The Role Of Tau In The Onset And Progression Of Alzheimer's Disease Within The Cyclical Immunoreactive Theory Of AD

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Abstract: The causal mechanism from which Alzheimer's Disease (AD) originates has yet to be illuminated in full, although significant progress has been made in that very direction. Ideas have been put forth since the disease's founding by Dr. Alois Alzheimer over 100 years ago that have implicated the beta amyloid (Aβ) peptide in the onset and progression of the disease in its exclusively elderly population of patients, as aggregations of this antimicrobial protein formed plaques in the autopsied brain of the earliest studied AD brain and in all of those that have come after her. Because increased availability of improved technology has allowed for greater observational tracing of the disease, it has come to be known that the quantity of Aβ deposition is directly proportional to the severity of the behavioral symptoms observed of the patient in question. This left little doubt as to whether or not Aβ played an important role in the exacerbation of AD, and it is on these grounds that ideas such as the common amyloid cascade hypothesis have been put forth. While incomplete, these long standing frameworks for thinking about the intricacies and causal mechanisms of AD have given way to more complete theories on the matter such as the cyclical immunoreactive theory of AD. Nonetheless, all plausible frameworks surrounding the onset and progression of AD afford the majority of their focus to Aβ, while ignoring some of the more peripheral, though important elements of AD. Perhaps the only rival to Aβ in terms of prevalence, consistent presence, and potential causal involvement is the tau protein. Having also been observed very early on in the autopsied brains of AD patients by Dr. Alzheimer the microtubule associated protein (MAP) tau has been shown to aggregate in a manner similar to that of Aβ in the AD brain. These accumulations of the pathological protein are called neurofibrillary tangles (NFTs), and no doubt play a role similar to Aβ plaques in the slow yet consistent progression of the neurodegenerative disease. This text will assess the role of the tau protein in the brain of AD patients, and review relevant studies on the subject all with the aim of defining its role within the context of what is thus far the most complete framework for diagnosing and describing the intricacies of AD.

Keywords: Alzheimer's, Tau, Proteins, Neurodegeneration, Neuroscience, Neuropathology

Introduction:

Tau is a microtubule binding protein (MAP), meaning that it plays a critical role in the stabilization of neuronal microtubules, as well as being an important regulator and the most key component of neurofibrillary tangles, which are, in short, deposed aggregates of the tau protein in the AD brain (Lewis & Dickenson, 2016; Iqbal et al., 2010). Despite the fact that it is less discussed than Aβ plaques and their deposition, tau protein aggregates have been critical, exacerbation components of AD since the beginning of the disease's anti-human campaign, and were observed at virtually the same time, by Dr. Alois Alzheimer, as the first Aβ plaques were discovered and studied in the autopsied brain of a former dementia patient (Stelzmann et al., 1995). But, despite clear, observed tangles in neurofibrillary fibers which manifest themselves as blockage-causing aggregations, their composition would not be known for nearly seventy more years, given that the tau protein's discovery was first made public in a 1975 study, in which they were identified as heat stable proteins and deemed necessary for the assembly of microtubules, which they'd discovered by subjecting vials of tubulin collected from porcine brain samples to intermittent cycles of polymerization, which is simply any process that involves the chemical combination of smaller monomers into larger polymers (Weingarten et al., 1975).

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Since then, significant study was allocated to understanding the function of the protein, due principally to the fact that it aligned itself with other MAP species in terms of structure and function, namely MAP2 and MAP4 which exist in the MAP Type II class of microtubule associated proteins along with tau (Al-Bassam et al., 2002). These proteins are exclusive to nerve cells in mammals (Kar et al., 2003). MAP2 specifically, is found primarily in dendrites and its primary function, to stabilize microtubules through conserved C-terminal microtubule binding domain and N-terminal domains which project from the proteins, being analogous to that of tau, which serves the same function through the same means in the axon (Kar et al., 2003; Kinoshita, Habermann, & Hyman, 2003). But, upon further investigation, it would become clear that tau differed from its fellow Type II MAP variants in a very significant, though not fully understood way. While it was well documented by Dr. Alois Alzheimer himself, and reinforced in the many years to follow, that there was a clear correlation between the prevalence of NFTs and the severity of AD, the component pieces of these tangles were not known until eleven years after tau's discovery, when it was revealed that the protein was discovered to be the primary ingredient in these NFTs (Grundke-Iqbal et al., 1986). This revelation marked a turning point in the perceived importance of the tau protein, as the MAP, once thought to simply play a menial role in the formation of larger, more relevant neuronally supportive structures as is the case with other Type II MAPs, is instead on par with Aβ as one of the driving factors behind the onset and progression of the disease that affects one in every nine Americans and remains the sixth leading cause of death. This newfound relevance piqued the interest of countless researchers in the field of AD, as the potential for breakthroughs in terms of the mechanisms that facilitate the neurotoxicity that is characteristic of AD represented a gold mine for intellectual

clout. From the researching frenzy that ensued and the incessant publication on the subject, the leading theory which served to implicate tau as the primary causal mechanism of AD was the tau propagation hypothesis, which, at its most basic argues for the fact that tau spreads (is propagated by) the intraneuronal transfer AD-pathological neurons, and this transfer follows a consistent, predictable tract from the entorhinal cortex, to the hippocampus, and up into the neocortex. Hyperphosphorylation, the process by which phosphate is added to an organic compound at many sites, facilitates the transformation of this protein into the NFTs, which are the tau equivalent to Aβ aggregations (Iqbal et al., 2010). The theory has budded into a legitimately plausible mechanisms by which tau may catalyze the pathological spread of AD, but, much like its Aβ counterpart, the specific intricacies of its pathological function,, namely how it contributes to neuronal toxicity, has continually evaded the observational findings of AD researchers. Although there is clear correlation between the aggregation of tau and the spread of AD throughout the diseased brain, the way in which it facilitates neurodegeneration remain misunderstood.

Tau Propagation

Microtubule polymerization, the process by which alpha and beta tubulin conjoin to form protofilaments that formulate in a lateral fashion thus making a basic hollow structure, is one of the primary functions of the tau protein. It was also shown by Grundke-Iqbal et al. that the au protein is critical for maintaining the stability of microtubules in various conditions. Tau functions properly only under the strong and intricate regulation of various physiological mechanisms including nitration and phosphorylation, amongst many others (Morris et al., 2011). It is well known, via experimental disruption to these regulatory mechanisms, that interruptions or alterations to the processes which the efficacy of the tau protein is so dependent on can facilitate pathological tendencies of tau and its isoforms. The very progression of tau-protein buildup is inversely related to the health dependent neurons which serve too many critical functions to name. As mentioned, phosphorylation is a normal process which is typical of healthy tau, as well as other MAPs and interaction with alpha- and beta-tubulin are critical to elicit the normative, supportive function of the tau protein. But mutations which impede the normalcy of this function serve to exacerbate the phosphorylation of tau to a pathological extent, at which point the proteins enter a state of hyperphosphorylation, which occurs pre-clinically at serine 119, 202 and 409, and then later at serine 396 and threonine 231 (Mohandas, Rajmohan, & Raghunath, 2009). This hyperphosphorylation of tau to an excessive extent results in the formation of paired helical filaments (PHF), which entangle themselves and form the aggregations of tau referred to as NFTs (Mohandas, Rajmohan, & Raghunath, January 2009). Aside from hyperphosphorylation however, the mechanism by which tau spreads must be recognized to fully understand the means by which the mutated tau is pathological. The tau propagation hypothesis argues that the tau protein is propagated intraneuronally, meaning that it spreads via transfer from one neuron to the next (Iqbal et al., 2010). This bears clinical significance, under the assumption that tau aggregates do indeed play a role in the pathological progression of AD, as it would mean the normal neuronal plasticity observed in the human brain would facilitate the means of its own destruction. It has been observed that tau interacts with annexins, the binding proteins of the plasma membrane, and it is thought that this may be the causal factor, or at least one of the causal factors that allows for the Tau protein to be distributed intracellularly (Gauthier-Kemper et al., 2018). What's more, the aforementioned Morris et al., 2011, speaks to the dynamic nature of the tau protein, highlighting the fact that it has been observed to interact with many binding partners, of which annexins are only one. This speaks to how dynamic the tau protein truly is, manner in which it differs from its MAP counterparts, and it allows for the presupposition that this flexibility in function may also play a major role in its extracellular existence (Morris et al., 2011). Braak & Braak (1991), showed, via cross-sectional study of the tau pathology in an AD ridden brain, that tau spreads in a predictable fashion along a neural network, a fact that is made relevant when it is observed in conjunction with the fact the NFT's spread in a virtually identical manner in all observed cases of AD, from the transentorhinal cortex out into other areas of the cerebral cortex (Braak & Braak, 1991). Given the fact that these NFT's are composed of aggregated PHFs, which themselves are hyperphosphorylated variants of the tau protein, the idea that their spread throughout the human brain would be directly correlated with the neural networks along which the tau protein consistently travels is certainly indicative of the fact that its is this transfer from one neuron to the next that leads to the proteins eventual hyperphosphorylation, aggregation, and extracellular deposition in the same manner as defined by Braak staging (Braak & Braak, 1991). The increased presence of the constituent protein can, with relative certainty, predict the presence of AD indicating features, i.e. the tau protein signifying the presence of NFTs or the Aβ peptide secretion via astrogliosis responses predicting the presence of amyloid plaques (Morris et al., 2011, Iacobelli, 2021). Because both of these constituent components, Aβ and hyperphosphorylated tau, increase in secretion and extracellular deposition, even prior to their aggregation into Aβ plaques and NFTs respectively, it is a guarantee that the mechanism which serves to secrete and propagate the spread of these proteins plays a critical, and likely causal role in the onset and progression of AD. In 2009, Frost et al., was able to indicate that when a a tau seed was placed in a culture medium, endocytosis, which is the process by which living cells take up matter by enfolding its own membrane so as to create a vacuole, occurs and this forms new tau aggregates within brain cells (Frost et al., 2009). Due to the fact that tau misfolding occurs from a very localized beginning in specifically diseased areas, to much larger, extracellular portions of the brian, Frost et al., argued that these tau aggregates, which exist extracellularly in their pathological state, can pass their pathological, misfolded state to the inside of a neuron or glial brain cell, from the outside (Frost et al., 2009). As mentioned, the team of researchers managed to effectively show that extracellular tau aggregates are taken up by cells via endocytosis, which then induces the fibrillization of full-length tau. They effectively showed that these fibrils could be used to seed tau monomers, and most importantly, the

study substantiated the idea that tau pathology could be transmitted intracellularly, at least within the context of the study(Frost et al., 2009). Cells that were either transfected (the infecting of a cell with free nucleic acid) with MTBR-YFP (microtubule binding region, the main functional area of the tau protein, which has been tagged with a YFP fluorescent) or mCherry (which they label as a fluorescent-red protein variant) were co-cultured over a twenty four hour period, and it was observed that the co-cultured cells had a much higher rate of dual-fluorescence, the positive presence of both YFP and mCherry, than the control groups which were MTBR-YFP and mCherry each cultured independently and then mixed together. This finding implies that the transfer of MTBR-YFP aggregates to cells that expressed mCherry had occurred (Frost et al., 2009). In a further effort to determine whether or not the transfer of these tau aggregates from one co-cultured cell to another is dependent on an inducer, a material/substance whose presence elicits a biochemical process, the team of researchers co-cultured another set of cells of full length tau-YFP, as opposed to just MTBR-YFP, and mCherry to see if the same effect of spontaneous intracellular transfer was observed. The misfolding of the full length tau-YFP was elicited by exposing it to the microtubule binding region tau aggregates for a fixed period (Frost et al., 2009). This exposure facilitated that pathological aggregation of the full length tau protein and, as was observed using fluorescent microscopy, the spontaneous transfer of those aggregates into the cells that expressed mCherry at a rate very similar to that of the original trail which involved just MTBR-YFP and no misfolding. Thus, if full length tau is induced to elicit its misfolding, it will spontaneously transfer between co-cultured cells just as spontaneously formed MTBR-YFP tau intracellular inclusions will transfer between co-cultured cells (Frost et al., 2009). It was shown by Iba et al. (2013) that when transgenically modified mice, who in this case were encoded with a human tau isoform (1N4R) using a cDNA encoding, with a pathogenic tau mutation (P301S), were intracellularly inoculated with synthetic preformed fibrils that were assembled from recombinant tau proteins or truncated tau that contained four MTBR repeats, NFT-like intracellular inclusions were quickly propagated from sites of infection to other regions of the brain, in manner the mimics that of tau pathologies observed in humans (Iba et al., 2013). Aside from aggregation of tau being a characteristic of AD in humans, there are several sub-factors that distinguish the AD-specific tau pathology from that of pathogenic tau observed in nature or in other human diseases. For purposes of comparison, Iba et al., used mice who contained a spontaneously occurring pathological tau mutation (PS19), but it was quickly observed that the tau pathology of these mice does not resemble that of the human form, while the mice on whom the study was performed, had a more AD-like tauopathy, given the fact that several of these sub-factors aligned with those observed in human NFTs (Iba et al., 2013). Among them, the tau aggregates observed in the mice from the study were Thioflavin S positive, meaning that when the aggregates were histologically stained, the observation of Thioflavin S indicates the presence of amyloid, which we know goes hand in hand with tau proteins in every observed case of AD. In addition, the NFTs in the transgenically modified mice of the study were acetylated, which among many other functions, neutralizes the positive charge of lysine which impacts the way that the tau interacts with its environment, and certainly contributes to its pathological nature (Iba et al., 2013). This study, as well as two similar studies preceding it which were of the same nature but focused on α-synuclein fibrils and Aβ fibrils that found virtually the same result (Luk et al., 2012; Stöhr et al., 2012), reinforce the idea that fibrillar, misfolded proteins can be transmitted at a high rate and, in specific cases of misfolding that are pathological for at least the tau protein and β-amyloid, this exponentially expanding neuropathology may play a causal, or at least exacerbation role in an AD infected brain (Iba et al., 2013). Ultimately, the greatest achievement of these studies is the fact that they have effectively proven that tau is indeed propagated along its predictable tract throughout the AD brain via intraneuronal transfer, thus substantiating the core tenant of the tau propagation hypothesis.

How Tau Contributes To Neuotoxicity

While significant discussion has thus far been afforded to the mechanisms by which tau is propagated throughout the AD brain, which we now know to be through intraneuronal transfer, little has been said about how the accumulation of tau contributes to neurodegeneration. While we have thus far touched on the fact that tau mutations lead to abnormally high rates of phosphorylation (hyperphosphorylation), which form paired helical filaments (PHFs), which then accumulate and entangle to form aggregates of the hyperphosphorylated tau called neurofibrillary tangles (NFTs), we have yet to shed light on the specific means by which the spread of tau and the formation of these aggregates actually contribute to neuronal toxicity and exacerbate neurodegeneration, principally due to the fact that this process remains unclear. THat said, there have been significant advances in the field and certain studies have offered insight as to how tau and its pathologically mutated isoforms contribute to neurodegeneration and negative behavioral ramifications associated with AD. The leading point of view on the matter is the idea that NFTs, because they tend to form in the synaptic pathways, block action potentials and thus prevent neurons from firing, hence limiting the neuronal plasticity that is characteristic of a healthy human brain. Few breakthrough studies have served to validate this assumption, although a 2011 study by Moreno et al. utilized tau protein injections from humans into the presynaptic terminals of the axons from giant squid synapses, to study the way in which the synapse release and neuronal firing processes would be affected (Moreno et al., 2011). In short, the study showed that there is a rapid hyperphosphorylation of the tau, as is the case with pathological tau in the AD brain, as well as a near immediate blockage of synaptic release (Moreno et al., 2011). While this finding was repeatable and tells of how tau affects synaptic release, it is difficult to draw conclusions from this study alone, and the process by which tau limits neuroplasticity remains unclear. That said, another proposed mechanism of tau-related AD pathology is the senescence of glial cells which is characterized primarily by the arrest of the cell-cycle which is irreversible and can be induced by a wide variety of intrinsic and extrinsic factors (Bussain et al., 2018). Among these triggering mechanisms may be the expression of the

tau protein. It is known that when senescent cells express an inhibitory protein, $P^{16INK4A}$, the protein has been shown to actively facilitate natural tissue degeneration, a process which has been linked directly to neurodegenerative disease like atherosclerosis and osteoarthritis, although it is not unreasonable to assume that a similar process could not also be the causal force behind AD (Bussain et al., 2018). The 2018 study by Bussain et al. establishes a correlation between the aggregation of senescent glial cells and cognitive decline that is characteristic of the neurodegeneration observed in AD and other disease whose hallmark is cognitive decline. Specifically, the $MAPT^{301S}PS19$, a type of tau mentioned earlier in the text, was used to transgenically modify mice such that they resembled having a tau-dependent neurodegenerative disease (Bussain et al., 2018). Observation of gthe transgenically modified mice over a period of time showed that they tended to accumulate the $P^{16INK4A}$senescent astrocytes and microglia (Bussain et al., 2018). Given the fact that we know that senescent cells which express this protein have an increased aptitude for facilitating neurodegeneration, specifically in the tissues that house these $P^{16INK4A}$-expressing cells, it is very reasonable to assume that senescent cells which express this protein, especially astrocytes and microglia, may also play a significant role in the onset and progression of AD. In addition, because it is known that glial cells, specifically astrocytes, are the primary secretors of tau's counterpart Aβ (Iacobelli, 2021), thai study represents a correlation, and possibly a common causal mechanism for both Aβ and tau, although more study must be done on this topic. A fellow 2018 study would go on to show that in tauopathies, the tau protein loses a great deal of its normal functionality, namely its ability to bind and detach from microtubules (Perez et al., 2018). This review summates evidence and proposes that tau, when pathologically mutated is spread through prion-like propagation, which still involves intracellular transmission, but would involve the exchange of tau seed from donor to recipient cells, as well as the exponential, pathogenic spread of prion-like mutations to normal tau proteins, a process of transformation and breadth-expansion which Musher et al., refers to as recruitment (Mudher etal., 2017; Perez et al., 2018). That said, the evidence for this process is less substantial, than for the tau propagation hypothesis, and while worthy of review, is not the subject of this particular text.

Conclusion

Ultimately, while this brief synopsis of the role of tau in relation to its intracellular propagation in the AD brain, is important for highlighting a few key discoveries on the mechanisms by which tau may play a directly pathogenic role in the onset and progression of AD, more study is necessary on the subject. A linkage between tau and Aβ secretion and aggregation should be examined, specifically in relation to senescent cells and the presence of the $P^{16INK4A}$protein and its expression in astrocytes and microglia, as the link between astrocytic expression of this protein along with Aβ may serve as the grounds for a linked causal mechanism that fits within the framework of a plausible for theory for the onset and progression of AD such as the cyclical immunoreactive theory of AD.

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