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UNTANGLING THE ROLE OF TAU IN ALZHEIMER'S DISEASE: A UNIFYING HYPOTHESIS

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Abstract

Recent investigations into the etiology and pathogenesis of Alzheimer's disease (AD) in the past few years have expanded to include previously unexplored and/or disconnected aspects of AD and related conditions at both the cellular and systemic levels of organization. These include how AD-associated abnormalities affect the cell cycle and neuronal differentiation state and how they recruit signal transduction, membrane trafficking and protein transcytosis mechanisms to produce a neurotoxic syndrome capable of spreading itself throughout the brain. The recent expansion of AD research into intercellular and new aspects of cellular degenerative mechanisms is causing a systemic re-evaluation of AD pathogenesis, including the roles played by well-studied elements, such as the generation of Aβ and tau protein aggregates. It is also changing our view of neurodegenerative diseases as a whole. Here we propose a conceptual framework to account for some of the emerging aspects of the role of tau in AD pathogenesis.

Keywords

• Tauopathy • Secretion • Alzheimer's disease pathogenesis • Tau lesion spread • Neurodegeneration • Tauopathy models • Tauopathy hypothesis

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Abbreviations:

AD - Alzheimer's disease
FAD - familial Alzheimer's disease
LOAD - late-onset Alzheimer's disease
APP - amyloid precursor protein
NFT - neurofibrillary tangle
PHF - paired helical filaments
Aβ - beta-amyloid peptide
CTE - chronic traumatic encephalopathy
CNS - central nervous system
CSF - cerebrospinal fluid
ROS - reactive oxygen species
MT - microtubule
ECF - extracellular fluid
MTBR - microtubule binding repeat
MAP - microtubule associated protein

Introduction / historical perspective

In the quarter century that has passed since the proteins that constitute the defining lesions (senile plaques, SP, and neurofibrillary tangles, NFT) of Alzheimer's disease (AD) were first characterized in detail, we have learned immensely more about the misprocessing of these proteins (amyloid beta, Aβ, and tau, respectively) that results in their aggregation into at the cellular and molecular levels of analysis. However, key aspects of the etiology and pathogenesis of AD itself - and particularly the most prevalent late-onset form of AD (late-onset AD, or LOAD) - remain unclear. These uncertainties have if anything increased over time, with more recent studies either calling into question the relevance of both SP and NFT to the neurodegenerative process or demonstrating the potential importance of other AD-associated neurodegenerative changes (e.g. cell cycle re-entry, loss of neuronal polarity) that have little apparent relevance to Aβ and/or tau aggregation. In this review, we attempt a synthesis between these lines of investigation with previously established views of disease mechanisms in AD that offers a new perspective on the direction of neurodegenerative disease research.

For most of the 100+ years since the publication of the case report of "dementia praecox" by Alois Alzheimer in 1907 [1], AD was considered to be a rare familial condition (FAD) featuring an autosomal dominant inheritance pattern, a midlife onset followed by rapid cognitive decline and a characteristic neuropathological proliferation of cerebral SP and NFT. During this period AD was studied and its lesions characterized by investigators using traditional clinical [2,3] genetic [4-7] neurohistochemical [8,9] and ultrastructural [10] approaches, with almost nothing being known about its etiology or pathogenesis beyond some indications that AD was associated with damage to cholinergic pathways [11,12]. It was not until the mid 1980s that it became clear that most cases of senile dementia (i.e. "senility") were neurologically indistinguishable from AD, prompting a detailed molecular characterization of the main component proteins of SP (β-amyloid or Aβ) [13] and NFT (tau) [14-19], which in turn quickly focused attention on the genetics, biogenesis, function and potential neurotoxicity of these agents. This was particularly true of Aβ and its generation via the proteolytic cleavage of its parent protein (amyloid precursor protein or APP) [20]. By 1991, the demonstration of a direct link between mutations in APP and the FAD syndrome in several families [21-23] led directly to the development of the amyloid cascade hypothesis.

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The amyloid cascade hypothesis

The amyloid cascade hypothesis (first put forward by Hardy, Selkoe, Bayreuther and colleagues in the early 1990s) was the first modern attempt to define the etiology of FAD in specific terms [24,25]. It was based on several landmark studies of families with autosomally dominant AD traceable to chromosome 21. It accounted for the increased amount and/or toxicity generated by the so-called "framing" mutations in APP [21,23], and was consistent with the long known link between Down's syndrome (trisomy 21) and AD [4]. By the mid 1990s, the original genetic basis for the amyloid cascade hypothesis (i.e. that the cleavage of APP by β and γ secretases (at the N- and C-termini of Aβ, respectively was the cause of at least some forms of familial AD). A central role for Aβ generation in AD was consistent with early acetylcholine pathway associated damage [26], known genetic and environmental risk factors, including the ApoE4 allele [27,28] and head trauma [29,30]. Furthermore, the toxicity of Aβ had also been largely supported by results from both cell culture [31,32] and in a transgenic mouse model [33]. The subsequent identification of presenilins 1 and 2 (the most common source of FAD mutations overall) as an element in the γ secretase complex [34] confirmed earlier results and established the value and importance of the amyloid cascade hypothesis to understanding AD. This hypothesis was the basis for the generation of the first AD mouse model (the so-called "Athena mouse"), in which Aβ was strongly overexpressed in the CNS, resulting in the development of significant plaque pathology closely resembling that seen in AD and Down's Syndrome brain [33]. The numerous CNS plaques found in Athena mice were accompanied by changes in tau phosphorylation resembling early "pre-tangle" neurofibrillary pathology in humans; these mice also replicated some of the earliest cognitive deficiencies typically seen with human AD. While these findings appeared to be a strong validation of the Amyloid Cascade Hypothesis to many at the time, the failure of other AD features (e.g. widespread neuron loss, the development of NFT) to develop in these mice was later seen to be evidence that factors in addition to APP misprocessing and plaque formation are required to explain the full spectrum of AD-related changes.

Tau - the amyloid cascade hypothesis is incomplete

The focus on Aβ pathobiology that was the prevailing state of affairs through the mid-1990s was by no means absolute; much effort at this time was also directed at the characterization of NFT, which by this time had been shown to be somatodendritically localized, hyperphosphorylated, aggregated forms of tau - a cytoskeletal protein hitherto largely associated with axonal microtubules in the CNS [14,15,35-39]. Phosphorylation-regulated binding of tau to microtubules [40] was known to occur via the microtubule-binding region (MTBR), a set 3 or 4 conserved tandem repeat motifs in the tau C-terminal domain [41,42]. In AD, phosphorylated tau aggregates consisting primarily of the MTBR were found to make up "paired helical filaments" (PHF), the key structural component of NFT [43-45]. The best evidence for a central role of tau in AD pathogenesis was the result of a series of studies by Heiko and Eva Braak and colleagues that demonstrated a progressive sequence of neurofibrillary pathology illustrating the spread of NFT in the CNS [18]. This work established a timeline for NFT lesion progression through the CNS in AD that was tightly correlated to the initial presentation and progression of clinical symptoms [46,47]. This "Braak pattern" of NFT development begins in the limbic cortex of the temporal lobe and progresses to association (polymodal) areas of the neocortex, leaving primary sensory and motor areas unaffected until end stage disease has set in. Despite the tight correlation between tau pathology (i.e. NFT distribution) and clinical presentation of AD, interest in the role played by tau in AD pathogenesis was initially limited by 1) the failure to identify mutations in the *TAU* gene that could be directly linked to FAD and 2) the inability of tau overexpression to cause neurotoxicity in cell culture models [48]. It was not until a) the identification of both exonic and intronic tau mutations as being responsible for the familial forms of a subset of non-AD neurodegenerative syndromes [49-51] and b) the successful production of cellular [52] and transgenic [53-56] models capable of replicating pathology resembling that of tauopathies *in situ* that general interest in tau as a central agent of AD pathogenesis renewed. These studies showed that tau is itself toxic and thus may be responsible for AD-associated neurodegeneration, thus for the first time tying NFT distribution directly to AD neuropathology. Furthermore, it became clear that mutations in tau induce changes in tau associated with both NFT formation and neurodegenerative disease [54,57]. These included the failure of mutant tau isoforms to bind MT strongly [58,59] and their increased tendency to aggregate [60,61], and become hyperphosphorylated [62]. In addition, tau derived from NFT can sequester normal tau and other MAPs [28,63] hence providing a route to "loss of function" defects in neuronal function. These findings solidified the status of tau aggregates and factors leading to tau aggregate formation as players in AD pathogenesis [65-69]. However, the ability of intronic mutations to induce dominant familial tauopathy syndromes by creating an imbalance between three and four-repeat tau isoforms [70-72] also demonstrated that tau toxicity is dependent on an extremely subtle interplay between the parameters associated with MT:tau binding, tau:tau binding, and tau hyperphosphorylation.

Most evidence before 2002 suggested that tau toxicity was exclusively mediated by the tau C-terminal domain and in particular the MTBR, since this region comprises the "core" of PHF and thus is essential for NFT formation [73,74]. The importance of the MTBR was particularly emphasized by the near-exclusive localization of exonic tauopathy point mutations to the MTBR-coding regions, indicating a central role for this part of tau in the pathogenesis of non-AD tauopathies as well as in AD. However, most studies of tau MTBR function had shown a very tight correlation between aggregation propensity, phosphorylation state, and tau:MT binding affinity, making it difficult to separate the contribution of each of these factors to the cytotoxicity induced by tau aggregation.

Still, a significant interaction between the tau N-terminal projection domain and the plasma membrane and in particular src family kinases had also been identified [75] and shown to be associated to be neurofibrillary pathology in AD [76-79]. Such results served as a reminder that MTBR-mediated tau aggregation, however important, could not be considered in isolation from other *cis*-acting factors that must also be involved in tau-associated neuropathogenesis.

Hints of other links to Alzheimer's disease mechanisms

While demonstrations that mutations in the *APP* and *tau* genes cause familial AD and non-AD tauopathies (respectively) had established central roles for these proteins in tauopathy pathogenesis, a number of other possible players in AD pathobiology had also been identified by the late 1990s that have since proven important in our understanding of the roles played by both Aβ and tau in neurodegeneration. One of the most surprising of these was the appearance of epitopes hitherto associated with the cell cycle in mature neurons during the earliest stages of neurofibrillary degeneration [80-83]. Other very early (pre-fibrillar) disease-associated changes include lysosomal hypertrophy [84,85] as well as the colocalization of a variety of development-associated regulatory proteins, including GSK3β, CDK5, MARK kinases, CRMP2, and GAP43 [86-90]. Additional abnormalities associated with pre-fibrillar neurons include evidence for the reactivation of developmental programs normally associated with tau, especially those associated with axonal identity [91,92], and other aspects of axonogenesis [93-96]. Moreover, it emerged that the primary genetic and environmental risk factors for developing LOAD were (respectively) the ApoE4 allele [27], and severe or repeated head trauma [97-99]. The latter was also known to cause non AD neurofibrillary conditions such as *dementia pugilistica* [97,98], which later became associated with other contact sports and battlefield injuries as chronic traumatic encephalopathy (CTE) [99]. Finally, the ability of wild type (WT) tau species to induce degeneration in both cellular and murine transgenic *in situ* [52,53], but not in cell culture lines had not (and has not since) been satisfactorily explained. This ability appears to imply that tau toxicity is dependent on the full differentiation of certain neuronal characteristics (i.e. fully differentiated synapses and axons and dendrites) that can only be found *in situ* [48,52] or in mature primary neuronal cultures, and offers hints as to how other unexplained aspects of AD cytopathology such as cell cycle re-entry may be related to overall disease cytopathogenesis, as discussed further below. All of these findings contributed to an emerging picture of AD as a condition of complex etiology rather than one based only on misprocessing APP and/or tau.

The new point of departure - tau aggregation/phosphorylation drives toxicity in AD

The treaty is signed (ca. 2004) - tau is downstream of Aβ

During the past 10-15 years, there has been an important shift in research focus from individual aspects of AD pathogenesis toward a more integrated approach to the study of AD pathogenesis. A prime driver of this change in perspective has been a general acceptance that a) the central etiological event in AD (LOAD as well as FAD) is the generation of β-amyloid peptide from its precursor (APP), and also that b) tau misprocessing serves as the proximate cause of neurotoxicity in nearly all experimental circumstances and is thus very likely to do so in AD as well. This second point was established by demonstrations both *in situ* [55] and in primary neuronal culture [100,101] that the presence of human tau is a necessary and sufficient condition for toxicity induced by Aβ. While tau overexpression in an *in situ* cellular model had caused clear tau-specific neurodegeneration [52], murine transgenic models that expressed WT human tau at physiological levels caused only minimal somatic tau accumulation with no apparent toxicity [102,103] and mild overexpression (5x) of WT tau produced some tau aggregates in elderly mice [53], which left open the possibility (at least for for some) that tau-induced toxicity might be of limited relevance to human disease. However, Götz and coworkers showed that cerebral microinjection into WT tau-expressing mice readily induced NFT formation in the vicinity of the injection site [55]. This suggested that Aβ might be playing a role comparable to that of tauopathy mutations in the exacerbation of toxicity-associated characteristics of tau protein resulting in NFT formation. This was consistent with earlier findings that Aβ induced tau phosphorylation and MT loss in cell culture [31] in a manner similar to that of tauopathy mutations [51,61,104,105]. An essential role for tau in mediating Aβ toxicity was directly demonstrated in an experiment by Rapoport and coworkers, who used primary cortical neurons taken from a tau KO mouse [106] to show that Aβ toxicity was completely dependent on tau expression [100]. Interestingly, the tau KO mouse used in this experiment showed relatively normal CNS development combined with an upregulation of MAP1A, suggesting that the roles played by tau in neurodevelopment (discussed below) are not unique to tau; knockdown experiments directed at tau in primary hippocampal neurons in culture have had similar results [107]. The nature of Aβ-induced changes to tau includes an increase in caspase and calpain-mediated tau truncation [108-112], which causes increased aggregation of C-terminal (or MTBR)-containing tau fragments [113-116]. Since tau is inherently prone to fibrillization [116] and since the tau proteins comprising PHF and NFT appear to evolve over time from full length to truncated species containing mainly the MTBR domain [117], it seems very likely that Aβ drives NFT formation via a truncation mediated mechanism. Studies of tau aggregate development transgenic mice [118] and flies [119] offer additional support for the view that much, if not all, Aβ neurotoxicity is mediated by the presence of either mouse or human tau isoforms. Tau has thus become a bridge between the Aβ and AD-specific phenotypes with Aβ as the catalyst for a tau-centered toxicity cascade. This has both unified diverse research foci and formed the basis for the current view of AD pathogenesis [120].

The establishment of tau-induced toxicity as the proximate cause of AD cytotoxicity subsequently resulted in a general increase in

attention given to tau-associated pathological mechanisms in the field. Much of the recent evolution of our current view of tau is due to a re-examination of non-MT associated tau functions in the light of new information that has emerged concerning the nature of tau-induced toxicity. The interaction of the tau N-terminal projection domain with the plasma membrane [75] and non-receptor tyrosine kinases such as fyn and src [76] are examples of such functions. In general, non-MT-associated tau functions can be characterized as involving an alternative association of either MTBR region [94,121,122] or N-terminal domains of tau with subcortical actin [75], actin-associated proteins such as dynactin [123-125] and membrane associated proteins involved in signal transduction such as fyn and src [126]. Additional non-MT interactions of tau occur with chaperone proteins such as Pin1 [127] ChIP [128] and HSPc70 [129]. All of these interactions now appear to play some role in tau pathobiology, but their relationships to tau aggregation and NFT formation remain somewhat unclear. Most tau-related research effort is still devoted to characterizing the mechanisms responsible for the hyperphosphorylation and proteolytic cleavage of tau and the correlation of these events with both the dissociation of tau from axonal microtubules and with aggregation itself [66-69,130,131]. It is increasingly clear that all of these events are associated with "pre-tangle" formation in neurons in the early stages of degeneration, and that abnormal tau phosphorylation is tightly associated with aggregate formation and that both aggregation and hyperphosphorylation are themselves exacerbated by the dissociation of tau from MT. However, since the association of tau with MT appears to be extremely dynamic in at least some circumstances [132], it has been difficult to assign a sequence of changes that lead to disease-associated toxicity based on causality. Similarly, the dissociation of tau from MT also makes tau a better substrate for caspases/calpains and thus more likely to undergo proteolotyic cleavage into N- and C-terminal fragments, possibly accounting for the progressive proteolytic removal of N- and C-terminal epitopes during the evolution of NFT in human brain [117]. Cleavage has been shown to favor the hyperphosphorylation of AD-associated sites in the MTBR-flanking regions as well as the oligomerization/aggregation of tau, as has the presence of tauopathy mutations, all of which appear to favor MT phosphorylation. Systematic dissection of the tau C-terminal domain in cell culture, mouse transgenic and *in vitro* models by the Mandelkow group and others has elucidated the molecular nature of tau:tau interactions and identified a 100 amino acid segment encompassing the MTBR as an aggregation-prone tau species responsible for toxicity [115-117,133]. The well-established disruption of the autophagolysosome protein turnover mechanism in the early stages of AD cytopathogenesis [84,85,134-136] may be another consequence of the inability of protein turnover mechanisms to eliminate tau aggregates, leading to toxicity via the formation of reactive oxidative species (ROS). Overall, while tau aggregate formation appears to be central in the generation of tau toxicity, the specific roles of hyperphosphorylation and aggregation have yet to be clarified. In particular, the importance of whether tau is associated with MT or some alternative cellular structure has emerged as a clear point of demarcation between normal and pathological tau processing.

Current issues in our understanding of tauopathy neuropathogenesis

Despite the increasingly detailed characterization of tau aggregate formation and its association with toxicity, there remain several other aspects of tau biology whose contributions to degeneration-associated toxicity remain unresolved. The ability of tau fragments containing only the N-terminal projection domain (and lacking the MTBR) to induce downstream tau toxicity in cell culture models [101,137] suggest that alternative toxicity pathways exist for tau that do not involve the MTBR, and therefore most probably do not involve tau oligomerization. Moreover, N terminal fragment toxicity appears to account for much of the cytotoxicity of extracellularly applied Aβ in at least some experimental models [101] and act via a receptor-mediated mechanism [106,109,133,138,139]. Such findings appear to challenge tau aggregate formation as the central mechanism mediating tau toxicity at least in AD, if not in other tauopathies. Other unresolved issues surrounding tau toxicity in neurodegenerative disease include a) the degree to which the abnormal reactivation of developmental functions (e.g. cell cycle regulation, neuronal polarization), b) the mechanism of tau secretion and its relationship to neurodegenerative disease and c) the mechanism of lesion spreading in tauopathy and its role in disease pathogenesis. Other areas of active research interest include the following:

Where in the cell do tangles form, and do tangles matter?

Although it now seems clear that tau is abnormally processed in the adult CNS when it ceases to bind to MT in the "classical" manner, the actual mechanism of tau aggregation into neurofibrillary tangles and where it occurs in the cell remain unclear. While it has generally been assumed that NFT formation occurs in the cytosol, many cellularly relevant mechanisms of tau aggregate formation involve polyanionic membrane components, such as heparan sulfate proteoglycans and fatty acids. This suggests that critical steps in NFT formation might require association with membrane, and might even occur within membrane-bound vesicles, as discussed below. More fundamentally, NFT and other tau aggregates containing lesions have always been the most prominent hallmarks of tauopathy neuropathology, and their development appears to follow clinical disease progression fairly closely [18,46]. Correlative studies suggest that the presence of NFT within neurons leads eventually to MT loss from dendrites [17] neuron death and "ghost tangle" formation [16,18,140]. In the late '90s, an important study by Iqbal and coworkers showed that tau aggregates sequester non-tau MAPs in AD, which could induce cytotoxic changes via the loss of MT function [63]. All of this was consistent with the once universal view that NFT are themselves toxic to the neurons that bear them. However, more recent studies in inducible mouse tau transgenics

have suggested that tangles themselves may be relatively benign. The advent of inducible tauopathy murine models expressing toxic human tau species (e.g. P301L tau) has made it possible to separate NFT formation from pre-tangle changes. Such studies have shown that cognitive changes associated with NFT formation can be at least partially reversed by stopping tau induction after dementia onset, but that the tangles remain present [141,142]. In non-murine tauopathy models such as the fruit fly and lamprey systems, tau aggregate formation occurs, but, as with the inducible mouse models, their presence appears irrelevant to direct measures of toxicity, such as cell death [143-145]. Moreover, the hyperphosphorylation associated with tau aggregation in NFT appears (paradoxically) to have neuroprotective effects in tauopathy fly lines, apparently by making neurons less susceptible to apoptosis [146,147]. Thus, while oligomeric precursors to NFT are now the best characterized likely mediators of tau toxicity in the cytopathogenesis of tauopathies [66-69,131,148-154], it is still unclear whether and to what extent large tau aggregates such as NFT are actually involved in mediating tau toxicity in human neurodegenerative disease.

Whither the cell cycle?

Research directed at elucidating the roles played by apoptotic changes in AD suggests that cell cycle re-entry may be of central importance in the mechanism of neurodegeneration, possibly involving the reactivation of normal developmental functions of both tau and APP. The initial steps of tau misprocessing involve its disassociation from MT and its phosphorylation by a wide variety of ser/thr/tyr kinases. Many of these kinases have also been shown to play important roles in regulating mitotic activity and/or early stages of neuronal differentiation [131,155-158]. The reactivation of genes associated with cell cycle re-entry and early stages of neurodifferentiation [86-90] in the aging brain may account for the appearance of apoptotic elements during the course of neurofibrillary degeneration in AD. That said, the slow time course of NFT formation [159,160] makes it unlikely that the classic apoptotic cascade is directly responsible for neuronal death in AD. However, the activation of "executioner" caspases and the generation of reactive oxygen species (ROS) associated with mitochondrial damage are centrally involved in both apoptosis and AD-associated neurodegeneration [161-163], suggesting that cell cycle re-entry caused by Aβ/tau misprocessing in the aging CNS may cause a partial activation of the apoptotic cascade that contributes to long term neurodegeneration.

Does tau aggregate formation require the involvement of membrane and or membrane proteins?

It has generally been assumed that the formation of tau aggregates occurs directly via oligomerization to granular aggregates or "pre-tangles" in the cytosol [130,146-148] although this process has not been extensively characterized in cellular tauopathy models. However, the links between misprocessed tau and src family kinases, lipid rafts and membrane trafficking [126,145], protein oligomerization with both endosome and exosome formation [163-165] and the recent demonstration of exosome-localized tau [166] complicates our understanding of tau aggregation mechanisms. It is possible that tau oligomerization and the subsequent formation of NFT might also involve the endocytosis of membrane-associated tau that has been oligomerized either via interactions with membrane associated proteoglycans [60,167,168] or other elements [169-171]. Experimental tau aggregate formation *in vitro* can be induced by MTBR-mediated tau:tau interactions or membrane-associated elements such as fatty acids [172,173], heparan sulfate proteoglycans [122,167] and other polyanions such as mRNA [174]. Disease-associated tau interactions with the membrane have also been showed *in vivo* [168], and may involve the tau N-terminus interacting with and being phosphorylated by srk family kinases such as fyn [75-77,175]. This pathway is consistent with demonstrations by LeClerc and coworkers showing that in both tau overexpression and in AD, tau becomes localized to the Golgi despite its lack of an ER-targeting signal sequence [176,177]. Finally, there is increasing evidence that vulnerable cellular protein turnover pathways (e.g. macroautophagy) are damaged and diverted by an excess of non-MT-associated tau [175,180-182]. Proteomic analysis of a neuroblastoma exosomal-associated proteome consistent with this is presented in Figure 1. Interestingly, recent reports of vesicle-mediated tau transport [178], vesicle associated tau secretion [166,179] and the possibility that AD and other tauopathies develop by interneuronal propagation of aggregated tau species in the brain [183-185] either indicate or assume that tau-membrane interaction plays a central role in disease pathogenesis. All of these indications favor serious consideration of endocytosis-mediated mechanisms as contributors to tau oligomerization and/or the seeding and growth of NFT and other large tau aggregates, as well as to tau secretion and lesion spreading mechanisms (discussed further below).

Mechanisms of lesion spreading in tauopathy – differential vulnerability and interneuronal transfer

Interneuronal aspects of tauopathy have until very recently been considered to be prohibitively complex for a systematic analysis based on cellular mechanisms. However, there has generally been agreement that the highly stereotyped and disease-specific sequences in which specific parts of the brain become involved as the tauopathy develops can only be accounted for by a combination of two factors – differential vulnerability to tauopathy and direct interneuronal transfer of toxic factors associated with tau-induced toxicity. It has been suspected for a number of years that the first neurons to degenerate in AD and non-AD tauopathies may have specific physiologic characteristics that might make them more vulnerable to neurofibrillary degeneration than other neuron types, and that this might at least partly account for the lesion development patterns observed. An example of selective vulnerability of cortical neurons to neurofibrillary changes is the

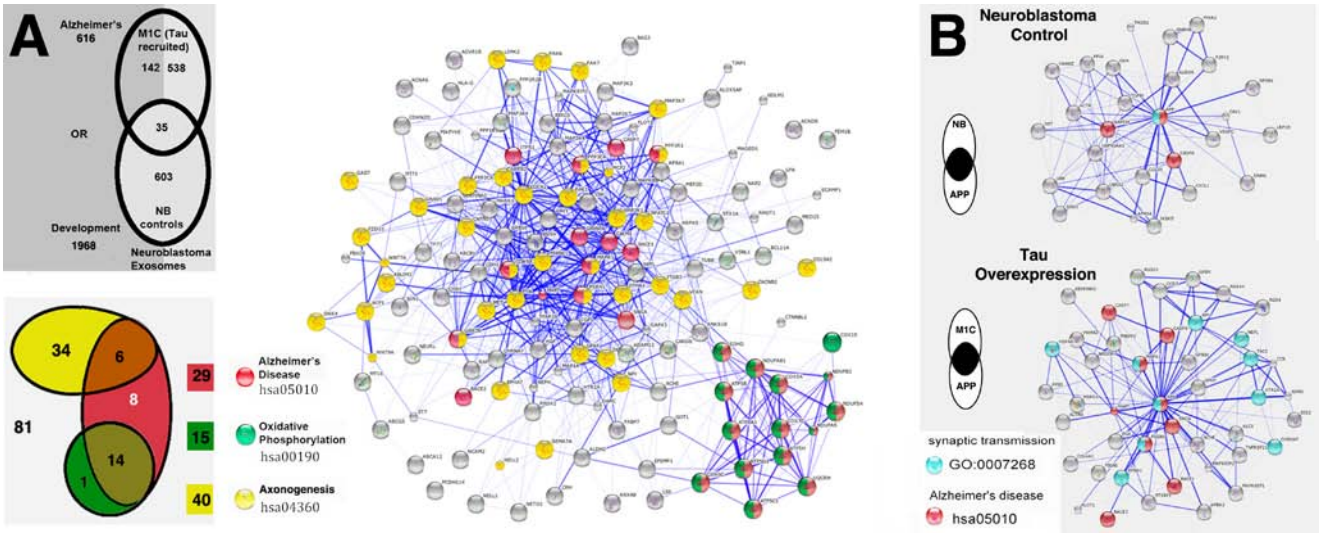

Figure 1. Proteomic analysis of exosomes in neuroblastoma cells overexpressing 4R0N tau suggests links between tau secretion, AD, autophagy abnormalities and APP misprocessing. A proteome of 669 proteins from exosome samples taken from M1C neuroblastoma cells was identified by mass spectometic analysis as described [166]. Prescreening was done using a large panel of 616 AD associated proteins [187] and 1968 general neurodevelopmental proteins based on String interactors [188] with axonogenesis and morphogenesis-associated proteins. These included tissue morphogen pathways (wnt, fzd, Ssh, Hox, Notch), growh factor pathways (EGF, FGF, NGF, PDGF, BDGF) and axonal guidance pathways (semaphorins, netrins, ephrins and slit). Panel A: summarizes the results of GO based analysis of this proteome using the online String 9.05 program [187]. Proteins present in this dataset and absent from a control neuroblastoma exosomal dataset (638 proteins) [188] produced a set of 142 proteins unique to the exosomal proteome of M1C cells induced to overexpress 4R0N tau [166]. The Venn diagram (A, bottom) summarizes the GO term characterization of this dataset using much more restrictively defined protein sets. Proteins associated with AD (hsa05010), mitochondria (oxidative phosphorylation – hsa 00190) and axonogenesis (hsa04360), showed highly significant recruitment into this proteome. Panel B: Connectivity analysis of the 142 protein dataset described in A. The strength and degree of relatedness between proteins (identified by gene name) is given by the length and thickness of the blue lines. Note that the AD signal recruited by tau overexpression recruits mitochondrial proteins normally not present in exosomes (red/green hatched proteins) suggesting the diversion of autophagosome contents into exosomes (exophagy) [181]. An entirely separate subset of AD-associated proteins (yellow/red hatch) co-localized significantly with proteins involved in axonogenesis. Panel C: Interestingly, tau overexpression results in the significant enrichment of APP-associated proteins (the top 500 APP interactors identified by String) relative to the control neuroblastoma exosomal proteome ($p < 0.01$, Fisher's Exact test). This was accompanied by a significant increase in the proportion of AD associated (red) and synapse associated (blue) proteins, suggesting that abnormal tau localization to the membrane caused by overexpression [145,179,190,191] potentiates AD-associate misprocessing of APP, possibly in a synapse-associated context.

selective decrease in dendritic spine density seen with age in temporal limbic loci [186]. These changes appear to be correlated with age-related sex hormone level decreases, which could exacerbate early synaptic damage associated with Aβ accumulation in AD [229]. Similarly, high levels of synaptic and dendritic plasticity may impart vulnerability of certain cortical brain regions to tauopathy, at least in AD, as highly plastic regions such as the hippocampus and neocortical "association" areas appears to be subject to NFT formation early in AD [18,140] while the relatively "hard wired" primary sensory and motor cortices rarely exhibit neurofibrillary degeneration until very late stages [80]. Interestingly, alterations in spine structure and other plasticity-associated changes caused by tau misprocessing [236,237] may well involve the small amount of tau that is normally localized to the postsynaptic region in dendrites, as inducible P301L (rTg4510) mice show transient increases in behavioral plasticity before the onset of P301L tau-induced neurodegeneration [238], a finding that is consistent with the reduced MT binding of P301L tau, which presumably is therefore more likely to associate with perimembranous actin cytoskeleton rather than axonal MT.

While these studies strongly suggest that selective vulnerability of specific brain loci to neurodegeneration probably contributes to tauopathy pathogenesis, a much greater amount of attention has been paid to the possibility that the lesion development pattern seen in AD and non-AD tauopathies is due to the actual physical transfer of toxic tau species from one neuron to another. This issue has been addressed in two somewhat different ways by investigators using different disease models, with some addressing the mechanisms by which tau may be secreted to and taken up from the extracellular space and others focusing on the possibility that tau (and possibly other aggregation-prone proteins involved in neurodegeneration) may act as "prions". As it is difficult to trace secreted tau in murine transgenic models, tau secretion mechanisms have been investigated and characterized at the cellular level *in situ* primarily in the lamprey cellular tauopathy model, in which tau overexpression is generated cell-autonomously, resulting in unambiguous secretion [52,143,179,190,191]. More recently, studies of tau secretion have also been pursued in cell culture as well [166,178,209,239]. It now appears that tau can be secreted from neurons in situ by multiple cellular pathways [179,192] and that the presence or absence of the MTBR is an important determinant of both the secretion

mechanism [178] and the resulting pattern of extracellular accumulation and transport [193]. In the lamprey model, tau secretion occurs before the onset of degenerative cellular changes [192,193], suggesting that extracellular tau in AD brain and CSF is very likely due to secretion rather than passive release from dead or dying neurons as has been commonly been assumed [166,194]. The propensity of tau to oligomerize may well be a factor in favoring its secretion, since the presence of tauopathy mutations also favor secretion [183,192,193] and uptake [195]. Dimeric and trimeric CSF species have also been observed in early stage AD patients [166], suggesting that oligomerization may occur with secretion. However, the role played by oligomerization in tau secretion (and thus in lesion spreading) is still unclear, since treatment of tau-overexpressing neurons with antiaggregating drugs greatly increases the efficacy of secretion *in situ* [191,196], but oligomerized tau appears to be preferentially taken up from the medium in some cell culture models [195,208]. Tau now appears to be secreted at least in part via the exosome pathway [166] as are other aggregation-prone proteins associated with neurodegenerative disease such as β-amyloid [197], α-synuclein [198] and prion protein [199]. Ongoing proteomic analysis of exosomal proteins recruited by tau into this secretion pathway in our laboratory suggests that tau misprocessing could drive secretion via a mechanism involving elements of synaptic function, APP misprocessing, and the diversion of autophagal lysosome contents into the exosomal secretion pathway (Figure 1).

Is tau a prion?

A major recent focus of interest have been the question of whether tau toxicity is propagated interneuronally via a prion-like mechanism involving a "templated" induction of specific toxic conformations in normal tau proteins in recipient neurons, and thus spreading toxicity and neurofibrillary lesions throughout the brain. While this mechanism has hitherto been considered unique to prion diseases [199-201], the Braak sequence of lesion progression in AD [18] and similar sequences for other tauopathies [18,202-206] have long hinted at trans-synaptic mechanisms of lesion spreading, and very recently evidence has accumulated in both cellular [194,207-209] and transgenic [183-185,210,211] tauopathy models that supports the existence of tau:tau interactions that result in the transformation of normal tau isoforms into toxic species. Moreover, tau lesion spreading patterns within the brains of mouse tauopathy models [184,185,211,239] and the existence of common molecular characteristics between tau, the prion protein and other aggregation prone proteins including Aβ [175,200,201] suggests that this mechanism could well be operative in human tauopathy [183,184,213]. There are also a number of parallels between transsynaptic lesion spreading patterns in tauopathy with the protein-mediated interneuronal transfer that is characteristic of prion-based disorders such as transmissible spongiform encephalopathies (e.g. Creutzfeld-Jakob disease, fatal familial insomnia), which certainly suggests that it could be relevant to human neurodegenerative disease [240]. However, it is very difficult to show that such a mechanism can (and more importantly that it *does*) account for neurodegenerative disease pathogenesis, as was evident during the protracted and highly contentious investigations that ultimately vindicated the "prion hypothesis" with respect to the pathogenesis of prion diseases. While demonstrations of tau lesion spreading in models to date have been convincing, it is important to note that such models were specially designed to enhance prion-like tau lesion propagation, and there is not yet any real evidence that tau aggregate propagation in models actually reflects the operation of similar mechanisms in human disease, or even that tau aggregates are themselves toxic (as opposed to aggregation-inducing) *in situ*. Indeed, it is quite possible that the interneuronal transfer of tau protein could induce toxicity without involving aggregation, especially since Aβ toxicity can be mediated by tau without requiring the presence of the aggregation-prone tau MTBR region. Such an "MTBR minus" propagation mechanism might involve receptor-mediated calcium dysregulation through the activation of calpains and caspases, which could in turn induce tau lesion formation in the receiving cell [108,109,138,139,213,214]. This type of mechanism would be consistent with reports that tau binds to NMDA and muscarinic acetylcholine receptors, causing changes in intracellular calcium levels [109,138,139,195,214]. It is worth noting in this context that both C and N-terminal tau fragments could possibly mediate neurofibrillary lesion spread in tauopathies via templated misfolding, oligomer-associated secretion, and/or calcium dysregulation mechanisms, respectively [213].

A unifying hypothesis of FAD and LOAD cytopathogenesis centered on tau

A central question emerging from recent investigations of tauopathy pathogenesis is how our now more detailed understanding of "conventional" mechanisms such as tau aggregation and tau phosphorylation can integrate elements such as tau secretion, cell cycle re-entry and neuronal polarity loss into a coherent unitary hypothesis. Another issue to be resolved is the mechanistic relationship that (presumably) exists between familial and sporadic AD and non-AD tauopathies. The traditional route to understanding neurodegenerative disease etiology and pathogenesis has generally been to first investigate familial, early onset variants of these conditions, whose mechanisms tend to be defined in terms of one or a few genes and then to extrapolate the mechanisms identified to sporadic variants of the disease. It the case of AD, it is now clear that the central initiating factor in FAD is an increase in the amount and/or toxicity of Aβ in vulnerable parts of the brain, and that the major proximate cause of neurodegeneration is the misprocessing of tau protein via interactions with Aβ. There is accumulating evidence that several other abnormalities (e.g. cell cycle re-entry, polarity loss, and aberrant re-activation of development programs) also play a central role in the pathogenesis of AD. Here we

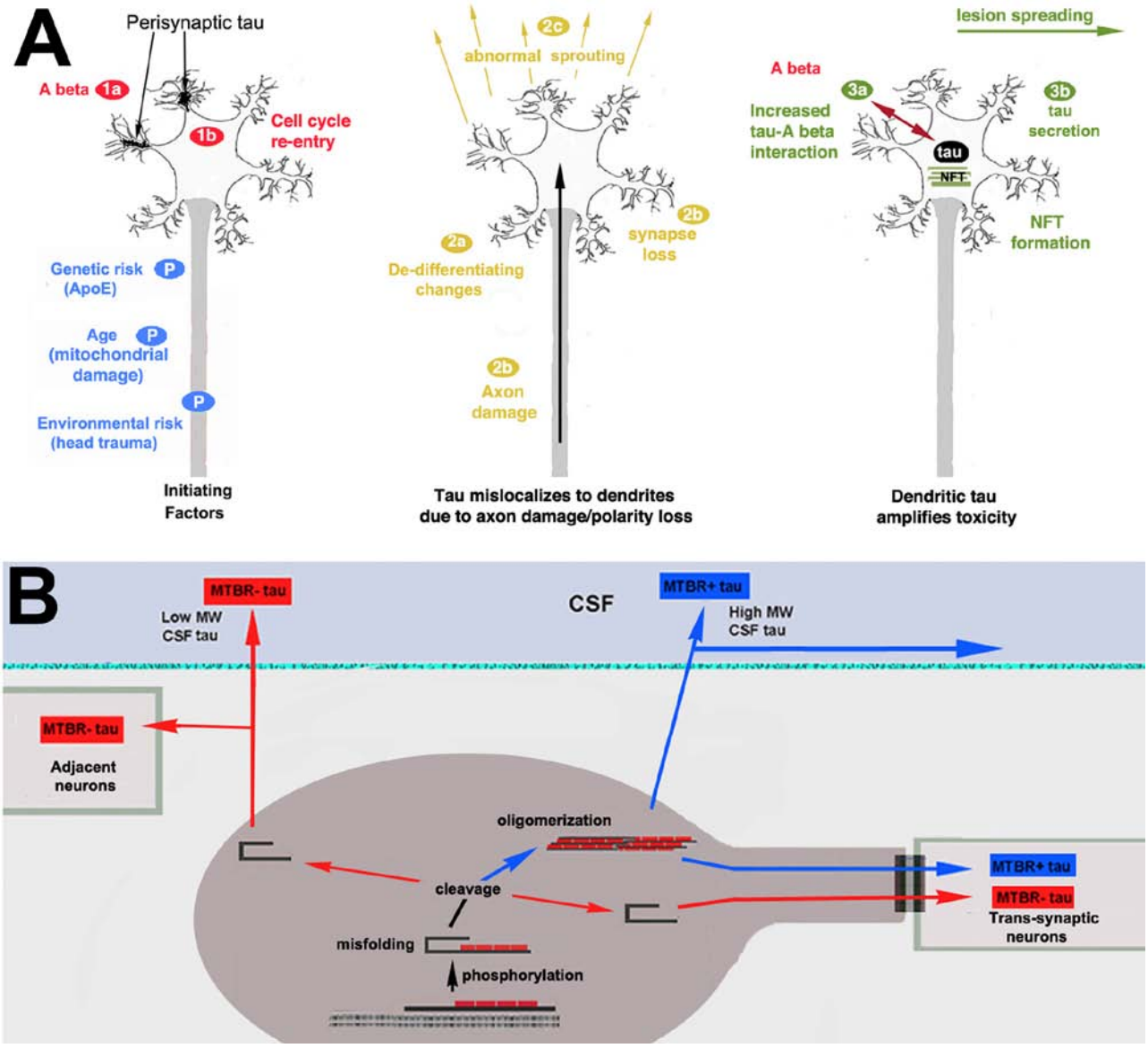

Figure 2. Hypothesized sequence of cellular events in tauopathy. We propose that tau misprocessing mediates Aβ initiated changes (AD) or directly induces (non-AD tauopathy) a cascade of toxic changes resulting in neurodegeneration via a hypothetical sequence of events as described. This sequence would account for and integrate Aβ synaptotoxicity, cell cycle re-entry mechanisms and aggregate formation in the context of both known predisposing genetic and environmental factors in LOAD and the unique distribution of tau in mature cortical neurons, where it resides primarily in the axon but also in perisynaptic zones within dendrites. Panel A: A-beta based abnormalities serve as the primary initiating factor of tau toxicity in familial AD (left). Age and genetic background-related factors (ApoE4 allele, tau haplotype) in combination with environmental predisposing factors (P) (traumatic head injury) precipitate the onset of LOAD. The initiating event (1a) involves APP misprocessing to A-beta in synapses and endosomes, occurring in the context of tau normally present in the postsynaptic density. Both of these are associated with cell cycle re-entry (1b), which sets off de-differentiation-related changes (2a) that damage that preferentially damage terminally differentiated neuronal structures such as axons, dendrites and synapses and compromise the localization of tau to the axon (2b). The failure of tau localization mechanisms that normally route most tau proteins to the axon [214, 215] prompt the reactivation of developmental programs such as the aberrant outgrowth of axon-like processes (2c). Furthermore, abnormal accumulation of phosphorylated, non-MT-associated tau in the soma results in its abnormal transport into dendrites [179], where it interacts with somatodendritic signaling pathways (3). This eventually results in amplified tau-Aβ toxic interactions (3a) and other toxicity associated events (3b) such as tau secretion and tau aggregate formation. This sequence of events is attended by the progressive accumulation of toxic tau cleavage fragments, oligomers and (possibly) prion-like misfolded tau species. Panel B: A detailed view of the cellular consequences of somatodendritic tau accumulation described in A. Somatodendritic tau misprocessing leading to toxicity, aggregate formation and interneuronal lesion propagation in tauopathy. Non-MT-associated tau becomes phosphorylated at multiples sites and vulnerable to proteolytic cleavage which generates toxic C-terminal (MTBR+) and N terminal (MTBR-) fragments. These are transferred trans-synaptically secreted to the extracellular space, the CSF and the ventricular and meningeal surfaces of the brain, where they are associated with and may mediate the interneuronal spreading of tau pathology [192,206].

present a hypothetical sequence of events (labeled 1-3 in Figure 2a) that integrates APP misprocessing, tau abnormalities, and ancillary factors in AD pathogenesis, together with mechanisms by which LOAD risk factors (P) could exacerbate this process. A summary of this hypothesis is given in Figure 2.

Predisposing risk factors to the development of LOAD

The most important risk factors for developing LOAD are (presumably) the various abnormalities introduced into vulnerable neurons by the aging process. The best established examples of age-associated neuronal dysfunction include accumulated oxidative damage to key organelles such as mitochondria [161,162] and the accumulation of misfolded/aggregated proteins that have not been cleared by normal cellular mechanisms [134]. Additional genetic factors for LOAD include ApoE allele status [27], and various gene dosage factors related to overall genetic background including the H1 haplotype [217,218] and chromosome 21 abnormalities [219,220]. Such factors include the regulation of tau splicing and the expression levels of key tau kinases (e.g. GSK3β, CDK5). These may also involve synaptic plasticity which may in turn cause downstream changes in developmental functions that appear to be affected in AD. Major environmental risk factors for LOAD include axonal damage as a consequence of cerebral injuries, typically in conjunction with repeated head trauma seen in contact sports and military action [99,221]. Axonal damage was among the first identified features of LOAD pathology [34] and subsequent studies using axotomy models established a link between the loss of overall neuronal polarity and perisomatic axonal injury [222-225]. We propose that an interplay between predisposing factors such as axon injury or reduced mitochondrial function amplify axonal changes due to tau misprocessing, neuronal de-differentiation and Aβ generation [226-230]. These factors may then initiate a cascade of events leading to plaque/tangle generation and neurodegeneration.

1 Aβ generation near dendrites disrupts synaptic function and associated signal transduction

Abnormal or excessive Aβ production in the vicinity of vulnerable neurons triggers the cascade of events leading to FAD and it is generally been assumed that these factors are exacerbated by vulnerabilities due to aging in LOAD. A large number of cellular and *in situ* studies have established that the localization and accumulation of extracellular Aβ produces multiple degenerative toxic changes resulting in localized synaptic dystrophy and loss [230-232]. Other perisynaptic effects of Aβ may include the generation of toxic tau fragments from the small proportion of neuronal tau that is normally associated with somatodendritic post-synaptic elements [233] and appears to play a role in the plasticity mechanisms characteristic to vulnerable neuronal populations, such as pyramidal neurons. The well-established dependence of Aβ-induced neurotoxicity on the presence of tau suggests that downstream neurodegenerative events appear to require the presence of a small but critical amount of somatodendritic, non-MT-associated tau [234-237], although it remains unclear whether this tau is derived from resident post-synaptic tau or abnormal accumulations of tau that would normally be targeted to the axon. This tau could serve as a primer for Aβ-induced neurotoxicity. Finally, an ongoing proteometric study in our laboratory shows that tau overexpression is associated with a significant recruitment of APP interactors and synapse associated proteins to the exosomal proteome, raising the possibility that tau abnormalities induced by Aβ might exacerbate Aβ production as well (Figure 1b).

2a Synaptic Aβ/tau interaction induces de-differentiation via cell cycle re-entry and impairs axonal function and identity

Although it is unclear how an initial Aβ-triggered insult to synaptic integrity ultimately induces NFT formation and cytodegeneration in AD, a variety of factors appear to precede and contribute to the downstream neurofibrillary changes that are ultimately associated with neuronal death. These include the appearance of apoptotic and mitotic markers in "pre-tangle" neurons [155-157] and the activation of development-associated signal transduction pathways resulting in aberrant cellular changes normally associated with development, such as neuropil thread formation [17,19,241,242]. Tau kinases such as CDK5, GSK3β and Mark1 normally play critical roles in cell cycle control, establishment of neuronal polarity and axonal outgrowth [243-246], so their roles in tau toxicity may therefore be due to aberrant activation of these same functions during the course of AD pathogenesis [147,247-249] An unusual aspect of tau toxicity is its apparent dependence on the terminally differentiated neuronal state, as shown by the relative resistance of cultured neurons to tau-induced neurodegeneration [48] when compared to *in situ* tau overexpression. These changes may be exacerbated and even prompted by glia-mediated changes affecting glutamate reuptake and inflammation-mediated changes to microglia induced by Aβ toxicity [250,251]. One intriguing possibility is that tau toxicity not induces but is also exacerbated by changes associated with cell cycle re-entry. It is tempting to suppose that the neurodegenerative changes that are typically seen in early stages of AD are in fact prompted by a "loss of the differentiated state" set in motion by cell cycle re-entry. This could be expected to cause the loss of certain aspects of the neuronal phenotype, such as synapses and neuronal polarity. Thus apoptosis, cell cycle re-entry, de-differentiation and tau mislocalization could be interrelated events consequent to the initiation of the neurodegenerative cascade in AD.

2b Axonal injury and neuronal polarity loss impairs axonal tau localization

We propose that damage to axons and axonal function by tau misprocessing causes the impairment of tau localization to axonal MT. We suggest that this might occur via a number of mechanisms, but that neuronal de-differentiation and the loss of axonal identity

leading to polarity loss is induced by abortive cell cycle re-entry events and is amplified by dysfunctional interaction of misprocessed tau with axonal MT in AD. This would be further exacerbated by known predisposing factors in LOAD, which include antecedent axonal injury caused by head trauma [225,253-257] and reduced mitochondrial efficiency and localization [257]. Damage to axonal identity could account for the failure of normal tau localization to the axon and the apparent activation of a variety of tau-associated developmental events, such as the growth of axon-like neurites (neuropil threads) [242]. The observations that neuropil threads frequently originate from dendrites [17,19,241] and the aberrant re-activation of development programs associated with neuronal polarization are consistent with a role for neuronal polarity loss in AD pathogenesis [86-90,243]. Tau kinases such as GSK3β, MARK1, PKA, and Cdk5 play central roles in cell cycle regulation and neuronal polarity and are associated with tau-induced neurodegeneration. Moreover, the activation of these kinases may account for the synergistic relationship between head trauma and AD [99], since head injuries typically are associated with axonal damage and loss as discussed above [225,253-257]. A variety of axonal injury models have shown that both axonal stretch injury and axotomy result in cytoskeletal collapse and may in turn induce a secondary proximal "virtual axotomy" that could account for subsequent somatodendritic tau accumulation. The entry of calcium into stretched or severed axons destabilizes axonal MT, thereby releasing axonal tau and exposing it to a variety of disease-associated modifications (hyperphosphorylation, proteolytic cleavage, and anomalous interactions with AD-associated signal transduction pathways). Another expected consequence of de-differentiation accompanying cell cycle re-entry is the synaptic dysfunction characteristic of non-AD tauopathies as well as AD. Synapse development is the final step in terminal neuronal differentiation, a status reflected by the complete absence of cell line models from the literature; it is investigated only in primary cultures capable of near complete differentiation as neurons [258]. While synaptic degeneration and loss of neuronal polarity are associated with APP dysfunction as well as tau and thus presumably can occur as a consequence of localized Aβ toxicity acting via tau [259], it is possible that de-differentiation might potentiate such synaptic injury and might account for it entirely in non-AD tauopathies where abnormal Aβ deposition is absent.

3a Amplified toxic interactions between Aβ and accumulating somatodendritic tau drive NFT formation

One of the best established toxic consequences of perisynaptic Aβ deposition is synaptic dysfunction and loss. This may occur as the result of excitotoxic effects of external Aβ via synaptic and perisynaptic glutamate receptors, or via endocytotic Aβ/APP uptake mediated by the activation of fyn or related src family kinases. We propose that somatodendritic tau accumulation in AD results from a number of antecedent changes that may include axonal injury, Ca^{2+} dysregulation, de-differentiation, inhibition of fast axonal transport by abnormal tau interactions with MT [260]. In FAD, this could amplify an initial toxic interaction that occurred between Aβ and post-synaptic density associated tau by increasing the amount of tau locally available for these pathways, resulting in increased NFT growth and other abnormalities associated with localized dendritic tau accumulation, including MT loss, tau secretion and progressive dendritic degeneration [179].

3bDendritic tau accumulation leads to tau secretion via multiple mechanisms

Amplified toxic interaction between Aβ and tau (directly [261] or via intermediates [262,263] very likely occurs in the endosome in the context of Aβ generation from APP and oligomer formation [175] and the exosome-mediated secretion of membrane proteins [197] and thus may account for the seeding of cellular tau aggregates as well as mediating tau lesion spread [163] especially as association of tau with cellular membranes and membrane elements favors tau oligomerization [171-173]. Both secretion and trans-synaptic tau movement have been associated with the presence of tauopathy mutations [183,192], suggesting that either the oligomerization or enhanced proteolytic cleavage of tau associated with these mutations result in the formation of more toxic N- and C-terminal fragments, which then may be secreted, possibly via multiple pathways [193]. Both types of fragment may also play a role in tau aggregate formation and lesion transfer. Murine transgenic tauopathy models expressing tauopathic exonic point mutations show somatodendritic tau accumulation and progressive toxicity, supporting the presence of Aβ-independent synaptotoxicity pathways. Moreover, proteomic analysis of the effect of tau overexpression in neuroblastoma cultures shows increased recruitment of APP and synapse-associated proteins to the proteome of exosomally secreted proteins (Figure 1a). Tau also recruits a significant number of intrinsic mitochondrial proteins to the exosomal proteome (Figure 1b), which might account for both the disruption of autophagy in AD and the presence of autophagy-associated proteins in the granulovacuolar lesions typically seen in AD neuropathology [264].

Conclusion

For the past few years, the consensus view of the role played by tau in neurodegenerative disease is that tau toxicity is induced by disease-related abnormalities that cause the release of tau from MT. It is now generally accepted that tau can disrupt neuronal function both by acquiring toxic properties associated primarily with tau hyperphosphorylation, tau:tau misfolding and oligomerization and tau cleavage and by interfering with normal neuronal functions such as macroautophagy and MT-mediated intracellular transport that may affect key neuronal properties (neuronal polarity), as outlined in Figure 2. Much tau research effort remains devoted to the investigation of mechanisms responsible for tau hyperphosphorylation, proteolytic cleavage and oligomerization/aggregation. This has recently expanded to include what appear to be similar mechanisms underlying synergistic roles played by other aggregation-

prone proteins in driving these changes in tau during neurodegeneration. The discovery of additional binding partners and cellular functions for tau in both normal and disease-associated circumstances, especially involving tau domains outside of the MTBR, has generated the current interest in mechanisms of tau secretion, tau lesion propagation and the long elusive interneuronal aspects of neurodegenerative disease.

It is now clear that tau is far more than an axon-specific MAP, as was once assumed, and that it has a multiplicity of developmental as well as homeostatic functions, not only in neurons but also in other cell types. However, its link to axonal function remains uniquely strong among aggregation-prone proteins and may have great significance to its role in tau-associated disease mechanisms. We propose that the reactivation of developmental tau functions in mature neurons combined with a failure of terminally differentiated axonal and synaptic functions that exposes non MT-associated somatodendritic tau to dendrite-specific signaling are responsible for tau neurotoxicity (via cleavage, misfolding, oligomerization other modification of tau) and in so doing, facilitates the spreading of tau lesions to other parts of the brain.

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