Unusual Biophysics and Strange Biology of Intrinsic Disorder

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Intrinsically disordered proteins (IDPs) lack stable tertiary and/or secondary structure under physiological conditions in vitro, often resembling 'protein clouds'. Computational studies revealed that IDPs are highly abundant in nature, as ~25-30% of eukaryotic proteins are mostly disordered, and >50% of eukaryotic proteins and > 70% of signaling proteins have long disordered regions. The functional repertoire of IDPs is complementary to that of ordered proteins, with IDPs being commonly involved in regulation, signaling and control pathways, where binding to multiple partners and high-specificity/low-affinity interactions play a crucial role. It is suggested that 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 be highly responsive to change in their environment and to fold in a template-dependent manner. All this requires a close attention to the odd biophysics of IDPs. In this talk, some key biophysical features of IDPs will be covered. In addition to the peculiar sequence characteristics these unusual biophysical features include sequential, structural, and spatiotemporal heterogeneity of IDPs; their rough and relatively flat energy landscapes; their ability to undergo both induced folding and induced unfolding; the ability to interact specifically with structurally unrelated partners; the ability to gain different structures at binding to different partners; and the ability to keep essential amount of disorder even in the bound form. IDPs are also characterized by the “turned-out” response to the changes in their environment. It is proposed that the heterogeneous spatiotemporal structure of IDPs/IDPRs can be described as a set of foldons, inducible foldons, semi-foldons and non-foldons. They may lose their function when folded, and activation of some IDPs is associated with the awaking of the dormant disorder.