Article

Open questions: Reflections on intrinsically disordered proteins

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Abstract

Intrinsically Disordered Proteins or Regions (IDPs) are proteins that lack a predetermined 3D structure playing key cellular functions including regulation, signaling, and protein-protein/DNA interaction. IDPs are often involved in diseases such as cancer, cardiovascular and neurodegenerative diseases, and diabetes. IDPs have been shown to be attractive therapeutic targets and drug development. Intrigued by these controversial observations, some questions are raised: how IDPs are so common even under the scenario that they are unstable and linked to misfolding and diseases? Does the cellular regulation depend on disorder?

Keywords disorder; diseases; protein; regulation.

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1 The Intrinsically Disordered Proteins: The Genius of The Weird

Previously, it was admitted that structure ensures function. This classical paradigm was challenged by the discovery of the intrinsically disordered proteins (IDPs) in many organisms (Fig. 1).

IDPs are unstructured proteins in physiological conditions. They are fully or partially unstructured. IDPs are often associated to low complexity regions. IDPs were neglected, not performing important functions within the organisms. Extensive researches revealed that IDPs are ubiquitous and they play key regulatory and signaling functions such as transcription regulation, cell cycle, chaperone activity, stress tolerance, signaling cascades and molecular interactions. Due to their structural flexibility and ability to bind different binding sites, IDPs are able to recognize and interact with multiple partners (Tompa et al., 2011).

In our thoughts, order often spells equilibrium, a source of health. Why has organism used the disorder? And how does it occur in the crucial functions? After all, are IDPs disordered really?

The field of research is rapidly evolving and provides surprising results. What is the nature hiding more from us?

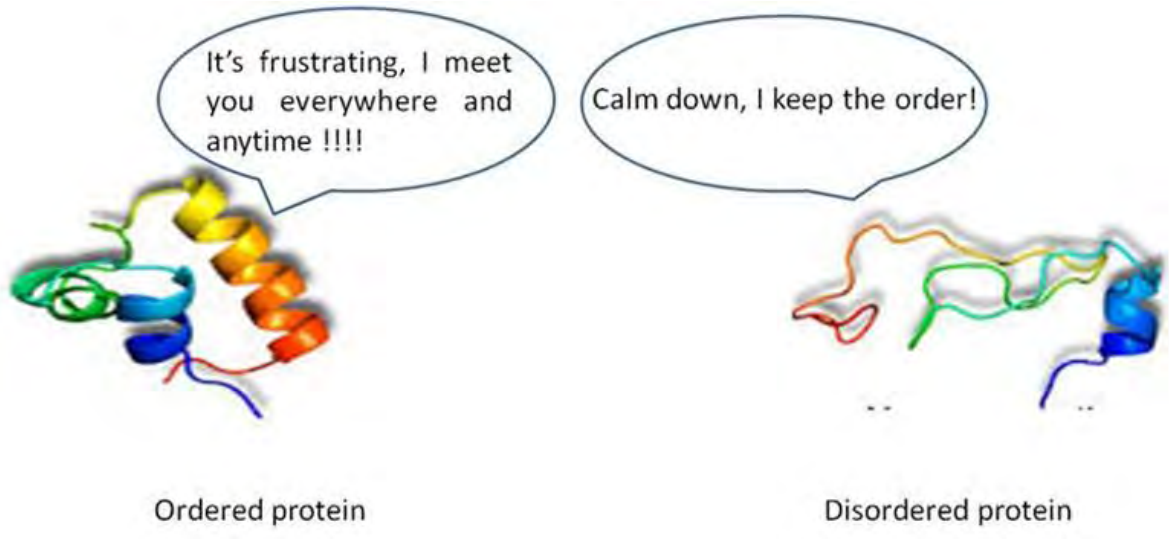

Fig. 1 Imaginary conversation between ordered protein and disordered protein.

2 When Intrinsically Disordered Proteins Turn To Therapeutic Targets

The intrinsically disordered proteins (IDPs) are involved in various diseases including cancers, neurological diseases, cardiovascular diseases, and diabetes (Uversky, 2015) which made them attractive therapeutic targets. The strategies developed and designed small molecules target particularly the hydrophobic regions of IDPs hampering DNA/protein-IDP interactions. Some successful targeting of IDPs in different cancers were reported in Santofimia-Castaño et al. (2020). The roles of IDPs in neurodegeneration and protein dysfunction diseases with their specificities as potential drug targets are discussed in Uversky (2020). Moreover, recent study revealed that the human disordered biased charged proteins might be potential markers for diagnostic and drug targets (Choura and Rebaï, 2020) .

3 Evolution of The Intrinsically Disordered Proteins: Out of The Ordinary

As it is conventional, evolutionary conserved regions correspond to functional and/or structural domains. Conversely, the intrinsically disordered proteins do not have a defined structure, the alignment and the analysis of such proteins from different species show high variation in the amino acid sequence and very little conservation in the disordered regions.

Paradoxally, the IDPs are involved in key cellular processes and they are common in all organisms. IDPs occur in 2.0% of archaean, 4.2% of eubacterial and 33.0% of eukaryotic proteins (Ward et al., 2004). Recently, it was reported that wheat and barley contain 27% and 28.9% of IDPs respectively (Choura et al., 2020).

Some binding sites in IDPs are conserved and others are not. They can readily emerge and disappear over the course of protein evolution. Moreover, many binding sites remain to be identified which may explain the sequence heterogeneity of the sequence conservation of IDPs (Ota and Fukuchi, 2017)

Furthermore, it was found that the intrinsically disordered protein regions in the coronavirus designated as SARS-CoV-2, are functionally important and commonly used for interaction with specific partners. The disordered regions in viral proteins are associated with the viral infectivity and pathogenicity (Giri et al., 2021). The structural flexibility may suggest one of the reasons behind the vulnerability of the infected patients with comorbidities.

4 Conclusion

In summary, the past decade has provided many exciting scientific findings and obliged to reconsider the protein structure-function paradigm. Disorder is a conserved phenomenon. Disorder complexity is multi-parametric trait. Yet, many questions still unanswered. A possible answer is all a question of equilibrium between disorder and order.

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