PERSPECTIVE

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Disorder in the lifetime of a protein

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Intrinsic disorder is everywhere and is inevitable. The non-folding propensity is inherent for numerous natural polypeptide chains, and many functional proteins and protein regions are intrinsically disordered. Furthermore, at particular moments in their life, most notably during their synthesis and degradation, all ordered proteins are at least partially unfolded (disordered). Also, there is a widely spread phenomenon of conditional (functional or transient) disorder, where functions of many ordered proteins require local or even global unfolding of their unique structures. Finally, extrinsic disorder (i.e., intrinsic disorder in functional partners of ordered proteins) should be taken into account too. Therefore, even if a protein is completely devoid of intrinsically disordered regions in its mature form (which is a rather exceptional situation), it faces different forms of disorder (intrinsic, extrinsic, or induced disorder) at all the stages of its functional life, from birth to death. The goal of this article is to briefly introduce this concept of disorder in the lifetime of a protein.

Keywords: intrinsically disordered protein region; protein function; nascent polypeptide chain; protein degradation; protein biosynthesis

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Last decade and a half in protein science clearly represents a triumphal procession of the protein intrinsic disorder phenomenon.[1-5] The scale and rate of penetration of the intrinsic disorder concept to the modern protein science are really astonishing. What started as a set of anecdotes and obscure exceptions with purely academic interest suddenly metamorphed to the extremely exciting field, which is completely transforming our understanding of protein structure and function. The exceptionality of intrinsic disorder is changing. It is clear now that intrinsically disordered proteins (IDPs) and proteins with long IDP regions (IDPRs) are not rare exceptions, but are exceptionally common in nature, with the abundance of IDPs/IDPRs being typically correlated with the evolutionary complexity of the organisms.[6-12] Curiously, even in the protein data bank (PDB), this preeminent source of protein structural knowledge, the information about IDPRs is exceptionally common, since only ~7% of proteins in the corresponding PDB structures contain complete sequences, and only ~25% of the total data set have > 95% of their lengths observed in the corresponding PDB structures, with the remaining proteins possessing unobserved regions of various length that frequently correspond to IDPRs.[13] IDPs possess exceptional structural heterogeneity, ranging from completely structure-less, coil-like conformational ensembles to compact molten globule-like structural ensembles of whole proteins, to proteins with a mosaic or hybrid structure containing both ordered and disordered regions.[5,14-17] The functional repertoire of these proteins is exceptionally broad and complements activities of ordered proteins and domains.[18-34] Exceptional binding plasticity and promiscuity of IDPs/IDPRs,[35,36] where a single IDPR can bind to multiple partners gaining very different structures in the bound state,[33,37,38] define the abundance of intrinsic disorder among hub proteins and their binding partners in various protein-protein interaction networks.[27,39-43]

Therefore, there is no doubt that intrinsic disorder is abundant and functionally important. However, it appears that all

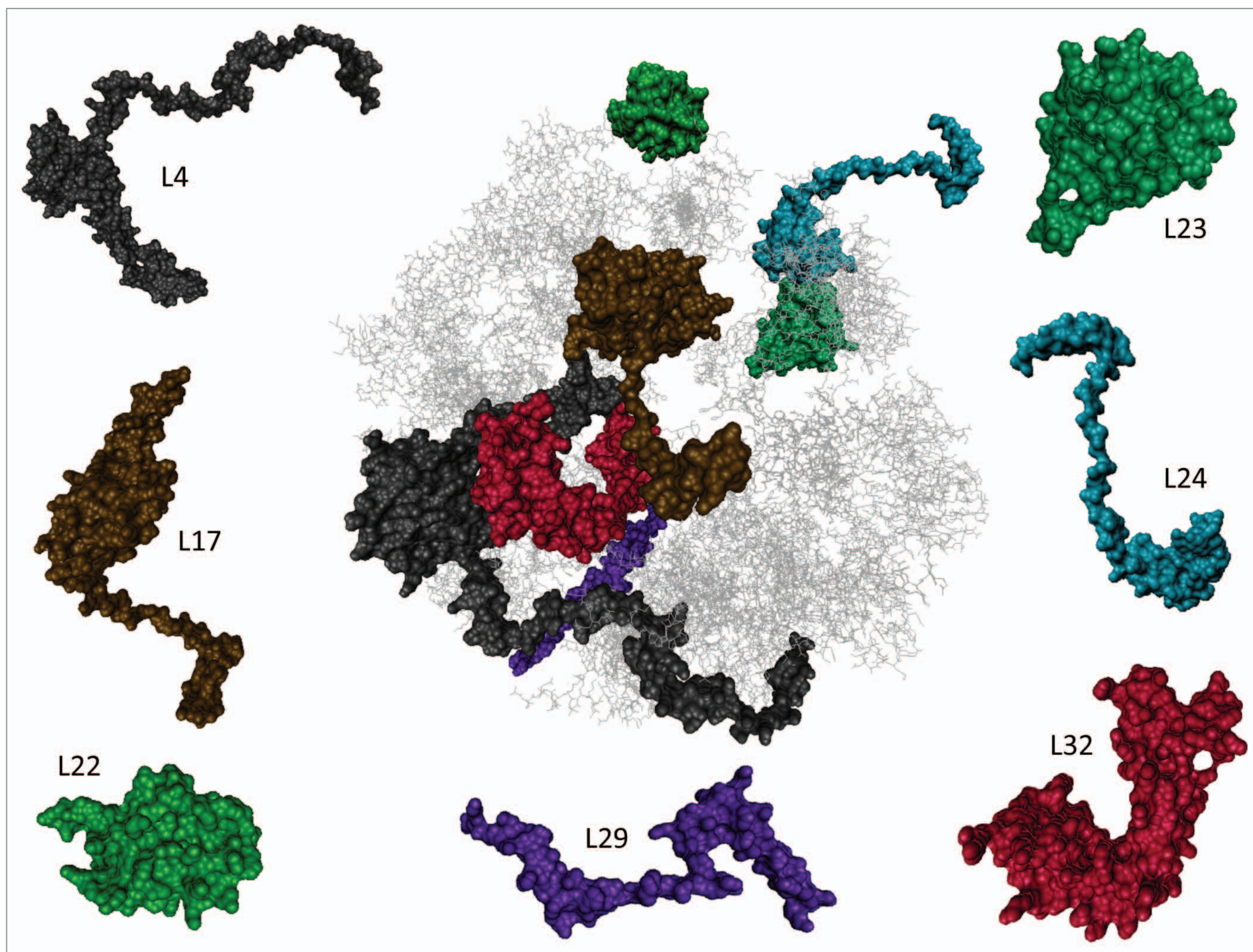

Figure 1. Localization of the ribosomal proteins at a ring around the tunnel exit site of the ribosome. The proteinaceous constituent of the yeast *Saccharomyces cerevisiae* 60*S* ribosomal subunit is shown (PDB ID: 3U5E). The crystal structure of the 60S ribosome is shown at the center of the plot as a gray mesh, with the ribosomal proteins L4, L17, L22, L23, L24, L29, and L32 are depicted as surfaces of different color. Individual structures of these proteins are shown around the central complex.

proteins (even those rare exceptions that are completely ordered in their functional state) face intrinsic disorder at all the stages of their functional lives. In fact, the protein birth place is the ribosomal exit tunnel, which is 100 Å long, extending from the peptidyl transferase center to the solvent side of the large ribosomal subunit, and ranges in diameter from:10 to 28 Å along its length.[44] When a nascent polypeptide chain enters the world, it faces a ring around the tunnel exit site of the ribosome that comprises of L4, L17, L22, L23, L24, L29, and L32 ribosomal proteins, of which L22 is known to interact with specific nascent chains to regulate translation.[45] Therefore, the first encounter of the newly synthesized protein with the outside world is the ribosome-embedded cradle containing a significant number of IDPs or hybrid proteins composing ordered and disordered domains and regions. **Figure 1** illustrates this point by representing the proteinaceous constituent of the yeast *Saccharomyces cerevisiae* 60*S* ribosomal subunit (PDB ID: 3U5E). The crystal structure of the 60S ribosome is shown at the center of the plot as a gray mesh, whereas the aforementioned ribosomal proteins L4, L17, L22, L23, L24, L29, and L32 are depicted as surfaces (clouds) of different color. Individual structures of these proteins are shown around the central complex. Visual analysis of these structures indicates that almost all of these proteins (except for L22 and L23) possess very unusual shapes which are not consistent with simple globular structure, which suggests that these and many other ribosomal proteins fold at binding.[46] In fact, such peculiar non-globular shapes suggest that many ribosomal proteins form the so-called 2-state (or disordered) complexes, where the monomers unfold upon complex separation. Therefore, individual chains in such complexes are disordered in their unbound forms and fold at complex formation. This behavior is different from that of the so-called 3-state (or ordered) complexes, individual chains of which are independently folded even in the unbound state.[47,48] Furthermore, although L22 possesses a globular shape within the ribosome, its N- and C-terminal tails

(residues 1–8 and 109–121) are so-called regions of missing electron density which correspond to protein segments that retain high conformational flexibility in their bound forms, precluding them from being detected in crystallography experiments.[46] Also, a very significant part of L24 (residues 99–155) is a long region of missing electron density. All this clearly shows that the mentioned cradle of a nascent polypeptide chain is fuzzy and fluffy, being enriched in IDPs/IDPRs.

At the next stage of the protein's life, a newly synthesized polypeptide chain leaves the ribosome and meets chaperones and nanny-proteins that guard and babysat this chain before it properly folds and matures. The major function of protein chaperones in relation to the newly synthesized proteins is to ensure proper folding of a target protein, whereas nanny-proteins serve to protect newly synthesized proteins from degradation-by-default via the 20S proteasome pathway by transient binding and masking of the susceptible segments which inhibits their degradation.[49] Many of the molecular chaperones and nanny-proteins are IDPs or hybrid proteins.[49-54]

Furthermore, many protein functions are dependent on intrinsic disorder, and activation and regulation of a myriad of proteins are controlled by various IDPs.[18-20,22,26-28,34,36,55,56] Of particular interest is an intriguing phenomenon of functional unfolding or transient disorder of originally ordered proteins.[5,15,57,58] Here, functions of some ordered proteins rely on the decrease in the amount of their ordered structure; i.e., these functions require local or even global functional unfolding of a unique protein structure. The important features of these functional alterations are their induced nature and transient character. In other words, the function-related changes in these so-called conditionally disordered proteins[59] are induced by transient alterations in their environment or by modification of their structures. They are reversed as soon as the environment is restored or the modification is removed.[58] This cryptic disorder can be awoken by a wide spectrum of factors, which crudely can be grouped into 2 major classes, passive and active.[58] Passive factors include environmental factors independent on any specific interactions between the protein and its partners. These factors correspond to changes of some global parameters of the protein environment, such as changes in pH, temperature, the redox potential, application of mechanical force, or light exposure. On the contrary, active factors typically involve some specific interactions of a protein with its environment and include interactions with membrane, ligands, other protein nucleic acids, or various posttranslational modifications or release of autoinhibition.[58] Some of the illustrative examples of transiently or conditionally disordered proteins are: acid-activated chaperone HdeA,[60-62] many pH-sensors (e.g., sodium proton antiporters[63-65] and inward rectifier K^+ ROMK channels[66-68]), pH-sensing envelope proteins of several viral families,[68,69] the temperature-activated *Saccharomyces cerevisiae* holdase Hsp26 and wheat holdase Hsp16.9,[69] oxidative stress-activated holdase Hsp33,[70-75] mechanosensitive channels,[76] photosensoring proteins (e.g., photoactive yellow protein),[77,78] proteins translocating through the membrane (e.g., various colicines,[79] ricin,[80-82] and some transport proteins[83]), proteins interacting with various small molecules,[84,85] proteins interacting with other proteins (e.g., targets of the mitochondrial import machinery complex[86]), many post-translationally modified proteins, and proteins activated by the release of autoinhibition.[87-89] For more information about these intriguing membres of the protein kingdom see recent comprehensive review.[58]

Finally, even on the deathbed, many proteins face intrinsic disorder. Here, intrinsic disorder plays a role in protein digestion by various proteases that are highly sensitive to the presence of disoder in target proteins,[19,90-94] and also in the controlled degradation via proteasome, which acts as an active unfoldase. In fact, ATP-dependent proteases (proteasomes in eukaryotes and proteasome analogs such as the ClpAP, ClpXP, HslUV, Lon, and FtsH proteases in prokaryotes) are crucial for the timely and controlled degradation of regulatory proteins, as well as of misfolded or damaged polypeptides. Furthermore, they are responsible for the production of antigenic peptides. All of these ATP-dependent proteases are large protein assemblies, which are typically barrel-shaped. The proteolytic sites of these proteases are located within the central core and are accessible only through a narrow translocation channel aligned with the long axes of the particles.[95] A crucial functional step of these ATP-dependent proteases is the active unfolding of their protein substrates, as demonstrated for ClpAP,[96] ClpXP,[97] FtsH,[97] Lon,[98] the archaebacterial proteasome-regulatory ATPase complex PAN,[99] and the eukaryotic proteasome.[100] It is likely that these proteases unfold their substrates mechanically by pulling the polypeptide chain into their channel. This conclusion follows from the observation that during degradation of a protein by the ATP-dependent protease, unfolding occurs together with translocation of the polypeptide chain into the degradation channel.[86] Also, it was pointed out that the proteolysis of tightly folded proteins by the proteasome is accelerated greatly when an unstructured region is attached to the substrate.[101] Here, the disordered initiation site serves as a component of the targeting signal for degradation, being recognized and degraded first, leading to the sequential digestion of the rest of the target protein.[101]

Concluding, it seems that there is no single protein that would escape one or another form of disorder during its lifetime. Obviously many proteins are intrinsically disordered through their entire lives. However, even fully ordered proteins have to be disordered during their birth and death. This disorder is due to either the under-folding of a nascent polypeptide chain or the proteasome-induced unfolding of the degradation target. Many proteins are known to fold into ordered structure between these events and several remain disordered during that time. However all proteins need to become disordered during the exit from the ribosome tunnel and while entering the chamber of death, the proteasome tunnel. Furthermore, many ordered proteins undergo functional unfolding or possess transient disorder. Functions of these proteins require local or even global unfolding of their unique structures. Illustrative examples of such conditionally disordered proteins include protein translocating through a membrane, some activated states, and local

transient unfolding. Finally, many protein functions are dependent on intrinsic disorder in their partners, and activation and regulation of a myriad of proteins are controlled by various IDPs. In other words, we are dealing here with extrinsic disorder (i.e., intrinsic disorder in functional partners of ordered proteins). In summary, the protein lifetime is rather disordered, and any given protein constantly experiences disorder in one or another form.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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