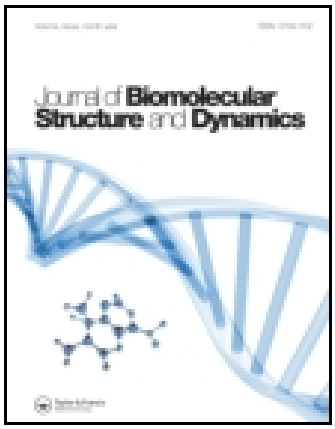

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Comment

The Yeast Prion Case: Could There be a Uniform Concept Underlying Complex Protein Folding?

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To date, there have been many hypotheses on protein folding and certain progress surely has been made, such as Anfinsen's dogma (1), Levinthal paradox (2). Recently, Mittal *et al*. analyzed close to 4,000 folded proteins from their published crystal structures in the protein data bank (PDB) with a bioinformatics and computational method, and innovatively proposed that 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 (3). Contrary to all prevalent views, this hypothesis actually negated the roles of specific amino-acid interactions and the sequence order of the amino acids in protein folding. In this connection, it should be noted that preferential interactions between amino acids are the basis for introducing knowledge-based potentials, which in turn provide the underpinning for present day three-dimensional protein structure prediction by modeling and simulation (4-7 and references therein). Although their data analysis approaches seem scientifically correct, the "unified conclusion" drawn from a quantity of statistic data may not explain principles complied by every individual protein for its folding. Nevertheless, spatial distribution of neighborhoods for all amino-acids, rather than residues adjacent along the primary sequence, determine the protein folding, as proposed by Mittal *et al.* is a meaningful finding.

It is the study of the properties of protein folding in certain types of proteins that is being used to deduce the common properties shared by other proteins; such studies has already laid the foundation for almost every hypothesis on protein folding. For example, the reason why Anfinsen's dogma is widely accepted is that it is deduced from the study on the features of ribonuclease molecule (1). On the other hand, the inspiration of Mittal *et al*. was originated from Chargaff's Rules, a statement on DNA composition properties. It is well known that DNA is composed by only 4 kinds of nucleotides while the types of amino acids in proteins are as many as 20. Furthermore, DNA composition is relatively simple and conservative in all species; but the structure of protein is far more complicated in that different proteins have different structures even in the same species, and the structure of a protein with the same function is different in different species. Therefore, it is extremely difficult trying to use one uniform concept to explain all kinds of protein foldings and structural features.

For a decade, our group has been constantly devoted to the study on protein misfolding diseases. The conformational conversion of amyloid proteins, especially prions, is associated with numerous protein aggregation pathologies and infectious properties. We will comment on this issue based on the data obtained from molecular biological and molecular dynamic prion protein studies.

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Each prion protein contains one prion-forming domain (PrD), essential to its aggregation. It is found that in the PrDs of Ure2p, Sup35p and Rnq1p, the first three yeast prion proteins to be identified, the glutamine (Q) and asparagine (N) content is unusually high (48% for Ure2p-1–89, 46% for Sup35p and 43% for Rnq1p) (8-10). Mutagenesis studies of Sup35p and Ure2p have confirmed the important role played by the Q/Ns content in prion formation (8, 9). Based on the special amino acid Q/Ns' content and other factors to compose prion, Lindquist and her co-workers conducted a bioinformatic proteome-wide survey to score every PrD in yeast and revealed that ~ 200 proteins have candidate PrDs, in which the amyloid and prion-forming properties of the 100 highest-scored PrDs were tested (11). They identified 24 proteins that satisfied the criterion for prion behavior, of which several were proved to be prion (New1p, Swi1p, Mot3p and Cyc8p). Their study has suggested that specific amino-acids could contribute to the structural feature of a certain protein.

Subsequently, Wickner and his team used Ure2p as a model system and randomly shuffled the order of amino acids of its PrD while keeping the amino acid composition (12). Five Ure2p variants were generated. Test performed *in vitro* shows that the prion domains of all five have readily formed amyloid fibers under native conditions. Meanwhile, four of them formed stable prions *in vivo*, and the fifth formed unstable prions that could only be maintained and transmitted under selective conditions. Liu *et al.* studied Sup35p and shuffled its PrD without altering its amino acid composition, which even formed amyloid fiber *in vitro* (13). The study on the prion formation of shuffled PrD of Sup35p *in vivo* was conducted by Wickner's group (14). Seven shuffled variants were generated, five of which expressed normally *in vivo*. And for these five, it was found that four of them formed stable prions and the fifth formed unstable prion. It needs to be pointed out that their results suggested that the Sup35p oligopeptide repeats (PQGGYQQYN, which is repeatedly expressed in prion domain of Sup35p) were not indispensable for prion formation. These oligopeptide repeats were first found in mammalian prion protein and were thought to influence their conformational conversion to the prion state (15).

Moreover, our group has used the molecular dynamics simulation to study the aggregation characters of a short 7 peptide fragment (GNNQQNY) in yeast prion Sup35p which could form amyloid fibrils (16, 17). The seven amino-acid residues were reorganized randomly into 9 different fragments (shown in Table I), without changing any amino acid content. We performed 20ns simulation for each fragment system at pH 7 and temperature 330 K. The RMSD (Root Mean Square Derivative) value of each fragment system after the simulation was quite close, between 3.214 and 4.473, which indicated that the structural diversity of each fragment were very similar. Hereafter we calculated aggregation time of each fragment system and found that these nine systems aggregated into one cluster eventually despite different time they spent. Although changing the permutation of the seven amino-acid residues has made impacts on the aggregation speeds of nine systems, their aggregation properties have not been influenced. Both Wickner and our groups' results indicated that the aggregation properties of prion proteins are independent to the order of amino-acid sequences.

Table I
The sequences of 9 randomly reorganized 7 peptides and the computation after simulation.

	Sequence	RMSD (Å)	Aggregation Time* (ns)
wt	GNNQQNY	3.214	5.91
1	GQNQNNY	4.391	4.95
2	GNQNQNY	3.494	1.97
3	GNNQNQY	4.073	11.89
4	GQNNQNY	4.473	1.89
5	GQNNNQY	3.634	4.87
6	GNQNNQY	4.399	3.99
7	GQQNNNY	3.539	9.24
8	GNQQNNY	3.686	7.58
9	GNNNQQY	3.833	6.39

*Aggregation time, the time that each fragment system aggregate to one cluster.

Our opinion for the thesis of Mittal *et al*. comes from data on only one kind of specific proteins. Results obtained cannot be employed to prove that all the protein folding features of all proteins may be in accordance with this principle. We believe that special amino-acids should be crucial for the structural features of certain type of proteins, and it might only be in a limited fixed type of proteins that the occurrence of amino-acids (stoichiometry) determines the structural features. However, it is still open to question whether stoichiometry driven protein folding is a universal concept that applies to all proteins.

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