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ALZHEIMER DISEASE

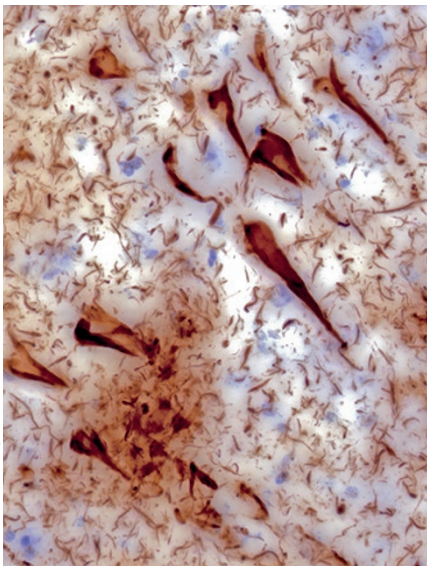
Evidence for trans-synaptic and exo-synaptic tau propagation in Alzheimer disease

The idea that tau pathology can spread through the brain in a prion-like fashion is gaining acceptance, and two recent studies shed new light on the underlying mechanisms. Writing in *Nature Communications*, Bradley Hyman and colleagues report trans-synaptic transmission of a phosphorylated high-molecular-weight (HMW) form of tau, and in *Nature Neuroscience*, Tsuneya Ikezu and colleagues propose an important role for microglia and exosomes in tau propagation.

Intracellular neurofibrillary tangles consisting of hyperphosphorylated tau are one of the two main pathological hallmarks of Alzheimer disease (AD), the other being amyloid-β plaques. The spread of tau pathology through the brain, starting in the entorhinal cortex and subsequently manifesting in the hippocampus and neocortex, mirrors the emergence of cognitive deficits. Evidence is growing that tau oligomers released from 'donor' neurons can be taken up by 'recipient' neurons, where they act as templates—or 'seeds'—to induce misfolding of native tau.

"We used a new set of experimental tools, including microfluidic devices that separated donor neuronal cell bodies and axons from recipient neurons by hydrostatic pressure gradients," explains Hyman. "This tool allowed us to biochemically separate and characterize different forms of tau derived from both transgenic animal models and human neuropathological specimens."

In postmortem cortical extracts from individuals with AD, the researchers identified a soluble phosphorylated HMW tau species that was efficiently taken up by neurons. A similar HMW species was detected in interstitial fluid from a transgenic mouse model of tauopathy. Experiments in the microfluidic culture device confirmed that HMW tau could be transmitted trans-synaptically between neurons.



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"We suggest that the release and uptake of this form of tau is an important step in the spread of disease from one brain area to another," says Hyman. "Since that spread likely underlies clinical progression of symptoms, targeting the mechanisms of the spreading might stabilize disease."

The study by Hyman and colleagues was based on the premise that the mechanism of tau propagation is predominantly trans-synaptic, but the paper from Ikezu and co-workers challenges this assumption. "Tau pathology does not always progress through neuroanatomical connections," points out Ikezu. "For example, tau accumulation in layer II of the entorhinal cortex region does not directly connect to the CA1 region of the hippocampus, where tau accumulation is commonly seen as the pathology progresses." Such observations prompted Ikezu's team to ask whether a nonsynaptic tau propagation pathway might exist.

The investigators generated a transgenic mouse model that expressed human Pro301Leu mutant tau under the control of the synapsin-1 promoter, which led to neuron-specific expression of the protein. This model displayed rapid spread of mutant tau from the entorhinal cortex to the dentate gyrus, thereby recapitulating the pattern of tau propagation that has been observed in the human brain, but within a time frame that was more amenable to laboratory investigation.

The team discovered that propagation of mutant tau between these two brain regions depended on the presence of microglia, the resident phagocytes of the brain. When the tyrosine kinase inhibitor PLX3397 was used to deplete microglia, tau propagation was halted. Furthermore, suppression of exosome synthesis by the sphingomyelin-2 inhibitor GW4869 led to a reduction in tau propagation in the dentate gyrus but, interestingly, not in the entorhinal cortex. This latter observation indicates the existence of regional variations in the predominant tau propagation mechanism in the brain.

"The most significant finding from this study is that tau can propagate from neuron to neuron via the exo-synaptic pathway, which involves phagocytic microglia and secretion of exosomes," concludes Ikezu. "This is consistent with prior studies describing the existence of tau in exosomes isolated from the cerebrospinal fluid of patients with AD."

The findings of the two studies suggest new avenues for the development of therapeutic strategies to halt the spread of tau pathology in the brain. Hyman and colleagues propose the HMW tau species as a target, whereas Ikezu and co-workers plan to further explore the therapeutic potential of PLX3397 and GW4869.

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Original articles Takeda, S. *et al.* Neuronal uptake and propagation of a rare phosphorylated high-molecular-weight tau derived from Alzheimer's disease brain. *Nat. Commun.* **6**, 8490 (2015) | Asai, H. *et al.* Depletion of microglia and inhibition of exosome synthesis halt tau propagation. *Nat. Neurosci.* doi:10.1038/nn.4132