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Origins of Alzheimer's Disease: Reconciling CSF biomarker and neuropathology data regarding the temporal sequence of A β and tau involvement

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Abstract

Purpose of Review—To address the temporal sequencing of involvement of A β and tau in the pathogenesis of AD, and reconcile apparently conflicting neuropathologic and biomarker data.

Recent Findings—While neuropathologic studies show that limbic system tau pathology occurs ubiquitously in middle aged individuals before the appearance of amyloid plaques, biomarker studies in living subjects suggest that A β pathology is the initiating event in AD and precedes CSF tau changes. Evidence from neuropathologic, biomarker, genetic, and cellular/mouse studies shows that tau accumulation in limbic regions occurs slowly with age and does not induce widespread neurodegeneration, but that A β interacts with tau in some way to accelerate neurofibrillary pathology and induce neurodegeneration.

Summary—A β aggregation is the key initial trigger of AD pathologic changes, and interacts with tau to exacerbate age-related tauopathy and induce neurodegeneration.

Keywords

tau; amyloid; biomarkers; neurofibrillary tangle; A β

Introduction

Amyloid-beta (A β) and tau are the primary constituents of the two hallmark pathologic lesions of Alzheimer's Disease (AD), the amyloid plaque and the neurofibrillary tangle (NFT), respectively. A debate has raged for decades regarding which is the true pathogenic cause of AD. With the advent of reliable cerebrospinal fluid (CSF) and imaging biomarkers for AD, there has been an explosion of data on the antemortem biochemical and pathological changes associated with brain aging and AD. This biomarker data has illuminated a prototypical sequence of pathogenic protein changes in the CSF, with decreases in the CSF level of A β ₄₂, indicative of cerebral A β plaque deposition, as the earliest change associated with incipient AD, preceding symptom onset by up to ~15 years [1,2]. Increased CSF total and phosphorylated tau (tau and p-tau) appear later in the disease course and while preceding cognitive decline, their increase appears to occur ~3-5 years prior to the onset of cognitive decline and brain atrophy, suggesting that tau and p-tau elevation represent markers of neurodegeneration. These findings are in keeping with the “amyloid hypothesis”, which posits that A β is the primary pathogenic protein in AD which initiates a series of

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pathogenic events, including tau phosphorylation and formation of neurofibrillary tangles, ultimately resulting in neurodegeneration and dementia[3]. However, neuropathologic studies of normal aging and AD progression show that tau phosphorylation and NFTs are seen in the entorhinal cortex in many middle aged, asymptomatic individuals, and that tau pathology progresses through the limbic system and becomes ubiquitous by age 60, therefore preceding any signs of amyloid pathology in most people [4,5*]. These observations have prompted considerable debate about the origins of AD[6]. Herein we summarize evidence from human neuropathological, biomarker, and genetic studies, as well as data from cellular and mouse models, which provide an explanation of these seemingly disparate findings and support the model in which A β accumulation and aggregation serves as the initiator of AD pathogenesis, and interaction between A β and tau is critical for neurodegeneration.

CSF Biomarkers

Several cerebrospinal fluid (CSF) biomarkers of AD pathogenesis have been rigorously examined, chief among them the key pathological proteins in AD, A β and tau. CSF sampling for measurement of A β , tau, and p-tau allows for longitudinal analysis of biochemical changes in living humans throughout the course of AD. Based on CSF biomarker data from thousands of participants, a model of progression from normal aging to AD has been developed in which decreases in CSF A β_{42} occurs first, due to amyloid plaques sequestering soluble A β_{42} [7,8]. This occurs up to ~15 years prior to the onset of symptoms, while elevations in CSF tau and p-tau tend to appear near the onset of cognitive symptoms and subsequently correlate closely with markers of neurodegeneration, such as hippocampal atrophy and cortical hypometabolism[1,2,7,9*,10]. In general, CSF A β_{42} levels decline and reach their nadir years prior to the onset of cognitive changes, remaining low as clinical AD progresses. CSF tau and p-tau are generally normal in asymptomatic patients, initially even those with low A β . However, they begin to rise during the period of preclinical AD ~3-5 years prior to cognitive decline, as neurodegeneration ensues[9*,11,12]. The appearance of fibrillar amyloid plaques on PET imaging using amyloid-binding tracers (such as Pittsburgh Compound B) probably lags slightly behind CSF A β_{42} changes, but precedes CSF tau elevations and cognitive decline, and is closely correlated with diminished CSF A β_{42} and with the combination of elevated CSF tau and p-tau together with low CSF A β_{42} [7,13,14]. There was a modest age-related increase in CSF tau and p-tau levels in cognitively-normal subjects, but neither tau or p-tau levels reached the threshold to be considered abnormal in any of these individuals, while 19% reached the pathologic threshold for CSF A β [15]. Thus, the prevailing biomarker data suggests that a marked decline in A β_{42} and the appearance of amyloid plaques on imaging are the first signs of incipient AD in living humans, with subsequent (and perhaps consequent) changes in tau which coincide with neurodegeneration.

Neuropathology

Neuropathologic analysis of brains from cognitively normal individuals and patients with AD differs from the biomarker data with respect to the temporal appearance of A β and tau pathology. Braak and Braak first demonstrated that tau pathology (hyperphosphorylated tau and NFTs) was present in limbic regions of young, cognitively normal individuals, and usually preceded any amyloid pathology, and became more dense and widespread in the neocortex in dementia [4]. This landmark study defined six stages of tauopathy which progresses temporally from the medial temporal lobe to the cortex. NFTs primarily affect the entorhinal cortex early (Stages I and II), followed by hippocampal CA1 subfield (Stage II-IV), the temporal cortex by stage V, and diffuse neocortical regions in stage V-VI. Subsequently, numerous studies of cognitively normal individuals have shown that NFTs are nearly ubiquitously present in the entorhinal cortex and other limbic structures

(including hippocampal CA1) in middle age [16-19]. Tau hyperphosphorylation is seen in the EC of nearly every person older than 30, and stage I-II NFT pathology is seen in >70% of persons over 50, while stage V-VI pathology is rarely seen before age 60 and is present in only ~25% of people over 80 [4,20]. Recently, the locus coeruleus (LC) has been proposed as the earliest site of tau pathology, as 22/42 very young cognitively normal young subjects (ages 4-29) showed tau hyperphosphorylation isolated to LC, all in the absence of amyloid pathology [21]. In a second study examining several specific brain regions, 30% of cognitively normal subjects under the age of 50 showed hyperphosphorylated tau or NFTs exclusively in the LC among the regions examined, which included the entorhinal cortex [22]. Because NFTs are known to correlate closely anatomically with neuronal loss in AD [23], these observations have prompted the hypothesis that brainstem and/or EC neurofibrillary pathology represents the origins of AD [5*].

The work of Price and Morris suggests an alternative interpretation [18]. In a detailed neuropathologic evaluation of 39 patients with carefully verified cognitive status for many visits during life and documented clinical status with the Clinical Dementia Rating (CDR), they also observed ubiquitous limbic tau pathology in asymptomatic subjects (CDR 0), and found that amyloid deposits often occurred much later in life. They also noted that while tau pathology progressed very slowly in cognitively normal subjects without amyloid pathology, the severity and rate of accumulation of NFTs was markedly increased in individuals with concomitant A β pathology. They concluded that limbic tau pathology occurs slowly as a part of the aging process, but is inadequate to induce significant neurodegeneration [18,24]. However, A β accumulation, which occurs in temporally and anatomically distinct manner from tauopathy, serves to accelerate tau pathology and facilitates neurodegeneration. In keeping with this concept, studies examining neuropathologic changes in cognitively normal elderly [17] and patients with amnesic mild cognitive impairment [25] showed that every patient with NFT pathology with Braak stage >3 had concomitant amyloid plaques, while tau pathology of Braak stage III or less was almost ubiquitously seen in the absence of amyloid. Furthermore, while tau pathology is abundant in the EC and CA1 region in normal adults, there is no evidence of neuronal loss in these regions with normal aging, suggesting that age-related tau accumulation is insufficient to cause significant neurodegeneration [26,27]. However, neurodegeneration does occur prominently in both the EC and CA1 in AD patients with amyloid plaques [26,27]. Finally, the presence of “neuritic plaques”, which contain both tau and amyloid pathology, correlate more closely with neuronal loss and dementia in AD than either plaques or tangles alone [28], supporting the concept that the interaction between A β and tau is a driving force for neurodegeneration in AD.

Human Genetics

The analysis of pathology from humans with autosomal dominant mutations in the gene encoding tau (*MAPT*), or genes regulating A β production (*APP*, *PSEN1*, *PSEN2*) also provides important insights into the relative contributions of tau and A β to AD. Several families with a fronto-temporal dementia due to mutations in the *MAPT* gene have been described, all of which harbor severe NFT pathology, but few of which show major amyloid pathology [29,30]. Sparse plaques have been described in a few of these patients, particularly those with onset later in life or with an ApoE4 allele, suggesting co-existent but unrelated amyloid pathology [30]. However, many cases of dementia caused by *MAPT* mutation are accompanied by no increase in plaques [29,31]. Thus, it appears that *MAPT* mutations cause tauopathy without inducing A β pathology. Conversely, patients with autosomal dominant AD caused by mutations in *APP*, *PSEN1*, or *PSEN2*, all of which directly modulate A β ₄₂ versus A β ₄₀ production, develop severe amyloid plaque pathology as well as severe neocortical NFT pathology similar to that seen in sporadic AD, demonstrating that A β can

induce tau pathology in humans [32]. In keeping with these findings, Kauwe et al identified single nucleotide polymorphisms (SNPs) in the *MAPT* gene which are associated with higher CSF p-tau levels and early age-of-onset of AD, but only in individuals with evidence of brain A β pathology [33]. Finally, the apolipoprotein E4 allele, which is the major genetic risk factor for sporadic AD, is associated with pathogenic changes in CSF A β ₄₂ but not in tau in cognitively-normal subjects [13,34]. Thus, human genetic studies provide strong evidence that A β is upstream of tau pathology in the development of AD.

Cellular and Mouse Models

Evidence from cellular and animal models of AD also support the hypothesis that A β is the initiator of AD pathology, and that A β -tau interactions are critical to AD-related neurodegeneration. While murine A β and tau do not form plaques and tangles, numerous mouse models have been generated which express human mutant APP and develop plaque pathology, or human mutant tau which develop NFTs.

Cell culture studies employ neurons derived from these mice, or wild type cells exposed to exogenous A β . Several studies have demonstrated that application of exogenous A β to cultured neurons can induce tau pathology. Incubation of primary neuronal cultures with synthetic fibrillar A β caused tau phosphorylation and neuritic dystrophy [35], while exposure to synthetic A β oligomers also induced tau phosphorylation, tau mislocalization, dendritic spine loss, and microtubule damage [36]. In mice, injection of synthetic A β fibrils into the brain of mutant tau-expressing mice (P301L) caused a dramatic increase in NFT pathology [37]. Lewis et al generated mice expressing both human mutant tau and APP, and observed marked increases in NFT pathology in these double transgenics as compared to mutant tau mice alone, with no change in A β pathology [38]. In mice expressing mutant human tau, co-expression of mutant human APP accelerated NFT formation and exacerbated the spread of tauopathy, while introduction of mutant tau did not accelerate A β pathology, again suggesting that A β triggers tau pathology, but that tau pathology does not influence A β [39].

Furthermore, cellular and mouse studies suggest that tau may be required for some forms of A β toxicity. Rappaport et al initially demonstrated that primary neurons from tau knockout mice were resistant to neuritic degeneration induced by synthetic A β [40]. A β dimers isolated from human AD cortex also induce tau phosphorylation and neuritic pathology in cultured neurons, an effect which was exacerbated by tau overexpression and abrogated by siRNA-mediated tau knockdown [41*]. A β -mediated axonal transport deficits in cultured neurons were also alleviated by tau knockdown [42]. Roberson et al showed that behavioral deficits and early mortality observed in mice expressing mutant human APP (hAPP) were rescued if tau was genetically deleted, and that an intermediate level of protection was seen in hAPP mice with hemizygous tau deletion [43]. In these experiments, tau deletion again had no effect on A β pathology. Explorations into the mechanisms by which tau mediates A β toxicity have been limited to a few specific animal models, but have implicated the Src kinase Fyn as a potential link between A β and Tau [44,45]. These studies suggest that tau facilitates interaction between Fyn and the NMDA receptor in dendrites, and that tau deletion prevents A β -mediated synaptotoxicity, which is NMDA receptor-Fyn dependent [46]. While fascinating, it remains to be determined if this mechanism is at play in human AD. Regardless of mechanism, it is clear that cellular and animal models strongly suggest that A β is upstream of tau pathology, and that tau plays a critical role in A β toxicity.

Conclusion

Taken in total, the data presented herein suggest that tauopathy begins early in life and accumulates slowly with age, while the appearance of amyloid pathology is a punctuated event later in life which sets in motion a cascade of events leading to AD. While age-related tau pathology in the limbic system may be inadequate to cause cell death by itself, it may sensitize these regions to neurodegeneration once toxic A β species begin to accumulate, explaining the close spatial correlation between NFTs and neuronal loss in AD. Mouse studies concur with this model, suggesting that A β can directly induce tau pathology and that tau may play a critical role in A β toxicity. Accordingly, both A β and tau represent attractive therapeutic targets for the prevention of AD.

While the existing data are compelling, many important questions remain. As mentioned earlier, human pathological data shows that tau and A β pathology initially progress in a spatially independent manner [18]. While tauopathy appears first in the brainstem and medial temporal lobe, A β accumulates in cortical regions associated with the default mode network (DMN) [47]. Thus, the initial mechanisms leading to A β and tau aggregation and potentially spreading are likely unique. Evidence suggests that A β deposition occurs most readily in the DMN likely as a result of high synaptic activity [48, 49]. The molecular mechanisms governing the spatial regulation of tau propagation are unknown, but may be related to trans-synaptic spread [50-52]. The appearance of A β pathology seems to accelerate tauopathy, but this acceleration occurs in the usual pattern seen in the absence of plaques, just to a more severe degree [18].

How then can A β facilitate tauopathy if the two pathological processes are spatially separated and mechanistically unique? The answer remains elusive, but one might speculate that tauopathy occurs as a result of age along a pre-defined spatial path starting in the brainstem and medial temporal lobe. A β pathology begins in the DMN, which has considerable synaptic connectivity with the hippocampus [53], suggesting that A β might affect the medial temporal lobe via trans-synaptic mechanisms/processes [54]. This in turn could stimulate tauopathy, accelerating tangle formation and spread along its usual spatial course. Alternatively, A β might stimulate tau propagation via paracrine mechanisms, perhaps by altering metabolic processes throughout the brain, or by causing remote changes in brain redox state or inflammation [55-57]. The elucidation of the mechanisms by which A β accelerates tauopathy holds considerable therapeutic potential.

What are the substrates of age-related limbic tau accumulation, can this process be prevented, and would early prevention of limbic tauopathy prevent AD later in life? Recent evidence suggests that tau pathology may display transcellular propagation, and that tau aggregates may display “prion-like” behavior, moving from one neuron to the next and inducing tau aggregation in the recipient cell [50-52]. However, it remains to be determined if transcellular tau propagation occurs in humans, and if so, if it represents a pathogenic process. It is important to determine if A β influences transcellular tau propagation, and if so, how? Finally, does A β toxicity in human AD brain rely in part on tau, and if so, does Fyn play a role? The answers to these and related questions might inform the next generation of AD therapies.

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Key Points

1. Neurofibrillary tangles accumulate in a confined manner in limbic regions including the entorhinal cortex and hippocampal CA1 as part of normal aging.
2. A β aggregation and accumulation represents the initial pathogenic trigger of AD, and interacts with tau to exacerbate neurofibrillary pathology and induce its spread to the neocortex.
3. Decreases in CSF A β_{42} are the first hallmark of AD and precede an increase in CSF tau, which serves as a later biomarker of neurodegeneration.
4. Animal models suggest that A β induces tau pathology, and that tau is required for some aspects of A β toxicity.