Cookson, M Alpha-Synuclein and neuronal cell death *Molecular Neurodegeneration* 2009: 4:9 1-13
What is the Link Between Protein Aggregation and Interneuronal Lesion Propagation in Neurodegenerative Disease?

[51] Cotman, S.L., Halfter, W., and Cole, G.J. Agrin binds to β-amyloid (Aβ), accelerates Aβ fibril formation, and is localized to Aβ deposits in Alzheimer’s disease brain. *Mol. Cell Neurosci.* 2000; 15: 183–210.

[52] Cohlberg, J.A., Li, J., Uversky, V.N., and Fink, A.L. Heparin and other glycosaminoglycans stimulate the formation of amyloid fibrils from α-synuclein in vitro. *Biochemistry,* 2002 41: 1612–1621.

[53] Cushman M, Johnson B, King O, Gitler A, and J Shorter Prion-like disorders: blurring the divide between transmissibility and infectivity *Journal of Cell Science* 2010 123: 1191-1201 2Cohlberg

[54] Dawson HN, Cantillana V, Jansen M, Wang H, Vitek MP, Wilcock DM, Lynch JR, Laskowitz DT. Loss of tau elicits axonal degeneration in a mouse model of Alzheimer’s disease. *Neuroscience.* 2010;169(1):516-31.

[55] Dawson HN, Ferreira A, Eyster MV, Ghoshal N, Binder LI, Vitek MP Inhibition of neuronal maturation in primary hippocampal neurons from tau deficient mice. *J Cell Sci* 2001 121:1249-1257.

[56] Deleault NR, Lucassen RW, Supattapone S RNA molecules stimulate prion protein conversion. *Nature* 2003 425:717–720.

[57] Desplats P, et al. Inclusion formation and neuronal cell death through neuron-to-neuron transmission of α-synuclein. *Proc Natl Acad Sci USA* 2009 106:13004–13005.

[58] Dickson, D.W. Tau and synuclein and their role in neuropathology. *Brain Pathol.* 1999. 9, 657–661.

[59] Dickson DW, Neuropathology of non Alzheimer degenerative disorders, *Int J Clin Exp Pathol,* 3, 2010, pp. 1-22.

[60] DiTella M, Feiguin F, Morfini G, Caceres A. Microfilament associated growth cone component depends upon tau for its intracellular localization. *Cell Motil Cytoskel* 1994; 29:124–130.

[61] Dixit R, Ross JL, Goldman YE, Holzbaur EL. Differential regulation of dynein and kinesin motor proteins by tau. *Science* 2008; 319:1086-9.

[62] Dudek SM, Johnson GV. Transglutaminase catalyzes the formation of sodium dodecyl sulfate-insoluble, Alz-50-reactive polymers of tau. *J Neurochem* 1993; 61:1229-62.

[63] Dugger BN, Tu M, Murray ME, Dickson DW: Disease specificity and pathologic progression of tau pathology in brainstem nuclei of Alzheimer’s disease and progressive supranuclear palsy. *Neurosci Lett*; 2011; 491(2):122-6.

[64] Ehehalt R, Keller P, Haass C, Thiele C, Simons KAmyloidogenic processing of the Alzheimer beta-amyloid precursor protein depends on lipid rafts. *J Cell Biol* 2003 160:120–123.

[65] Eisele,Y.S., U. Obermuller, G. Heilbronner, F. Baumann, S.A. Kaeser and H. Wolburg et al., Peripherally applied Abeta-containing inoculates induce cerebral beta-amyloidosis, *Science* 2010; 330: 980–982.

[66] El-Agnaf, O. , Jakes R, Curran, MD. and Wallace, A. Effects of the mutations Ala30 to Pro and Ala53 to Thr on the physical and morphological properties of alpha synuclein protein implicated in Parkinson’s disease. *FEBS Lett.* 1998; 440: 67-70.

[67] Elbaum-Garfinkle S, Ramlall T, Rhoades E. The role of the lipid bilayer in tau aggregation. *Biophys J.* 2010 98:2722-30.

[68] Emmanouilidou E, Melachroinou K, Roumeliotis T, Garbis SD, Ntzouni M, Margaritis LH, Stefanis L, Vekrellis K. Cell-produced alpha-synuclein is secreted in a calcium-
dependent manner by exosomes and impacts neuronal survival. *J Neurosci.* 2010; 30:6838-51.

[69] Esposito A, Dohm CP, Kermer P, Bähr M, Wouters FS. 2007 Alpha-Synuclein and its disease-related mutants interact differentially with the microtubule protein tau and associate with the actin cytoskeleton. *Neurobiol Dis.* 26(3):521-31.

[70] Fang, Y., Wu, N., Gan, X., Yan, W., Morrell, J. C., and Gould, S. J. (2007). Higher-order oligomerization targets plasma membrane proteins and HIV gag to exosomes. *PLoS Biol* 5, e158.

[71] Fein JA, Sokolow S, Miller CA, Vinters HV, Yang F, Cole GM, Gyllys KH. Co-localization of amyloid beta and tau pathology in Alzheimer’s disease synaptosomes. *Am. J. Pathol* 2008; 172: 1683-1692.

[72] Fenrich KK, Skelton N, MacDermid VE, Meehan CF, Armstrong S et al. Axonal regeneration and development of de novo axons from distal dendrites of adult feline commissural interneurons after a proximal axotomy. *J Comp Neurol* 2007; 502:1079–1097.

[73] Fevrier B, Vilette D, Archer F, Loew D, Faigle W, Vidal M, Laude H, Raposo G. Cells release prions in association with exosomes. *Proc Natl Acad Sci USA* 2004; 101: 9683-9688.

[74] Fevrier, B., and Raposo, G. Exosomes: endosomal-derived vesicles shipping extracellular messages. *Curr Opin Cell Biol* 2004; 16: 415-421.

[75] Fortin DL, Troyer MD, Nakamura K, Kubo S, Anthony MD, Edwards RH: Lipid rafts mediate the synaptic localization of alphasynuclein. *J Neurosci* 2004; 24:6715-6723.

[76] Fournier J-G, Escaign-Haye F, Villetmeur TBD and Robain O Ultrastructural localisation of cellular prion protein in synaptic boutons of normal hamster hippocampus. *CR Acad Sci (Paris)*, 1995; 318, 339–344.

[77] Freedman, S. D., Katz, M. H., Parker, E. M., and Gelrud, A. Endocytosis at the apical plasma membrane of pancreatic acinar cells is regulated by tyrosine kinases. *Am J Physiol* 1999; 276, C306-311.

[78] Friedrich RP, Tepper K, Rönincke R, Soom M, Westermann M, Reymann K, Kaether C, Fändrich M. Mechanism of amyloid plaque formation suggests an intracellular basis of Abeta pathogenicity. *Proc Natl Acad Sci U S A*. 2010 107(5):1942-7.

[79] Frost B, Jacks RL, Diamond MI. Propagation of tau misfolding from the outside to the inside of a cell. *J Biol Chem* 2009; 284: 12845-12852.

[80] Fujiwara, H., Hasegawa, M., Dohmae, N., Kawashima, A., Masliah, E., Goldberg, M.S., Shen, J., Takio, K., Iwatsubo, T. alpha-synuclein is phosphorylated in synucleinopathy lesions. *Nat. Cell Biol.* 2002; 4, 160–164.

[81] Giasson BI, Forman M, Capobianco R, Limido L, Hauw JJ, Haïk S, Fociani P, Bugiani O, Tagliavini, F. Tauopathy in human and experimental variant Creutzfeldt-Jakob disease. *Neurobiol. Aging*, 2008 , 29:1864-1873.

[82] Giasson BI, Forman M, Higuchi M, Golbe L, Graves C, Kotzbauer P, Trojanowski JQ, Lee V.M-Y. Initiation and synergistic fibrillization of tau and alpha synuclein. *Science* 2003; 300: 636-640.
What is the Link Between Protein Aggregation and Interneuronal Lesion Propagation in Neurodegenerative Disease?

[84] Glabe, C.G., Kayed, R., Sokolov, Y., Hall, J., 2004. Common structure and mechanism of soluble amyloid oligomer pathogenesis in degenerative diseases. Neurobiol. Aging 25, 75.

[85] Gomez-Ramos A, Diaz-Hernandez M, Cuadros R, Hernandez F, Avila, J. Extracellular tau is toxic to neuronal cells. FEBS Lett. 2006; 580: 4842–4850.

[86] Gotz J, Probst A, Spillantini MG, Schafer T, Jakes R, Burki K, Goedert M. Somatodendritic localization and hyperphosphorylation of tau protein in transgenic mice expressing the longest human brain tau isoform, Embo J. 1995; 14: 1304-1313.

[87] Gotz J, Chen F, van Dorpe J, Nitsch RM: Formation of neurofibrillary tangles in P301l tau transgenic mice induced by Abeta 1-42 fibrils. Science 2001; 293: 1601-1605.

[88] Grune T, Botzen D, Engels M, Voss P, Kaiser B, Jung T, Grimm S, Ernag G, Davies KJ. (2010) Tau protein degradation is catalyzed by the ATP/ubiquitin-independent 20S proteasome under normal cell conditions. Arch Biochem Biophys. 500(2):181-8.

[89] Grundke-Iqbal I, Iqbal K, Tung YC, Quinlan M, Wisniewski HM, Binder LI. Abnormal phosphorylation of the microtubule-associated protein tau in Alzheimer cytoskeletal pathology. Proc Natl Acad Sci USA 2106; 83: 4913- 4917.

[90] Guillontet-Bongaarts AL, Garcia-Sierra F, Reynolds MR, Horowitz PM, Fu Y, Wang T, Cahill ME, Bigio HE, Berry RW, Binder LI. Tau truncation during neurofibrillary tangle evolution in Alzheimer's disease. Neurobiol Aging 2005; 26:1015-22.

[91] Goedert M, Jakos R, Spillantini MG, Hasegawa M, Smith MJ, Crowther RA. Assembly of microtubule-associated protein tau into Alzheimer-like filaments induced by sulphated glycosaminoglycans. Nature 1996; 383: 550-553.

[92] Gonzalez-Billault C, Engelke M, Jimenez-Mateos EM, Wandosell F, Caceres A, Avila J. Participation of structural microtubule-associated proteins (MAPs) in the development of neuronal polarity. J Neurosci Res 2002; 67: 713–719.

[93] Guo JT, Arai J, Miklossy J, McGeer P. Tau and A beta forms 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: 1953-1958.

[94] Haass C, Lemere CA, Capell A, Citron M, Seubert P, Schenk D, Lannfelt L, Selkoe DJ. 1995. The Swedish mutation causes early-onset Alzheimer’s disease by ß-secretase cleavage within the secretory pathway. Nat Med 1: 1291–1296.

[95] Haïk S, Privat N, Adjou KT, Szadovitch V, Dormont D, Duyckaerts C, Hauw JJ. Alpha-synuclein-immunoreactive deposits in human and animal prion diseases. Acta Neuropathol. 2002 103(5):516-20.

[96] Hall GF. Cellular responses of identified lamprey central neurons to axonal and dendritic injury. Ann NY Acad Sci 1993; 679: 43-64.

[97] Hall GF. Neuronal Morphology: Development and maintenance of neuronal polarity. Encyclopedia of Neuroscience, ed Adelman & Smith 1999; 1409-1413.

[98] Hall GF, Poulos A, Cohen MJ. Sprouts emerging from the dendrites of axotomized lamprey central neurons have axonlike ultrastructure. J Neurosci 1989; 9: 588-599.

[99] Hall, G. F. and K. S. Kosik Axotomy-induced neurofilament phosphorylation is inhibited in situ by microinjection of PKA and PKC inhibitors into identified lamprey neurons. Neuron 1993; 10: 613-625.

[100] Hall GF, Yao J. and Lee G. Tau overexpressed in identified lamprey neurons in situ is spatially segregated by phosphorylation state, forms hyperphosphorylated, dense
aggregations and induces neurodegeneration. *Proc Nat Acad Sci USA* 1997; 94: 4733-4738.

[101] Hall GF, Yao J, Selzer M, Kosik KS. Cytoskeletal correlates to cell polarity loss following axotomy of lamprey central neurons *J Neurocytol* 1997; 26: 733-753.

[102] Hall GF, Lee S, Yao, J. Neurofibrillary degeneration can be arrested in an in vivo cellular model of human tauopathy by application of a compound which inhibits tau filament formation in vitro. *J. Mol. Neurosci* 2002; 19: 253-260.

[103] Hall GF, Chu B, Lee G, Yao J. Human tau filaments induce microtubule and synapse loss in vertebrate central neurons. *J Cell Sci* 2000; 120: 1373-1387.

[104] Hamano T, Gendron TF, Causevic E, Yen SH, Lin WL, Isidoro C, Deture M, Ko LW. Autophagic-lysosomal perturbation enhances tau aggregation in transfectants with induced wild-type tau expression. *Eur J Neurosci* 2008; 27: 1119-30.

[105] Hara T, Nakamura K, Matsui M, Yamamoto A, Nakahara Y, Suzuki-Migishima R, Yokoyama M, Mishima K, Saito I, Okano H et al.: Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice. *Nature* 2006, 441:885-889.

[106] Hasegawa M, Smith MJ. Goedert M. Tau proteins with FTDP-17 mutations have a reduced ability to promote microtubule assembly. *FEBS Lett* 1998; 437: 207-210.

[107] He HJ, Wang XS, Pan R, Wang DL, Liu MN, He RQ. The proline rich domain of tau plays a role in interactions with actin. *BMC Cell Biol* 2009; 10: 81-93.

[108] Helmke S, Pfenninger KH (1995) Growth cone enrichment and cytoskeletal association of non-receptor tyrosine kinases. *Cell Motil Cytoskeleton* 30, 194-207.

[109] Higashi S, Iseki E, Yamamoto R, Minegishi M, Hino H, Fujisawa K, Togo T, Katsuse O, Uchikado H, Furukawa Y, Kosaka K, Arai H. Concurrence of TDP-43, tau and alpha-synuclein pathology in brains of Alzheimer's disease and dementia with Lewy bodies. *Brain Res* 2007; 1254: 284-294.

[110] Ho GJ, Hashimoto M, Adame A, Izu M, Alford MF, Thal LJ, Hansen LA, Masliah E. Altered p59Fyn kinase expression accompanies disease progression in Alzheimer's disease: implications for its functional role. *Neurobiol Aging* 2005; 26:625-35.

[111] Hooper NM. Glypican-1 facilitates prion conversion in lipid rafts. 2011 *J Neurochem.* 16(5):721-5.

[112] Horowitz PM, LaPointe N, Guillozet-Bongaarts AL, Berry RW, Binder LI. N-terminal fragments of tau inhibit full-length tau polymerization in vitro. *Biochemistry* 2006; 45: 12859-12866.

[113] Hundt C et al. (2001) Identification of interaction domains of the prion protein with its 37-kDa/67-kDa laminin receptor. *EMBO J*, 20, 5876-5886.

[114] Ihara, Y. Massive somatodendritic sprouting of cortical neurons in Alzheimer's Disease. *Brain Res* 2108; 459: 138-144.

[115] Ishikura N, Clever J, Bouzamondo-Bernstein E, Samaya E, Prusiner SB, Huang E, DeArmond SJ. Notch-1 activation and dendritic atrophy in prion diseases. *PNAS*. 2005;102:886-891.

[116] Iqbal KC, Alonso A, Chen S, Chohan MO, El-Akkad E, Gong CX, Khatoon S, Li B, Liu F, Rahman A, Tanimukai H, Grundke-Iqbal I. Tau pathology in Alzheimer disease and other tauopathies. *Bioclin. Biophys. Acta.* 2005; 1739: 210-210.

[117] Ittner LM, Ke YD, Delerue F, Bi M, Gladbach A, van Eersel J, Wölfing H, Chieng BC, Christie MJ, Napier IA, Eckert A, Staufenbiel M et al. Dendritic function of tau mediates amyloid-beta toxicity in Alzheimer's disease mouse models. *Cell* 2010; 142: 387-97.
What is the Link Between Protein Aggregation and Interneuronal Lesion Propagation in Neurodegenerative Disease?

[118] Johnson GV, Cox TM, Lockhart JP, Zimmerman MD, Miller ML, Powers R. Transglutaminase activity is increased in Alzheimer's disease brain. *Brain Res* 1997; 751: 323-329.

[119] Kampers T, Friedhoff P, Biernat J, Mandelkow EM. RNA stimulates aggregation of microtubule-associated protein-tau into Alzheimer-like paired helical filaments, *FEBS Lett* 1997; 399: 344–349.

[120] Kawarabayashi T, Shoji M, Younkin L, Wen-Lang L, Dickson D, Murakami T, Matsubara E, Abe K, Ashe K. Younkin S. Dimeric amyloid beta protein rapidly accumulates in lipid rafts followed by apolipoprotein E and phosphorylated tau accumulation in the Tg2576 mouse model of Alzheimer's disease. *J. Neurosci.* 2004; 24: 3801–3809.

[121] Kazmierczak A, Strosznajder JB, Adamczyk A. 2008 A-Synuclein enhances secretion and toxicity of amyloid beta peptides in PC12 cells. *Neurochem Int.* 53(6-8):263-9.

[122] Kempf M, Clement A, Faissner A, Lee G, Brandt R. Tau binds to the distal axon early in development of polarity in a microtubule- and microfilament-dependent manner. *J Neurosci* 1996; 16:5583-5592.

[123] Kim W, Lee S, Jung C, Ahmed A, Lee G, Hall GF. Interneuronal transfer of human tau between Lamprey central neurons in situ. *J Alz Dis* 2010; 19:647-64.

[124] Kim W, Lee S, Hall GF. Secretion of human tau fragments resembling CSF-tau in Alzheimer's disease is modulated by the presence of the exon 2 insert. *FEBS Lett* 2010; 584:3085-8.

[125] King ME, Kan H, Baas PW, Erisir A, Glabe C, Bloom GS. Tau-dependent microtubule disassembly initiated by prefibrillar beta-amyloid. *J Cell Biol* 2006; 175: 541–546.

[126] Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, Yokochi M, Mizuno Y, Shimizu N. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. *Nature.* 1998 392(6676):605-8

[127] Koo EH, Sisodia SS, Archer DR, Martin LJ, Weidemann A, Beyreuther K, et al. Precursor of amyloid protein in Alzheimer disease undergoes fast anterograde axonal transport. *Proc Natl Acad Sci USA* 1990; 87:1561–5.

[128] Kordower, J., Y Chu, R Hauser, T Freeman and CW Olanow (2008) Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease *Nature Medicine* 14, 504–506.

[129] Khurana V, Elson-Schwab I, Fulga TA, Sharp KA, Loewen CA, Mulkearns E, Tyynelä J, Scherzer CR, Feany MB: Lysosomal dysfunction promotes cleavage and neurotoxicity of tau in vivo. *PLoS Genet*; 2010; 6(7):e1001026

[130] Lachenal, Gaelle (2011) Release of exosomes from differentiated neurons and its regulation by synaptic glutamatergic activity. *Molecular and Cellular Neuroscience* 46(2)

[131] Lambert MP, Barlow AK, Chromy BA, Edwards C, Freed R, Liosatos M, Morgan TE, Rozovsky I, Trommer B, Viola KL, Wals P, Zhang C, Finch CE, Krafft GA, Klein WL. Diffusible, nonfibrillar ligands derived from Abeta1-42 are potent central nervous system neurotoxins. *Proc Natl Acad Sci USA* 1998; 95: 6448–6453.

[132] LaMonte BH, Wallace KE, Holloway BA, Shelly SS, Ascano J, Tokito M, Van Winkle T, Howland DS, Holzbaur EL: Disruption of dynein/dynactin inhibits axonal transport in motor neurons causing late-onset progressive degeneration. *Neuron* 2002, 34:715-727.
[133] Lashuel, H.A., Petre, B.M., Wall, J., Simon, M., Nowak, R.J., Walz, T., Lansbury Jr., P.T., 2002. Alph-synuclein, especially the Parkinson’s disease-associated mutants, forms pore-like annular and tubular protofibrils. J. Mol. Biol. 322, 1089–1102.

[134] Lauren, J, Gimbel, DA, Nygaard HB, Gilbert JW and Strittmatter SM. Cellular prion protein mediates impairment of synaptic plasticity by amyloid-beta oligomers. Nature 2009; 457:1128-32.

[135] Lazarov O, Lee M, Peterson DA, and Sisodia, SS. Evidence that synaptically released beta-amyloid accumulates as extracellular deposits in the hippocampus of transgenic mice. J. Neurosci. 2002; 22: 9785-9793.

[136] Lebouvier T, Scales TM, Hanger DP, Geahlen RL, Lardeux B, Reynolds CH, Anderton BH, Derkinderen P. The microtubule-associated protein tau is phosphorylated by Syk. Biochim Biophys Acta 2008; 1783: 188–92

[137] Lee G, Newman ST, Gard DL, Band H, Panchamoorthy G. Tau interacts with src-family non-receptor tyrosine kinases. J. Cell Sci 1998; 111: 3167-3177.

[138] Lee G, Thangavel R, Sharma VM, Litersky JM, Bhaskar K, Fang SM. Do LH, Andreadis A, Van Hoesen G, and Ksiezak-Reding H. Phosphorylation of tau by lyn: implications for Alzheimer’s disease. J. Neurosci 2004; 24: 2304–2312.

[139] Lee HJ, Choi C, Lee SJ. Membrane-bound alpha-synuclein has a high aggregation propensity and the ability to seed the aggregation of the cytosolic form. J. Biol. Chem. 2002; 277 (1): 671–8.

[140] Lee HJ, Patel S, and Lee, SJ Intravesicular localization and exocytosis of α-synuclein and its aggregates. J. Neurosci., 2005; 25, 6016–6024.

[141] Lee S, Jung C, Lee G, and Hall GF Exonic point mutations of human tau enhance its toxicity and cause characteristic changes in neuronal morphology, tau distribution and tau phosphorylation in the lamprey cellular model of tauopathy. J. Alz. Dis., 2009; 16, 99-111.

[142] Lee S, Kim W, Li Z and Hall GF Accumulation of vesicle-associated human tau in distal dendrites drives degeneration and tau secretion in an in situ cellular tauopathy model Int J. Alz Dis 2011 accepted.

[143] Lee VM, Goedert M, Trojanowski JQ. Neurodegenerative tauopathies. Annu Rev Neurosci 2001; 24:1121-59.

[144] Linda H, Risling M, Cullheim S. ‘Dendraxons’ in regenerating motoneurons in the cat: do dendrites generate new axons after central axotomy? Brain Res 2112; 358:329–333.

[145] Lindwasser W and M Resh Multimerization of Human Immunodeficiency Virus Type 1 Gag Promotes Its Localization to Barges, Raft-Like Membrane Microdomains J.Virol, 2001; 75: 7913-7924

[146] Litman P, Barg J, Rindzoonski L, Ginzburg I. Subcellular localization of tau mRNA in differentiating neuronal cell culture: Implications for neuronal polarity. Neuron 1993; 10: 627-638.

[147] Liu, Y. and Szaro, B. hnRNP K Post-transcriptionally Co-regulates Multiple Cytoskeletal Genes Needed for Axonogenesis Development (in press)

[148] Maas, T., Eidenmuller, J., and Brandt, R. (2000) Tau’s interaction with the neural membrane cortex is regulated by phosphorylation at sites that are modified in paired helical filaments. J. Biol. Chem. 275, 15733–15740.

www.intechopen.com
[149] Mahfoud R, Garmy N, Maresca M, Yahi N, Puigserver A and J. Fantini, Identification of a common sphingolipid-binding domain in Alzheimer, prion, and HIV-1 proteins, *J. Biol. Chem.* 2002; 277: 11292–11296.

[150] Maroteaux L, Campanelli JT, Scheller RH: Synuclein: a neuronspecific protein localized to the nucleus and presynaptic nerve terminal. *J Neurosci* 2108, 8:2804-2815.

[151] McKee AC, Kowall NW, Kosik KS. Microtubular reorganization and dendritic growth response in Alzheimer's disease *Ann Neurol.* 1989; 26: 652-659.

[152] McKee AC, Cantu R, Nowinski C, et al. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. *J Neuropathol Exp Neurol* 2009; 68:709–35.

[153] Menzies F, Moreau, K. and D. Rubinsztein Protein misfolding disorders and macroautophagy *Current Opinion in Cell Biology* 2011; 23:190–197

[154] Michiorri S, Gelmetti V, Giarda E, Lombardi F, Romano F, Marongiu R, Nerini-Molteni S, Sale P, Vago R, Arena G et al.: The Parkinson-associated protein PINK1 interacts with Beclin1 and promotes autophagy. *Cell Death Differ* 2010; 17: 962-974.

[155] Minami S, Hoe H, Burns M, Matsuoka Y and G Rebeck Fyn kinase regulates phosphorylation and localization of APP and Dab1 to lipid rafts *J. Neurochem.* 2011; 125: 879–890

[156] Mocanu MM, Nissen A, Eckermann K, Khlistunova I, Biernat J, Drexler D, Petrova O, et al. The potential for beta-structure in the repeat domain of tau protein determines aggregation, synaptic decay, neuronal loss, and coassembly with endogenous Tau in inducible mouse models of tauopathy. *J Neurosci* 2008; 28: 737-748.

[157] Morfini GA, Burns M, Binder LI, Kanaan NM, LaPointe N, Bosco DA, et al. Axonal transport defects in neurodegenerative diseases. *J Neurosci* 2009; 29: 12776-86.

[158] Mori H., Kondo J., and Ihara Y. (2107). Ubiquitin is a component of paired helical filaments in Alzheimer's disease, *Science*235, 1641–1644.

[159] Morita T, Sobue K. Specification of Neuronal Polarity Regulated by Local Translation of CRMP2 and Tau via the mTOR-p70S6K Pathway *J. Biol Chem* 2009; 284: 27734–27745.

[160] Mufson EJ, Kroin JS, Sendera TJ, Sobreviela T. Distribution and retrograde transport of trophic factors in the central nervous system: functional implications for the treatment of neurodegenerative diseases. *Prog Neurobiol* 1999; 57: 451–484.

[161] Nemes Z, Devreeese B, Steinert PM, Van Beeumen J. Fusus L. Cross-linking of ubiquitin, HSP27, parkin, and alpha-synuclein by gamma-glutamyl-epsilon-lysine bonds in Alzheimer’s neurofibrillary tangles. *FASEB J.* 2004; 18:1205–7.

[162] Newell, KL, Boyer P, Gomez-Tortosa, E, Hobbs W, Hedley-Whyte, ET, Vonsattel, JP, Hyman, BT. alpha-Synuclein immunoreactivity is present in axonal swellings in neuroaxonal dystrophy and acute traumatic brain injury. *J. Neuropathol. Exp. Neurol.* 1999; 58, 1353–1358.

[163] Nickel W. Unconventional secretory routes: direct protein export across the plasma membrane of mammalian cells. *Traffic* 2005; 6: 607–614.

[164] Nixon, R. A. (2005). Endosome function and dysfunction in Alzheimer's disease and other neurodegenerative diseases. *Neurobiol Aging* 26, 373–382.

[165] Nixon RA, Wegiel J, Kumar A, Yu WH, Peterhoff C, Cataldo A, Cuervo AM. Extensive involvement of autophagy in Alzheimer disease: an immuno-electron microscopy study. *J Neuropathol Exp Neurol* 2005; 64: 120–122.
[166] Nybakken K, Perrimon N. Heparan sulfate proteoglycan modulation of developmental signaling in Drosophila Biochimica et Biophysica Acta 2002; 1573: 280–291

[167] Pan, T., S. Kondo, W. Le, J. Jankovic, The role of autophagy–lysosome pathway in neurodegeneration associated with Parkinson's disease, Brain 131 (2008) 1969–1978.

[168] Parchi P, Castellani R, Capellari S, Ghetti B, Young K, et al. Molecular basis of phenotypic variability in sporadic Creutzfeldt-Jakob disease. Annal Neurol. 1996;39:767–778.

[169] Park SY, Ferreira A. The generation of a 17 kDa neurotoxic fragment: an alternative mechanism by which tau mediates beta-amyloid-induced neurodegeneration. J Neurosci 2005; 25: 5365-5375.

[170] Patterson, K. C Remmer, Y Fu, S Brooker, N Kanaan, L Vana, S Ward, J Reyes, K Philibert, M Glucksman, and LI Binder Characterization of Prefibrillar Tau Oligomers in Vitro and in Alzheimer Disease J. Biol. Chem. 2011 286: 23063-23076.

[171] Pérez, MR, Cuadros M, Benítez J, Jiménez J. Interaction of Alzheimer's disease amyloid β peptide fragment 25-35 with tau protein, and with a tau peptide containing the microtubule binding domain J Alz Dis 2004; 6: 461-467.

[172] Perez MR, Zheng H, Lex H, Van der Ploeg T and Koo E. The b-Amyloid Precursor Protein of Alzheimer’s Disease Enhances Neuron Viability and Modulates Neuronal Polarity J. Neurosci. 1997; 17(24):9407–9414

[173] Perrin RJ, Woods WS, Clayton DF, George JM (2001) Exposure to long chain polyunsaturated fatty acids triggers rapid multimerization of synucleins. J Biol Chem 276: 41958–41962.

[174] Perry G, Kawai M, Tabaton M, Onorato M, Mulvihill P, Richey P, Morandi A, Connolly JA, Gambetti P. Neuropil threads of Alzheimer's disease show a marked alteration of the normal cytoskeleton. J Neurosci 1991; 11:1748-1755.

[175] Prusiner SB, Scott MR, DeArmond SJ and Cohen FE (1998) Prion protein biology. Cell, 93, 337–348.

[176] Rajendran L, Honsho M, Zahn TR, Keller P, Geiger KD, Verkade P, Simons K. Alzheimer's disease beta-amyloid peptides are released in association with exosomes. Proc Natl Acad Sci USA 2006; 103: 11242-11247.

[177] Rapoport M, Dawson HN, Binder LI, Vitek MP, Ferreira A. Tau is essential to beta-amyloid-induced neurotoxicity. Proc Natl Acad Sci USA 2002; 99: 6364–6369.

[178] Ravikumar B, Acevedo-Arozena A, Imarisio S, Berger Z, Vacher C, O’Kane CJ, Brown SD, Rubinsztain DC: Dynein mutations impair autophagic clearance of aggregate-prone proteins. Nat Genet 2005, 37:771-776.

[179] Reynolds CH, Garwood CJ, Wray S, Price C, Kellie S, Perera T, Zvelebil M, Yang A, Sheppard PW, Varndell IM, et al.: Phosphorylation regulates tau interactions with Src homology 3 domains of phosphatidylinositol 3-kinase, phospholipase Cgamma1, Grb2, and Src family kinases. J Biol Chem 2008, 283:18177-18186.

[180] Roberson ED, Scearce-Levie K, Palop JJ, Yan F, Cheng IH, Wu T, Gerstein H, Yu GQ, Mucke L. Reducing endogenous tau ameliorates amyloid beta-induced deficits in an Alzheimer’s disease mouse model. Science 2007; 316: 750-754.

[181] Roberts TK, Eugenin EA, Morgello S, Clements JE, Zink MC, Berman JW. PrPC, the cellular isoform of the human prion protein, is a novel biomarker of HIV-associated neurocognitive impairment and mediates neuroinflammation. Am J Pathol. 2010; 177(4):1848-60.
[182] Rock KL, Gramm C, Rothstein L, Clark K, Stein R, Dick L, Hwang D, Goldberg AL. (1994) Inhibitors of the proteasome block the degradation of most cell proteins and the generation of peptides presented on MHC class I molecules. Cell 78(5): 761-71.

[183] Rose PK, MacDermid V, Joshi M, Neuber-Hess M. Emergence of axons from distal dendrites of adult mammalian neurons following a permanent axotomy. Eur J Neurosci 2001; 13:1236-1246.

[184] Roy, S., Zhang, B, Lee, V. M.-Y. & Trojanowski, J. Q. Axonal transport defects: a common theme in neurodegenerative diseases. Acta Neuropathol. 109, 5-13 (2005).

[185] Saman S. and Hall GF (2011) Analysis of tau associated proteins in secreted exosomes - clues to tau-mediated neurodegeneration? Alzheimer's and Dementia, in press.

[186] Samsonov A, Yu JZ, Rasenick M, Popov SV. Tau interaction with microtubules in vivo. J Cell Sci 2004; 124: 6129-41

[187] Sandal M, Valle F, Tessari I, Mammi S, Bergantino E, Musiani F, Brucale M, Bubacco L, Samori B (2008). Conformational equilibria in monomeric α-synuclein at the single-molecule level. PLoS Biol. 6 (1): e6.

[188] Santuccione A, Sytnyk V, Leshchyns'ka I, Schachner M. Prion protein recruits its neuronal receptor NCAM to lipid rafts to activate p59fyn and to enhance neurite outgrowth. J Cell Biol 2005; 169: 341–354.

[189] Sarkar M, Kuret J, Lee G. Two motifs within the tau microtubule binding domain mediate its association with the hsc70 molecular chaperone. J Neurosci Res 2008; 86: 2763-73.

[190] Schindowski K, Belarbi K, Buee L. Neurotrophics factors in Alzheimer’s disease: role of axonal transport Genes, Brain and Behavior 2008; 7(Suppl. 1): 43–56.

[191] Schneider, A. et al. (2008) Flotillin-dependent clustering of the amyloid precursor protein regulates its endocytosis and amyloidogenic processing in neurons. J. Neurosci. 28, 2874–2882

[192] Shmerling, D. et al. Expression of amino-terminallytruncated PrP in the mouse leading to ataxia and specific cerebellar lesions. Cell 93, 203–214 (1998).

[193] Simons M, Keller P, De Strooper B, Beyreuther K, Dotti CG, Simons K.Cholesterol depletion inhibits the generation of beta-amyloid in hippocampal neurons. Proc Natl Acad Sci USA 1998; 95:6460-4.

[194] Singleton, RH., Zhu J, Stone JR., Povlishock JT. Traumatically induced axotomy adjacent to the soma does not result in acute neuronal death. J Neurosci 2002; 22: 791–802.

[195] Soper, J. H., Roy, S., Stieber, A., Lee, E., Wilson, R. B., Trojanowski, J. Q., Burd, C. G. and Lee, V. M.(2008). Alpha-synuclein-induced aggregation of cytoplasmic vesicles in Saccharomyces cerevisiae. Mol. Biol. Cell 19, 1093-1103.

[196] Soto C, Estrada L. Protein Misfolding and Neurodegeneration Arch Neurol. 2008 65(2):184-189

[197] Spillantini, M.G., Bird, T.D., Ghatti, B. Frontotemporal dementia and parkinsonism linked to chromosome 17: a new group of tauopathies. Brain Pathol. 1998; 8 (2): 387-402.

[198] Spillantini, M. G., Tolnay, M., Love, S. & Goedert, M. Microtubule-associated protein tau, heparan sulphate and alpha synuclein in several neurodegenerative diseases with dementia. Acta Neuropathol.1999; 97: 585-594.

[199] Stamer K, Vogel R, Thies E, Mandelkow E, Mandelkow EM. Tau blocks traffic of organelles, neurofilaments, and APP vesicles in neurons and enhances oxidative stress. J. Cell Biol 2002; 156: 1121-1063.
[200] Stokin GB, Lillo C, Falzone TL, Brusch RG, Rockenstein E, Mount SL, Raman R, Davies P, Masliah E. Williams DS, Goldstein LS. Axonopathy and transport deficits early in the pathogenesis of Alzheimer’s disease. *Science* 2005; 307: 1282–1288.

[201] Stone MC, Nguyen MM, Tao J, Allender D.L, Rolls MM. Global Up-Regulation of Microtubule Dynamics and Polarity Reversal during Regeneration of an Axon from a Dendrite. *Mol Biol Cell* 2010; 21: 767–777.

[202] Stoothoff W, Johnson GV. Tau phosphorylation: physiological and pathological consequences *Biochimica et Biophysica Acta* 2005 1739 280-297. 

[203] Su JH, Deng G, Cotman CW. Transneuronal degeneration in the spread of Alzheimer’s disease pathology: immunohistochemical evidence for the transmission of tau hyperphosphorylation. *Neurobiol Dis* 1997; 4: 365–375.

[204] Sunyach C, Jen A, Deng J, FitzGerald KT, Frobert Y, Grassi J, McCaffrey MW, Morris R. The mechanism of internalization of glycosylphosphatidylinositol-anchored prion protein. *EMBO J* 2003; 22: 3591–3601.

[205] Sverdlov, M., Shajahan, A. N., and Minshall, R. D. Tyrosine phosphorylation dependence of caveolae-mediated endocytosis. *J Cell Mol Med* 2007; 11: 1239-1340.

[206] Sverdlov RH, Khan SM. A “mitochondrial cascade hypothesis” for sporadic Alzheimer’s disease. *Med Hypotheses.* 2004; 63:8–20.

[207] Takashima A., Murayama M., Murayama O., Kohno T., Honda T., Yasutake K., et al. Presenilin 1 associates with glycogen synthase kinase-3 beta and its substrate tau. *Proc. Natl. Acad. Sci. USA* 1998; 95: 9637–9641.

[208] Taraboulos A, Scott M, Semenov A, Avrahami D, Laszlo L, Prusiner SB, Avraham D (1995) Cholesterol depletion and modification of COOH-terminal targeting sequence of the prion protein inhibit formation of the scrapie isoform. *J Cell Biol* 129:121–132.

[209] Taylor, D and N Hooper Role of lipid rafts in the processing of the pathogenic prion and Alzheimer’s amyloid-beta proteins. *Seminars in Cell & Developmental Biology* 18 (2007) 638–648.

[210] Tournaviti, S., Hannemann, S., Terjung, S., Kitzing, T. M., Stegmayer, C., Ritzerfeld, J., Walther, P., Grosse, R., Nickel, W., and Fackler, O. T. (2007). SH4-domain-induced plasma membrane dynamization promotes bleb-associated cell motility. *J Cell Sci* 120, 3820-3829.

[211] Uchida Y, Ohshima T, Sasaki Y, Suzuki H, Yanai S, Yamashita N, Nakamura F, Takei K, Ihara Y, Mikoshiba K, et al. Semaphorin3A signalling is mediated via sequential Cdk5 and GSK3beta phosphorylation of CRMP2: implication of common phosphorylating mechanism underlying axon guidance and Alzheimer’s disease. *Genes Cells* 2005; 10:165–179.

[212] Uryu K, Chen XH, Martinez D, et al. Multiple proteins implicated in neurodegenerative diseases accumulate in axons after brain trauma in humans. *Exp Neurol* 2007; 208:185–92.

[213] Uversky VN. Neuropathology, biochemistry, and biophysics of alpha-synuclein aggregation. *J. Neurochem.* 2007; 103 (1): 17–37.

[214] Uversky VN, Fink AL Amino acid determinants of alpha-synuclein aggregation: putting together pieces of the puzzle *FEBS Lett.* 2002; 522(1-3):9-13.

[215] Vella L, R Sharples, R Nisbet, R Cappai and A Hill The role of exosomes in the processing of proteins associated with neurodegenerative diseases, *Eur. Biophys. J.* 2007; 37: 323–332.
What is the Link Between Protein Aggregation and Interneuronal Lesion Propagation in Neurodegenerative Disease?

[216] Wang XF, Dong CF, Zhang J, Wan YZ, Li F, Huang YX, Han L, Shan B., Gao C, Han J, Dong XP. Human tau protein forms complex with PrP and some GSS- and fCJD-related PrP mutants possess stronger binding activities with tau in vitro. *Mol. Cell Biochem.* 2010; 310: 49-55.

[217] Waxman EA, Giasson BI: Induction of intracellular tau aggregation is promoted by α-synuclein seeds and provides novel insights into the hyperphosphorylation of tau. *J Neurosci* 2011 31(21):7604-18

[218] Webb JL, Ravikumar B, Atkins J, Skepper JN, Rubinsztein DC: Alpha-Synuclein is degraded by both autophagy and the proteasome. *J Biol Chem* 2003, 278:25009-25013.

[219] Weinreb, PH, Zhen, W, Poon, AW, Conway, KA. & Lansbury, PT. 1996 NACP, a protein implicated in Alzheimer’s disease and learning, is natively unfolded. *Biochemistry* 1996; 35, 13710-13715.

[220] Williams AL, Jahreiss S. Sarkar S. Saiki FM, Menzies B. Ravikumar B, Rubinsztein DC. Aggregate-prone proteins are cleared from the cytosol by autophagy: therapeutic implications. *Curr Top Dev Biol* 2006; 76: 89–101.

[221] Williamson R, Scales T, Clark BR, Gibb G, Reynolds CH, Kellie S, Bird IN, Varndell IM, Sheppard PW, Everall I, Anderton BH: Rapid tyrosine phosphorylation of neuronal proteins including tau and focal adhesion kinase in response to amyloid-beta peptide exposure: involvement of Src family protein kinases. *J Neurosci* 2002, 22:10-20.

[222] Wilson, D. M. & Binder, L. I. Free fatty acids stimulate the polymerization of tau and amyloid beta peptides. *Am. J. Pathol.* 1997; 161;: 2321-2335.

[223] Woodring PJ, Litwack ED, O’Leary DD, Lucero GR, Wang JY, Hunter T (2002) Modulation of the F-actin cytoskeleton by c-Abl tyrosine kinase in cell spreading and neurite extension. *J Cell Biol* 156, 879-892.

[224] Wu, B, B Decourt, M Zabidi, L Wuethrich, W Kim, Z Zhou, K MacIsaac, and D Suter Microtubule-mediated Src Tyrosine Kinase Trafficking in Neuronal Growth Cones. *Molec. Biol Cell* 2008; 19, 4611-4627.

[225] Yin S. et al. Human prion proteins with pathogenic m10utations have common conformational changes resulting in enhanced binding to glycosaminoglycans. *Proc. Natl. Acad. Sci. U. S. A.* 2007; 104: 7546–7551.

[226] Yin H, Kuret J. C-terminal truncation modulates both nucleation and extension phases of tau fibrillization. *FEBS Lett* 2006; 580: 211-215.

[227] Yonetani M, Nonaka T, Masuda M, Inukai Y, Oikawa T, Hisanaga S, Hasegawa M. 2009 Conversion of wild-type alpha-synuclein into mutant-type fibrils and its propagation in the presence of A30P mutant. *J. Biol. Chem* 284(12):7940-50.

[228] Yoshida, H., A. Watanabe, and Y. Ihara. Collapsin response mediator protein-2 is associated with neurofibrillary tangles in Alzheimer’s disease. *J Biol Chem* 1998; 273: 9761–9768.

[229] Yue Z, Wang QJ, Komatsu M. Neuronal autophagy: going the distance to the axon. *Autophagy*. 2008; 4(1):94-6.

[230] Zabrocki P, Bastaens I, Delay C, Bammens T, Ghillebert R, Pellens K, De Virgilio C, Van Leuven F, Winderickx J: Phosphorylation, lipid raft interaction and traffic of alpha-synuclein in a yeast model for Parkinsonism. *Biochim Biophys Acta* 2008, 1783:1767-1780.
[231] Zahn R. The octapeptide repeats in mammalian prion protein constitute a pH-dependent folding and aggregation site. *J Mol Biol.* 2003; 334(3): 477-88.

[232] Zehe C., Engling A., Wegehingel S., Schäfer T., and Nickel W. Cell-surface heparan sulfate proteoglycans are essential components of the unconventional export machinery of FGF-2. *Proc. Natl. Acad. Sci. U S A* 2006; 103: 15479-15484.

[233] Zhu M, Li J, Fink AL (2003). The association of alpha-synuclein with membranes affects bilayer structure, stability, and fibril formation. *J. Biol. Chem.* 278 (41): 40186–97.

[234] Zilka N, Filipcik P, Koson P, Fialova L, Skrabana R, Zilkova M, Rolkova G, Kontsekova E, Novak M. Truncated tau from sporadic Alzheimer's disease suffices to drive neurofibrillary degeneration in vivo. *FEBS Lett* 2006; 580:3582-8.

[235] Zmuda J, Rivas R. Actin disruption alters the localization of tau in the growth cones of cerebellar granule neurons *J Cell Sci* 2000; 120: 2797-2809.
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