# A new perspective on the role of phosphorylation in Alzheimer's and other tau pathologies

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**Video Abstract**

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# Abstract

Normally bound to the microtubules that give neurons their structure, the protein tau becomes detached in the brains of patients with Alzheimer's disease. That leads to the fibrillary tangles that have become the hallmark of the disease. Most textbooks explain that post-translational modifications, or PTMs, in the form of excessive phosphorylation trigger the formation and growth of these bundles. But new findings propose a subtle though crucial refinement. Researchers from the Brain Mind Institute at the EPFL in Switzerland have discovered that while phosphorylation does trigger tau detachment, it doesn't appear to promote tangle growth. It actually protects against it. Their findings offer a new perspective on the role of phosphorylation in tau pathologies, while encouraging the design of therapeutics that target tau detachment. Numerous studies have homed in on hyperphosphorylation as a trigger for tau pathologies. Unfortunately, they've done so with relatively poor resolution. Existing tools and methods tend to blanket tau with PTMs, unable to target any single site independently or to introduce phosphorylation at multiple sites with precision. The authors of the new study overcame that limitation by leveraging a chemical synthetic strategy they've recently developed. The approach uses K18 as a model for the tau protein. K18 is the fragment of the protein that contains all four repeats involved in the binding of tau to microtubules, as well as several PTM sites linked to tau aggregation and pathology formation in Alzheimer's disease. By building K18 one amino acid at a time, the team could study the effects of phosphorylation at single or multiple sites on the protein. They generated K18 with 1, 2, 3 or 4 phosphorylation sites and assessed the effects of single or multiple phosphorylation on K18 aggregation, microtubule binding and seeding activity. They found that phosphorylation at multiple sites (state known as hyperphosphorylation) inhibits tau aggregation and binding to microtubules. Phosphorylation atserine 262 in particular appears to play a dominant role in disrupting tau's ability to aggregate, bind to microtubules, and promote microtubule polymerization. Findings also showed that incubation of hyperphosphorylated variants of K18 did not enhance aggregation or produce the seeding activity typically associated with tau fibrillization in cells. Rather, it was suppressed. In fact, this activity was increasingly dulled with an uptick in the number of phosphorylated sites. This stands in contrast to the prevailing hypothesis that hyperphosphorylation necessarily leads to tau fibrillization. The team's work suggests that some hyperphosphorylation patterns may occur after tau fibrillization or as a cellular response to aggregation. It also underscores the critical importance of revisiting the role of phosphorylation in regulating tau's normal functions and its role in the pathogenesis of disease. Inhibitors of kinases that regulate phosphorylation-dependent disassociation of tau from microtubules could provide a viable strategy for stabilizing the native state of tau and inhibiting its aggregation. Studies are currently underway to explore this approach and to map the different phosphorylation events that directly or indirectly disrupt the binding of tau to microtubules.