Protein Folding: Grand Challenge of Nature

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Protein folding is a longstanding challenge in structural biology. No one knows how to predict the correct native structure or folding of a protein from the primary amino acid sequence unless that sequence has significant homology with another protein of known 3D structure. Concerning 1D-3D structure/folding prediction in proteins, one remarkable research work “A Stoichiometry Driven Universal Spatial Organization of Backbones of Folded Proteins: Are there Chargaff’s Rules for Protein Folding?” has recently been published by Mittal et al. in 2010 in this Journal (1). The work opens an unanticipated window into the new biostatistics methods on protein folding. After rigorous investigation on close to four thousand crystal structures (of protein), the authors conclude “Protein folding is a direct consequence of a narrow band of stoichiometric occurrences of amino-acids in primary sequences, regardless of the size and the fold of a protein”. Contrary to all prevalent views, the authors also emphasized: “preferential interactions” between amino-acids do not drive protein folding. In this connection, it should be noted that that preferential interactions between amino acids are the basis for introducing knowledge-based potentials, which in turn provide the underpinning for present day 3D protein structure prediction by modeling and simulation (2-5 and references therein). Perhaps the actual rules of protein folding still remain elusive; however, this work contributes new information on bio-mathematical expression and adds a new dimension that could lead to solutions to problems presented by structural biology.

Though the research work of Mittal et al. may provide some light on the recognition of protein fold from their primary amino acid sequences, it has several limitations. Several points in Mittal et al. appear to conflict with existing concepts. In the prediction of protein folding, the contribution of side chains (polar/non-polar, acidic and basic) in the primary sequence seems missing in this work, and this should be clarified. The hydrophobic, hydrophilic, van der Waals and H-bonding interaction may control the folding mechanism by fixing the orientation of side chains in proteins (6-8). The side chains (polar, acidic or basic) interact with the aqueous medium and play a major role in shaping the protein, the hydrophobicity of amino acids tend to drive them from exterior to interior. The charge – charge, charge – dipole and dipole – dipole interaction of side chains may calibrate the fold recognition. So, the essence of side chain could be to gear the folding topology of protein, i.e., folding topology is not geared by protein backbone alone as advocated by Mittal et al. The dynamical results reveal that the backbone is incapable to build the actual fold of a protein, perhaps the side chain with backbone amino acids produce the folds (9). During dynamics, the fold of protein structure undergoes the conformational changes which may be identical or not with its x-ray structure. All the atoms (backbone and side chain) move anisotropically, and the direction of motion in protein is determined by non-bonded interaction of sidechains. This motion is anharmonic at biological temperature, usually due to

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side chain hopping between two or more alternative minima (10-12). Moreover, the loop–flap dynamics demand that the backbone behave as rigid bodies (minimum RMSF) whereas the displacement of loop is possible due to the reorientation of sidechains (13). Hence, in addition to the C-alpha atoms, the sidechain could influence the shape, size and fold of a protein. On the basis of the above arguments, it is doubtful or not clear, whether the correct fold recognition is provided by the stoichiometry driven folding thesis of Mittal et al.

Again, another important point, the influence of topology to protein folding has not been mentioned by the authors. Protein-folding rates and mechanisms are largely determined by a protein’s topology rather than its inter-atomic interactions. In the several crystal structures, the large changes in amino-acid sequence do not alter the overall topology of a protein and evolution has not optimized protein sequences for rapid folding (14). The observation that some structurally related proteins with little or no sequence similarity have very similar type of fold, makes the situation more complicated.

Nevertheless, some single-point mutation in a protein perturbs the secondary, tertiary, and quaternary structures, thus inducing new folding (15). The backbone of protein could not control the folding mechanism, perhaps a conflict in side chain orientation causes a misfold (16, 17). Again in some multi nuclear metalloproteins, the occupancy of metal ions within the protein are controlled by side chains, not by backbone, and sometime the selectivity of metal ions (18) are also governed by protein folding. In addition, continuum models of water do not account for the discrete nature of water molecules, which may lead to differences in protein folding dynamics (19) such as a cooperative expulsion of water upon folding. The authors’ view on this aspect is not clear.

Undoubtedly, the work of Mittal et al. will be very effective to provide impetus for further investigation in protein research.

References