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Alzheimer disease
A tale of two prions

Justin M. Nussbaum,[1,2,†] Matthew E. Seward[1,2] and George S. Bloom[1,2,*]

[1]Department of Biology; University of Virginia; Charlottesville, VA USA; [2]Department of Cell Biology; University of Virginia; Charlottesville, VA USA;

[†]Current affiliation: Department of Stem Cell Biology and Regenerative Medicine; Lerner Research Institute; Cleveland Clinic; Cleveland, OH USA

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Abbreviations: Aβ, amyloid-β; AD, Alzheimer disease; CSF, cerebrospinal fluid; EC, entorhinal cortex; KO, knockout; MAP, microtubule-associated protein; MT, microtubule; pE, pyroglutamate or pyroglutamylated; PHF, paired helical filament; WT, wild type

Alzheimer disease (AD) has traditionally been thought to involve the misfolding and aggregation of two different factors that contribute in parallel to pathogenesis: amyloid-β (Aβ) peptides, which represent proteolytic fragments of the transmembrane amyloid precursor protein, and tau, which normally functions as a neuronally enriched, microtubule-associated protein that predominantly accumulates in axons. Recent evidence has challenged this model, however, by revealing numerous functional interactions between Aβ and tau in the context of pathogenic mechanisms for AD. Moreover, the propagation of toxic, misfolded Aβ and tau bears a striking resemblance to the propagation of toxic, misfolded forms of the canonical prion protein, PrP, and misfolded Aβ has been shown to induce tau misfolding in vitro through direct, intermolecular interaction. In this review we discuss evidence for the prion-like properties of both Aβ and tau individually, as well as the intriguing possibility that misfolded Aβ acts as a template for tau misfolding in vivo.

Introduction

Alzheimer disease (AD) is a slowly progressing neurodegenerative disorder characterized by the misfolding, aggregation and gain of toxicity of amyloid-β (Aβ) and tau in the brain.[1,2] Aggregated Aβ, in the form of densely packed fibrils, accumulates extracellularly in structures known as amyloid plaques. The tau aggregates also correspond to tightly packed filaments, but in contrast to plaques, they accumulate intracellularly in diseased neurons, where they are known as neurofibrillary tangles (NFTs). The term paired helical filament, or PHF, is often used to describe the individual tau filaments found in NFTs.

Aβ comprises a family of ~40 amino acid long peptide cleavage products of the transmembrane amyloid precursor protein and has no known essential function in normal physiology, but has long been regarded as a primary cause of AD.[3,4] The original focus on large, fibrillar Aβ aggregates as possible causative agents for the memory and cognitive decline associated with AD has gradually shifted over the past decade to the realization that smaller, soluble Aβ oligomers are more relevant culprits. Compared with fibrillar Aβ, soluble Aβ oligomers correlate better with neurotoxicity in vivo and are far more toxic than Aβ fibrils to cultured neurons.[5-12]

Tau was discovered nearly 40 years ago as a microtubule-associated protein (MAP) that stimulates tubulin polymerization,[13] but it was not until a decade later that its presence in NFTs was first described.[14-16] Surprisingly, beyond its generic MAP function as a stimulator of microtubule (MT) assembly, the only known specific function of tau is that it impedes the movement of kinesin MT motor proteins and their attached cargoes along MTs.[17-20] Historically, tau has received much less attention than Aβ in the AD field, despite the fact that a spectrum of neurodegenerative disorders known collectively as non-Alzheimer tauopathies are invariably characterized by PHF accumulation in the brain and can be caused by any of dozens of tau mutations.[21] PHF tau is abnormally phosphorylated at dozens of sites,[22] some of which appear in vivo in both human AD cases and transgenic mice before the tau assembles into filaments.[23]

About three decades after Prusiner first described prion driven infection in Creutzfeldt-Jacob disease[24] and speculated that a similar infectious process may apply to AD,[25] a recent wave of evidence has demonstrated striking biochemical and cell biological similarities between AD and classical prion diseases. In contrast to PrP-based disorders, such as mad cow disease, scrapie and kuru, AD does not appear to be communicable between individuals, but a growing body of data indicate that misfolded, toxic oligomers of Aβ and tau spread through the brain from neuron to nearby neuron much much like misfolded PrP.[25-32] For both Aβ[8,33] and tau,[34-38] moreover, misfolded forms of the peptide or protein can be taken up by neurons containing otherwise normal Aβ or tau, which as a result then misfold, become toxic and spread to other neurons.

In addition to in vivo histopathology evidence,[33,35,36,38] several groups recently demonstrated biochemical mechanisms for prion-like propagation of Aβ and tau,[9,39-42] and of additional

*Correspondence to: George S. Bloom; Email: gsb4g@virginia.edu
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proteins whose misfolding into β-sheet-rich structures underlies other well-known neurodegenerative diseases.[26-28,30,32] Most intriguing in this regard is evidence for Aβ-tau interactions, both physically[43,44] and in cell signaling.[5,9,11,39,45-52] AD can thus be regarded as a disease that requires prion-like behavior of two distinct proteins.

Aβ and Tau Spread Stereotypically Through the Brain

One line of evidence suggesting prion-like mechanisms in AD comes from histological studies showing that aggregated forms of both Aβ and tau spread through the brain by following typecast neuroanatomical patterns. Perceptions about the exact details of these patterns have evolved somewhat over the years, but plaques and tangles do not follow identical blueprints for dispersing through the brain. Plaques first appear in the basal temporal neocortex, then advance to the entorhinal and hippocampal regions before finally spreading throughout the neocortx.[53] This progression might be explained by the movement of Aβ through anterograde transport and synaptic exchange mechanisms from regions where Aβ aggregation is initiated into nearby areas receiving axonal input from contaminated regions. Consistent with this hypothesis is the recent demonstration that cultured neurons can accomplish direct cell-to-cell transfer of Aβ oligomers.[8] This intercellular transfer mechanism, in combination with ongoing production of new Aβ monomers and the fragmentation of fibrils and large oligomers into smaller but more numerous seeds that can initiate Aβ aggregation, could fuel the growth of more Aβ oligomers and fibrils.

In contrast to plaques, abnormal tau first appears in proximal axons within the locus coeruleus,[54] when it becomes immunoreactive with the AT8 monoclonal antibody, which detects tau phosphorylated at S202 and T205.[23] Evidently, tau at this stage has not yet assembled into PHFs, but instead is in a soluble, pre-NFT state. As AD progresses from pre-symptomatic to clinically detectable stages, the pattern of AT8-positive tau expands first to distal axonal and somatodendritic compartments within affected locus coeruleus neurons, and then sequentially to the entorhinal cortex (EC), dentate gyrus, CA1 region of the hippocampus and the neocortex. Superimposed on this spreading of abnormal tau is its gradual acquisition of additional phosphoepitopes that are diagnostic of diseased neurons, and its conversion into PHFs.[34] Interestingly, despite compelling evidence that Aβ is upstream of tau in AD pathogenesis,[5,9,11,39,45-52] abnormal, pre-NFT tau is usually detectable before plaques.[55,56] This may symbolize that soluble, oligomeric Aβ, rather than plaques, provoke tau pathology, and that the pattern of plaque spreading simply reflects net rates of insoluble Aβ accumulation within various regions of brain over time.

Two groups, using very similar approaches, recently published compelling experimental evidence that the spatiotemporal spread of tau in AD brain also involves transfer of tau from neuron to neuron along defined synaptic circuits.[36,38] Both groups targeted expression of a human tau transgene specifically in the EC of mice. In both cases, the transgene encoded tau with a P301L mutation that adopts an AD-like phosphorylation profile, forms PHFs and causes the non-Alzheimer tauopathy, FTDP-17, with full penetrance in humans.[57,58] As the mice aged, they showed progressive tau pathology that began in the EC and subsequently followed the same path of axonal circuitry into the hippocampus as seen in human AD. Notably, this occurred without any detectable expression of human tau mRNA or protein outside of the EC. In other words, the toxic, mutant human tau that was expressed exclusively in the EC caused the endogenous mouse tau to misfold and become toxic, and then spread along synaptic circuits to the hippocampus. Besides confirming that tau pathology spreads along pre-determined, interconnected, neuroanatomical tracks, these data imply a prion-like process whereby misfolded "bad" tau can provoke the toxic misfolding of "good" tau. One important issue that remains to be determined is the mode of neuron-to-neuron transmission of misfolded tau. For example, the available data do not discriminate among models in which toxic tau is transferred from diseased to healthy neurons at synapses, via cycles of exocytosis and endocytosis, via intercellular bridges or by some combination of these or other potential mechanisms that can be imagined.

Aβ as a Prion

While progression of Aβ aggregation in human AD brain has fueled speculation of prionlike mechanisms of misfolding, recent in vivo and in vitro data have provided direct evidence for prion activity of Aβ, and have suggested specific biochemical and biophysical mechanisms to explain Aβ pathology. The strongest in vivo evidence comes from a large body of work demonstrating that injection of misfolded Aβ from either biological or synthetic sources at specific loci in the brains of AD model mice accelerates the appearance of aggregated, transgenically expressed Aβ throughout the brain.[42,59-62] While these seed-induced Aβ deposits are initially observed in tissue directly surrounding sites of seeding, spreading eventually occurs along axonally connected regions and in separate locations, suggesting that both axonal transport and extracellular routes play a role in the spreading of Aβ throughout the brain.

Building on this substantial body of in vivo data are several lines of in vitro biochemical and biophysical investigation that have provided direct evidence for specific mechanisms in the propagation of Aβ misfolding. Researchers throughout the AD field have long noted anecdotally that purified Aβ often seems to behave in unpredictable ways that suggest an aggregation mechanism capable of following multiple paths. These suspicions were recently confirmed when aliquots of monomeric Aβ from a single pool were aggregated separately, leading to formation of many structurally and immunologically distinct, aliquot-specific Aβ oligomers.[63] These experiments also demonstrated that exposing specific preformed Aβ oligomer species to monomeric Aβ promotes the aggregation of monomers into oligomeric species of the same size range and immunoreactivity. A straightforward interpretation of these data suggests a model in which the specific folding patterns of oligomers formed early in the aggregation process self-propagate by increasing

the probability of similar folding patterns occurring in newly formed oligomers.

While numerous studies of Aβ have relied on the use of oligomers made from synthetic versions of the conventional peptides, Aβ1-40 and Aβ1-42, Aβ isolated from biological samples, especially from AD brain, typically show much stronger bioactivity across a wide range of assays.[47,64-66] This may be due, at least in part, to biologically produced Aβ comprising a rich variety of peptide species, including Aβ1-40 and Aβ1-42, that are distinguished from each other by their bioactivities and potency, N-terminal truncations, C-terminal truncations or extensions, and post-translational modifications of amino acids within the peptide backbone. Indeed, a recent study of the Aβ peptides present in cerebrospinal fluid (CSF) samples revealed more than 20 molecularly distinct peptide species.[67] As described in the next paragraph, at least one naturally occurring variant of Aβ is both exceptionally toxic and prion-like. It is therefore possible that low abundance, highly potent, infectious forms of Aβ isolated from brain tissue or cell cultures can explain the enhanced potency of biologically produced, vs. synthetic Aβ.

We recently described a specific, prion-like mechanism of "intermolecular infectivity" involving Aβ3(pE)-42,[9] which lacks the first two amino acids found in Aβ1-40 and Aβ1-42, and whose initial residue is enzymatically modified from glutamate to pyroglutamylate (pE) by glutaminyl cyclase.[68] We found that Aβ3(pE)-42 can induce Aβ1-42 to form low-*n* oligomers that are ~10-fold more cytotoxic to neurons than otherwise comparable oligomers made from Aβ1-42, alone.

Formation of the cytotoxic oligomers typically involved co-incubation of synthetic Aβ3(pE)-42 with a 19-fold molar excess of synthetic Aβ1-42 for 24 h before dilution into primary neuron cultures. Remarkably, if the two peptides were incubated separately for 24 h and then were mixed together at a 1:19 molar ratio of Aβ3(pE)-42 relative to Aβ1-42, the mixtures had negligible cytotoxicity, like that associated with oligomers made from Aβ1-42 alone. Furthermore, cytotoxic mixed oligomers could be serially diluted into freshly dissolved Aβ1-42 monomers with only slight loss of cytotoxicity after each passage. Even after the Aβ3(pE)-42 concentration was serially passaged three times to drop its level from 5% to 0.000625% of the total Aβ present, the final product was nearly 2/3 as cytotoxic as the starting material containing 5% Aβ3(pE)-42. The cytotoxic oligomers, which appeared to be predominantly dimers and trimers, were immunologically distinct from comparably sized oligomers made exclusively from Aβ1–42. These data signify template mediated protein-misfolding by a process in which the original template, Aβ3(pE)-42, can transfer its distinct conformation and cytotoxic properties to Aβ1-42, which then can act as a template itself to induce further, prion-like propagation of toxic Aβ oligomers.[9]

The in vivo relevance of these results was established by multiple lines of additional evidence. Most notably, putative dimers and trimers containing both conventional and pE-modified Aβ species were detected more commonly in brain cytosol collected post-mortem from AD patients than from normal age-matched controls, and transgenic mice that produced Aβ3(pE)-x experienced massive gliosis and neuron death in the hippocampus by three months of age. Strikingly, the Aβ3(pE)-x levels in these mice were just a few percent of what is commonly found in human AD brain, and neither gliosis nor neuron loss occurred in otherwise identical mice that lacked functional tau genes. The phenotype of the pE-Aβ-producing, tau knockout (KO) mice mimicked the response of primary neurons obtained from tau KO, but otherwise normal mice to cytotoxic oligomers of 5% Aβ3(pE)-42 plus 95% Aβ1–42. Unlike wild type (WT) neurons, the tau KO neurons were not killed by the mixed oligomers.[9] These collective in vitro and in vivo results emphasize the exceptional potency of pE-modified Aβ and the tau requirement for its cytotoxicity.

Tau as a Prion

Several lines of evidence have recently demonstrated the ability of filamentous tau polymers to propagate by a nucleated assembly mechanism. Monomeric tau is a soluble, natively unfolded protein[69] that does not readily form filaments in vitro unless induced to misfold and polymerize by strongly anionic agents, such as arachidonic acid,[70] heparin[71] or RNA.[72] Small oligomers, especially tau dimers, are intermediates in the filament assembly process.[44,73] Once filament polymerization has occurred, sonication can fracture the filaments into shorter, more numerous structures that can seed the assembly of additional tau monomers.[74] Tau filaments therefore have the ability to self-propagate.

Pre-aggregated tau, comprising filaments and apparent oligomers, is able to enter cultured cells and then cause the intracellular tau that they express to misfold and aggregate as well.[75,76] This general principle has also been demonstrated in vivo through experiments showing that intracerebral injection of aggregation-prone P301S mutant tau can induce the spreading of NFT formation throughout the cortex of mice expressing wild-type human tau, which does not form NFTs spontaneously.[35] Given the small amount of initially injected material in these experiments, the data indicate that WT human tau was able to adopt at least some critical properties of the aggregated, mutant human tau to continue propagation throughout the brain. The aforementioned studies of P301L tau being expressed exclusively in the EC of transgenic mice, but driving tau pathology into hippocampal structures[36,38] constitute further evidence for prion-like behavior of misfolded tau.

The possibility that tau oligomers serve as agents for the spread of tau pathology must be seriously considered as well. Such oligomers have been detected immunologically in AD brain, most notably in neurons that had not yet accumulated NFTs.[73,77] Furthermore, intracerebral injection of tau oligomers, but neither monomeric nor fibrillar tau, has been shown to be neurotoxic, to cause synaptic and mitochondrial dysfunction, and to impair memory.[78]

Are Tau Prions Seeded by Aβ Prions?

Several groups have described adverse Aβ effects that depend on tau, thereby placing Aβ upstream of tau in AD pathogenesis and establishing tau as an essential protein in development of the

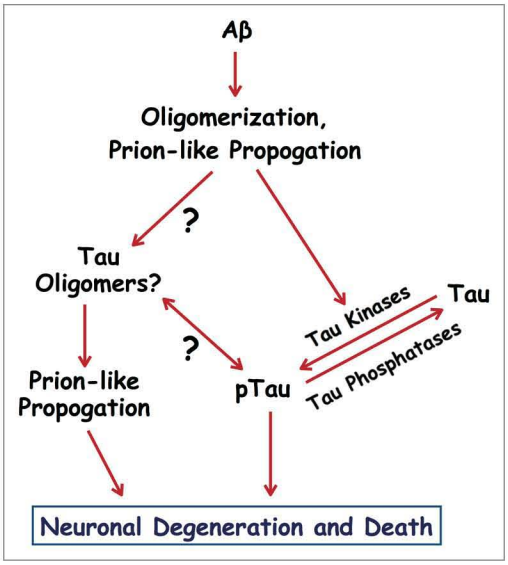

Figure 1. Prion-like mechanisms in Alzheimer disease. Amyloid-β (Aβ) peptides can form toxic oligomers that are able to propogate by a prion-like mechanism of template-mediated protein misfolding. Aβ oligomers can activate tau kinases, which then catalyze pathogenic phosphorylation of tau (pTau), and may also serve as prion-like seeds that induce tau to oligomerize. Tau oligomers also self-propogate by a prion-like mechanism, and along with pathogenically phosphorylated tau, drive the degeneration and death of neurons involved in memory and cognition. The temporal and functional relationships between pathogenic phosphorylation and oligomerization of tau remain to be determined.

disease.[5,9,11,46,48-50,79,80] At least some of these Aβ-tau connections are indirect, such as Aβ induced activation of protein kinases, which then catalyze abnormal tau phosphorylation.[11,45,47,51,52] There is also evidence, though, for a direct pathogenic connection between Aβ and tau. In the absence of any other proteins or peptides, Aβ can bind to tau[43] and tau monomers can be induced to oligomerize in vitro after exposure to low substoichiometric levels of Aβ oligomers.[44] These findings raise the obvious possibility that, in vivo, Aβ oligomers seed the initial formation of tau oligomers, which can then self-propagate in the absence of additional input from Aβ (**Fig. 1**). If such a phenomenon were to occur in vivo, it would represent a seminal step in AD pathogenesis. It might explain, moreover, why so many heroic efforts to target Aβ therapeutically in clinical trials have failed so far. This may be because all experimental patients in such trials must first have received a clinical diagnosis of AD, which can only be made long after tau pathology is already well underway and self-sustaining.

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