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Euro Dementia: Targeting Prion-like Cis Phosphorylated Tau Pathology in Neurodegenerative Diseases-Onder Albayram- Havard Medical School

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Abstract

Overview of Prions and Neurodegenerative Disease: The accumulation of protein aggregates is a common feature of many neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD) and frontotemporal dementia (FTD), Each type of aggregate has one type of protein as its major component, with amyloid-β, hyperphosphorylated tau and α-synuclein being the most commonly observed. These proteins undergo a transformation from a soluble monomer to an insoluble, aggregated state through a number of intermediates . Researchers have speculated that the protein deposits found in these neurodegenerative diseases may develop and spread throughout the brain in a very manner analogous to it of aggregation of the prion protein (PrP) in transmissible spongiform encephalopathies (TSEs), such as Creutzfeldt-Jakob disease (CJD). Many recent studies in rodents, as well as in humans , support the notion that AD pathology propagates in a prion-like fashion. Elowever, there is no evidence suggesting that non-TSE neurodegenerative diseases, including AD, can be transferred between individuals in any case other than direct injection of diseased brain extracts, hence the use of "prion-like."

Structure and Toxicity of Pathological Tau: Native tau contains a relatively loose, unstructured protein with little α-helix and β-sheet structure. In the adult human brain, tau protein appears as six isoforms, all derived from a single gene by alternative splicing. Three of these isoforms contain three repeats (3R-τ) of a sequence thought to be involved in binding to microtubules; the other three isoforms contain an additional fourth repeat of the region, coded by exon 10 (4R-τ). The repeat region of tau is positioned between two basic, proline rich regions. Many of these prolines are preceded by a serine or threonine, allowing for phosphorylation. Dimerization due to disulfide cross-linking has been proposed to be a first step in the formation of NFTs, and only occurs when lysines in the microtubule binding repeat regions are phosphorylated . This in turn disrupts tau's function on microtubules and alters its protein stability, eventually leading to aggregation and tangle formation.

Neurofibrillary tangles are a neuropathological hallmark of tauopathies AD and other tauopathies and were previously believed to be the toxic species. However, recent studies have demonstrated that necrobosis occurs before tangle formation, meaning some earlier intermediate must be the source of tau toxicity. The culmination of many years of increasing research into the toxicity of tau aggregation in neurodegenerative disease has led to the proposal that soluble, oligomeric kinds of hyperphosphorylated tau (p-tau) are likely the most toxic entities in disease. These p-tau oligomers are able to enter and exit cells in vitro, and are believed to be a serious species accountable for propagation, although the exact mechanism is continues to be unknown. Evidence suggests that these multimeric tau oligomers may act as templates for the misfolding of native tau, thereby seeding the spread of the toxic kind of the protein and initiating disease progression in a manner analogous to that of prions . Additionally, these oligomers have repeatedly been found to induce necrobiosis in numerous tauopathies and can propagate through the brain causing synaptic and mitochondrial dysfunction associated with memory deficits .

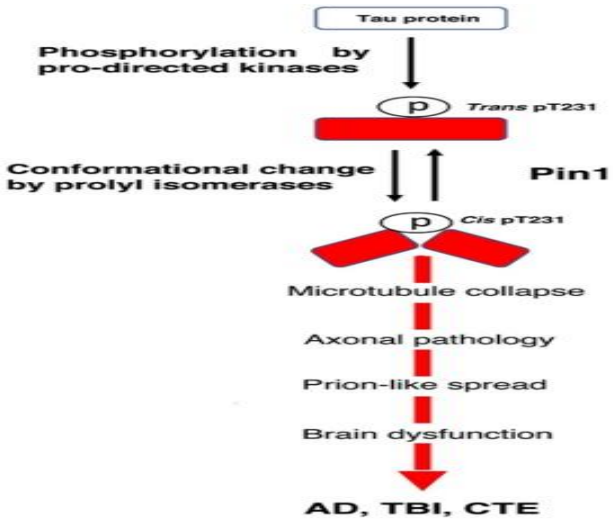

Figure 1: Upon phosphorylation of tau on the Thr231-Pro motif, Pin1 converts cis to trans of p-tau at a much higher frequency, although it can catalyze both directions. When

Pin1 becomes down-regulated or when cis p-tau is produced in abnormally high quantities, as we see in the case in TBI and AD, the cis conformation begins to accumulate in the brain. Unlike trans p-tau, which may bind and promote microtubule assembly, is liable to protein dephosphorylation and degradation and immune to protein aggregation, and does not cause neurodegeneration, cis p-tau cannot bind and promote microtubule assembly, is immune to protein dephosphorylation and degradation, prone to protein aggregation, and cause and spread neurodegeneration.

Alzheimer's Disease: The work from our lab and others has uncovered the extensive contribution ofPin1 to the development of AD pathology. Pin1 promoter polymorphisms resulting in decreased Pin1 levels are associated with an increased risk for late-onset AD. In contrast, Pin1 SNPs resulting in reduced Pin1 inhibition are related to with a delayed onset of AD . In a normal human brain, Pin1 expression was relatively low in regions of the hippocampus that are susceptible to NFT-related neurodegeneration in AD (CA1 and subiculum), while Pin1 expression was higher in regions that are generally spared (CA4, CA3, CA2, presubiculum) .In the brains of human AD patients, the majority of pyramidal neurons (96%) with relatively high Pin1 expression lacked tau tangles, and most pyramidal neurons (71%) with relatively low Pin1 expression had tangles . Furthermore, Pin1 co-localizes and co-purifies with NFTs, and can directly restore the ability of tau to bind microtubules and promote microtubule activity . Finally, levels of p-Thr231 tau correlate with the progression of AD, and Pin1 is strongly correlated with dephosphorylation of tau at Thr231

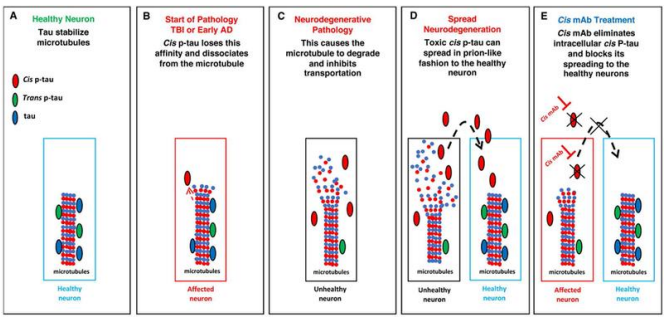

Figure 2: Healthy tau contains a high affinity for microtubules, promoting their assembly and assisting in the transportation of various proteins and nutrients along the axon. (B) Cis p-tau loses this affinity and dissociates from the microtubule. (C) The tau which dissociates from the microtubule also develops a much better affinity for itself and begins to aggregate, and really seeds itself in a manner like to the prion protein. This essentially means toxic tau can convert other healthy tau in the brain into the toxic cis conformation, causing a systematic and predictable spread of tau pathology. This cis P-tau is also the missing step in the process of neurodegeneration. (D) The isomerization causes healthy, physiological trans tau to become a toxic cis form, which is capable of causing and spread neurodegeneration and eventual tau tangles in tauopathies. (E) The flexibility of cis p-tau to cause and spread neurodegeneration is effectively neutralized by cis p-tau antibody, which targets intracellular cis P-tau for proteasome-mediated degradation and preventing extracellular cis P-tau from spreading to other neurons.

Traumatic Brain Injury and Chronic Traumatic Encephalopathy: Traumatic brain injury (TBI) and chronic traumatic encephalopathy (CTE) are closely related tauopathies that have significant potential for studying the toxicity and spread of tau in controlled conditions. Repetitive mild TBI (rmTBI), or single moderate/severe TBI (ssTBI), may cause acute and potentially long-lasting neurological dysfunction, including the development of CTE. Additionally, TBI is an established environmental risk factor for AD

Therapy: Studies have revealed the potential of antibody treatments in neutralizing toxic cis p-tau, thereby halting, or or a minimum of significantly delaying, neurodegeneration. This therapy has so far proved successful in mouse models of TBI. Periodic treatment with a cis p-tau monoclonal antibody treatment over 4 months not only eliminated spreading of cis p-tau, axonal pathology and astrogliosis into the hippocampus without affecting physiologic trails p-tau, but also prevented tau oligomerization, tangle formation, and APP accumulation. Shorter courses of treatment (between 5 and 10 days) with delayed administration also proved effective at eliminating cis p-tau induction.A humanized version of the cis p-tau antibody could prove extremely useful in treating the wide range of neurodegenerative diseases associated with toxic tau.

Conclusion: For many years NFTs were the most subject of study in research done on tau toxicity in neurodegenerative diseases. Recently evidence has pointed to an intermediate in the aggregation process, like soluble cis p-tau, as a more likely candidate for the toxic species in common tauopathies. As more research has been done on tau aggregation intermediates, the prion-like nature of tau has been made apparent.

Note: This work is partly presented at 11th International Conference on Alzheimers Disease & Dementia, Vienna, Austria