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Truncation: A possible mechanism for diversity in Alpha-synuclein prion-like properties

Parkinson's disease (PD) is the most common neurodegenerative movement disorder, which is characterized by motor disturbances such as tremor and bradykinesia resulting from severe degeneration of nigral dopaminergic neurons. The pathological hallmark of PD is the presence of aggregated α-synuclein (α-syn). Numerous studies support that these aggregated α-syn can propagate in diseased brains via the neural network in a prion-like manner. The α-syn aggregates found in sporadic α-synucleinopathies such as PD, dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) have different structural and biophysical properties, which enables them to produce distinct disease phenotypes. However, the mechanism for the generation of the structural variants of α-syn aggregates in sporadic α-synucleinopathies is still unclear.

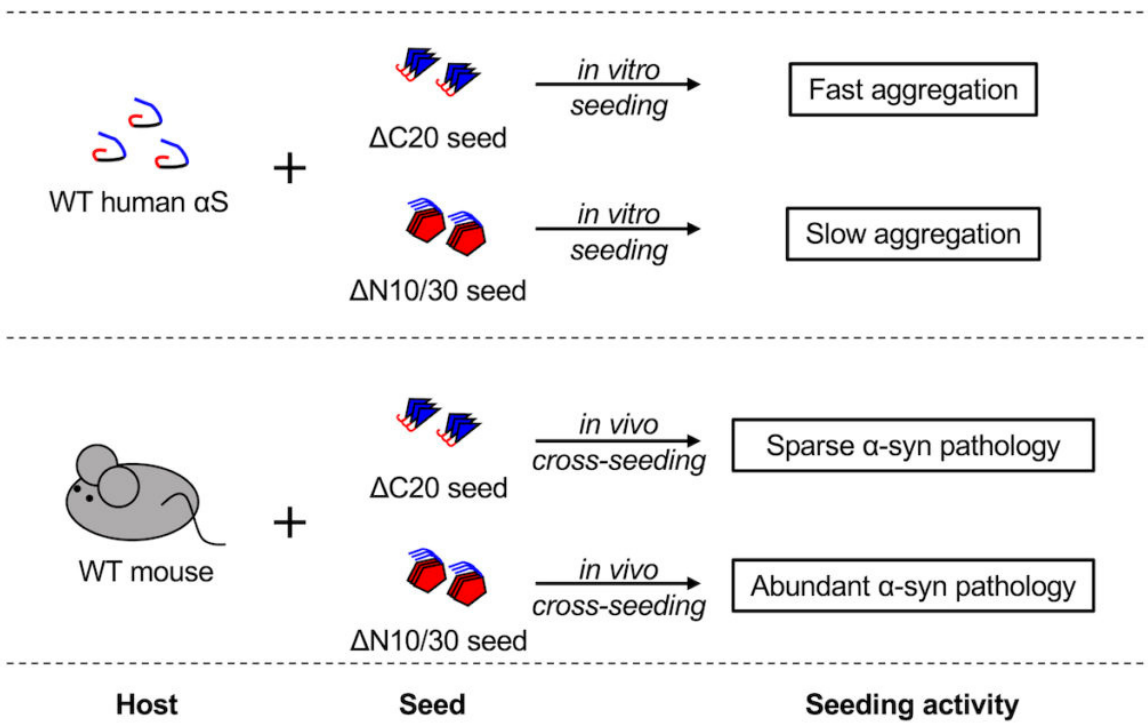

Fig. 1. Schematic representation of the effect of truncation on prion-like properties of α-synuclein.
WT; wild-type, ΔC20: C-terminal 20-residue truncated human α-syn fibrils, ΔN10/30: N-terminal 10-/30-residue truncated human α-syn fibrils

In the present study, we investigated the effect of truncation on prion-like properties of α-syn in vitro and in vivo. Previous studies have shown that both N- or C-terminally truncated species of α-syn are detected in both patients and healthy individuals and that aggregation of α-syn is frequently exacerbated by the truncation of α-syn. Most of the previous studies have focused on the C-terminal truncation, but familial PD-related point mutations are located in the N-terminal region; this observation suggests the importance of the N-terminal region in pathogenic aggregation of α-syn. Therefore, we generated synthetic fibrils from a series of both N-

and C-terminal deletion variants of the human α-syn protein. First, we examined their seeding activities for full-length human α-syn in vitro using thioflavin T assay. The C-terminal 20-residue truncated human α-syn fibrils (DC20) showed higher capacity to seed the aggregation of full-length human α-syn, whereas other types of truncated α-syn fibrils caused slower aggregation (Fig. 1). We then inoculated the wild-type and truncated human α-syn fibrils into the striatum of the wild-type mice. Subsequently, we investigated the ability to induce phosphorylated α-syn aggregates histochemically and biochemically. Consistent with previous studies, wild-type human α-syn fibrils triggered little phosphorylated α-syn pathology in the wild-type mouse brain, suggesting the presence of species barrier commonly observed in the prion-like propagation. C-terminal truncated human α-syn fibrils also induced only sparse phosphorylated α-syn pathology limited in the injection site. Alternatively, we observed abundant and widespread phosphorylated α-syn pathology in mice treated with N-terminally truncated human α-syn fibrils (DN10 and DN30); this suggests the presence of a lower species barrier between these truncated human α-syn and mouse α-syn (Fig. 1). The structural compatibility between the seed and host proteins is important for cross-seeding activity; therefore, we then examined the patterns of proteolytic cleavage of these fibrils. As expected, wild-type human and wild-type mouse α-syn fibrils showed different cleavage patterns. Interestingly, the cleavage patterns of N-terminally truncated human α-syn fibrils and wild-type mouse fibrils were very similar, indicating that these fibrils share similar structural properties. Unlike N-terminal 10- or 30-residue truncated α-syn fibrils, N-terminal 20-residue truncated α-syn fibrils could not induce abundant phosphorylated α-syn pathology. We found that the former two truncated fibrils were more sensitive to chemical denaturants than the later fibril, suggesting that the higher fragility of fibrils enhanced the cross-seeding activities. Taken together, these results indicate that N-terminal truncation can drastically alter the structural properties of human α-syn fibrils and reduce the species barrier between the human and mouse.

In summary, the present study showed that both N- and C-terminal truncations have an important role in structural properties of α-syn fibrils that lead to phenotypic diversity of α-synucleinopathies.

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