ABSTRACT

In a last few decade, a new concept of protein has emerged, called the intrinsically disordered proteins (IDPs) or intrinsically disordered regions of proteins (IDRs) which lack stable conformations under normal physiological condition and yet are fully functional. IDPs are part of several important cellular activities. They often engage in low affinity high specificity interactions which brilliantly makes them fit for multiple partner binding interactions like the ones found in cell signalling and regulation. IDPs are extensively found in eukaryotes compared to prokaryotes associating increase in disorderedness with increase in cellular complexity. The current study provides a structural, functional and evolutionary perspective of IDPs. IDPs have been characterised for the first time in view of the neighbouring residues of IDRs (NRIs). This study finds that NRIs behave as a bridging element between the flexible IDRs and the rigid bulk residues. The unique characteristics of NRIs are important to maintain the structural pliability of IDRs. The evolutionary behaviour of IDPs based on structural and functional classification of IDRs is studied as well. It is found that the small IDRs are better conserved than the long IDRs or full IDPs. Conservation and coevolution are found not to be affected by interacting partners of IDPs, though functional classes show distinct variation in the evolutionary signals. Functional classes which require structural flexibility as the principal component are better conserved than other classes. Disorder promoting amino acids evolve faster than order promoting amino acids. Strong preferences of forming coevolving pairs with same amino acid are observed in Pro, Gly, Ile and Phe. Owing to the role of imparting structural flexibility by Pro and Gly and making important contacts at the IDP-partner interface by hydrophobic residues like Ile and Phe, this coevolving nature is an important finding towards the evolution of IDPs. Fused in sarcoma protein (FUS) is an IDP which mis-localises in the cytoplasm causing neurodegenerative disease, amyotrophic lateral sclerosis (ALS) and fronto-temporal lobar degeneration (FTLD). This study reports the conformational dynamics exhibited by RNA recognition motif (RRM) domain and nuclear localisation signal (NLS) domain of FUS in terms of macromolecular recognition and interaction. The significant role of flexible loops along with the absence of conventional residues in RRM domain of FUS has been elucidated in this study. This study also explains the effect of P525L mutation on the dynamics of FUS NLS bound to nuclear transport protein

Karyopherin β2 (Kapβ2). The probable effects of the mutation on NLS are structural distortions at N-terminal of Kapβ2 and weaker binding of NLS with Kapβ2. The above reasons may affect the binding of FUS NLS with Kapβ2 which in turn might causes cytoplasmic mis-localisation of FUS causing ALS/FTLD. This study sheds light on structural architecture, functional dynamics and evolution of IDPs which can significantly contribute our understanding to this exponentially growing area of research in IDPs.

Keywords: Intrinsically disordered proteins, structural flexibility, evolutionary signal, macromolecular interactions, molecular dynamics