

IEEE 7th BIBE Invited Tutorial Lecture: Intrinsically Disordered Proteins in Human Diseases

October 14-17, 2007, Harvard Medical School Conference Center, Boston, MA

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Abstract— Intrinsically disordered proteins lack stable tertiary and/or secondary structure under physiological conditions *in vitro*. They are highly abundant in nature, with ~25-30% of eukaryotic proteins being mostly disordered, and with >50% of eukaryotic proteins and > 70% of signaling proteins having long disordered regions. Functional repertoire of intrinsically disordered proteins is very broad and complements functions of ordered proteins. Often, intrinsically disordered proteins are involved in regulation, signaling and control pathways, where binding to multiple partners and high-specificity/low-affinity interactions play a crucial role. We have found that out of the 711 Swiss-Prot functional keywords associated with at least 20 proteins, 262 were strongly positively correlated with long intrinsically disordered regions, and 302 were strongly negatively correlated. It is suggested that functions of intrinsically disordered proteins 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 intrinsically disordered proteins possess an exceptional ability to fold in a template-dependent manner. Intrinsically disordered proteins are key players in protein-protein interaction networks being highly abundant among hubs. Furthermore, regions of mRNA which undergo alternative splicing code for disordered proteins much more often than they code for structured proteins. This association of alternative splicing and intrinsic disorder helps proteins to avoid folding difficulties and provides a novel mechanism for developing tissue-specific protein interaction networks. Numerous intrinsically disordered proteins are associated with such human diseases as cancer, cardiovascular disease, amyloidoses, neurodegenerative diseases, diabetes and others. Our bioinformatics analysis revealed that many human diseases are strongly correlated with proteins predicted to be disordered. Contrary to this, we did not find disease associated proteins to be strongly correlated with absence of disorder. 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. Intrinsically disordered proteins, 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.



Dr. Uversky received broad training, with an MS in Physics (Leningrad State University, Russia, 1986), a PhD (Moscow Institute of Technical Physics, 1991) and a DSc in Biophysics (Institute of Experimental and Theoretical Biophysics, Russian Academy of Sciences, 1998) and with pre- and postdoctoral research in Structural Biology, Biochemistry and Biophysics (1991-1998, Institute of Protein Research, Russian Academy of Sciences). From 1985 until 1998, Dr. Uversky used molecular biophysics methods to study protein folding. In 1998, he started to investigate protein misfolding. Working on protein folding-misfolding, Dr. Uversky found that many biologically active proteins do not have rigid structure and are often involved in human diseases. He is known for his work on structural characterization of partially folded proteins, for development of novel tools to study protein folding, misfolding and non-folding, and for a model of protein amyloidogenesis involving the pre-molten globular (disordered) state. While he continues to use biophysics, more recently Dr. Uversky has focused on the development and use of bioinformatics methods for the study of intrinsically disordered proteins.