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Investigating the Aggregation of ?-synuclein Variants and Their Interactions with a Molecular Tweezer

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Abstract

The protein ?-synuclein (?-syn) self-assembles under abnormal conditions into toxic aggregates thought to be a central cause of pathology in neurodegenerative diseases such as Parkinson's Disease (PD). A promising approach for treating PD is to inhibit the abnormal self-assembly of ?-syn in the brain by using small molecules called "molecular tweezers" that the Bitan laboratory has been developing. Molecular tweezers bind to lysine (Lys) residues and prevent both hydrophobic and electrostatic interactions that are key to abnormal self-assembly. The molecular tweezer CLR01 inhibits the self-assembly of ?-syn *in vitro* and *in vivo* by preferentially binding to Lys at positions 10 and/or 12 and at the region spanning residues 43-58. This leads me to investigate how effective CLR01 is in preventing aggregation when the amino acid at the binding site is substituted, by using Lys to Ala variants of ?-syn at positions 43 and 58. I hypothesize that CLR01 will prevent more effectively aggregation in the wild type (WT) than it will in the two variants because essential binding sites will be missing in these variants. As my main experimental method, I use the Thioflavin-T fluorescence assay to measure the amount and kinetics of ?-pleated sheet formation, which is analogous to ?-syn aggregation regardless of the absence or concentration of CLR01. This study will provide insight into the preferred binding site of CLR01 and the behavior of ?-syn containing amino acid substitutions and thus will increase our understanding of this important mechanism underlying PD and potentially direct future drug development efforts.

KEYWORDS: Parkinson's disease; ?-synuclein; CLR01; ?-pleated sheet formation; amyloid

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ABSTRACT

The protein α-synuclein (α-syn) self-assembles under abnormal conditions into toxic aggregates thought to be a central cause of pathology in neurodegenerative diseases such as Parkinson's Disease (PD). A promising approach for treating PD is to inhibit the abnormal self-assembly of α-syn in the brain by using small molecules called "molecular tweezers" that the Bitan laboratory has been developing. Molecular tweezers bind to lysine (Lys) residues and prevent both hydrophobic and electrostatic interactions that are key to abnormal self-assembly. The molecular tweezer CLR01 inhibits the self-assembly of α-syn *in vitro* and *in vivo* by preferentially binding to Lys at positions 10 and/or 12 and at the region spanning residues 43-58. This leads me to investigate how effective CLR01 is in preventing aggregation when the amino acid at the binding site is substituted, by using Lys to Ala variants of α-syn at positions 43 and 58. I hypothesize that CLR01 will prevent more effectively aggregation in the wild type (WT) than it will in the two variants because essential binding sites will be missing in these variants. As my main experimental method, I use the Thioflavin-T fluorescence assay to measure the amount and kinetics of □-pleated sheet formation, which is analogous to α-syn aggregation regardless of the absence or concentration of CLR01. This study will provide insight into the preferred binding site of CLR01 and the behavior of α-syn containing amino acid substitutions and thus will increase our understanding of this important mechanism underlying PD and potentially direct future drug development efforts.

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