Amyloid Oligomers: Precursors, Competitors or Inhibitors of Mature Fibril Formation?

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Principal Investigators

MUSCHOL, MARTIN

Institution

UNIVERSITY OF SOUTH FLORIDA

Contact information of lead PI
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Research Abstract

? DESCRIPTION (provided by applicant): Amyloid Oligomers: Precursors, Competitors or Inhibitors of Mature Fibril Formation? Project Summary Deposits of amyloid fibrils, insoluble protein fibrils with cross beta-sheet structure, are characteristic of numerous human disorders, including Alzheimer’s disease, Parkinson’s diseases and type II diabetes. Research over the past decade has implicated amyloid oligomers, which are early-stage assembly intermediates, instead of the late-stage mature fibrils as the molecular species responsible for cell toxicity.

Hence, elucidating the mechanisms that regulate the assembly of toxic oligomers and their transformation into relatively benign amyloid fibrils can inform rational drug design and even approaches towards therapeutic interventions. The focus of the proposed research is on the role of amyloid oligomers in the fibril assembly process. Using the Alzheimer-disease peptide A?(1-40) and the model amyloid lysozyme we will determine whether toxic oligomers are a required prerequisite of amyloid fibril growth or an off-pathway by-product competing with fibril formation. In addition, we will investigate our observation that these toxic oligomers, at elevated concentrations, could retard the formation of comparatively benign fibrils. The specific experiments outlined below will utilize fluorescence spectroscopy, static and dynamic light scattering, electron and atomic force microscopy, Fourier-Transform infrared spectroscopy and selective fluorescence labeling of proteins. The proposal has three specific aims. In aim 1 we will ascertain whether amyloid oligomers compete with or, instead, are required precursors of amyloid fibril formation. We will perform these experiments under two types of experimental conditions that allow us to test whether amyloid oligomers can undergo fast or slow structural reconfiguration into amyloid fibrils. While experiment in aim 1 relied on intimate knowledge of the “”assembly phase space”” for lysozyme amyloids, in aim 2 we will perform selective fluorescence labeling of amyloid oligomers and track whether they are the direct precursors or competitors of mature amyloid fibril formation. This approach allows us to include the Alzheimer peptide A?(1-40) into our study. Under aim 3 we will quantify preliminary observation that amyloid oligomers can, under some circumstances, actively inhibit the process of mature fibril nucleation. Such “”self-inhibition”” of fibril formation by oligomers could significantly increase th period over which oligomers can induce cell pathology. We will investigate molecular crowding, solution viscosity and gelation as potential mechanisms mediating the observed inhibition.

Further information available at:

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