Comment

New Direction to the Solution of Protein Folding Problem

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Recently we saw an interesting paper entitled “A Stoichiometry Driven Universal Spatial Organization of Backbones of Folded Proteins: Are there Chargaff’s Rules for Protein Folding?” by Aditya Mittal, B. Jayram, Sandhya Shenoy and Tejdeep Singh Bawa which appeared in the Journal of Biomolecular Structure and Dynamics (1). The paper comes up with a very revolutionary idea about protein folding. The authors point out that the frequencies of amino acids in the primary structures of proteins guide the folding patterns of the proteins. This very idea is quite contrary to the existing belief of the theory behind protein folding. According to the current understanding behind the mechanism of protein folding, the process of protein folding relies predominantly on non-covalent interactions between the side chains of amino acid residues in proteins (2-10) as well as with the surrounding environment in which the proteins reside. This preferential interaction between amino acids is the basis of the development of knowledge-based potentials and protein structure prediction which is common place nowadays by modeling and simulations. (11, 12 and references therein).

The authors in the paper observed, on the basis of their analysis of the crystal structures of proteins in the protein data bank (PDB), that the frequencies of amino acid residues in proteins govern the folding patterns of proteins. This is quite interesting and, if substantiated in future research, would change the whole scenario of the computational prediction of protein folding. Prediction of protein folding from the amino acid sequence of proteins depends basically on the extent of sequence similarity between the query protein and the template (13-15). As per the observations of the paper in question, proteins with similar amino acid frequency would likely to have similar folding patterns. We have a few questions regarding the hypothesis.

Is there any direct correlation between the amino acid residue frequency and the secondary structures of proteins? If so, then it would be a very essential step towards in-silico protein development. Next question is how does the amino acid sequence frequency determine the interaction patterns in proteins? The pattern of amino acid sequence frequency, while governing the folding patterns of proteins, should also interfere with the interaction patterns of proteins. If indeed this is the case, then this would shed light in the elucidation of the underlying mechanisms of different diseases. But one big question then is what are the effects of the cellular environments on protein folding? According to the results of the paper in question, minimization of the surface to volume ratio of proteins (based on the side chains of the constituting amino acid residues of the proteins) by exclusion of surrounding water molecules, is the most important parameter of the folding process. This correlates with the existing views of the mechanism of protein folding. As per the results of this paper, proteins

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are found to be enriched in hydrophobic amino acid residues (Leu, Ala, Val) and Glycine and depleted in aromatic amino acid residues (Phe, Trp, Tyr). It is well known that hydrophobic amino acid residues generally constitute the structural scaffolds of proteins, but aromatic amino acid residues also stabilize proteins by cation-pi interactions with basic amino acid residues (Lys, Arg) present in proteins (4-10). The average percentage of Cys residues is very low (second to the minimum which is Trp). Therefore the number of covalent disulfide bonds in proteins is much less. This supports the existing view of the molecular mechanism of protein folding, which suggests the preponderance of non-covalent interactions in proteins. Also the average percentages of polar and charged amino acid residues are much less. The less number of charged or polar amino acid residues in proteins means less interactions with the surrounding aqueous milieu and that means less surface-to-volume ratio. However, we are curious to know what the correlation is between the frequency of amino acid residues in proteins and the numerous intermediates that proteins have before getting converted to the natively folded form from the unfolded states; whether it would be possible to predict the structural aspects of the intermediates from the amino acid frequencies of the proteins. If that is possible then the mystery behind protein folding mechanisms could be solved. But it should also be noted that crystal structures are just some snapshots of the dynamic behavior of the ever changing macromolecules in cells (16-18). Therefore it is still far from certain what is actually happening inside the cells. The paper in question suggests an interesting and novel way of analyzing the mystery behind protein folding.

Further validation of the hypothesis presented in the paper may be achieved by determining the structures of proteins from their amino acid residue frequency.

References