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Nano-assembly of amyloid β peptide: Role of the hairpin fold

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Abstract:

Statement of the Problem: Increasing evidence suggests that the self-assembly of amyloid β(Aβ) protein underlies the early onset of Alzheimer's disease (AD). Given that small Aβ nano-assemblies (oligomers) are the most neurotoxic species, they have become the major target for the development of treatments and early diagnostic tools for AD. However, advances surrounding this are blocked by the lack of structure intrinsic to Aβ oligomers, as they are transient states of Aβ aggregation kinetics; making traditional structural approaches non-amenable. We have previously developed single-molecule approaches capable of probing of aμ□□o□□□□□□□□□ dimers. Here, we extended our approaches to higher order oligomers. We hypothesized that the folding pattern of amyloid protein defines the aggregation pathway.

Methodology & Theoretical Orientation: In this study, we tested this hypothesis using Aβ(14-23) peptide in linear form and its tandem assembled in the hairpin-type shape. We combined two experimental approaches and molecular dynamics simulations to characterize molecular interactions and the stability of complexes between Aβ (14-23) hairpin and Aβ (14-23) monomer, as well as the interactions between two hairpins.

Findings: The lifetime measurements demonstrate that the Aβ (14-23) hairpin and a Aβ(14-23) monomer assemble in a very stable complex when compared with homologous ensembles. We measured the strength of hairpin-hairpin and hairpin-monomer interactions which demonstrated that the hairpin-monomer interaction is stronger compared with the hairpin-hairpin assembly; data that is fully in line with the lifetime measurements. Aggregation studies demonstrate that the Aβ(14-23) monomer formed fibrils and the hairpin formed spherical structures. However, their mixture formed neither fibrils nor spherical structures, but rather disk shaped nanostructures.

Conclusion & Significance: Overall, our study provides new insight into the role of the monomer structure on the self-assembly process that contributes to the formation of disease aggregates. Importantly, the developed experimental approaches and validation approaches for computational analyses are not limited to amyloid proteins, but can also be applied to other molecular systems.

Biography:

Yuri L Lyubchenko is a Professor of Pharmaceutical Sciences at the University of Nebraska Medical Center, USA. His research focuses on understanding fundamental mechanisms underlying health and disease, which are keys to developing new and more effective diagnostics and medications. This primarily basic research allows him not only to identify new drug targets for small molecule drugs, it also leads to development of the nanotools and methods to discover novel approaches for diagnostic, treatment and disease prevention and to more rapidly determine their effi cacy at the molecular level.

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