would come from the effects of water. Furthermore, the independent observations that Gaillard *et al*. use to argue in favor of melt predict a sheet-like melt network would not cause anisotropic conductivity, especially if the conduction arises from highly conductive carbonatite melts.

If Gaillard *et al*.'s explanation is correct, then small volumes of carbonatite melt are rafted away from the ridge crest. For the melt to conduct, it needs to be interconnected throughout the mantle—and there is good reason to expect it to be interconnected (*16*). Carbonatites are highly buoyant (*17*) and, in general, interconnected melt is thought to be mobile. Yet, if the conductor away from the ridge crest on the East Pacific Rise is caused by carbonatite melt, then this trace amount of melt appears to be trapped: The overlying 60 to 70 km of mantle are highly resistive, show no sign of melt, and thus appear to prevent upward flow. Similarly, the deeper conductor across the Pacific Basin appears to be stable. Substantial volumes of melt could be floating about in the asthenosphere (the actively convecting part of the mantle), and its fate merits further investigation. Perhaps it plays a role in seamount formation. Perhaps it is released through faults in the overriding lithosphere. Or perhaps it stays put.

Resolving the water/melt controversy may be tricky: It is difficult to conceive of a field experiment that could rule one mechanism in or out. Areas with temperatures below the mantle melting point would also be too cold for the water mechanism to affect conductivity, and the interdependence between melting and water content similarly make it difficult to untangle the two. But regardless of this debate, at least the deep melt fractions inferred from geophysics can now be revised, and petrologists and geophysicists can move several steps closer to agreement.

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BIOCHEMISTRY

Controlled Chaos

The availability and abundance of intrinsically disordered proteins inside a cell is under tight control.

Vladimir N. Uversky[1,2] and A. Keith Dunker[1]

The cornerstone of modern protein structural biology is the sequence-structure-function paradigm, according to which a protein's function depends on its folding into a unique three-dimensional structure. Thus, proteins are traditionally viewed as rigid or semi-rigid "blocks," whose specificity and catalytic power are determined by the unique fit of a correct substrate onto the preformed and sturdy surface of the enzyme's active site (*1*). But the discovery of proteins that are wholly disordered or contain lengthy disordered segments, yet are functional (*2*–*6*), has wreaked havoc on the lock-and-key world view that demands highly organized proteins. Such disordered proteins are abundant, diverse, vital, dynamic, and chaotic, and on page 1365 of this issue, Gsponer *et al*. (*7*) reveal how these disorganized proteins are tightly controlled inside the cell.

The concept of ill-structured but functional proteins has raised many questions. For example, although some disordered proteins (and disordered regions within proteins) have been characterized in vitro, whether they are "real" and exist in vivo has not been clear. The abundance of these proteins and protein regions in various proteomes, their structural and dynamical properties, and their functional repertoire have not been understood. It also remains unknown whether intrinsic disorder in a protein is encoded by the amino acid sequence, or what the turnover rates are of such proteins in a cell. More generally, it is not clear how intrinsically disordered proteins are regulated inside the cell.

Bioinformatics has begun to play a crucial role in shaping the study of intrinsically disordered proteins, bringing coherence to proteins that were previously viewed as individual outliers (*8*). Disorderedness is now linked to amino acid sequence. Intrinsically disordered proteins (and regions) are generally enriched in most polar and charged residues and are depleted of hydrophobic residues (other than proline), and this distinction forms the basis of computational tools for disorder prediction (*4*, *5*, *8*, *9*).

The main functions of intrinsically disordered proteins include transducing intracellular signals, regulating processes including the cell division cycle, and recognizing various binding partners (e.g., ligands, other proteins, and nucleic acids). These are complementary to the common catalysis and transport activities of proteins with well-defined, stable three-dimensional structures (*3*, *5*, *6*, *10*–*12*). Structurally, intrinsically disordered proteins range from completely unstructured polypeptides to extended partially structured forms to compact disordered ensembles containing substantial secondary structure (*10*, *11*). Intrinsically disordered regions are highly abundant in nature [>50% of eukaryotic proteins likely contain at least one disordered region ≥30 amino acids in length (*5*)]. Furthermore, many proteins encoded by various genomes are likely to be wholly disordered [e.g., >20% of eukaryotic proteins are expected to be mostly disordered (*13*)].

The rates (*14*) and patterns (*15*) of amino acid substitutions within intrinsically disordered proteins over evolutionary time are distinct from those within structured proteins and are consistent with lack of structure. Therefore, these evolutionary characteristics support the existence of disorder inside the cell. Also, polypeptide segments that are present in some proteins but absent in others as a result of alternative splicing of the encoding messenger RNA (mRNA) are much more often intrinsically disordered than ordered (*16*). Furthermore, new segments that become

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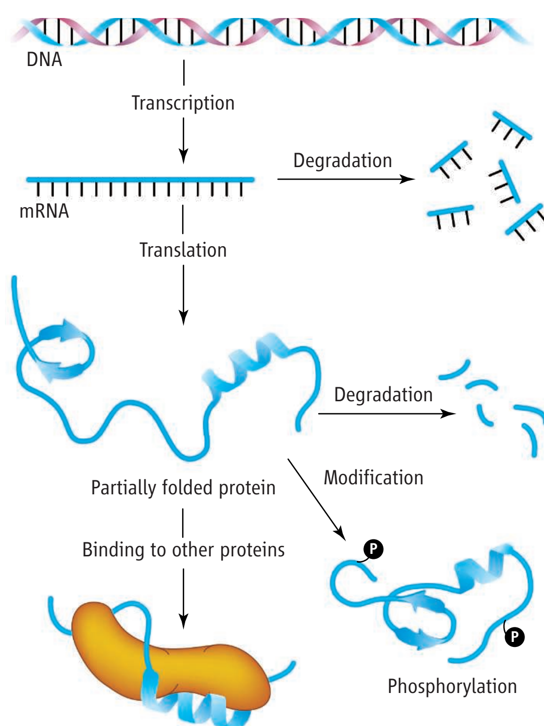
added to proteins (probably through the conversion of a noncoding DNA sequence to a coding sequence) typically lack structure and fall into the class of intrinsically disordered regions (*17*). Thus, it is not surprising that proteins and protein regions that are disordered are often associated with human diseases (*18*).

Gsponer *et al*. assigned all proteins of the budding yeast *Saccharomyces cerevisiae* to one of three groups according to their predicted levels of intrinsic disorder: highly ordered proteins (0 to 10% predicted disorder), moderately disordered proteins (10 to 30% predicted disorder), and highly disordered proteins (30 to 100% predicted disorder). The authors then evaluated correlations between these groups and the various steps of protein synthesis and degradation.

To collate the transcription of genes encoding intrinsically disordered and ordered proteins, Gsponer *et al*. compared the synthesis and degradation rates of the corresponding mRNAs. Although the rates of transcription of genes encoding both classes of proteins were comparable, mRNAs encoding intrinsically disordered proteins were generally less abundant because of their increased degradation (see the figure).



Disorder management. As a result of fast mRNA degradation, slow translation of mRNA into protein, and fast protein degradation, the overall amount of intrinsically disordered proteins inside a cell is less, and their half-lives are generally shorter, than those of ordered proteins. However, some disordered proteins can be present at high quantities and for long periods of time if they are modified (such as by phosphorylation) or interact with some specific binding partners.

At the protein level, intrinsically disordered proteins were less abundant than ordered proteins because of their lower rates of synthesis and shorter half-lives. Because the stability of certain proteins can be modulated by chemical modifications such as phosphorylation (*19*), Gsponer *et al*. examined a specific enzyme-substrate network in yeast. Intrinsically disordered proteins were substrates of twice as many kinases (enzymes that phosphorylate proteins) as were ordered proteins. The majority of kinases whose substrates were mostly intrinsically disordered proteins either were regulated in a manner that depended on the stage of the cell division cycle or were activated upon exposure to particular stimuli or stress. Therefore, protein modifications not only may serve as important regulatory mechanisms for the fine-tuning the functions of intrinsically disordered proteins, but may also be necessary to tightly control the availability of these proteins under different conditions.

Comparable trends were found in proteins of the fission yeast *Schizosaccharomyces pombe* and in proteins of *Homo sapiens*, suggesting that unicellular and multicellular eukaryotes regulate the availability of intrinsically disordered proteins similarly. Overall, Gsponer *et al*. demonstrate evolutionarily conserved tight control of synthesis and clearance of most intrinsically disordered proteins. This stringent regulation is directly related to the involvement of such proteins in cell signaling, in which it is crucial that proteins be available in appropriate amounts yet not be present longer than needed. In addition, some intrinsically disordered proteins could be present in cells in large amounts and/or for long periods of time because of either specific chemical modifications or interactions with other factors that promote changes in their cellular localization or protect them from degradation (*5*, *19*, *20*).

The observations made by Gsponer *et al.* clearly show that the chaos seemingly introduced into the protein world by the discovery of these proteins is under tight control. These findings are in a good agreement with a recently published study showing that both the measured amount of RNA in a bacterium (*Escherichia coli*) and the predicted amount of protein expression correlate positively with the predicted fraction of disordered regions in *E. coli* proteins (*21*). The disorder predictions match with the experimentally elucidated disordered regions for several highly expressed proteins that were predicted to have a high degree of disorder. It was proposed that higher synthesis and degradation rates could make the amount of intrinsically disordered proteins very sensitive to the environment, with slight changes in either production or degradation leading to significant shifts in the amount of protein present.

The discovery of new functions of intrinsically disordered proteins is a goal for the future, as well as a better understanding of how these proteins have evolved. Another important aim will be the elaboration of new experimental methods and computational tools for the discovery and structural and functional characterization of intrinsically disordered proteins and regions, both inside cells and in a crowded milieu in vitro. Uncovering the interplay between intrinsic protein disorder and the pathogenesis of human diseases has just begun.

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