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In silico Evaluation of Anti-cancer Peptides on BRCA1 Targeting

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ABSTRACT

In silico docking techniques are being at this instant have great investigation utensil for molecular analysis. The principle binding situate of this protein would be BRCT considered for expression and regulation of BRCA1. The BRCA1 C Terminus (BRCT) domain is a family of evolutionarily related proteins. The present study focus on docking and toxicity scrutiny of well descriptive peptides and the results suggested that Z Dock score suggested higher score with peptide p-ACC1 and ATRIP peptide and the toxicity examination were carried out using ToxinPred on line tool suggested that ATRIP peptide has lesser toxicity controversy with peptide p-ACC1 has greater toxicity. Further concluded ATRIP and p-ACC1 suggested for further studies.

Key words: Peptides, toxicity, docking, interactions, BRCA1

INTRODUCTION

The breast cancer is the most commonly diagnosed cancer after non melanoma skin cancer and it is the second leading cause of cancer deaths after lung cancer. In 2013, an estimated 234,580 new cases diagnosed and 40,030 deaths from breast cancer occur. The BRCA1 is a human caretaker gene chiefly institute in breast and ovarian cancers. Its protein, also called by the synonym breast cancer type 1 susceptibility protein. The primary tumor suppressing task of BRCA1 relates to the maintenance of genomic integrity through multiple roles such as regulation of DNA replication, repair and transcription, in toting up to various cell cycle check points (Henderson, 2012), controlling of lipogenesis and transcriptional regulation. Very recent provided substantiation indicating, BRCA1 also involving in chromatin unfolding (Greenwood, 2002; Jagatheesh and Elangovan, 2013). The principle binding situate of this protein would be BRCT considered for expression and regulation of BRCA1. The BRCA1 C Terminus (BRCT) domain is a family of evolutionarily related proteins. The BRCT domain (after the C-terminal domain of a breast cancer susceptibility protein) is found predominantly in proteins, involved in many of vital functions of BRCA1, for example as found in the breast cancer DNA-repair protein BRCA1 and checkpoint control during the transition from G2 to M phase of the cell cycle. The domain is an approximately 100 amino acids, tandem repeat which appears to act as a phospho-protein binding domain. Phosphoserine is a component of many proteins as the result of post-translational modifications peptide-protein interactions are ubiquitous in the living cell and form a key component of the overall protein-protein interaction network. These interactions are drawing increasing interest due to their part in signaling and regulation and are thus striking targets for computational structural modeling (London *et al*., 2012). The current scenario of *in silico* docking tools for protein-peptide interactions are appreciated candidate for predicting enhanced interactions (Jayaraj *et al*., 2013). However, the abilities of peptides to translocate through cell membranes can be accompained by

toxic effects resulting from membrane perturbation at higher peptide concentrations. Therefore, we investigate selected cell penetrating peptide for its interactions with BRCA1 on BRCT domain and toxicity of four peptides with well-documented for their potential anti cancer property possessing phosphoserine.

MATERIALS AND METHODS

Hardware and software: Docking calculation was carried out on HP Intel® Xeon® processor E3-1200v2 family with 16 Gb RAM, 1 TB Hard disk, NVIDIA Quadro 2000, windows 7 ultimate 64 bit. Accelrys Discovery Studio Client 3.5 used for docking preparation, Biosolve IT and GOLD 5.1 are docking softwares used for binding energy calculation.

Identification of target protein: The crystal structure of the peptide target of BRCT domain was salvaged from RCSB Protein Data Bank [PDB ID-1VKX] (http://www.pdb.org).

Protein-protein docking

Selection of peptide: Four well known peptides for the target of BRCA1 without bearing in mind the primitive future mechanism were selected as follows:

- **MDC1:** The MDC1 peptide holds phosphoserine which smooth the progress of interaction with BRCT domain. The MDC1-BRCT binds pSer-Gln-Glu-Tyr-COO(-) at the C terminus of the histone variant gamma H2AX via direct recognition of the C-terminal carboxylate while BRCA1 recognizes pSer-X-X-Phe motifs either at C-terminal or internal sites within target proteins may assist protein signaling at DNA damage foci through specific interaction with serine-phosphorylated protein partner (Campbell *et al*., 2010)
- **BATT:** The BRCA1 BRCTs also interrelate with BAAT1 and the BRCA1-associated protein required for ATM commencement, it's also recognized as BRAT1. Phosphorylation of Ser239 in human BRCA1 is recognized specifically by the BRCA1 BRCT domains, whereas a S239A substitution abrogates the BRCA1 binding to BATT1 and leads to a G2-M checkpoint defect, indicating that this interaction is essential for the ATR function in checkpoint control (Liu and Ladias, 2013)
- **ATRIP:** The BRCA1-C complex is composed of CtIP and the MRN complex and is formed in a cell cycle-dependent manner during S and G2 phases of the cell cycle. The BRCA1-C is involved in DNA end resection to generate ssDNA needed for HR-mediated DNA repair. In addition to these well-studied complexes, the BRCA1 BRCTs also interact with ATRIP (PEACpSPQFG) may possess vital role in cell cycle checkpoint (Shen and Tong, 2008)
- **p-ACC1:** Shen and Tong (2008) suggested the crystal structure at 3.2 Å resolutions of human BRCA1 BRCT domains in complex with a phospho-peptide from human which provides molecular evidence for direct interactions between BRCA1 and ACC1. The p-ACC1 peptide is bound in an extended conformation, located in a groove between the tandem BRCT domains

Protein docking using Z DOCK in accelrys discovery studio 3.5: The Z DOCK is a rigid body protein-protein docking algorithm based on Fast Fourier Transform correlation technique that is used to explore the rotational and translational space of a protein-protein system (Chen *et al*., 2003). Here, the crystal structure of BRCA1- BRCT domain used as a receptor protein and peptides as a ligand protein were subjected to dock in Z DOCK to calculate the binding energy.

Toxicity prediction: The toxicity analysis were performed by using ToxinPred, an *in silico* method using QMS calculator which allows the users to submit query peptide in FASTA format and to optimize the peptide sequence to get maximum/minimum/desired toxicity based upon the quantitative matrix based position specific scores. It will also help the user to tweak any residue from the predecessor peptide to attain the analog with desired property (highest/lowest toxicity) (Gupta *et al*., 2013).

RESULTS

The docking studies with Accelrys Discovery Studio 3.5 highest affinity between different peptides to BRCT domain are shown in Fig. 1. The pink and green manifestation in concert denotes the hydrogen bonding in this pACC1 shows higher degree of pink-green manifestation peptide MDC1 and pACC1 shows equal hydrogen bonding ability with BRCT domain. The Z rank score displayed in Table 1, donotes the attraction gain of hydrogen bonds by the result of interaction MDC1 and pACC1 have equal interactions hence ATRIP defeat the MDC1 with the score of 10.76Z score BATT1 peptide scores very poor Z score and it defeats rest of three peptides excluding pACC1 in the Z rank score. The QMS score analysis remains closer values rest of other three peptides excluding pACC1, it shows higher degree of toxicity with high maximum and minimum score shown in Table 2. Basically the quantitative matrix was generated by ToxinPred considering the probability or frequency of amino acid at particular position so the arrangement of amino acids are responsible of this scores.

Table 1: Z rank score by Accelrys discovery studio client 3.5

Peptide	Sequence of amino acids	Z rank score	Z score	Hydrogen bond interactions
MDC1	KKKTQApSQEY	-41.375	9.66	P: THR1898: OG1-C:SEP139: O1P
				P: GLY1899: N-C:SEP139: O2P
				P: ARG1932: NH1-C:GLU141: OE2
				P: ARG1933: NE-C: TYR142: O
				P: LYS1936: NZ-C:SEP139: O3P
				P: LEU2059: N-C:GLU141: OE1
				C: TYR142: N-P: ARG1933: O
				C: NH2143: N-P: CYS2042: O
BATT1	LQGDpSSLFVA	-60.322	8.08	P: ARG5: N-C: ASN1774: O
ATRIP	PEACpSPQFG	-50.727	10.76	C: LYS1648: NZ-P: PRO7: O
				C: THR1685: OG1-P:CYS5: SG
				P: CYS5: SG-C: ARG1649: O
				P: GLN8: N-C:MET1650: SD
				P: GLN8: N-C:MET1728: SD
				P: GLN8: NE2-C: LYS1648: O
pACC1	DSPPQpSPTFPEAGH	-74.097	13.34	C: LEU1657: N-P: SEP1263: O
				C: THR1658: N-P:GLN1262: OE1
				C: THR1658: OG1-P:GLN1262: OE1
				C: LYS1702: NZ-P: THR1265: O
				P: GLN1262: N-C: GLY1656: O
				P: GLN1262: NE2-C:GLU1661: OE2
				P: SEP1263: N-C: GLY1656: O
				P: GLU1268: N-C: LEU1676: O

P: Peptide, C: BRCT domain

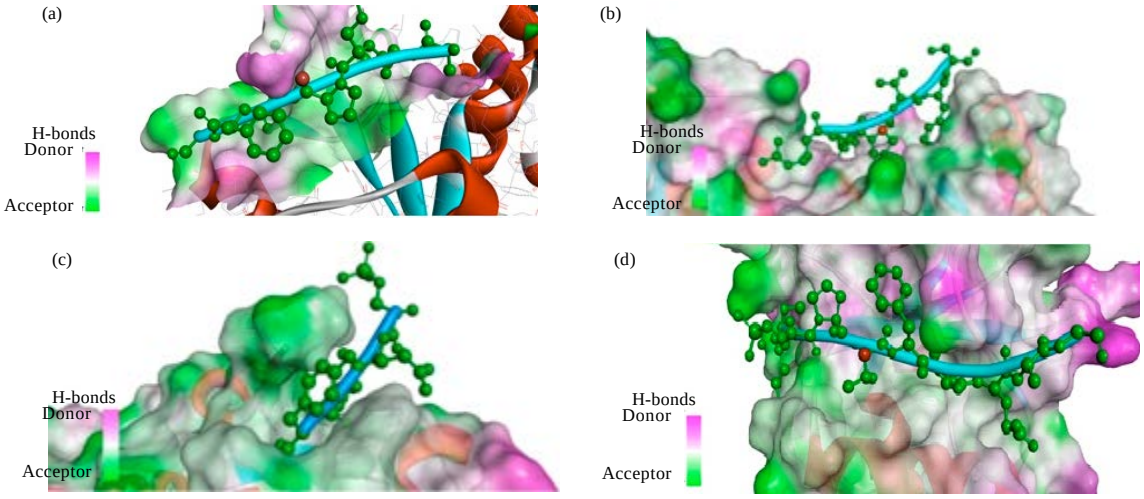

Fig. 1(a-d): Docking of peptides with BRCA1-BRCT domain (a) ATRIP, (b) BATT1, (c) MDC1 and (d) pACC1 peptide

Table 2: QMS score by ToxinPred

Peptide	Sum of origin score	Sum of maximum score	Sum of minimum score
MDC1	5.0	158.4	-81.0
BATT1	-2.1	158.4	-81.0
ATRIP	4.3	150.0	-76.4
pACC1	4.2	223.3	-100.1

DISCUSSION

The docking and toxicity studies may provide immense thought concerning therapeutic peptides ability for intended pharmacology. The Z DOCK protocol performs the initial global, systematic search for orientations of the two protein partners. Typically the larger protein (the receptor protein) is kept fixed while moving the smaller protein (the ligand protein) around the receptor protein. The Z DOCK uses a grid-based rigid body docking search in six dimensions utilizing the Fast Fourier Transform (FFT) technique for efficiency. The rotational search sampling grid can use a 15° grid which samples a total of 3600 docked poses, or a 6° grid which samples a total of 54,000 poses for more accurate results. So, the results optional the pACC1 furnish good Z score and Z rank score, basically Z rank score denotes optimized energy scoring function based on weighted energy terms of van der Waals, electrostatics and desolation chemical properties between two proteins. Here number of interaction does no matter but the force involved, bond angle and bond length mattes evidently the BATT1 peptide scored higher Z score when compared to other peptides which encompass further interactions this perhaps by reason of bond strength this is may be the bond which was found in between BATT1 and BRCT domain may formed the bond incompletely shielded from water attack. Dehydrons promotes the removal of water through proteins or ligand binding and notably exogenous dehydration enhances the electrostatic interactions.

The quantitative matrix score used to find the toxicity of cell penetrating peptides. The present study fallout recommended high toxicity score for peptide pACC1 with compared that of other peptides which are included in the study. Hence, the pACC1 posses below the score which

considered for lethal effect perhaps attributable to amino acid arrangements and it can be further conformed by wet lab analysis and further the toxicity may decreases by altering number of amino acids and functionalizations with different substrates possibly will increase bio affinity and decrease toxicity.

CONCLUSION

Pertaining to the docking studies peptide p-ACC1 and ATRIP peptide has greater therapeutic compass for further upon compared with other peptides. The toxicity of the same peptides besides is supposed to keep in mind and each step of studies should be with vigilantly for explore their potential.

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