

The role of structural disorder in protein-protein interactions

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Intrinsically disordered proteins (IDPs) have received increased attention lately, as it has become clear that the lack of a stable 3D structure is prevalent in the proteomes of higher organisms. Structural disorder is particularly prevalent in regulatory and signaling proteins, and IDPs often carry out their functions via protein-protein interactions (PPIs). In this work we have addressed the principles of the involvement of disorder in PPIs. We have shown that short linear recognition motifs of proteins tend to fall into locally disordered regions, and such regions provide efficient switches for the rapid evolutionary adaptation of interaction networks. The actual binding regions undergo disorder-to-order transition upon binding and adopt well-defined structures in the cognate complexes. Analysis of the secondary structural preferences of these regions has led to the unexpected finding that IDPs have a strong preference for their structures attained in the bound state, which suggests that their binding motifs might presage their final, partner-induced conformations. This fine balance between order and disorder is probably indicative of the thermodynamic and kinetic fine-tuning of recognition by IDPs, which is in line with their preferential functioning in interaction networks. Our studies on PPI networks have shown that disorder is higher in proteins with multiple interactions (hubs proteins) than in proteins with a few interactions. We also have studied atomic details of the interfaces, which suggests that IDPs use a unique strategy for recognition. They present a much higher proportion of their residues for interaction than their globular counterparts, and they tend to expose their hydrophobic residues for effective interaction with their partners. Overall, these and other observations corroborate our premise that involvement in rapid and regulated PPIs has been a key element in the evolutionary advance of protein disorder.