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Research Article

INSIGHT IN TO THE DIFFERENCES IN PATTERN OF INTERACTIONS IN HOMODIMERS

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ABSTRACT

Objective: Our study aims to identify the differences in number of cation-pi and aromatic-aromatic interactions in a set of homodimers with known folding data (2S, 3SMI and 3SDI) towards having a deep insight in to their folding and binding.

Methods: We have computed the contribution of cation–pi interactions for each protein in the data set using realistic electrostatics program CAPTURE. Aromatic- aromatic interactions of the proteins in the dataset are being identified using Protein Interactions Calculations (PIC) server.

Results: The energetic contributions of residues involved in cation–pi interaction have been computed using CAPTURE, and the results are tabulated in Table 2. The result shows that maximum number of cation – pi interactions occurs in 3S than in 2S homodimers. Aromatic –aromatic interactions have been studied using PIC server. The result shows that maximum number of aromatic-aromatic interactions is again in 3S homodimers than in 2S.

Conclusion: From the results obtained from our study, we find a number of energetically significant cation–pi interactions in the dataset. Analysis of cation–pi interaction energy revealed that there is stronger electrostatic energy than van der Waals energy. We compared the occurrence of six interaction pairs to understand which interaction pair is most preferred and found that preference of Arg–Tyr interactions is higher when compared to other interacting residues which suggest the importance of Arg–Tyr pair in the stability of proteins and we also find that the length of the protein has no significant effect on the number of interactions.

Keywords: Homodimers, Cation-pi, Aromatic-Aromatic, 2S, 3SMI and 3SDI.

INTRODUCTION

To understand the homodimer folding mechanism through 2state (2S) without stable intermediate, 3state with monomer intermediate (3SMI) and 3-state with dimer intermediate (3SDI) is interesting [1,2,3,4]. Thus it becomes critical to differentiate 2S, 3SMI and 3SDI homodimers using different interactions. The three dimensional structure of a protein is being described by number of interactions which include cation-π, Ar-Ar etc. Cation-π interactions plays major role in biological recognition [5-6].

Protein structures are stabilized by several non-covalent interactions, including electrostatic, hydrogen bonding, van der Waals and hydrophobic interactions. The cation–π interactions are also recognized to play an important role in the stability of proteins and protein–DNA complexes [7,8,9]. The importance of this interaction has been stressed by several researchers for their role in enhancement of the stability of thermophilic proteins [10-11], folding of polypeptides [12-13] and the stability of membrane protein structures [14-15].

The side-chains of phenylalanine and tyrosine residues in proteins are found to be involved in pairwise interactions. It has been suggested that aromatic-aromatic interactions are important in protein folding and stability. The non-bonded potential energy calculations indicate that a typical aromatic-aromatic interaction has an energy of between -1 and -2 kcal/mol and contributes between -0·6 and -1·3 kcal/mol to protein stability [16].

A large number of varieties of weak and strong non-covalent interactions contribute to the stability of proteins. Even though hydrogen bonds [17-18], salt bridges [19-20] and hydrophobic interactions are considered to be the major determinants of structural stability, non-canonical interactions have been shown to be of much greater importance than previously thought, particularly those interactions in which the π ring system serves as a hydrogen bond acceptor [21].

These non-canonical interactions involving the π ring system as hydrogen bond acceptor were first described by Wulf ***et al***.[22] through spectroscopic analysis of small molecules. The occurrence of C^{α}-H···O=C hydrogen bonds were documented by Sutor [23] and later studied in great detail by Desiraju and Steiner [24].

MATERIALS AND METHOD

Dataset

The dataset comprises 41 homodimers piled up with the individual function for each of the homodimer and tabulated. [Table 1]. They show regulatory and catalysis functions. The reason to known the individual function for data is to establish common understanding for a biological system, which makes the task even more challenging.

Data analysis tools

The **CAPTURE** tool from e-source (http:// capture.caltech.edu/) is used which can identify energetically significant cation-π interaction with in homodimers (2S and 3S). Protein interaction calculations (PIC) is a server which predicts different kind of interactions including disulphide bonds, hydrophobic interactions, ionic interactions, hydrogen bonds, aromatic–aromatic interactions, aromatic-sulphur interactions and cation-π interactions. The number of Cation pi and Aromatic-Aromatic interactions are organized in Table 2 and Table 3.

Table 2: Cation - Pi interactions in Homodimers

Folding state	NUM	Mean					
		TYR/LYS	TYR/ARG	TRP/ARG	PHE/LYS	PHE/ARG	TRP/LYS
2S<100	12	1	0.33	0.41	0.41	0.41	0.16
2S>100	13	2.66	3	0.5	1.16	1	0.41
3SMI	6	2.9	3	0.4	0.9	1.2	0.7
3SDI	10	5.33	5.33	0.66	2	4.5	0.33

Num = Number of Proteins in each subset,2S>100 = Homodimers in state with Monomer length >100

Table 1: Dataset for the study

S. No.	2S	Molecular Function	Classification
1	2cpg	DNA binding	Gene regulating Protein
2	1arr	DNA binding	Gene regulating Protein
3	1rop	DNA binding	Transcription regulation
4	5cro	DNA binding	Gene regulating Protein
5	1bfm	DNA binding	Histone Protein
6	1a7g	DNA binding	Transcription regulation
7	1vqb	DNA binding	DNA binding protein
8	1b8z	DNA binding	DNA binding protein
9	1ety	DNA binding	Transcription regulation
10	1y7q	DNA binding	Transcription regulation
11	1a8g	Aspartic type endopeptidase activity	Complex(acidproteinase/inhibitor)
12	1siv	DNA gyrase inhibitor activity	Plasmid
13	1vub	DNA gyrase inhibitor activity	Plasmid
14	1cmb	DNA binding	DNA binding protein
15	3ssi	None	Serine protease inhibitor
16	1wrp	DNA binding	DNA binding protein
17	1bet	Growth Factor	None
18	1oh0	Steroid delta isomerase activity	Isomerase
19	2gsr	Glutathione transferase activity	Complex(transferase/inhibitor)
20	1gsd	Glutathione transferase activity	Transferase
21	1gta	Glutathione transferase activity	Transferase
22	2bqp	Sugar binding	Sugar binding protein
23	1hti	Triose phosphate isomerase activity	Isomerase
24	1ee1	ATP binding	Ligase
25	1buo	Btb domain from PLZF protein	None
	3S		
26	1mul	DNA binding	DNA binding protein
27	1hqo	None	Signalling protein
28	1psc	Zinc ion binding	Hydrolase
29	1cm7	3-isopropylmalate dehydrogenase activity	Oxidoreductase
30	1aoz	Oxidoreductase activity	Oxidoreductase
31	1nl3	ATP binding	Protein Transport
32	1a43	None	Viral Protein
33	1qll	Calcium ion binding	Neurotoxin
34	1dfx	None	Electron Transport
35	1yai	Metal ion binding	Oxidoreductase
36	1spd	Metal ion binding	Oxidoreductase
37	1run	DNA binding	DNA binding protein
38	11gs	Glutathione transferase activity	Transferase
39	1tya	RNA binding	Ligase
40	1nd5	Acid Phosphatase activity	Hydrolase
41	2crk	Catalytic activity	Transferase

Table 3: Aromatic - Aromatic interactions in Homodimers

Folding state	NUM	Mean						
		TYR/PHE	TRP/TRP	TRP/TYR	PHE/PHE	PHE/TRP	TYR/TYR	PHE/TYR
2S<100	12	1.25	0.16	0.16	2.08	0	0.5	0.58
2S>100	13	3	0.08	0.6	0.58	1.16	1.16	0.5
3SMI	6	1.91	0.25	0.41	1.41	1.83	1.29	1.41
3SDI	10	2.5	0.16	0.83	3	1.16	0.83	1.5

Num = Number of Proteins in each subset, 2S>100 = Homodimers in state with Monomer length >100

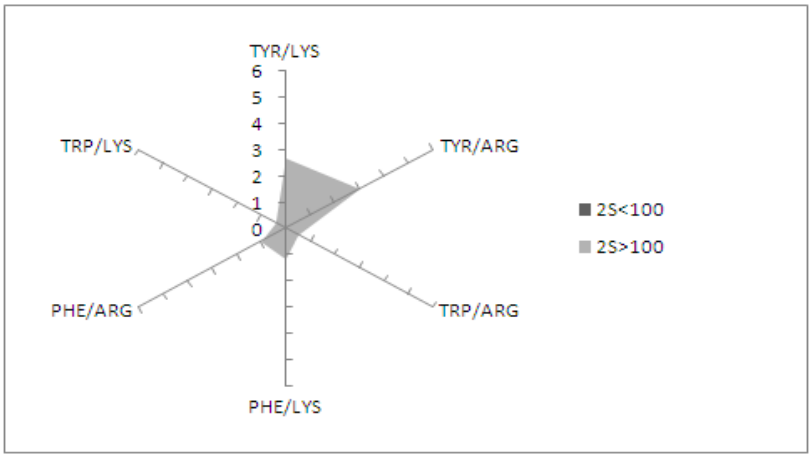

Fig. 1a: Radar diagram showing the Cation - Pi interaction of 2S Homodimers

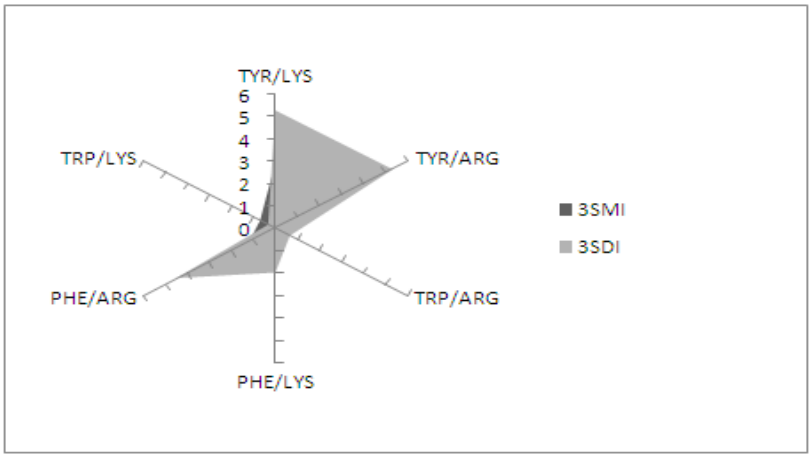

Fig. 1b: Radar diagram showing the Cation - Pi interaction of 3S Homodimers

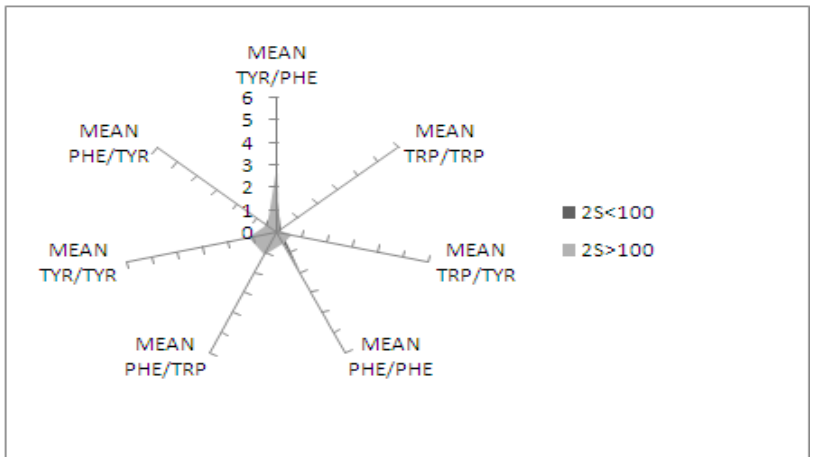

Fig. 2a: Radar diagram showing the aromatic-aromatic interaction of 2S Homodimers

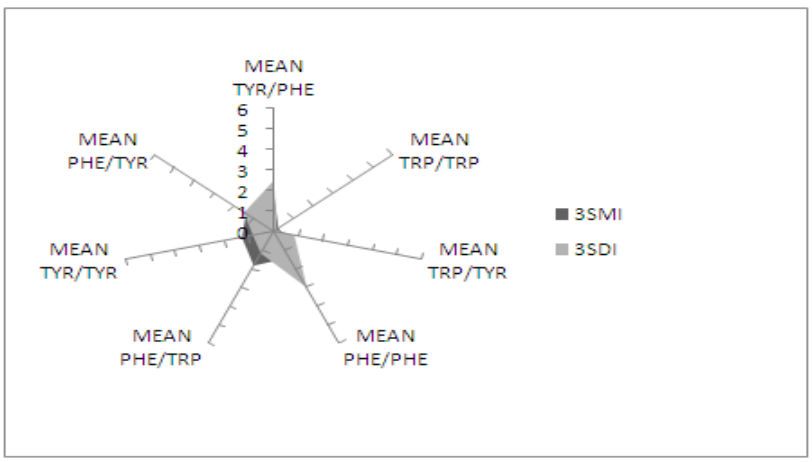

Fig. 2b: Radar diagram showing the aromatic-aromatic interaction of 3S Homodimers

RESULTS AND DISCUSSION

Fig. 1 shows the occurrence of Cation-Pi interactions in 2S (Fig. 1a) and 3S (Fig. 1b) proteins. The distribution in 3S is larger than 2S. This implies that large number of the Cation-pi interactions is occurring in 3S than 2S. Fig. 2 shows the occurrence of Aromatic-Aromatic interactions in 2S (Fig. 2a) and 3S (Fig.2b) proteins. The distribution in 3S is again larger than 2S. This implies those major portions of the Aromatic-Aromatic interactions are occurring in 3S. This information makes the classification of Homodimer folding in to 2S and 3S respectively. Further, we can see that both cation-pi and aromatic-aromatic interactions shows the ratio of occurrence as 3SDI>3SMI> (2S>100)> (2S<100).

CONCLUSION

The crucial role of homodimer as potential drug targets has been identified in recent studies. Hence it becomes highly essential to

have an understanding on structure and mechanism of Homodimer folding. Homodimer folding is usually studied using Biophysical techniques which are generally time consuming and tedious. Determination of folding mechanism for known homodimer structures using structural features is interesting. The accessible information on Homodimer folding and binding is coaxing in nature. 2S, 3SMI and 3SDI homodimers fold and bind through different mechanisms. This study depicts discernments of occurrence of 2S, 3SMI and 3SDI proteins on the basis of cation-pi and aromatic-aromatic interactions. Data from the study suggests that both cation-pi and aromatic-aromatic interactions shows the ratio of occurrence as 3SDI>3SMI> (2S>100)> (2S<100). Thus, it is possible to differentiate 2S from 3S proteins using these parameters.

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