9-30-2015

Preface to Special Topic: Amyloid Aggregation: Characterization, Function and Molecular Mechanisms

Bernard S. Gerstman
Department of Physics, Florida International University, gerstman@fiu.edu

Yifat Miller
Ben-Gurion University of the Negev

Preface to Special Topic: Amyloid Aggregation: Characterization, Function and Molecular Mechanisms

Bernard S. Gerstman[1,a] and Yifat Miller[2,3,a]
[1]*Department of Physics, Florida International University, Miami, Florida, USA*
[2]*Department of Chemistry, Ben-Gurion University of the Negev, Beér-Sheva 84105, Israel*
[3]*Ilse Katz Institute for Nanoscale Science and Technology, Ben-Gurion University of the Negev, Beér-Sheva 84105, Israel*

(Received 28 September 2015; accepted 28 September 2015; published online 30 September 2015)

[http://dx.doi.org/10.1063/1.4932621]

Amyloid aggregation is an intensively studied and fast growing field in science. The accumulation of amyloids in the brain is a hallmark of neurodegenerative diseases, such as Aβ in Alzheimer's Disease (AD) and α-synuclein (AS) in Parkinson's Disease (PD). Amylin or human islet amyloid polypeptide (hIAPP) molecules accumulate in the pancreatic β-cells and lead to the death of the cells in type 2 diabetes (T2D). In addition to their critical importance in health, amyloid aggregation manifests fascinating physics related to the dynamics of self-organization of polymers. This special issue deals with aggregation of these amyloids using both computational and experimental techniques. It focuses on the structures of self-assembled amyloids, the effects of various factors on amyloid aggregation, and presents insights into the mechanisms of amyloid aggregation.

This issue is composed of articles that deal with four main issues: the effects of temperature, pH, and concentration of Aβ on the kinetics of Aβ fibrillization using in vitro techniques, the effect of metal ions on Aβ aggregation using both experimental and computational tools, self-assembly of lysosomes and structural variation of AS using coarse-grained Monte Carlo simulations, and aggregation of the hIAPP dimer using computational techniques.

A systematic investigation of the effects of $A\beta_{42}$ peptide concentration, temperature, pH, added solvents and the ratio of $A\beta_{40}$ and $A\beta_{42}$ on the kinetics of Aβ fibrillization under agitated conditions had been studied by Tiiman et al. using in vitro techniques. In vitro fibrillization kinetics are studied in order to obtain valuable information about the characteristics of Aβ aggregation and to find clues for putative strategies to suppress amyloid aggregation.

Aβ plaque formation and oxidative stress are two key events in the pathology of AD, in which metal ions have been shown to play an important role. When Cu(II) reacts with Aβ, it forms aggregates and also generates reactive oxygen species (ROS). Cu(II) leads to different aggregation states depending on factors such as pH, amyloid concentration, metal-amyloid ratio, temperature, buffer conditions and stirring during incubation. A detailed review by Gamez and Caballero discusses the binding sites of Cu(II) in Aβ oligomers, the affinity of the Cu(II) to Aβ and the etiology of AD which is related to metal dyshomeostasis. This review focuses on experimental techniques and suggests that Cu(II) may prevent AD and illustrates several therapy approaches.

In recent years, the modeling of Cu-Aβ complexes has experienced significant advances. A detailed knowledge of the electronic and molecular structure of Cu(II)-Aβ complexes is thus important to get a better understanding of the role of these complexes in the development and progression of the AD. Various computational modeling methods are illustrated in the review by Ali-Torres et al. The challenges in studying the aggregation of Cu(II)-Aβ complexes using computational methods are discussed.

Various computational studies have been made to study aggregation of proteins without reference to specific proteins via simplified models with relatively small samples. Some of these studies include 'minimalist' models involving a few short chains and coarse-grained MD simulations on

[a]Correspondence should be addressed to: gerstman@fiu.edu, ymiller@bgu.ac.il

relatively small systems. Pandey et al. report on computational investigations on systems with larger, more realistic lysozyme proteins that contain 148 amino acids. Using a coarse-grained Monte Carlo simulation, they are able to track the changes in the underlying multi-scale dynamics of aggregation, such as its dimensionality, as a function of temperature, and the number of chains and concentration.

Finally, hIAPP is a peptide co-secreted with insulin from the pancreatic β-cells. Aggregation of hIAPP peptides leads to the loss of β-cells and consequently to the development of type 2 diabetes. The dimerization mechanism of hIAPP had been investigated by Chiu and de Pablo applying biased-exchange metadynamics. The dimerization mechanisms could be useful for designing strategies to inhibit hIAPP intermediates and therefore to prevent hIAPP aggregation.

These papers contribute to the advancement of a fundamental understanding of amyloid aggregation, and present the application of new techniques to study the function and the mechanisms of the process. Moreover, we believe that the papers in this special issue will be critically important for the next generation of researchers that will design novel molecules to inhibit amyloid aggregation.