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Untangling a Role for Tau in Synucleinopathies

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In this issue of *Biological Psychiatry*, Sengupta *et al.* (1) present novel evidence supporting a role for tau protein in the pathogenesis of Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Synucleinopathies are a group of neurodegenerative disorders characterized by the abnormal deposition of α -synuclein in filamentous intracellular inclusions called Lewy bodies. The most well-known synucleinopathy is PD, but other neurodegenerative diseases, including DLB and multiple system atrophy, also manifest abnormal α -synuclein deposition as a major pathologic feature. Neurofibrillary tangles composed of hyperphosphorylated tau protein, the major pathologic hallmark of tauopathies (e.g., Alzheimer's disease), have also been observed in brain specimens from patients with DLB and PD. Using Braak staging of neurofibrillary tangle pathology, clinicopathologic studies identified 18% and 75% of PD and DLB cases, respectively, as Braak stage IV or greater (2). Conversely, Lewy bodies are observed in 60% of patients with Alzheimer's disease (3). Although synucleinopathies and tauopathies are historically considered distinct disease entities, evidence now suggests that common mechanisms and interplay of α -synuclein and tau may determine susceptibility to developing disease (4). Additional data supporting a connection between α -synuclein and tau comes from genetic studies that link the *MAPT* gene encoding tau with an increased risk of PD (5). Although the co-occurrence of α -synuclein and tau pathologies has been widely reported, the functional consequences of the primary deposited protein on secondary pathology has been poorly investigated to date, and the common mechanisms remain to be elucidated Figure 1.

At the molecular level, α -synuclein and tau were first shown to interact physically in the late 1990s by Jensen *et al.* (6) with a binding inhibitory concentration of 50% of 50 pM. Although this observation has been confirmed in later studies using cellular models and brain tissue analyses (4), the relevance of an α -synuclein-tau interaction has still not been revealed. A possible physiologic function, such as modulation of cytoskeleton dynamics, has been proposed, but coexpression of tau and α -synuclein has proved deleterious in vitro and in vivo, suggesting that the interaction potentially exacerbates a pathologic process (4). One of the first proposed pathologic mechanisms for an α -synuclein-tau interaction was the α -synuclein-induced recruitment of kinases to potentiate abnormal tau phosphorylation (6). Later, using recombinant proteins, Waxman and Giasson (7) showed that tau aggregation could be specifically induced by α -synuclein and vice versa. Nübling *et al.* (8) were able to

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detect in vitro co-oligomerization of tau and α -synuclein using tagged recombinant proteins and fluorescent intensity distribution analysis. Sengupta *et al.*, in an analogous study using human brain tissues and oligomer-specific antibodies, present strong evidence for a detrimental α -synuclein-tau relationship via a co-oligomerization process.

Tau and α -synuclein are partially unfolded proteins that can form toxic oligomers and abnormal intracellular aggregates under pathologic conditions. A critical role for soluble amyloid oligomers in neurodegeneration has become an accepted hypothesis for multiple neurodegenerative diseases, including Alzheimer's disease, PD, DLB, and amyotrophic lateral sclerosis. A body of evidence points to oligomeric species as the culprits in pathogenesis, rather than the large fibrillar aggregates detected in postmortem histopathologic studies (9). The detection of oligomeric species is challenging, and specific tools for immunohistochemical detection of tau and α -synuclein oligomers have not been available to the scientific community until now. For the past several years, Kaye's group has been actively working on designing conformation-specific antibodies to enable efficient detection of oligomers associated with neurodegenerative disease. This group was previously successful in developing and characterizing a tau oligomer-specific antibody, known as T22 (10). In this issue of *Biological Psychiatry*, the group reports two newly developed antibodies, F8H7 and Syn33, specific for α -synuclein oligomers. These new conformation-specific antibodies are extensively and elegantly characterized in this priority communication. The authors demonstrate their high sensitivity for the oligomeric form of α -synuclein versus the monomeric form as well as selectivity over other amyloid oligomers (e.g., A β). Moreover, the group demonstrates the validity of the antibodies in myriad different applications, such as Western blot, enzyme-linked immunosorbent assay, coimmunoprecipitation, and particularly human tissue staining. Until now, available oligomer-specific antibodies offered limited specificity and sensitivity and rarely worked on fixed tissue samples. Lastly, these antibodies have been raised in different hosts and isotypes (polyclonal rabbit immunoglobulin G, a monoclonal mouse immunoglobulin M and immunoglobulin G), presenting the possibility to use them in combination or with sequence specific antibodies. Together, T22, F8H7, and Syn33 represent powerful new tools to study the possible synergic effect of tau and α -synuclein in diseases.

Sengupta *et al.* also offer a first glimpse of how these antibodies can help in understanding the role of tau and α -synuclein oligomers in neurodegeneration. Immunostaining of PD and DLB brain tissue with F8H7 and T22 reveals a significant level of tau oligomers in addition to α -synuclein oligomers compared with control cases. Colocalization of tau and α -synuclein oligomers was observed by confocal microscopy, identifying coaggregation of tau and α -synuclein in hybrid oligomers in the same neurons. Using coimmunoprecipitation followed by immunoblotting and atomic force microscopy, the authors confirm the presence of comorbid oligomers of α -synuclein and tau in patients with PD and DLB. This is the first time that hybrid oligomeric structures have been reported in diseased human brains, confirming the in vitro findings of Nübling *et al.* (8). This new finding suggests that a role for tau in synucleinopathies has probably been underestimated until now and points out the importance of understanding physiologic tau- α -synuclein interactions.

In conclusion, elucidating the mechanism by which tau and α -synuclein oligomers synergistically lead to hybrid oligomers is crucial and requires further study. For example, it would be useful to know how and to what extent tau oligomers or hybrid oligomers are pathogenic in synucleinopathies. Can hybrid oligomers of α -synuclein and tau seed further oligomer formation and aggregation? Also, with the current supposition that extracellular oligomers of α -synuclein and tau are important in disease progression, it will be important to determine if hybrid oligomers of α -synuclein and tau can be detected in the extracellular milieu, are transmitted trans-synaptically, and propagate pathology and neurodegeneration. Although the work of Sengupta *et al.* focuses on tau oligomers in brains of patients with PD and DLB, it opens the door to the next question—can hybrid oligomers be detected in brains of patients with Alzheimer's disease with T22 and F8H7? To address this question, the newly developed conformation-specific antibodies described herein will be invaluable tools to move the field of neurodegeneration forward.

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Figure 1.

Tau and α -synuclein interactions. Tau and α -synuclein are known to interact at the monomeric level and potentiate each other's aggregation into homomeric amyloid fibrils. Sengupta *et al.* demonstrate that under pathologic conditions, tau and α -synuclein also interact to form hybrid co-oligomers that can be recognized by a tau oligomer-specific antibody T22 and the α -synuclein oligomer-specific antibodies F8H7 or syn33.