Biophysical studies on the effects of in vivo Constituents on amyloid formation in Alzheimer's disease

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Abstract

Introduction: Alzheimer's disease (AD) is the most prevalent form of dementia which dysregulation of the amyloid-beta (Aβ) level leads to Aβ insoluble assemblies and, eventually, alternate with the normal neuronal conditions. Hence One of the grand challenges of biophysics is to understand the principles that govern formation of protein Aggregation like amyloid fibrils. So there is dire need to extend these investigations to in vivo conditions where amyloid formation is affected by a myriad of biochemical interactions.

Methods: Single molecule AFM force spectroscopy has been used to elucidate the role of cations on interpeptide interactions. moreover researchers developed a unique fluorescent assay to monitor fibril formation using to investigate pH effects on Aβ. Also Time-dependent fluorescence spectroscopic measurements carried out to investigate the fibrillation kinetics of islet amyloid polypeptide (IAPP) in the presence of different cosolvents.

Results and discussion: Histidine and lysine roots play an important role in the polymerization and growth of amyloids, and it has been found that pH below 7 have a positive effect on amyloid growth. AFM force spectroscopy revealed that Cu++ cations dramatically change the folding patent of Aβ42 within dimers. Stabilizing co-solvent hamper fibril elongation Conversely, destabilizing (urea) cosolvents leading to retardation of IAPP nuclei formation.

Conclusion: From a multitude of biophysical studies, which are mainly summarized, one knows that most, if not all of the molecules and ions composing the intra- and extracellular spaces have an influence on the thermodynamics and kinetics of amyloid aggregation. They can speed up aggregation.

Keywords: Alzheimer's, Amyloid formation, In vivo, Biophysical studies

Modulation of Ab aggregation by pH changes

The viability of cells is strongly dependent on the regulation of Ph. Kinetic fluorescence measurements demonstrate that the formation of both Ab oligomers and Ab fibrils is strongly influenced by pH.

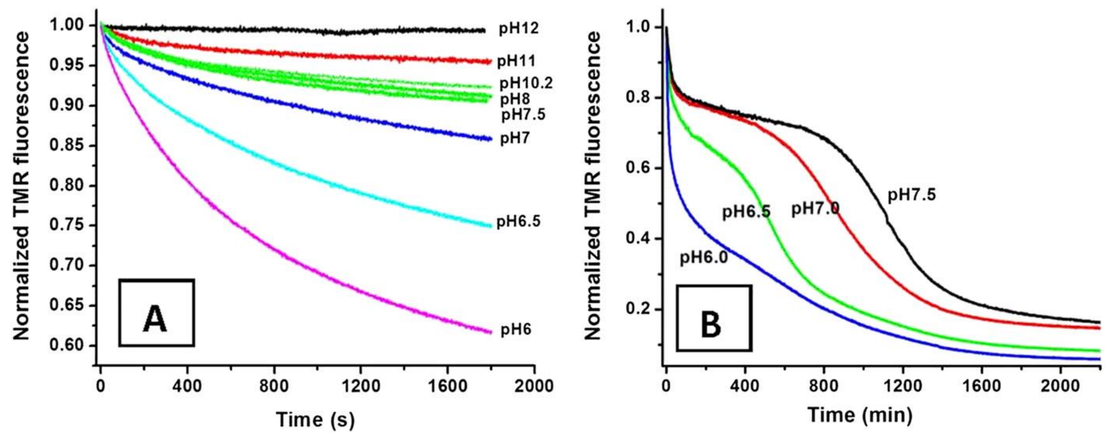
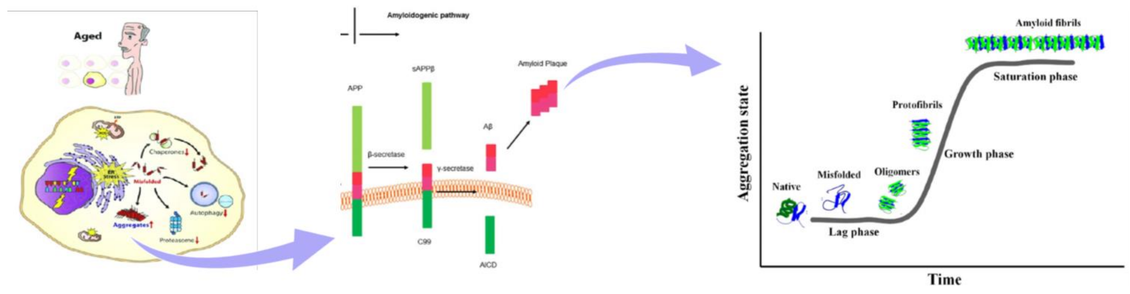


Fig. 5 pH dependence of oligomerization (A) and fibrillization (B) of tetramethylrhodamine (TMR)-amyloid β (Aβ)1–42.

Relationship between Aβ and Alzheimer's disease

Alzheimer's disease (AD) is most prevalent progressive neurodegenerative disorder, that slowly destroys the ability to carry out the simplest tasks. In year1979, amyloid fibrils were identified as the major cause of Alzheimer's disease. Amyloids are abnormal, extracellular, and insoluble fibers that are structurally made of beta plates. Unlike other filamentous proteins, they have no role in stability, motility or structure. The process of amyloid formation involves three phases: a lag phase, followed by an exponential growth phase, and finally a plateau regime. In the following, the most important in vivo conditions known to be related to amyloid diseases are reviewed:



Role of metal ions inamyloid formation

Aggregation of the amyloid β- protein (Aβ) is hallmarks of Alzheimer's disease. Process is dependent on the environmental conditions, including the presence of divalent cations, such as Cu2+. Cu2+ cations regulate early stages of Aβ aggregation, but the molecular mechanism of Cu2+ regulation is unknown. In this study was applied single molecule AFM force spectroscopy to elucidate the role of Cu2+ cations on interpeptide interactions. the combined AFM force spectroscopy and imaging analyses demonstrate that Cu2+ cations promote both the initial and the elongation stages of Aβ aggregation, but protein protonation diminishes the effect of Cu2+.

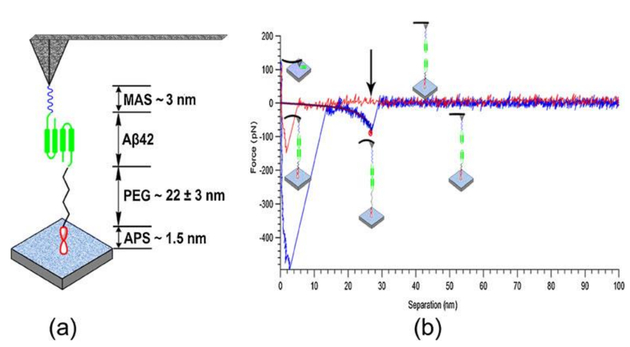
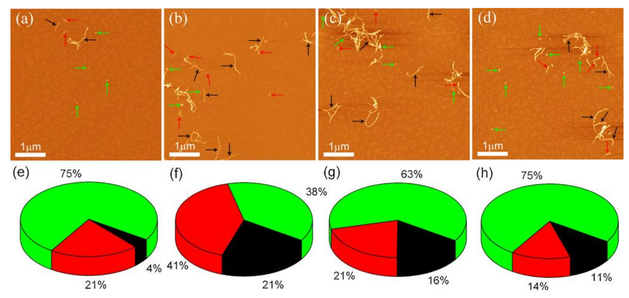


Fig. 5 Experimental setup of SMFS (a). One of the interacting Aβ42 molecules is immobilized on the APS modified mica surface via a long PEG linker. The counterpart Aβ42 molecule is anchored on the MAS functionalized AFM tip. A typical approach-retraction cycle of recorded rupture force curve (b). Red line is the approach force curve and blue line is the force curve for the retraction step followed by the approach.



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Cosolvent effects on the fibrillation reaction of APP

Owing to the presence of various types of osmolytes in the cellular environment, is study focuses on the impact of stabilizing (TMAO and) as well as destabilizing (urea) cosolvents on the aggregation and fibrillation reaction of the highly amyloidogenic amyloid polypeptide (APP).

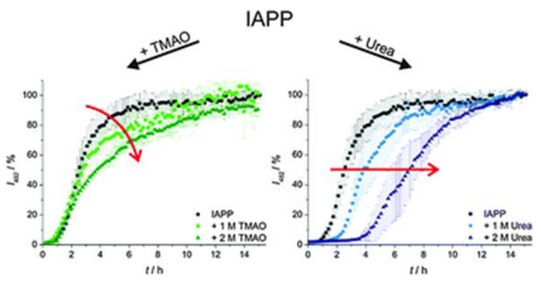

Fig. 2 Normalized fluorescence spectroscopic ThT intensity data of the aggregation of 10 mM IAPP in Presence of different concentrations (a) TMAO, (b) urea.

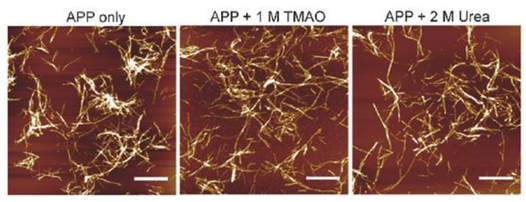

Fig. 3 AFM images showing the fibrillar structures of 50 mM APP after ~ 15h of incubation in solution in the absence and presence of cosolvents.

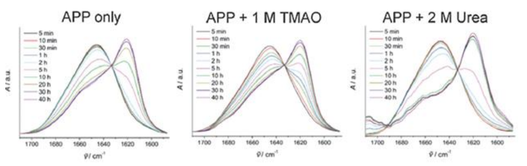

Fig. 4 Area-normalized ATR-FTIR spectra showing time-dependent shifts of the amide-I0 band of 10 mM APP in solution only and in solution containing 1 M TMAO, 2 M 13C-labeled urea and both.

Conclusion

- Depending on the type of cosolvent, a change in the lag time or growth rate of fibrils is observed. Mixtures of chaotropic and kosmotropic cosolvents exhibit a counteractive effect.
- The aggregation propensity of Aβ is highly dependent on pH .
- The pH-dependent protonation of His, His13, and His14 strongly affects the binding properties and coordination modes of Aβ with metal ions such as Cu2+, Fe2+ and Zn2+, and these interaction can induce dimerization. The release of metal ion from proteins can also create an acidic environment, and this positive feedback can further alter the aggregation state of Aβ.

Reference

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