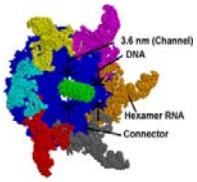

NIH Nanomedicine Development Center:

Phi29 DNA-Packaging Motor for Nanomedicine

Biomedical Engineering Research Seminar

Co-Sponsored by the NIH Nanomedicine Development Center and the Biomedical Engineering Department

Wednesday, October 14, 4:00 to 5:00 p.m. 6254 MSB

Nanoimaging and single molecule probing for the analysis of protein misfolding and aggregation

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Misfolding and aggregation of proteins are widespread phenomena leading to the development of numerous neurodegenerative disorders such as Parkinson's, Alzheimer's, and prion diseases to mention a few. Each of these diseases is linked primarily to misfolding of one particular protein. High-resolution methods such as x-ray crystallography, NMR, electron microscopy, and AFM have provided important information regarding the secondary structure of aggregated proteins and morphologies of self-assembled aggregates, but such fundamental questions as why the misfolded conformation of the protein is formed, and how the misfolded protein aggregates, remain unanswered. Misfolded states exist intermittently, so answering these questions requires the use of methods capable of probing transient conformations of proteins. To address this question, we need to utilize new techniques capable of probing transient misfolded conformations of single protein molecules. Our central hypothesis is that proteins in misfolded states are characterized by elevated interprotein interactions that can be detected by AFM force spectroscopy approach. Therefore, we developed nanoprobing AFM methodology capable of detecting and analyzing transient states misfolded states of the proteins that differ from normal states by the increased interactions.

In this talk I review our recent studies in which we applied the nanoprobing approach for analysis of misfolding of α-synuclein, amyloid β-peptide and prions at conditions facilitating the formation of misfolded states. These experiments revealed enormously high stability of misfolded dimers of all species suggesting their critical role in the early stages of the aggregates formation. A high stability of the misfolded dimers is unexpected finding that sheds a new light into the mechanism of the self-assembly of misfolded proteins into the disease related aggregates. We believe the further development of nanoimaging and nanoprobing methods will lead to innovative single nanotechnologies with the prospects to diagnose, prevent, and cure protein misfolding diseases.