4ae Thermodynamic and Kinetic Modeling of Protein Phase Transition Related to Diseases and Drug Development through Control of Protein-Protein Interactions

Sungmun Lee

My future research focuses on understanding and controlling phase transitions of abnormal proteins associated with various diseases. In order to find out the general characteristics of protein aggregation, protein phase diagrams will be established for the proteins showing abnormal protein aggregation such as β-amyloid (Alzheimer's disease), α-synuclein (Parkinson's disease), polyglutamine (Huntington's disease), and prion protein (Creutzfeldt-Jacob disease). Protein phase transitions are determined by protein type, concentration and environmental conditions such as temperature, pH, and ionic strength. Kinetic parameters of protein aggregation will be estimated at physiological condition, and free energy of each phase will be calculated at specific conditions as well as physiological condition. The next goal of my research is to find out the drug candidates which prevent protein aggregation and toxicity. Drug candidates can be selected by the prediction of protein-protein interaction. Drug activities to prevent protein aggregation and toxicity will be tested experimentally. Protein-protein interaction will be predicted by various docking methods. Protein aggregation rate can be determined experimentally by turbidity assay or dye methods. Biological activities of protein aggregates can be obtained by cell viability assay. This research can be applied to drug development, protein separation, and protein structure studies (x-ray crystallography). My future research plans draw on expertise gained during my research experiences in all cross-disciplinary areas. During my graduate studies, research has focused on understanding and trying to control the aggregation of β-amyloid. I have examined the structure, size and stability of β-amyloid aggregates and intermediates using electron microscope (EM), Fast Protein Liquid Chromatography (FPLC), Circular dichroism (CD), urea unfolding, and hydrogen exchange/mass spectrometry (HX-MS), and related the results of these studies to biological activity of β-amyloid. I found that different β-amyloid incubation conditions in vitro affected both the rate of β-amyloid fibril formation and the conformation of intermediates in the aggregation pathway. The stability of β-amyloid could be related to the biological activities of β-amyloid. Based on the experimental data, thermodynamic diagram has been proposed and kinetic study has been done. I have also examined the ability of chaperones which interact with partly folded intermediate states of proteins to prevent incorrect folding and aggregation. I have found that one small heat shock proteins (sHsp) called Hsp20 is able to prevent both β-amyloid aggregation and toxicity. The characterization of protein-protein interaction has been investigated experimentally by using mass spectrometry (MS) and atomic force microscopy (AFM). The binding affinity between β-amyloid and sHsps was estimated by protein docking program. These tools and experiences will enable me to guide a research group in the development of the next generation of drugs and test those drugs for use in a number of diseases of protein aggregation.