Molecular mechanism of amyloid beta aggregation

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Question
Principal Investigators
Related
Institution
Contact information of lead PI
Country

European Commission

Title of project or programme

Molecular mechanism of amyloid beta aggregation

Source of funding information

European Commission FP7-Seventh Framework Programme

Total sum awarded (Euro)

€ 2,499,920

Start date of award

01/02/2014

Total duration of award in years

5.0

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords
Research Abstract

Generation of toxic oligomers during aggregation of amyloid beta peptide (Abeta42) into amyloid fibrils is a central event in Alzheimer disease. Understanding the aggregation process is therefore one important step towards therapy and diagnosis of the disease. We propose a physical chemistry approach with the goal of finding the molecular mechanisms behind the process in terms of the underlying microscopic steps and the molecular driving forces governing each step. We will use methodology developed recently in our laboratory yielding unprecedented reproducibility in the kinetic data. The methodology relies on optimization of every step from production and purification to isolation of highly pure monomeric peptide, and inertness and minimized area of all surfaces. We will use cell viability studies to detect toxic

oligomeric species, and selective radio-labeling experiments to pinpoint the origin of those species. In order to obtain insight into the molecular determinants and the relative role of different kinds of intermolecular interactions for each microscopic step, we will study the concentration dependent aggregation kinetics as a function of extrinsic and intrinsic parameters. Extrinsic parameters include temperature, salt, pH, biological membranes, other proteins, and low and high Mw inhibitors. Intrinsic parameters include point mutations and sequence extension/truncation. We will perform detailed kinetic studies for each inhibitor to learn which step in the process is inhibited coupled to cell toxicity assays to learn whether the generation of toxic oligomers is limited. We will use spectroscopic techniques, dynamic light scattering, cryogenic transmission electron microscopy and mass spectrometry coupled to HD exchange to learn about structural transitions as a function of process progression under different conditions to favor different microscopic steps. The results may lead to improved diagnostics and therapeutics of Alzheimer disease.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
European Commission

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:
N/A