

TARGETING α -SYNUCLEIN AGGREGATION VIA hHEP1-MEDIATED PHASE SEPARATION: MECHANISTIC INSIGHTS INTO THE COCHAPERONE- α -SYNUCLEIN INTERACTION

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Abstract

INTRODUCTION: Parkinson's disease (PD) is a progressive neurodegenerative disorder marked by dopaminergic neuron loss in the substantia nigra. A key pathological feature is the intracellular aggregation of α -synuclein (α -Syn), a 14 kDa presynaptic protein. Under pathological conditions, α -Syn misfolds into β -sheet-rich structures that form toxic oligomers and fibrils. Peptides containing the GKNEE motif have shown anti-aggregation properties. Human Hsp70-escort protein 1 (hHEP1), a 124-residue cochaperone, possesses similar sequence motifs and structural features potentially relevant to α -Syn modulation. **OBJECTIVES:** To investigate whether hHEP1 inhibits α -Syn aggregation and to elucidate the underlying mechanism of this activity. **METHODS:** Recombinant α -Syn was incubated with increasing hHEP1 molar ratios (1:0.25 to 1:2). Aggregation was monitored via Thioflavin T fluorescence. Transmission electron microscopy (TEM) assessed fibril formation. To evaluate target specificity, hHEP1 was added at various time points post-aggregation initiation. LLPS behavior was tested in 30% PEG 4000 using fluorescence microscopy. **RESULTS/DISCUSSION:** hHEP1 delayed aggregation at substoichiometric levels and completely inhibited fibril formation at a 1:1 ratio. TEM showed only small oligomers at 1:1 and no fibrils at 1:2. Delayed hHEP1 addition had no inhibitory effect, indicating specificity for monomeric α -Syn. Under crowding conditions, hHEP1 formed phase-separated condensates, while α -Syn did not. However, α -Syn was recruited into hHEP1 droplets, suggesting a sequestration-based inhibitory mechanism. **CONCLUSION:** hHEP1 effectively inhibits α -Syn aggregation by interacting with its monomeric form and recruiting it into phase-separated compartments, preventing nucleation and fibril propagation. This highlights hHEP1 as a potential modulator of pathological α -Syn aggregation in PD.



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Track

- Protein structure, function, conversion, and dysfunction

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