Fyn-Tau-Amyloid: A Toxic Triad

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The axonal protein tau and amyloid β-peptide (Aβ) are key players in the pathogenesis of Alzheimer's disease, and tau mediates Aβ toxicity, but it is not clear how. Ittner et al. (2010) now report an unexpected physiological function for tau in neuronal dendrites that may explain how tau mediates Aβ toxicity.

Alzheimer's disease (AD) is a devastating public health problem for our aging societies. Although it is well established that amyloid β-peptide (Aβ) forms toxic oligomers in the brain (Haass and Selkoe, 2007), it is not clear how Aβ initiates the amyloid cascade and causes the death of neurons. Tau, an axonal protein, seems to be an executor of Aβ toxicity even though it is localized to axons, and Aβ toxicity is primarily triggered through interactions of Aβ oligomers with dendritic spines (Haass and Selkoe, 2007). Tau binds to microtubules, a process that is prevented by its abnormal phosphorylation during AD pathogenesis. Loss of microtubule binding by tau is thought to cause the disassembly of microtubules followed by the aggregation and deposition of tau in pathogenic neurofibrillary tangles. Although amyloid plaques and tau tangles are prominent markers of AD, one of the first and most obvious pathological abnormalities observed in brain tissue from AD patients is the relocalization of tau from axons to the somatodendritic compartment of neurons (Figure 1) (Ballatore et al., 2007). During brain development, tau and other microtubule-associated proteins are initially distributed ubiquitously throughout neurons, but then, as differentiation progresses, tau becomes sorted into axons (Figure 1). In AD and other neurodegenerative diseases involving tau (termed "tauopathies"), this neat sorting pattern breaks down (Ballatore et al., 2007), perhaps because abnormal phosphorylation of tau enables it to detach from microtubules and diffuse rapidly into other neuronal compartments (Konzack et al., 2007). In this issue of *Cell*, Ittner et al. (2010) now shed light on an unexpected dendritic function for normal tau that suggests how tau may mediate Aβ toxicity.

Most research on tau function has focused on whether it is important for microtubule stabilization, neurite outgrowth, or the formation of tracks for cargo transport along axons. The catastrophic redistribution of tau to the soma and dendrites of neurons in AD suggests that an efficient sorting mechanism normally keeps tau localized to axons. However, such "polarized" sorting like other cellular sorting pathways is never completely efficient, thus enabling small amounts of tau to become localized to the somatodendritic compartment even under physiological conditions. This led Ittner and colleagues to propose a microtubule-independent physiological function for tau that regulates signaling in dendritic spines. Their research was initially triggered by accumulating evidence that subacute seizures occur not only in transgenic mouse models of AD, but also in AD patients (Palop and Mucke, 2009). Interestingly, tau deficiency decreases seizures induced by the Aβ-mediated overstimulation of excitatory N-methyl-D-aspartate (NMDA) receptors and improves survival in a transgenic AD mouse model (Roberson et al., 2007).

It is well established that tau binds not only to microtubules but also to several nonreceptor tyrosine kinases including Fyn through its N-terminal domain (Lee et al., 1998). This enables tau to sequester Fyn and to alter its localization in the neuron. Fyn phosphorylates subunit 2 of the NMDA receptor, resulting in stabilization of this receptor's interaction with PSD95, a scaffolding protein in the dendritic spines of neurons. This stabilization, in turn, strengthens signaling by the excitotoxic neurotransmitter glutamate, which enhances Aβ toxicity (Figure 1). A tau-dependent increase in Fyn in dendritic spines could boost excitotoxic signaling, and, conversely, sequestration of Fyn by tau or downregulation of tau expression could mitigate excitotoxicity.

To address whether this is the case, Ittner and coworkers first generated transgenic mice that overexpressed a variant of tau (Δtau) that lacked the C terminus and thus could bind to Fyn but not to microtubules. Interestingly, Δtau was completely excluded from dendrites and accumulated within the soma (Figure 1). Moreover, Δtau efficiently competed with endogenous tau for binding to Fyn, resulting in sequestration of Fyn in the soma. Similarly, loss of tau also prevented postsynaptic targeting of Fyn, and loss of Fyn in the dendrites was enhanced when Δtau was expressed in mice deficient in normal tau. This suggests that the targeting of Fyn to dendrites depends on normal tau, a surprising finding for a protein believed to act only in axons. But how tau-based sorting of Fyn occurs and whether other proteins are required remain unclear.

Fyn phosphorylates NMDA receptor subunit 2 at tyrosine 1472 and stabilizes the interaction of this subunit with the postsynaptic protein PSD95 (Nakazawa et al., 2001). However, when Fyn is trapped within the soma by expression of Δtau or reduced expression of endogenous tau, there is decreased phosphorylation of

the NMDA receptor, the interaction of the receptor with PSD95 is destabilized, and excitotoxic signaling decreases. Excitotoxicity has been implicated in Aß-mediated toxicity, and a reduction in tau ameliorates the pathological action of Aβ in the AD transgenic mouse model (Roberson et al., 2007). Similarly, overexpression of Δtau in the AD mice prevented seizures and improved survival; indeed, these benefits were enhanced when expression of endogenous tau was reduced. Moreover, the AD mice overexpressing Δtau showed improvements in memory, suggesting that Aβ toxicity was reduced when Fyn levels decreased in the dendritic spines. This was independent of Aβ production or the overall amyloid plaque load.

Notably, there is an interesting twist to the Fyn-tau-microtubule story. In oligodendrocytes, tau is necessary for the outgrowth of cell processes and for transport of Fyn, which is important for myelinating neurons. Expression of the N-terminal domain of tau alone causes abnormal sorting of Fyn, resulting in poor myelination of neurons and seizures in rodents (Klein et al., 2002). Thus, there are two completely distinct settings for this potentially toxic triad, which implicates abnormal tau in seizure disorders as well as in neurodegenerative diseases.

But can the Fyn-tau connection in dendritic spines be exploited to develop new therapeutic strategies for treating AD? A peptide that blocks phosphorylation of NMDA receptors by Fyn protects neurons from excitotoxic damage (Aarts et al., 2002). Strikingly, when Ittner and colleagues treated their transgenic AD mice with this peptide, memory deficits were ameliorated and there was improved survival, similar to the results when Fyn was sequestered by Δtau.

The Ittner et al. study may provide a missing link between extracellular deposits of Aβ and intracellular tau and pinpoints tau and Fyn as possible mediators of Aβ toxicity. Although the idea is tantalizing, the actual colocalization of tau and Fyn within dendritic spines and their modes of action remain to be shown under physiological conditions. A major surprise of this study is that a normal physiological function of tau, regarded as an axonal protein, mediates Aβ toxicity at dendritic spines. Is this physiological function of tau affected during the earliest stages of AD? This may be the case, as redistribution of full-length tau (and possibly tau fragments) to the somatodendritic compartment occurs well before the formation of neurofibrillary tangles. The abnormal sorting of tau to the somatodendritic compartment may be due to changes in signaling cascades that alter kinase and phosphatase activities in those dendritic spines affected by Aβ, resulting in local changes in tau sorting and cytoskeletal rearrangements. But do tau and Fyn still interact after tau redistribution, given that the Fyn binding site on tau can be phosphorylated leading to disruption of this binding? If they do, then relocalized tau may boost Fyn action in dendrites and hence phosphorylation of NMDA receptors, thus enhancing excitotoxic signaling and increasing the sensitivity of neurons to Aβ (Figure 1). However, before targeting the tau-Fyn interaction for therapeutic purposes, we need to know more about the mechanism by which tau mediates the transport of Fyn to dendrites. If that transport mechanism is disturbed, what other neuronal functions would be affected? Clearly, not only Fyn, but also other signaling molecules containing SH3 domains bind to the PXXP motifs in the N-terminal domain of tau and of related microtubule-associated proteins; but we do not know whether inhibition of this binding would have deleterious effects. Also, is Δtau just a scavenger that when overexpressed sequesters Fyn? Could proteins other than tau perform this activity in vivo? The enhanced phenotypes upon reduction of endogenous tau seem to speak against this possibility. The provocative work of Ittner et al. raises new challenging questions, but also brings us a significant step closer to understanding AD pathophysiology. Hopefully, these findings will help in the design of new therapeutic strategies for reducing the synaptic dysfunction and neuronal loss of AD and other neurodegenerative diseases.

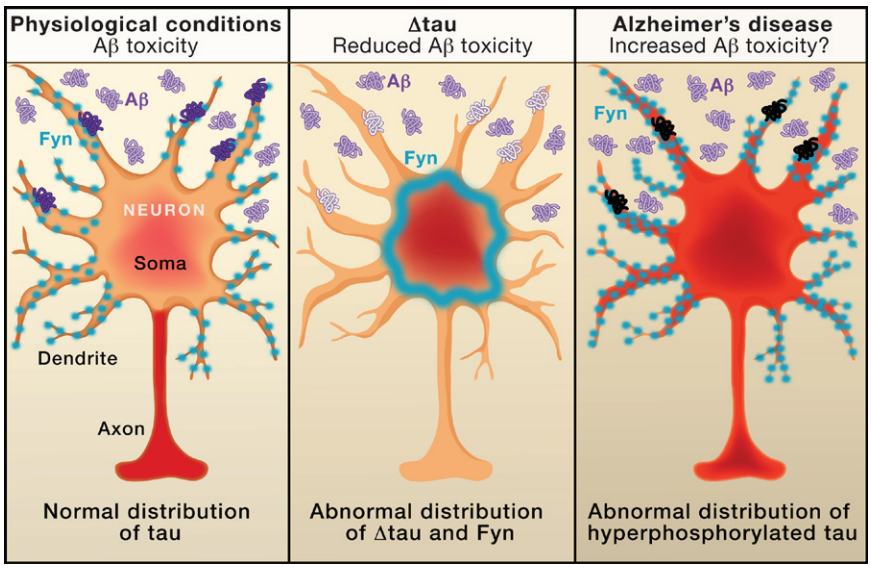

Figure 1. A Toxic Triad in Alzheimer's Disease.
Shown is the neuronal localization of tau protein (red) and Fyn kinase (blue) under physiological and pathological conditions.
(Left) Normal tau is primarily located in axons but also interacts with Fyn kinase and targets it to dendrites. Fyn kinase phosphorylates subunit 2 of the NMDA receptor in dendritic spines, which results in stabilization of the receptor's interaction with the postsynaptic density protein PSD95, leading to enhanced excitotoxicity. Excitotoxicity is known to increase the toxic effects of oligomers of Aβ (dark purple) on neurons.
(Middle) Overexpression of a Δtau variant lacking the C terminus, which binds to Fyn kinase but not to microtubules, results in the sequestration of Fyn in the soma, preventing Fyn from reaching the dendrites. Consequently, Fyn-mediated phosphorylation of NMDA receptors is decreased and Aβ-mediated toxicity is reduced (pale purple).
(Right) Enhanced redistribution of abnormally hyperphosphorylated tau from axons to the somatodendritic compartment during AD pathogenesis may increase tau-dependent sorting of Fyn to the dendrites, boosting excitotoxic signaling and increasing the toxic effects of Aβ (black) on neurons.

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Noncoding RNAs: The Missing "Linc" in p53-Mediated Repression

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The tumor suppressor protein p53 coordinates the cellular response to stress through regulation of gene expression. Now, Huarte et al. (2010) identify a long intergenic noncoding RNA as a new player in p53-mediated repression of genes involved in apoptosis.

The tumor suppressor protein p53 is one of the cell's most important barriers against oncogenic transformation. By regulating the expression of thousands of genes, either directly or indirectly, p53 profoundly influences cell fate in response to stress. Several decades of research have established p53 as a transcriptional activator with high sequence specificity. However, p53 clearly also represses at least as many genes as it activates, if not more. Despite this, the mechanism of repression is less well characterized than the transactivation mechanism by p53. Now, the informative study by Huarte et al. (2010) in this issue lays the framework for a new and elegant mechanism by which p53 globally downregulates a large subset of its repression targets. These authors show that the long intergenic RNA-p21 (lincRNA-p21), a bona fide downstream target of p53, is a key inhibitor of gene expression through its interaction with heterogeneous ribonucleoprotein K (hnRNP-K).

Although the first reports of gene repression by p53 focused on suppression of the basal transcriptional machinery, subsequent studies identified more precise mechanisms occurring at specific genes (reviewed in Laptenko and Prives, 2006). These include p53 interacting with and inhibiting specific transcription factors; displacement of specific activators from promoters due to the presence of overlapping binding sites; the recruitment by p53 of chromatin-modifying factors, such as histone deacetylases, which then block gene expression; and the binding of p53 to unique "repression" response elements. In addition, p53 may also inhibit genes indirectly by activating transcription of factors that block expression of specific genes. Most notably, many labs have demonstrated that the cell-cycle inhibitor p21 (especially within the context of Rb-family activation) is a critical mediator of p53-dependent transcriptional repression (Figure 1, top) (Barsotti and Prives, 2009, and references therein). Recently, studies indicate that p53 regulates microRNAs, which either degrade mRNA targets or inhibit their translation into protein. The p53 protein facilitates not only the transcriptional activation of microRNAs but also their processing into mature, active forms (Figure 1, middle) (Shi et al., 2010). Now, Huarte, Rinn, and their colleagues (Huarte et al., 2010) add an exciting new route through which p53 executes widespread gene repression, specifically by activating a long intergenic RNA (Figure 1, bottom).

LincRNAs are large RNA molecules (primary transcript ≥5 kb) that are evolutionarily conserved across mammalian genomes. Although these RNAs are transcribed by RNA polymerase II, 5′capped, and polyadenylated like normal mRNAs, they do not code for proteins (Guttman et al., 2009). Previous work by the Rinn group suggested that lincRNAs may repress transcription by targeting chromatin-modifying complexes to specific genomic loci (Khalil et al., 2009).

In their new work, Huarte et al. (2010) sought to identify specific lincRNAs that operate within the p53 pathway. They constructed a tiling microarray designed to detect the expression of ~400 lincRNAs. They then incubated this array with RNA