Structures and Propagation of Pathologically Relevant Amyloids in Alzheimers.

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USA

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Structures and Propagation of Pathologically Relevant Amyloids in Alzheimers.

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3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

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Research Abstract

? DESCRIPTION (provided by applicant): Amyloid fibrils of 42- and 40-residues Alzheimer’s ?-amyloid (A?) peptides represent two primary components of senile plaques, which are a

hallmark of Alzheimer’s disease (AD). As amyloid fibrils formed via self-assembly of A? show notable toxicity, neural cell deaths in AD have long been associated with A? amyloid fibrils. More recently, diffusible subfibrillar aggregates of A? were identified as a new suspect of AD since many of these diffusible A? aggregates show much higher toxicity than A? fibrils. Molecular structures of amyloid fibrils and diffusible aggregates of A? have attracted great attention. However, applications of traditional methods such as X-ray crystallography or solution NMR have been limited to non-crystalline amyloid aggregates. In particular, for more pathologically relevant 42-residue A? (A?42), only a few atomic-level structural details were known because of notoriously difficult sample preparation due to its high propensity to aggregate. Similarly, for A? mutants associated with early onset of AD, very little is known about structures of most pathogenic mutants such as E22G A? because they aggregate readily into heterogeneous aggregates, which are not suited for a structural analysis. Through this study, we will reveal atomic details of amyloid fibrils and spherical aggregates in order to highlight structural relationships and interactions between different amyloid aggregate species, in particular for A?42, which is considered to be more pathogenic than more abundant 40-residue A?40. As a vital tool for site- specific structural analysis for amyloid aggregates, we will use solid-state NMR (SSNMR), in a combination with transmission electron microscopy (TEM), MD simulations, and other biochemical/biophysical methods. Our studies entail the following three Specific Aims. (1) In Aim 1, we will establish preparation of homogenous amyloid fibrils optimized for structural analyses for A?42 and a pathogenic mutant E22G A?40. For the A?42 fibrils, we will elucidate atomic-level structural details by advanced SSNMR spectroscopy. The interactions of different A? species in AD will be modeled by cross-seeding experiments, which allow us to examine structural compatibility of two different A? species in fibrils. The aim will define structures and structural variations of A?42 fibrils while offering insight into how the structures can impact AD progression. (2) In Aim 2, we will examine atomic details of two distinctive diffusible A?42 aggregates. First, we will establish a synthetic reconstitute of highl toxic subfibrillar aggregate called amylospheroid (ASPD), which is found in AD brains. As the level of ASPD is correlated with the severity of AD, this study will reveal the first atomic detail a pathologically relevant amyloid oligomer in AD. We will also examine a similar spherical assembly called SPA, which has a larger size (20 nm diameter) and modest toxicity. (3) In Aim 3, we will profile structures and toxicity of brain-derived A?42 fibrils, which are replicated fro A?42 fibrils in AD brain. Through a comparison of ~30 brain samples, the aim will allow us to compare structures and toxicity of brain-derived amyloid fibrils in AD.

Lay Summary

PUBLIC HEALTH RELEVANCE: This project will address central problems associated with Alzheimer’s disease (AD) and amyloid-? (A?) protein that forms toxic fibrillar or spherical aggregates, which are linked to neural deaths in AD. The specific problems studied in this proposal include: how the structure of most pathologically relevant 42-residue A?42 differs from well characterized but less toxic 40-residue A?40 in fibril aggregates, how more toxic spherical aggregates of A?42 is structurally different from fibrillar aggregate for A?42. Besides in-vitro models, structures and toxicity of fibrillar aggregates replicated from human brain samples will be studied; the results will be directly relevant to understanding the mechanism and finding of new diagnosis for AD.

Further information available at:

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United States of America

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Alzheimer's disease & other dementias

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