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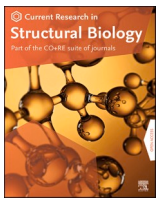

Shining light on the dark proteome with unstructural biology

Modern structural biology has moved away from the classic 1894 "lock-and-key" model, which viewed enzymes (and by analogy all other proteins) as rigid structures (Fischer, 1894), toward considering protein functionality as being driven by a spectrum of conformational states, spanning from highly ordered structures to various degrees of intrinsic disorder, where a protein can be intrinsically disordered as a whole or contain intrinsically disordered regions (Wright and Dyson, 1999; Uversky et al., 2000; Dunker et al., 2001; Tompa, 2002, 2011; van der Lee et al., 2014; Uversky, 2016, 2019; Gupta and Uversky, 2024; Kulkarni et al., 2025). Far from being mutually exclusive, order and disorder are complementary, acting in concert to facilitate biological activity, where ordered proteins often handle catalysis, whereas disordered proteins excel in signaling, regulation, and binding, offering high specificity with low affinity, allowing for rapid, reversible interactions (Uversky, 2019; Gupta and Uversky, 2024; DeForte and Uversky, 2016a; Bondos et al., 2021, 2022). This relationship is complex, as some proteins require (at least partial) unfolding to achieve functionality (Kulkarni et al., 2025; Bardwell and Jakob, 2012; Mitrea and Kriwacki, 2013; Reichmann and Jakob, 2013; Jakob et al., 2014; Devi et al., 2025; Uversky, 2015), while others, being inherently disordered, undergo binding-induced folding (Dunker et al., 2002a, 2002b; Wright and Dyson, 2009). Disordered proteins and regions possess high conformational plasticity supporting promiscuous binding and partner-specific folding (Dunker et al., 2001; Radivojac et al., 2007; Oldfield and Dunker, 2014; Uversky, 2013; Uversky and Dunker, 2010) and showing remarkable binding plasticity, being able to fold differently as a result of binding to different partners (Oldfield and Dunker, 2014; Dajani et al., 2003; Dyson and Wright, 2002; Hsu et al., 2013; Oldfield et al., 2008). Many IDPs and IDRs are capable of weak, transient, and multivalent interactions of the "palpation" type (so-called, low-affinity, high-avidity contacts), which represent the foundational mechanism for the liquid-liquid phase separation (LLPS) driving the biogenesis of various membrane-less organelles (MLOs) or biomolecular condensates (Uversky et al., 2015; Chong and Forman-Kay, 2016; Uversky, 2017; Darling et al., 2018, 2019; Feng et al., 2019; Owen and Shewmaker, 2019; Pancsa et al., 2019; Turoverov et al., 2019; Murthy and Fawzi, 2020; Rhine et al., 2020; Yoshizawa et al., 2020; Borcherds et al., 2021; Fonin et al., 2022).

Furthermore, many proteins exist on the boundary of order and disorder, featuring "dual-personality" fragments that can be ordered or disordered depending on environmental conditions or post-translational modifications (Zhang et al., 2007; DeForte and Uversky, 2016b). The order-disorder boundary (assuming that it is even exists) is further blurred by metamorphic (or fold-switching) proteins (which are also known as "turncoat" polypeptides (Zamora-Carreras et al., 2020)) demonstrating that a single amino acid sequence can possess multiple, stable, and distinct folded states, rather than just one (or none, as in intrinsically disordered proteins) (Zhang et al., 2007; DeForte and Uversky, 2016b; Zamora-Carreras et al., 2020; Goodchild et al., 2011; Lella and Mahalakshmi, 2017; Dishman and Volkman, 2018, 2023; Madhurima et al., 2021; LiWang and Orban, 2025; Chakravarty and Porter, 2026). All these lock-and-key deviants (which are not merely disordered but also include proteins that appear ordered and globular but have no similarity to any known structures) constitute the dark proteome, which is the vast, unexplored, or structurally uncharacterized portion of the protein universe (Ross, 2016; Kruger, 2016; Baboo and Cook, 2014; Bhowmick et al., 2016; Bitard-Feildel and Callebaut, 2017; Levitt, 2009; Perdigao et al., 2015, 2017). Because these proteins are resistant to current experimental structural analysis and lack suitable templates for homology modeling, the molecular basis of their functions remains poorly understood. This requires development and use of alternative, "unstructural" methods, such as nuclear magnetic resonance (NMR) spectroscopy, small-angle X-ray/neutron scattering (SAXS/SANS), single-molecule FRET (smFRET), cryo-electron microscopy (Cryo-EM) protein-protein interaction studies (e.g., cross-linking mass spectrometry), computational predictions and modeling of conformational ensembles, and "unstructural" bioinformatics. It is also crucial to recognize that all proteins (and not just intrinsically disordered ones) exist as dynamic, flexible ensembles in physiological conditions, rather than as single, rigid structures. Essentially, rather than being static objects, proteins are flexible systems that adapt to changing environments and interact dynamically with other molecules, such as ligands and other proteins.

This special issue provides a short glimpse into the dark proteome by presenting three articles. Mutations in the IQ motif and SEC7 domain-containing protein 2 (IQSEC2), a guanine exchange factor (GEF) controlling the activation of ADP-ribosylation factor 6 (ARF6) that mediates membrane trafficking and synaptic connections between neurons, are associated with the intellectual developmental disorder, X-linked 1 (XLID1), which is an X-linked genetic condition resulting in intellectual disability, developmental delays, autism spectrum disorder, and epilepsy (Shoubridge et al., 2010; Kalscheuer et al., 2015). The fact that IQSEC2 is a large, mostly disordered protein (Shokhen et al., 2024a) complicates drug development because it lacks a stable, 3D structure with traditional, well-defined binding pockets. To address these issues, Shokhen et al. used accelerated molecular dynamics (aMD) and

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statistical thermodynamics to map the protein's folding process and identify specific structural conformers (Shokhen et al., 2024b). The study found that IQSEC2 exists in a balance between folding and dimerization. These two competing processes likely act as a natural switch to regulate how effectively IQSEC2 activates ARF6, a key driver of synaptic connectivity (Shokhen et al., 2024b).

Yang et al. indicated although many methods and database provided the information for IDPs, they are mainly limited to determine the IDRs lacking knowledge of possible folding patterns (Yang et al., 2025a). To overcome this issue, these authors proposed a "protein structure fingerprint" technology to map the folding patterns of IDPs (Yang et al., 2025a). The methodology is based on the PFSC-PFVM (Protein Folding Shape Code to expose the differences of folding conformation for an IDP (Yang, 2008) – Protein Folding Variation Matrix to reveal local folding variations for an IDP solely based on sequence (Yang et al., 2022)) algorithms and FiveFold approach capable of predicting multiple conformational 3D structures for an IDP (Yang et al., 2025b). The resulting combined tool is able explicitly to expose the possible conformational structures of a query IDP (Yang et al., 2025a). While traditional methods often stop at identifying disordered regions, the proposed methodology allows researchers to explicitly visualize possible 3D conformational variations. By demonstrating application of the protein fingerprint technology on three human proteins (p53, α-synuclein, and protamine-2), the authors show how these algorithms can predict multiple structural states, helping bridge the gap between disordered structures and their biological functions (Yang et al., 2025a). This methodology enhances the ability to map the "disorder--to-function" relationship by providing a clearer picture of an IDP's ensemble of 3D structures.

Although capability to undergo LLPS and have various MLOs was considered a specific property of eukaryotic cells, it is recognized now that LLPS-driven protein condensation and MLO formation also occur in prokaryotic cells (bacteria and archaea), as well as in viruses (Abbondanzieri and Meyer, 2019; Azaldegui et al., 2021; Nandana and Schrader, 2021; Li et al., 2022; Kuczynska-Wisnik et al., 2023; Zhang et al., 2023; Guo et al., 2024; Yusuf et al., 2025; Zhao et al., 2025; Bianchi et al., 2023; Brocca et al., 2020). While bacterial LLPS is often difficult to study due to small cell size, the number of identified bacterial LLPS systems is growing, suggesting this mechanism is widely distributed throughout nature (Guo et al., 2024; Gao et al., 2021). In fact, bacterial cells use LLPS to form various liquid-like, membrane-less compartments (such as those containing RNA-binding proteins or enzymes) that facilitate spatiotemporal organization. An illustrative example is given by bacterial cell poles, which serve as critical organizational hubs that direct the localization of essential proteins. These spatially regulated proteins orchestrate fundamental processes, including cell cycle control, differentiation, chromosome dynamics, and motility (Treuner-Lange and Sogaard-Andersen, 2014; Surovtsev and Jacobs-Wagner, 2018; Laloux and Jacobs-Wagner, 2014). Using comprehensive bioinformatics analysis, Aldadah et al. revealed that bacterial cell pole-related proteins are often intrinsically disordered and associated with liquid-liquid phase separation (LLPS) to regulate essential cellular processes (Aldadah et al., 2025). This analysis established that among 19 studied proteins, 11 were highly disordered and 7 were moderately disordered, with TipN, PopZ, and PBP2A being capable of spontaneous phase separation, and others serving as droplet clients. Importantly, intrinsic disorder propensity and LLPS potential were shown to be evolutionary conserved, suggesting that LLPS is a common mechanism for organizing bacterial cell poles, with PopZ and TipN playing significant roles in stress resistance (Aldadah et al., 2025). These insights into bacterial polarity, growth, and protein localization offer potential new strategies for developing antimicrobial targets.

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