Meeting-Abstract

Saturday, February 2, 2008

Instrinsically Disordered Proteins Subgroup

2008 Annual Meeting Abstracts - a supplement of Biophysical Journal

3-Subg Protein Intrinsic Disorder and Oligomericity in Immune Signaling

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Recent structural and genomic data have clearly shown that many proteins contain long regions termed intrinsically disordered (ID) or unstructured that do not adopt any globular structures under native conditions. Intriguingly, a highly flexible, random coil-like conformation constitutes the native and functional state for many proteins known to be involved in cell signaling. Reports in recent years revealed that these long ID domains preferentially occur on the cytoplasmic side. Examples include key components of immune signaling: the cytoplasmic regions of the multichain immune recognition receptor (MIRR; i.e., T and B cell receptors, Fc receptors, etc.) signaling subunits. Surprisingly, these unstructured domains exhibit specific dimerization distinct from non-specific aggregation behavior seen in many systems. Circular dichroic analysis and diffusion and chemical shift mapping NMR data show that the dimerization of these molecules is not accompanied by a structural transition to a folded form. This finding opposes the generally accepted view on the behavior of ID proteins and provides evidence for the existence of specific dimerization interactions for these protein species, thus opening a new line of research in this new and quickly developing field. The unusual homotypic interactions between ID cytoplasmic domains of MIRR signaling proteins have been used to develop a novel model of immune signaling that has been successfully applied in different fields of immunology and pharmacology. Application of this model to platelet signaling has already led to the development of a novel concept of platelet inhibition and the invention of new platelet inhibitors.

4-Subg Intrinsically Disordered Proteins in Human Diseases

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Intrinsically disordered proteins (IDPs) lack stable tertiary and/or secondary structure under physiological conditions *in vitro*. They are highly abundant in nature and often they are involved in regulation, signaling and control pathways, where binding to multiple partners and high-specificity/low-affinity interactions play a crucial role. Functions of IDPs may arise from the specific disorder form, from inter-conversion of disordered forms, or from transitions between disordered and ordered conformations. The choice between these conformations is determined by the peculiarities of the protein environment, and many IDPs possess an exceptional ability to fold in a template-dependent manner. IDPs are key players in protein-protein interaction networks being highly abundant among hubs. Numerous IDPs are associated with such human diseases as cancer, cardiovascular disease, amyloidoses, neurodegenerative diseases, diabetes and others. Overall, there is an intriguing interconnection between intrinsic disorder, cell signaling and human diseases, which suggests that protein conformational diseases may result not only from protein misfolding, but also from misidentification and missignaling. IDPs, such as α-synuclein, tau protein, p53, BRCA1 and many other disease-associated hub proteins represent attractive targets for drugs modulating protein-protein interactions. Therefore, novel strategies for drug discovery are based on intrinsically disordered proteins.

Permeation Transport Subgroup

5-Subg Structure of the Na,K-pump with Occluded Rb Ions

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The Na,K-ATPase belonging to the P-type ATPase family uses energy derived from ATP to pump Na ions out of the cell and K ions into the cell across the plasma membrane. It is composed of alpha- and beta-subunits and interacts with regulatory FXYD proteins, such as the gamma-subunit in kidney. This lecture will present and discuss the recently determined X-ray crystal structure of the pig renal Na+,K+-ATPase at 3.5 Å resolution with bound potassium or rubidium ions. It provides the first view of the architecture of multi-subunit P-type ATPases and the first sight of occluded countertransported ions. The C-terminus shows unique structural features, whose functional consequences have been probed by mutagenesis studies. Other aspects of the structure also point to new regulatory principles.

Motility Subgroup

6-Subg Three-dimensional Reconstruction of Cardiac Muscle Myosin Filaments from a Mouse MyBP-C Knockout Model for Human Hypertrophic Cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is an inherited disease caused mainly by mutations in myosin and myosin binding protein-C (MyBP-C), proteins that together with titin form the thick filaments. The mechanisms by which these mutations cause HCM are unknown. Most MyBP-C mutations result in failure of MyBP-C to bind to the thick filament. To determine the structural effects of the absence of MyBP-C, we have analyzed thick filaments from a mouse MyBP-C knockout model for HCM (Harris et al., 2002. Circ Res. *90*:594). Filaments isolated from wild type and knockout hearts