Alzheimer disease (AD), the most common neurodegenerative disorder, is characterized by the accumulation of amyloid beta (Aβ) and tau into plaques and tangles, respectively. Other neurodegenerative disorders such as Parkinson disease (PD) and dementia with Lewy bodies (DLB), though distinct neurological disorders, have some common pathological features that may have an impact on the clinical characteristics of these diseases. However, the question of whether these disorders have a common pathophysiology remains. Clinton and colleagues recently reported a mouse model that exhibits the combined pathologies of AD, PD, and DLB, a finding that may shed some light on this issue. Using this mouse model, the authors demonstrate that the pathogenic proteins amyloid beta, tau, and alpha-synuclein interact synergistically to enhance the accumulation of one another and accelerate cognitive decline. These data indicate shared pathogenic mechanisms and suggest the possibility that therapeutic interventions successfully targeting one of these pathogenic proteins have implications for a number of related neurodegenerative disorders.
pathologies of Aβ, tau, and SNCA. This animal was generated by introducing a mutant human SNCA transgene (SNCA<sub>AS5T</sub>) into the 3xTg-AD triple-transgenic mouse (hAPP<sub>Sw</sub>/hTau<sub>P301L</sub>/hPS1<sub>M146V</sub>). The authors report that the resulting 4xTg mice exhibit increased insoluble Aβ and thioflavin-S-positive plaque pathology and increased insoluble tau and AT8 phosphorylated tau immunoreactivity compared with the 3xTg-AD mouse model, suggesting that the addition of SNCA promotes the accumulation of these pathogenic proteins. Additionally, the 4xTg mice exhibit increased insoluble SNCA, increased phosphorylated SNCA, and accelerated deposition of Lewy body inclusions compared with single-transgenic SNCA mice, suggesting an effect of Aβ and tau on SNCA pathology. Importantly, the 4xTg mice exhibit accelerated cognitive decline compared with 3xTg-AD mice and single-transgenic SNCA mice, suggesting that the exacerbated pathology is clinically relevant. The authors conclude that Aβ, tau, and SNCA can synergistically promote the aggregation and deposition of each other and thereby accelerate cognitive decline.

There are many animal models of neurodegenerative diseases, yet none fully reproduces the full neuropathological or clinical features of the human disease. The mouse model described above is unique because it exhibits all three proteinopathies clinically associated with AD, DLB, and PD. But what disease does this animal model represent? One might argue that it represents a composite of several distinct diseases – AD, DLB, PD, and tauopathies – that do not naturally occur together. The resulting pathologies may be driven separately by the different transgenes: plaque pathology by the AD-associated APP and PS1 mutations; tau pathology by the frontotemporal dementia with Parkinsonism-chromosome 17 (FTDP-17) mutation in tau; and Lewy body pathology by the familial PD-associated mutation in SNCA. However, this mouse model strongly suggests that an interaction among these proteins results in a behavioral manifestation that models the clinical characteristics of these diseases to some extent. Importantly, clinical research in humans indicates that these diseases may be linked by common pathological changes involving these proteins and that these changes have clear clinical effects.

The molecular mechanisms that promote the synergistic aggregation of Aβ, tau, and SNCA remain to be elucidated. These proteins, and their aggregated pathological forms, often do not reside in the same neurons or cellular compartments, making physical interactions problematic. Thus, one can hypothesize that there may be a common underlying pathogenic mechanism that independently promotes the aggregation of multiple proteins in susceptible cells. However, the data from Clinton and colleagues suggest a more direct cooperative interaction in which the aggregating proteins themselves may seed each other. Under pathological conditions, there may be aberrant co-localization of these proteins, as either oligomers or fibrils. These proteins may then act as seeds to promote the fibrillation of one another in a synergistic manner. The amyloidogenic nature of these proteins may play a role in this interaction. Such a seeding mechanism has been proposed to explain how tau and SNCA inclusions can co-localize in the same cells in several neurodegenerative diseases, including AD and DLB [16]. The authors propose a mechanism by which amyloidogenic SNCA forms a seed that then primes tau to acquire a conformational change allowing its polymerization. In support of this seeding mechanism is a finding by Yagi and colleagues [17] that the amyloid fibril formation of SNCA is enhanced by the preformed amyloid seeds of other proteins. Additional support comes from data demonstrating the co-localization of epitopes of tau and SNCA in Lewy bodies in some neurons [18] as well as the co-localization of Aβ and tau in neurofibrillary tangles and extracellular Aβ deposits (reviewed in [19]). Of particular clinical relevance is that interfering with this seeding process could impact the aggregation of multiple pathogenic proteins and, hopefully, impact the clinical progression of disease.

In summary, the study by Clinton and colleagues is a good example of how animal models studied in parallel with their human diseases can be complementary and provide novel information about the mechanisms of the disease process. In addition, such a model may provide opportunities for screening therapeutic interventions and validating diagnostic tests that could be useful for a number of closely related neurodegenerative diseases.

**Abbreviations**

Aβ, amyloid beta; AD, Alzheimer disease; AD-LBV, Alzheimer disease-Lewy body variant; CSF, cerebrospinal fluid; DLB, dementia with Lewy bodies; FTDP-17, frontotemporal dementia with Parkinsonism-chromosome 17; PD, Parkinson disease; PDD, dementia in Parkinson disease; SNCA, alpha-synuclein.

**Competing interests**

The authors declare that they have no competing interests.

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