DESCRIPTION FOR THE GENERAL PUBLIC

Proteins are directly involved in practically all functions of biological cells, including transcription and translation of the genetic code, metabolism, signaling, transport, and cell shaping. In fact, most events taking place in biological cells are either directly performed, regulated or catalyzed by proteins. Therefore, to understand the molecular principles of life, we need to have the knowledge about structures, interactions and motions of proteins.

Many cellular processes are executed and controlled by large, dynamic, multi-domain proteins. Examples include enzymatic catalysis, signal transduction, transport and degradation of biomolecules, cell adhesion, and many others. Contemporary structural biology is thus concerned with understanding ever larger, more complex, and more dynamic multi-domain proteins. The progress in this field of research depends sensitively on the development of appropriate methods. Our goal is to advance physical models and computational methods that will support biophysical and biochemical experiments in determining structures, dynamics and functions of multi-domain proteins.

The discovery of intrinsically disordered proteins questioned one of the basic paradigms of structural biology, which says that proteins need to be folded into strictly defined, stable, tertiary structures to perform their biological functions. This paradigm does not apply to intrinsically disordered proteins (IDPs), which despite the lack of stable tertiary structures under physiological conditions remain fully functional. In fact, the native state of an IDP under physiological conditions is an ensemble of inter-converting conformations.

An important class of IDPs are multi-domain proteins, in which the individual domains are connected by disordered regions of the polypeptide chain. Although abundant and critically important in cell physiology, such proteins often prove difficult to examine using conventional techniques of structural biology. This class of IDPs will be the subject of our project. We intend to study two different protein systems: (1) Multi-domain enzymes that are capable of degrading cellulose into monosaccharides. In particular, we will study endocellulases and exocellulases from the thermophilic bacterium *Clostridium thermocellum*. (2) Multi-domain adhesion proteins. In particular, we will focus on the complex of adhesion proteins CD47 and SIRPα.

The first part of this project concerns the influence of the disordered linkers on the activity of the multi-domain endocellulases and exocellulases. Our preliminary results suggest that the disordered regions in these enzymes serve not only as passive linkers connecting the adjacent domains but also as active modulators of the catalytic activity of the enzymatic domains. If this discovery is validated and understood, it will provide new possibilities of controlling the enzymatic activity of the endocellulases and exocellulases, which will have potential applications for improving biofuel production.

The second part of this project concerns the influence of disordered linkers on the binding of the trans-membrane receptor CD47 to the adhesion protein SIRPα. Our earlier works on membrane adhesion have shown that nanoscale fluctuations and flexibility of lipid membranes can lead to a cooperative binding of adhesion molecules. Here, we put forward the hypothesis that the flexibility of the disordered linkers can lead to an enhancement of the cooperativity effect.

The binding of CD47 to SIRPα has been found to play important roles in phagocytosis, auto-immunity and host defense. As such, the CD47-SIRPα complex has been recognized as a potential therapeutic target in cancer and inflammation. Therefore, our studies on the interactions of CD47 with SIRPα in the adhesion zone may have a direct influence on the advancement of new cancer treatments.