Pathways linking Aβ and tau pathologies

Frank M. LaFerla

Department of Neurobiology and Behavior and Institute for Memory Impairments and Neurological Disorders, University of California Irvine, Irvine, CA 92697, U.S.A.

Abstract

Aβ (amyloid β-peptide) and tau are the main proteins that misfold and accumulate in amyloid plaques and NFTs (neurofibrillary tangles) of Alzheimer’s disease and other neurological disorders. Historically, because plaques and NFTs accumulate in diverse cellular compartments, i.e. mainly extracellularly for plaques and intracellularly for NFTs, it was long presumed that the constituent proteins formed these lesions via unrelated pathways. Animal and cell studies over the last decade, however, have provided convincing evidence to show that Aβ can facilitate the development of tau pathology by altering several cell-dependent and -independent mechanisms. In the present article, results are reviewed from several laboratories that show that modulating Aβ pathology can directly affect the development of tau pathology, which has significant implications for the treatment of Alzheimer’s disease.

Introduction

Over 35 million people throughout the world are afflicted with AD (Alzheimer’s disease), the most common cause of dementia. The disease leads to a deterioration of memory, usually manifesting with deficits in episodic memory, followed by the decay in other cognitive domains and alterations in personality and mood. Death occurs on average 6 years after the onset of symptoms, but, on occasion, some individuals live with the disease for prolonged periods, sometimes exceeding 15 years. Age is the most common risk factor, and it is estimated that one-third of the population over the age of 85 years is affected, and it is likely that a remaining proportion are in the pre-symptomatic phases. Given the present demographics, it is anticipated that the prevalence of AD will grow 2–3-fold by the middle of this century, from the current 5.3 million cases to 13–16 million cases [1].

Pathologically, AD is characterized by the accumulation of Aβ (amyloid β-peptide) deposits, which, in the post-mortem brain, are mainly evident extracellularly in the form of diffuse and neuritic plaques. Evidence over the last decade and half, however, has also identified intraneuronal Aβ as playing a key pathophysiological role, and it is likely that this form of Aβ represents an early stage in the pathogenesis. NFTs (neurofibrillary tangles) are the second major pathological hallmark of AD, which are formed by the hyperphosphorylated microtubule-binding protein tau [2].

According to the amyloid cascade hypothesis, Aβ is the trigger responsible for the initiation of sporadic and familial AD [3]. The evidence initially supporting this hypothesis was based on the effect that mutations in genes linked to familial AD had on Aβ production or aggregation [4,5]. For idiopathic cases, it is likely that a failure in protein clearance mechanisms (i.e. enzymatic, autophagic, proteosomal or immunological), as opposed to overproduction of the protein responsible, accounts for the initiation of the disease. Although the hypothesis has been modified since its initial formulation, it is almost universally accepted, and, over the last decade, there has also been corroborating evidence from transgenic animal models. In the present review, the impact that Aβ has on the development of tau pathology is considered.

Biology of Aβ and tau

The Aβ peptide, which is the primary protein component of diffuse and neuritic plaques, originates via proteolysis from APP (amyloid precursor protein). The function of the APP holoprotein is not yet established, and mice lacking the APP gene show relatively minor neurological impairments. A potential role for APP was recently described in which APP binds to DR6 (death receptor 6), triggering axonal pruning [6]. Even though APP was first identified over three decades ago, no consensus has yet been reached regarding its functional role.

Aβ has been the central focal point of AD research for over a decade, and, as indicated above, is generally considered to be the upstream causative factor. Aβ can exist in several different physical states and compartments (i.e. monomeric, oligomeric or fibrillar; intracellular or extracellular), and it is critical to note that it has not yet been established which form of Aβ is the pathogenic culprit. It is quite plausible that all forms exert some pathobiological activity, which may vary during the different stages of the disease process. This point not only is relevant for academic reasons, but also may have profound implications for treatment, as the timing of therapeutic interventions that target different processes leading to Aβ generation or the different states of Aβ will prove to be critical. If Aβ is the trigger, then it suggests that anti-Aβ
therapies will probably be successful during the earliest stages of the disease, and that these agents will lose their effectiveness in more advanced stage patients. Only costly clinical trials, however, will be able to provide a definitive answer.

NFTs accumulate in other neurodegenerative disorders besides AD, including FTDP-17 (frontotemporal dementia with parkinsonism linked to chromosome 17), Pick’s disease, progressive supranuclear palsy and corticobasal degeneration [7]. The microtubule-associated protein tau is the main component of NFTs, and, in its normal state, it is a soluble protein that promotes microtubule assembly and stabilization. Pathological forms of tau are abnormally phosphorylated at certain residues, markedly reducing their affinity for microtubules, and the large unbound pool is then available to form filamentous structures. As with Aβ, it is not yet entirely established how misfolded forms of tau cause cellular toxicity. One pathway that has received considerable attention is transport, as studies suggest that hyperphosphorylated tau impedes axonal transport by interfering with motor proteins, before NFT formation [8].

The tau gene is not genetically linked to AD, but tau mutations do cause FTDP-17 [9], thereby establishing that alterations in tau itself are sufficient to cause neurodegeneration. As for the relationship between Aβ and tau in AD, the lack of genetic association with AD is consistent with tau lying downstream of Aβ in the neurodegenerative cascade, and indicates further that tau pathology can be triggered by different mechanisms, both dependent on and independent of Aβ. This observation should not be overinterpreted to mean that tau does not play a vital role in the neurodegenerative cascade leading to AD. In fact, given the classical role that tau plays in AD, it is surprising that more therapeutic interventions against tau have not been developed, although this seems to be slowly changing.

3 × Tg-AD mice
Creating mice that develop both Aβ and tau pathologies was an essential step in the process of investigating the molecular relationship between Aβ and tau. It also offered the added advantage of evaluating the effectiveness anti-AD interventions have on both lesions.

To develop a model with both plaques and NFTs, we opted to co-microinject two independent transgenes (encoding APPsw and tauP301L, both under the control of the Thy1.2 promoter) into single-cell embryos harvested from PS1M146V-knockin mice [10]. The resulting mice harboared three mutant transgenes, only two of which (APP and tau) were overexpressed, and hence we referred to the mice as 3 × Tg-AD mice. Because of the strategy employed to generate the 3 × Tg-AD mice, the mice are on the same genetic background (thereby avoiding an important confounding variable), they breed easily and efficiently (as easily as a single transgenic mouse) and exist in both a hemizygous and homozygous genotype (allowing one to assess the effects of doubling gene expression on cognition in mice of the same genetic background).

The 3 × Tg-AD mice develop both Aβ and tau pathology, and the temporal and regional pattern mimics that observed in the human AD brain. One noteworthy observation is that, despite equivalent overexpression of the human APP and human tau transgenes, Aβ deposition develops before NFT pathology, consistent with the amyloid cascade hypothesis. After developing intraneuronal Aβ and some extracellular plaques, conformational changes in tau, as is evident by MC1 immunostaining or immunoreactivity with phospho-specific tau markers, become apparent. There is a hierarchical pattern to the tau staining, with AT100 and MC1 immunostaining appearing to be the earliest tau-related changes, followed by phospho-specific markers such as AT8 and AT180, and then lastly PHF-1 immunoreactivity [10]. These results are consistent with a conformational change in tau representing an early stage in the progression of the pathology.

Evidence linking Aβ and tau pathology
If Aβ is the trigger for AD, it thus follows that the development of tau pathology, as well as the other degenerative changes in the brain, are a downstream consequence of the Aβ pathology. This does not mean that tau is irrelevant, particularly from a therapeutic viewpoint. In fact, it may be advantageous or even necessary to development therapies that mitigate the effects or preclude the formation of tau pathology. Along these lines, combination therapies may be required in the arsenal to treat AD.

There were three critical studies carried out in transgenic mice that were suggestive of a modulatory link between Aβ and tau. The first two were published concomitantly with Hutton and colleagues crossing mutant APP and mutant tau mice and showing that the newly formed double transgenic mice developed enhanced neurofibrillary pathology compared with single mutant tau mice [11]. The second study was published by Gotz et al. [12] and showed that administrating Aβ intracranially into mutant tau mice caused NFTs to form within the amygdala.

The third critical paper to support a modulatory link between Aβ and tau derived from my laboratory with the 3 × Tg-AD mice [13]. Rather than increasing the pathology by augmenting Aβ levels, clearing Aβ by passive immunotherapy caused a diminution in the pre-existing tau pathology. Temporal studies showed that the reduction in both Aβ and tau levels was hierarchical, as extracellular Aβ levels were reduced, followed by clearance of intraneuronal Aβ, and subsequently by the clearance of intracellular phospho-tau. Moreover, detailed pathological and biochemical analysis showed that, after the antibody dissipates, the Aβ pathology re-emerges before the tau pathology.

A critical finding with relevance to treating AD was the observation that the anti-Aβ antibody treatment was only effective at clearing early phospho-tau species and not hyperphosphorylated and silver-positive tau lesions. These findings are consistent with the existence of two different stages of tau pathology: an early stage, where tau accumulates in the somatodendritic compartment, is not stainable with
the Gallyas silver impregnation method in which tau can be cleared with anti-Aβ intervention, and a late stage in which tau is stained using the Gallyas method, but cannot be cleared by anti-Aβ interventions. Our studies also implicate the proteasome as a major factor in the clearance of the early tau lesions [13]. Follow-up studies also showed that oligomeric forms of Aβ were potent blockers of the proteasome, and are thus likely to be an early event in the pathogenesis of AD that could lead to the development of tau pathology [14].

Further genetic studies from our laboratory provided additional evidence that Aβ may trigger or facilitate the accumulation of tau pathology. For instance, we also developed double transgenic mice [mutant PS1 (presenilin 1)/mutant tau] that are on the same genetic background as the 3 × Tg-AD mice, but do not overexpress the human APP transgene, and consequently do not develop any Aβ pathology [15]. The steady-state levels of the tau gene are 6-fold greater than the endogenous mouse gene, mirroring the expression level of the 3 × Tg-AD mice. However, the mutant PS1/tau mice develop less severe tau pathology with a later onset compared with the 3 × Tg-AD mice, indicating that Aβ can modulate the onset and progression of tau pathology. The sum of a large body of work from the laboratory shows that there are a variety of cell-dependent and -independent pathways by which Aβ triggers the formation of tau pathology (Figure 1). For example, inflammation triggered by the accumulation of extracellular Aβ deposits alters the cytokine profile in the brain, creating an environment that is favourable to the formation of tau pathology [16]. Interestingly, work from our group suggests that different forms of Aβ may be responsible for inducing tau in different settings. Extracellular Aβ plays a role in the inflammation-mediated induction of tau, but oligomeric Aβ intraneuronally also appears to be critical for altering levels of CHIP [C-terminus of Hsc70 (heat-shock cognate 70)-interacting protein] and for inducing tau as well. Further work will be needed to elucidate the key molecular players that are responsible for the Aβ-mediated induction of tau.

**Funding**

This work was supported by the National Institutes of Health [grant numbers AG-027544, AG-021982 and AG16573].

**References**


Received 26 January 2010
doi:10.1042/BSTO380993