Amyloid-β_{42} Oligomer Structures from Fibrils: A Systematic Molecular Dynamics Study

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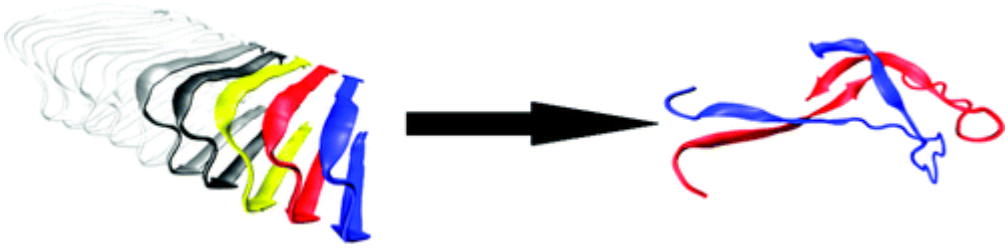
The formation of a so-called 'cross-β-sheet' structure with consecutive protein aggregation and amyloid deposition is a hallmark of several neurodegenerative disorders. These β-sheet aggregates are discussed as the primary cause for a number of protein-misfolding diseases, among whom Alzheimer's disease (AD) is the most prominent one. The 39- to 43-residue-long amyloid-β (Aβ) peptide, generated from the amyloid precursor protein, is the major component of AD-associated amyloid plaques consisting of protein fibrils.

Recent experimental data demonstrate that small, soluble $A\beta_{42}$ oligomers are the pathological effectors in Alzheimer's disease because they exhibit neurotoxic properties and also act as seed for fibril growth.[1,2]

One topic, which is not yet fully understood, is the structural similarities and differences between Aβ oligomers and the mature fibril. In light of the experimental observation that oligomers both play a role in initiating fibril growth and exhibit neurotoxic properties, it would be helpful to know whether the Aβ conformation detected in the mature fibril also represents a populated energy minimum for small oligomers or whether this topology is stable only in larger assemblies.

The aim of the present study was therefore to address the conformational stability of small oligomers starting from the fibril-bound conformation. For that purpose, all-atom molecular dynamics simulations of at least 100 ns in explicit solvent were performed at physiological temperatures for the Aβ monomer through pentamer starting from their fibrillar structure [3].

The structural differences detected between dimers and larger oligomers in our simulations [4] are also of interest for the design of anti-Alzheimer drugs, because they suggest that multiple drugs might be required to target the structurally different neurotoxic oligomers.



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