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PII: S0005-2736(18)30091-9
DOI: doi:10.1016/j.bbamem.2018.03.011
Reference: BBAMEM 82736

To appear in:

Received date: 31 December 2017
Revised date: 6 March 2018
Accepted date: 7 March 2018

Please cite this article as: Xinwei Ge, Yunxiang Sun, Feng Ding , Structures and dynamics of β-barrel oligomer intermediates of amyloid-beta16–22 aggregation. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Bbamem(2018), doi:10.1016/j.bbamem.2018.03.011

# Structures and Dynamics of β-barrel Oligomer Intermediates of Amyloid-beta16-22 Aggregation

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## Abstract

Accumulating evidence suggests that soluble oligomers are more toxic than final fibrils of amyloid aggregations. Among the mixture of inter-converting intermediates with continuous distribution of sizes and secondary structures, oligomers in the β-barrel conformation – a common class of protein folds with a closed β-sheet – have been postulated as the toxic species with well-defined three-dimensional structures to perform pathological functions. A common mechanism for amyloid toxicity, therefore, implies that all amyloid peptides should be able to form β-barrel oligomers as the aggregation intermediates. Here, we applied all-atom discrete molecular dynamics (DMD) simulations to evaluate the formation of β-barrel oligomers and characterize their structures and dynamics in the aggregation of a seven-residue amyloid peptide, corresponding to the amyloid core of amyloid-β with a sequence of $^{16}$KLVFFAE$^{22}$ (Aβ16-22). We carried out aggregation simulations with various numbers of peptides to study the size dependence of aggregation dynamics and assembly structures. Consistent with previous computational studies, we observed the formation of β-barrel oligomers in all-atom DMD simulations. Using a network-based approach to automatically identify β-barrel conformations, we systematically characterized β-barrels of various sizes. Our simulations revealed the conformational inter-conversion between β-barrels and double-layer β-sheets due to increased structural strains upon forming a closed β-barrel while maximizing backbone hydrogen bonds. The potential of mean force analysis further characterized the free energy barriers between these two states. The obtained structural and dynamic insights of β-barrel oligomers may help better understand the molecular mechanism of oligomer toxicities and design novel therapeutics targeting the toxic β-barrel oligomers.

## Introduction

Amyloid depositions of protein aggregation are associated with more than 25 degenerative diseases, including Alzheimer's disease [1, 2], Parkinson's disease [3, 4], prion conditions [5] and type-2 diabetes [6-8]. Despite differences in sequence and length of aggregating proteins, different amyloid proteins show similar all-or-none sigmoidal aggregation kinetics and common fibrillar morphology with the characteristic cross-β core of their final aggregates. These similarities together with the shared symptoms of different amyloid diseases suggest a potentially common mechanism for amyloid cytotoxicity [9-11]. Although mature fibrils were long suspected to be the toxic disease agents, more and more experimental studies with different amyloid proteins suggested that the small soluble oligomer intermediates populated during