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Post-translational modifications regulate α-synuclein aggregate structure and propagation properties

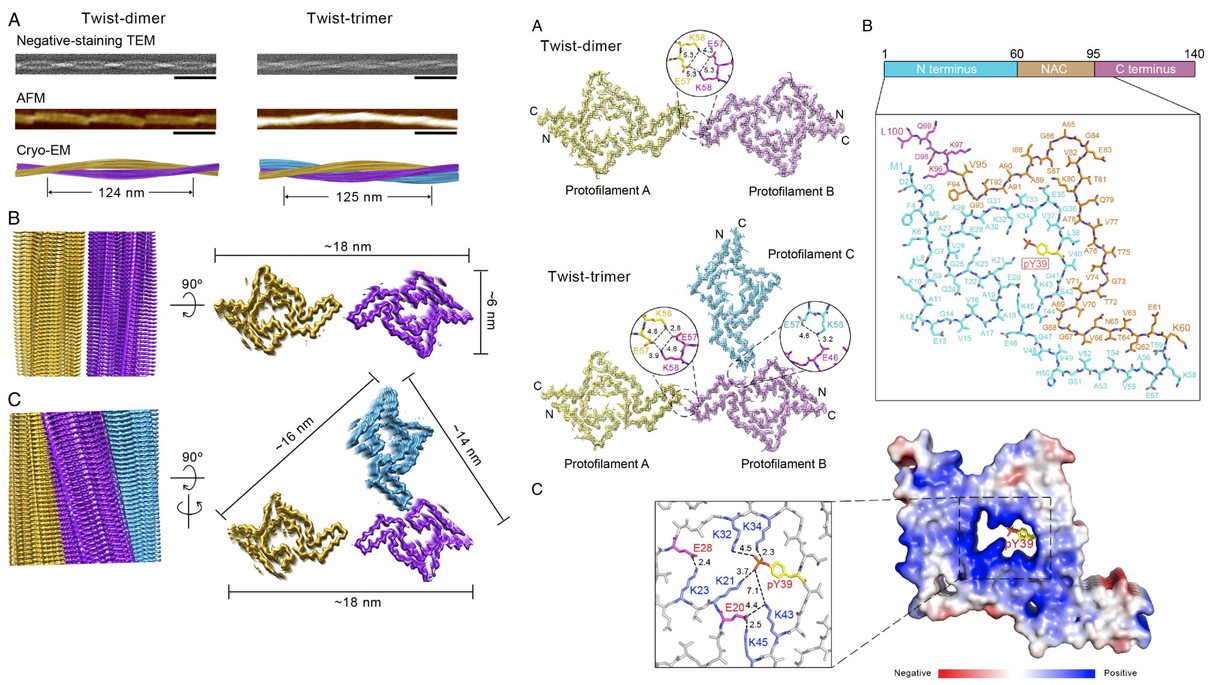
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One pathological hallmark of Parkinson's disease (PD) is α-synuclein (α-syn) forming pathological fibrils that propagate between neurons. Post-translational modifications (PTMs) critically regulate amyloid aggregation and fibril structure.

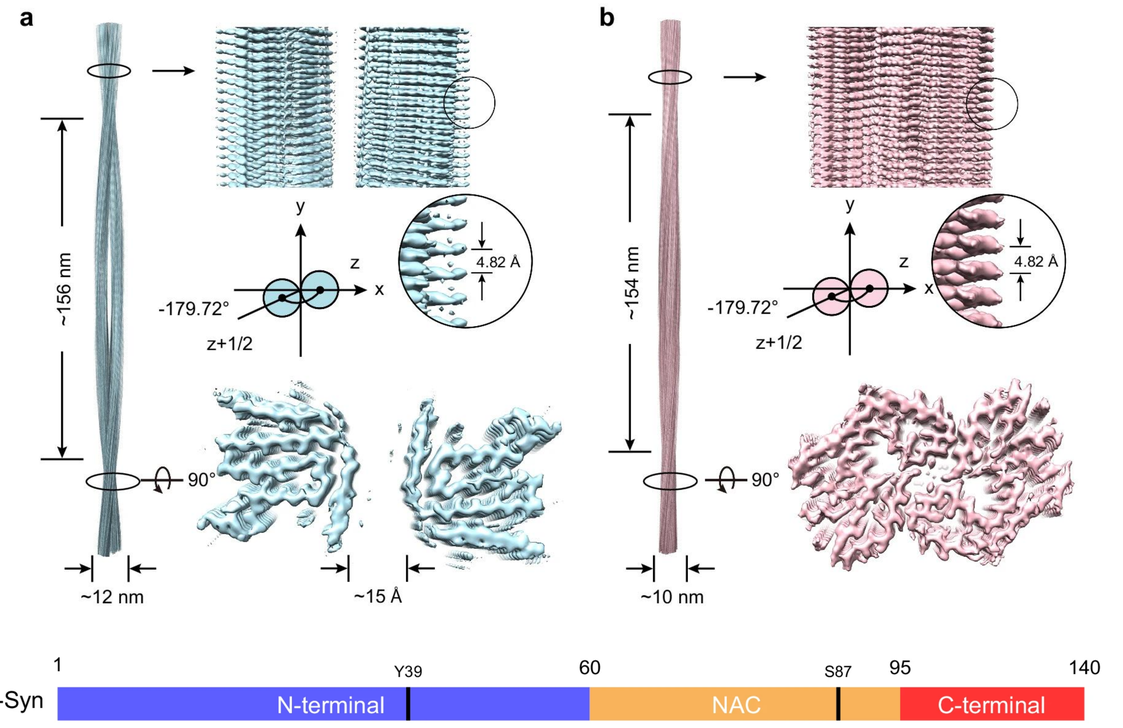
We determined the cryo-EM structure of α-syn fibrils phosphorylated at tyrosine 39 (pY39), revealing that phosphorylation acts as a "structural switch" driving pathogenic conformations. We further demonstrated that distinct PTMs at the same residue produce structural heterogeneity: Ser87 phosphorylation (pS87) and O-GlcNAc glycosylation (gS87) generate completely different fibril cores with distinct propagation properties.Mechanistically, we identified lymphocyte-activation gene 3 (LAG3) as a key receptor mediating pathological α-syn fibril endocytosis. The LAG3 D1 domain recognizes fibril β-sheet grooves through hydrophobic interactions, essential for transcellular transmission.

pY39 rearranges α-synuclein amyloid fibril structure

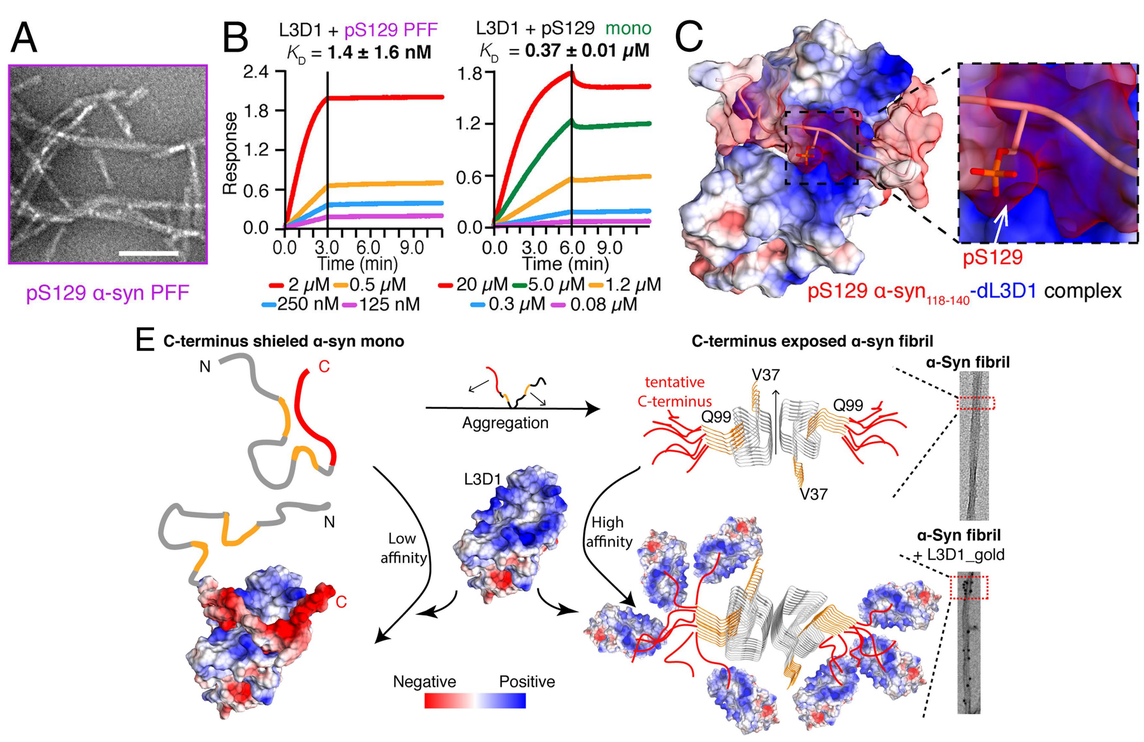


Cryo-EM polymorphs and fibril structure of pY39 α-syn (Proc. Natl. Acad. Sci. USA, 2020)

PTMs at the same site generate distinct fibril structures



pS129 enhances the binding of α-Syn fibril to LAG3



Mechanism of the preferential binding of L3D1 with α-syn fibrils (Proc. Natl. Acad. Sci. USA, 2021)

Comparison of α-syn fibril structures with different modifications (Nat. Commun., 2024)

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