Journal of Applied Pharmaceutical Science Vol. 7 (08), pp. 116-122, August, 2017
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2017.70816
ISSN 2231-3354

Computational modeling and analysis of prominent T-cell epitopes for assisting in designing vaccine of ZIKA virus

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ARTICLE INFO

Article history:
Received on: 07/04/2017
Accepted on: 09/05/2017
Available online: 30/08/2017

Key words:
Vaccine, Zika virus, T-cell epitope, MHC class II.

ABSTRACT

The Zika virus disease or Zika fever, regularly shows no or just mellow side effects, like an exceptionally gentle type of dengue fever. It spread eastwards from 2007-16 over the Pacific Ocean to the Americas, whereas in 2015 to 2016, Zika virus scourge achieved epidemic levels. In this study, the antigenic epitopes of Zika virus (ZIKV) were predicted and modeled. The highest binding scorers among the predicted ones and their correlating MHC class II alleles were further subjected to binding simulation studies. Immunoinformatics tools were applied to analyze the viral antigenic proteins that may be helpful in designing vaccine for ZIKV. The promiscuous epitopes of MHC class II were predicted from the viral proteins using ProPred, an immunoinformatics tool. The chosen epitopes and MHC alleles were modeled molecularly using PEP-FOLD3 and CPH model 3.2 servers respectively. The viral glycoprotein having epitope/peptide YRIMLSVHG bound to DRB1*01:01 MHC class II allele demonstrated the most noteworthy binding score. The anticipated peptide has high possibility of inducing T cell mediated immune response and it might be helpful in designing vaccines based on epitopes after continued future trials.

INTRODUCTION

Zika virus (ZIKV) is an arbovirus of the genus *Flavivirus* and the family *Flaviviridae* (Lanciotti *et al*., 2008). It is a positive-sense single-stranded RNA which incorporates a few other mosquito-borne infections of clinical significance such as dengue virus (DNV), yellow fever virus (YFV), and West Nile virus (WNV) (Lanciotti *et al*., 2008). The other individual from its clade, the Spondweni virus, is its nearest relative (Lanciotti *et al*., 2008; Kuno and Chang, 2007). The genome of Zika virus contains 10,794 nucleotides which encode 3,419 amino acids Kuno and Chang, 2007). The Zika virus is similar to other flavi-viruses, that is, it is made out of 2 non-coding regions (3' and 5') by which a polyprotein is encoded and a single open reading frame (ORF) is flanked. This encoded polyprotein gets cleaved into a triad of structural proteins, viz. precursor of membrane (prM), envelope (E) and capsid (C); and seven non-structural proteins (Kuno and Chang, 2007). The day-time active mosquitoes, predominantly of the *Aedes* (*Stegomyia*) genus, such as *A. aegypti* and *A. albopictus*, transmit the ZIKV (Malone *et al*., 2016). *Aedes* mosquitoes are generally circulated all around the globe, and most of the mosquito species inhabit warm subtropical and tropical local natural surroundings (Kraemer *et al*., 2015). *A. albopictus* does not yet give off an impression of being a noteworthy vector of ZIKV. But we can't ignore its role in the Gabon flare-up of 2007, it's widespread all through the US and absence of ZIKV when this particular species *Aedes sp.* was limited (Kraemer *et al*., 2015).

Inspite of various researches carried for treating ZIKV infection, there is no proper standard treatment available till date for curing this deadly infection. The administration is steady and incorporates rest, liquids, antipyretics, and analgesics. Headache medicines and other non-steroidal anti-inflammatory medications should not be taken until dengue is treated completely as this possesses the danger of hemorrhage (Kuno and Chang, 2007).

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So vaccine development against the ZIKV is very essential. The most antigenic part of a virus is its surface or envelope proteins which are often considered as a great contender for inoculation. The adaptive immune response primarily targets the envelope protein which mediates the viral entry which makes them crucial for vaccine development (Cerdeño-Tárraga *et al*., 2003; Trent and Qureshi, 1971). Over the past few years, immunologists have discovered the epitopes which can be identified by T cells and B cells are different and this has resulted in designing of more potent candidates for vaccine. Intercellular foreign antigenic peptides recognition majorly involves Major histocompatibility complex (MHC) and hence it takes part in developing both cell-mediated and humoral immune responses. Antigen-presenting cells (APCs) contain T cells on their surface which recognize antigenic fragments only when the exposed surface MHC molecules of all vertebrate cells are combined with them (Shekhar *et al*., 2012; Mohabatkar and Mohammadzadegan, 2007) .

The heterodimeric glycoproteins, MHC molecules, induce the activation of T cell by presenting a varied peptide set on the cell surrounding surface (Viret and Janeway, 1999; Tambunan and Parikesit, 2011). In a population with various alleles, the binding regions of an allele may not trigger the immune response due to high polymorphism of MHC molecules. So it's more necessary to identify viral peptides that are promiscuous and possess binding capacity with multiple MHC alleles (Tambunan and Parikesit, 2011).

Epitope or peptide-based vaccines are more specific, worthwhile, easily producible, safer and more time efficient than the conventional vaccines. The epitope or peptide-based vaccines can deliver high immunogen dosage at lower cost (Von Hoff *et al*., 2005; Tang *et al*., 2012). In order to design a potent synthetic peptide vaccine candidate, *In Silico* modeling techniques and immunoinformatics approaches have been applied including the use of bioinformatics software and tools which are based on various machine learning programs and other statistical approaches. The active candidate for vaccine must possess antigenicity and it must be responsible for pathogenicity (De Groot *et al*., 2002; Verma *et al*., 2011)

METHODS AND MATERIALS

Retrieving Zika virus envelope glycoprotein sequence and Protein antigenicity determination

Zika virus envelope (outer membrane) glycoprotein sequences were extracted in FASTA format from UniProtKB (http://www.uniprot.org/) (Gaunt *et al*., 2001). Theoretical isoelectric point (pI), molecular weight and amino acid compositions were computed by using the Expasy's ProtParam server for all the 40 glycoprotein sequences (Chandra *et al*., 2010). These sequences were then investigated with VaxiJen (http://www.ddg-pharmfac.net/vaxijen/VaxiJen/VaxiJen.html) with default parameters to discover its antigenicity, to predict the protective antigen as a vaccine (Doytchinova and Flower, 2007). Amongst all the antigenic proteins, the one having the highest antigenicity score was chosen to carry out further studies.

T-cell epitope-bound class II HLA expectation and identification

To identify the promiscuous T cell epitopes various distinctive prognosis procedures have been utilized. Epitopes are known as "promiscuous" when more than one MHC allele and more than one T cell clone can identify different T cell epitopes.

For the prediction of linear peptides as CD4+ T-cell epitopes for ZIKV envelope glycoprotein (GP) we picked abundant human leukocyte antigen class II alleles in humans (DRB1*07:01, DRB1*01:01, DRB1*04:01, DRB1*08:02, DRB1*03:01, DRB1*11:01, DRB1*15:01, DRB1*13:02)[19] and used ProPred (http://www.imtech.res.in/raghava/propred/), a graphical web-based tool which predicts those regions in an antigenic sequence which binds to MHC class-II. ProPred locates promiscuous binding sites in assistance with quantitative matrices. These binding regions are used for selecting candidates for vaccines (Gowthaman and Agrewala, 2007; Sturniolo *et al*., 1999). The predicted epitopes were further validated by using PREDIVAC (http://predivac.biosci.uq.edu.au/cgi-bin/binding.py), which predicts peptide binding of HLA class II on the basis of specificity-determining residue (SDR) concept covering 95% allelic variants of MHC class II (DR locus) and IEDB Analysis Resource (http://www.iedb.org/) which involves various MHC Class-II epitope prediction method, involving a consensus approximation combining NN-align, combinatorial library methods and SMM-align (Oyarzun *et al*., 2013). In this study, we have used the SMM prediction method.

Modeling favorable epitopes and MHC II alleles and their computational validations

The GP epitopes of ZIKV were modeled at PEPFOLD3 (http://bioserv.rpbs.univparisdiderot.fr/services/PEP-FOLD3/) for each MHC allele. In the Protein Data Bank (PDB) the 3-D structures of MHC alleles were inaccessible, so in order to secure their 3-D coordinate's files CPH model 3.2 server which uses their respective structural templates, was used. Afterwards, numerous online servers were used for verification and structural analysis of MHC alleles' structure. The servers being used are Errat, ProQ, ProSA, RAMPAGE, etc. Errat (http://services.mbi.ucla.edu/ERRAT/) is an algorithm for verification of protein structure which is used specifically for analyzing non-bonded interaction statistics between various atom types (Colovos and Yeates, 1993). ProQ (http://www.sbc.su.se/~bjornw/ProQ/ProQ.cgi) is a protein quality prediction tool that predicts the nature of a protein model on the basis of MaxSub and LG score, the two quality measures (Wallner and Elofsson, 2003). ProSA (https://prosa.services.came.sbg.ac.at/prosa.php) is a web-based tool which analyzes the structure of a protein (Wiederstein and Sippl, 2007). It determines the model quality both local and overall (Z-score) and for a particular protein structure it calculates an

overall quality score. RAMPAGE (http://mordred.bioc.cam.ac.uk/~rapper/rampage.php) is a web tool for assessing protein model on the basis of Ramachandran plot (Lovell *et al*., 2002).

Docking prediction of epitopes and alleles

After modeling the structure, chosen peptides and alleles were docked using rigid docking method with the assistance of PatchDock followed by refinement through FireDock to decide the values of binding score.

Epitope-HLA allele molecular dynamic simulation

The molecular dynamic simulation was performed by utilizing Desmond (Klepeis *et al*., 2009; Raj *et al*., 2015). Initial co-ordinates were obtained from the best peptide-allele complex for dynamics simulation process. The system building process was carried out by adding Simple Point Charge water model. Then the system was neutralized with the addition of counter ions followed by the system minimization step using Broyden-Fletcher-Gold farb-Shanno LBFGS algorithms. The whole system was further subjected for MD simulation studies for 20 ns at 300K & 1.0325 bar pressure and the RMSD was recorded to check the stability of the above said complex (Raj *et al*., 2016; Kamal *et al*., 2016).

RESULTS AND DISCUSSION

Recovery and prediction of antigenic Protein

Sequence analysis of envelope glycoprotein segregated from Zika virus was done on the basis of the structure. Fasta format of an aggregate of 40 polyproteins was recovered from UniProtKB. The physiochemical properties for all these 40 poyproteins hasve been summarized in Table 1. The protein having the highest immunogenicity was predicted using VaxiJen. The envelope protein, UniProtKB ID Q91KX7, was predicted with highest antigenicity with an aggregate score of 0.6269 at a threshold value of 0.4. This prediction corresponds to a previous observation where immunogenicity of the envelope glycoprotein was found (Roehrig *et al*., 1983).

Prediction and analysis of MHC Class II binding peptides

Based on the scores generated by the Propred (Table 2), peptides showing maximum binding with the same alleles of MHC II were taken.

Table 1: Physiochemical Properties of proteins.

Protein Designation	Accession No.	Size aa	Expected MW kDA	pI
Envelope protein	Q91KX7	276	30299.52	6.23
Envelope protein	A0A060H177	504	54380.19	6.51
Envelope protein	W8QIQ6	251	27562.29	5.82
Envelope protein	W8QIN8	251	27504.21	5.82
Envelope protein	A0A0N7HJ59	103	10840.53	8.87
Envelope protein	A0A0H4A724	110	11753.47	8.84
Envelope protein	W8R1P6	251	27532.20	5.82
Envelope protein	W8R1M7	251	27500.14	5.93
Envelope protein	A0A0N9ZT66	103	10840.53	8.87
Envelope protein	A0A0H4AEI9	110	11753.47	8.84
Envelope protein	W8Q7L0	251	27504.21	5.82
Envelope protein	W8Q6P9	251	27532.20	5.82
Envelope protein	W8QIP2	251	27544.27	5.82
Envelope protein	W8QFD0	251	27474.27	6.04
Envelope protein	W8Q6N7	251	27586.35	5.82
Envelope protein	W8R1N8	251	27504.21	5.82
Envelope protein	W8R1M9	251	27504.21	5.82
Envelope protein	W8Q7L5	251	27474.27	6.04
Envelope protein	W8QFD5	251	27522.22	5.93
Envelope protein	W8QFB7	251	27558.30	5.93
Envelope protein	W8QIM9	251	27603.34	5.94
Envelope protein	W8PAE0	280	30572.76	6.14
Envelope protein	W8QFC5	251	27512.27	5.82
Envelope protein	W8QIQ1	251	27405.26	5.71
Envelope protein	W8R1P2	251	27532.20	5.82
Envelope protein	W8Q6N2	251	27589.32	5.94
Envelope protein	W8QFD9	251	27546.29	5.82
Envelope protein	W8Q7L9	251	27535.22	5.71
Envelope protein	W8QFC1	251	27523.25	5.87
Envelope protein	W8Q6P1	251	27516.26	5.82
Envelope protein	W8Q7J5	251	27589.32	5.94
Envelope protein	W8Q6P5	251	27562.29	5.82
Envelope protein	A0A0P0A2N5	103	10840.48	8.53
Envelope protein	W8QIN4	251	27599.36	5.94
Envelope protein	W8QFB3	251	27599.35	5.87
Envelope protein	W8Q6N5	251	27504.21	5.82
Envelope protein	W8Q7K0	251	27504.21	5.82
Envelope protein	A0A142JYW4	120	12983.62	6.98
Envelope protein	W8QIP7	245	26804.44	5.75
Envelope protein	W8Q7K5	251	27523.25	5.87

Table 2: Scores generated by Propred.

Position	Epitope	Allele	Prediction	Score (%)
73	YRIMLSVHG	HLA- DRB1*01:01	ProPred, IEDB, PREDIVAC	63.33
		HLA- DRB1*11:01	ProPred, IEDB, PREDIVAC	36.14
		HLA- DRB1*13:02	ProPred, IEDB, PREDIVAC	53.41
228	LRLEGVSYS	HLA- DRB1*03:01	ProPred, IEDB, PREDIVAC	48.11
		HLA- DRB1*04:01	ProPred, IEDB, PREDIVAC	59.30
110	LGGFGSLGL	HLA- DRB1*15:01	ProPred, IEDB, PREDIVAC	62.24

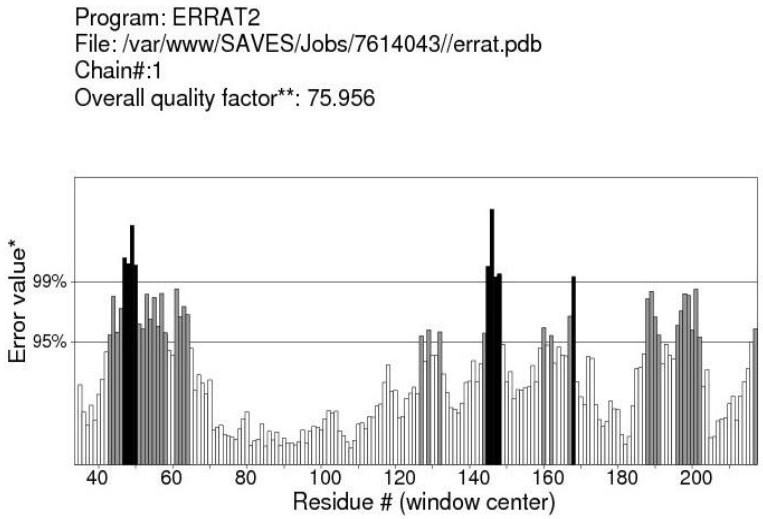

Fig. 1: The graphical representation of ERRAT result of DRB1*01:01 allele. On the error axis, two lines are drawn to show the certainty of which it is conceivable to reject regions that surpass that error values.

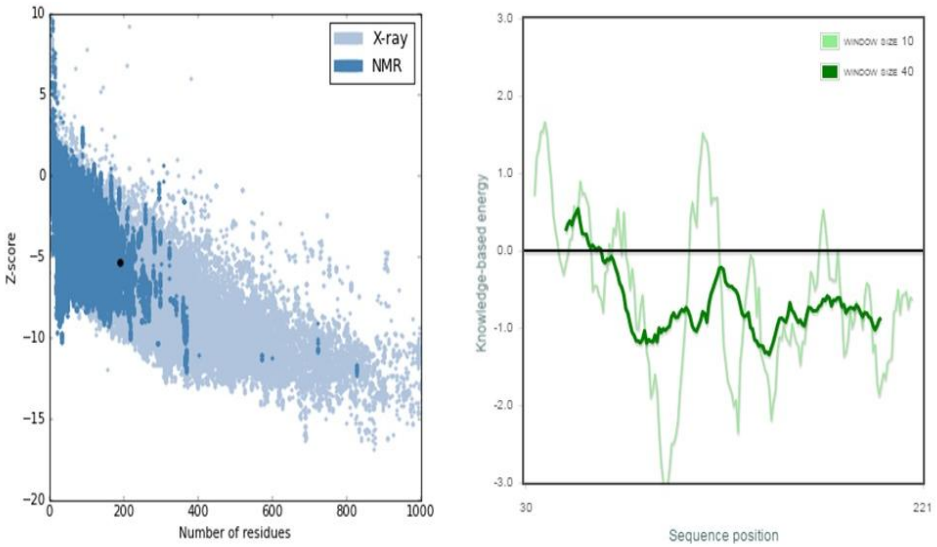

Fig. 2 ProSA result. (**a)** Z-score plot of DRB1*01:01 allele. **(b)** Graphical plot residue scores of DRB1*01:01 allele structure.

Target peptides and MHC II allele modeling and validation

PEP-FOLD3 and CPH model server were used to obtain 3-D coordinate file of favored peptides and allele respectively. The structures of DRB1*01:01, DRB1*15:01 and DRB1*04:01 alleles were validated through Errat, ProSA, RAMPAGE and ProQ. Errat was used to determine the general quality factor of an allele. It was 75.956 for DRB1*01:01(Fig. 1), 82.418 for DRB1*15:01 and 75.138 for DRB1*04:01. Quality predicted by ProQ was 'fairly good' for all the three alleles, DRB1*01:01, DRB1*15:01 and DRB1*04:01, with LG scores of 1.935, 2.125, 2.241, and MaxSub scores of 0.162, 0.175, 0.172 respectively. Utilizing ProSA, the computed Z-score of alleles DRB1*01:01, DRB1*15:01 and DRB1*04:01 was - 5.39 (Fig. 2.a & b), -5.18, -5.34 respectively and it resulted in considerably good model. Using RAMPAGE analysis, the favored region amino acid residues number was 179 (94.2 %), 178(94.2%), 179(95.7%) for DRB1*01:01 (Fig. 3), DRB1*15:01 and DRB1*04:01 alleles.

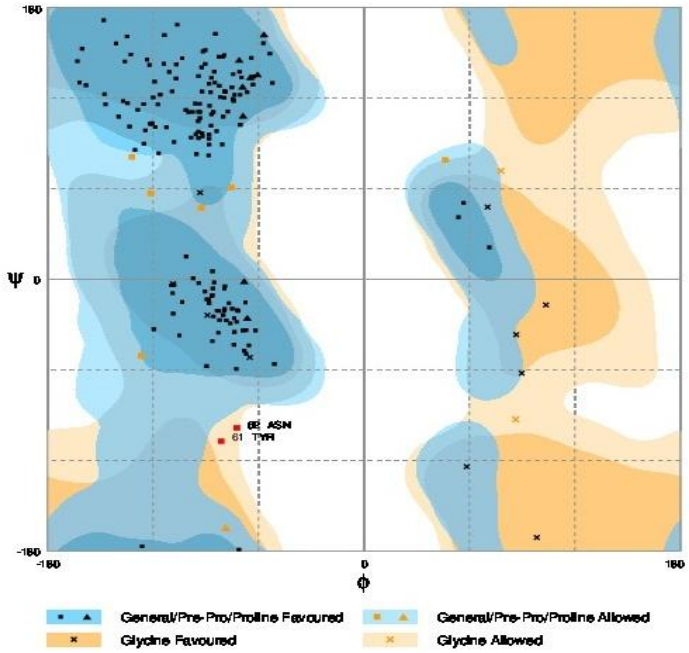

Fig.3 RAMPAGE demonstrating the residues in favored, allowed and outlier regions of DRB1*01:01 allele.

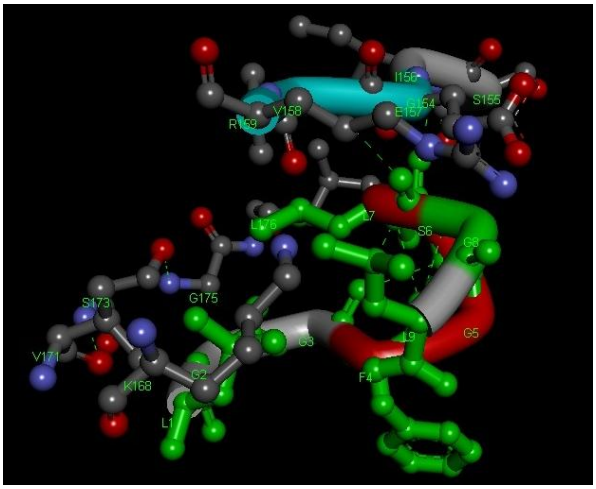

Fig.4 Docked epitope YRIMLSVHG-DRB1*01:01 allele complex by PatchDock and FireDock portraying the detailed position of amino acids alongside the arrangement of H-bonds.

Table 3: Docking and post docking results of epitopes with alleles.

Allele	Score	Area	Transformation	GE	Vdw Attractive	Vdw Repulsive	ACE	HB
DRB1*01:01	4852	530.80	-3.00 40.54 2.75 93.19 9.12 2.76	-57.31	-17.02	11.87	-13.46	-2.40
DRB1*04:01	5162	563.20	-1.50 1.01 2.23 87.26 4.91 -14.51	-49.87	-20.35	6.94	-12.81	-2.13
DRB1*15:01	6014	710.30	1.23 0.02 -0.23 19.61 28.87 113.67	-51.06	-24.06	12.26	-12.94	-0.78

Docking score determination by PatchDock and refinement of docking result by FireDock

Docking score investigations of epitopes YRIMLSVHG, LRLEGVSYS, LGGFGSLGL with DRB1*01:01, DRB1*04:01 and DRB1*15:01 alleles framed stable HLA–peptide complexes with the binding score of 4852, 5162 and 6032 respectively. Refinement through FireDock gave the global binding energy of -57.31, -49.87 and -51.06 respectively (Table 3).

Further we determined the contribution of the hydrogen bonds to the global binding energy utilizing FireDock, it was found to be -2.40, -2.13 and -0.78 respectively.

In this way, the epitope YRIMLSVHG with DRB1* 01:01 allele demonstrates the greatest chances of efficient binding as H-bonds may form. Hydrogen bonds are present on YRIMLSVHG-DRB1*01:01 complex at position S6, S155, G8, and E157 (Fig.4).

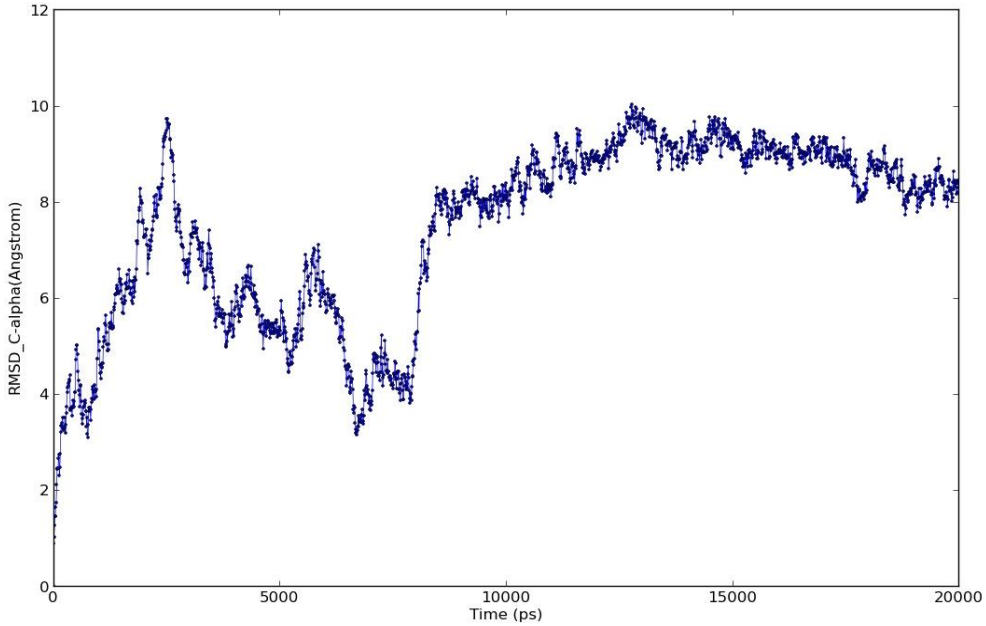

Fig. 5: Root Mean square deviation (RMSD) curve of peptide-allele complex during 20 ns MD simulation.

Allele-peptide complex analysis using molecular dynamics simulation

The best allele and peptide complex obtained through FireDock were subjected to molecular dynamics simulations. Peptide YRIMLSVHG-DRB1*01:01 allele complex at RMSD value of 9.8 Å shows the highest peak (Fig. 5). The mean RMSD obtained during MD trajectory of 20 ns was 7.438 Å with a standard deviation of 1.878 Å. As displayed in the graph, fluctuations occur mainly during initial phase up to 10 ns after that the graph shows consistent behavior which in turn reveals the stability of the complex during 10-20 ns simulation time.

CONCLUSION

The predicted epitopes from the genome/proteome sequences of the pathogens would greatly reduce the time as well as cost and be useful for experimental planning in the development of epitope vaccines. The predicted epitopes may be used for safe vaccine development against meningococcal diseases. The pathogenic activity of Zika Virus makes it difficult to develop novel vaccines. Vaccine development requires in-vivo and in-vitro experiments which are time-consuming. Virus growth and peptides' segregation on a vast cluster of tests is additionally an enormous what's more, legitimate limitation. The present study consolidates immunoinformatics approach for diminishing the time lost in the long array of experiments to maintain a strategic distance from hit and trial sets. A glycoprotein having 276 amino acids has the probability of holding an expansive number of epitopes. So out of many proteins, 276 amino acids long glycoprotein was taken to predict epitopes for T cell bound MHC II as a vaccine candidate for ZIKA envelope glycoprotein.

Vaccine designing and development against T cell epitopes appears convincing because the immune response evoked by it is long lasting and it also stimulates antigenic drift in which the memory response due to antibody can be easily escaped by the antigen (Trainor *et al*., 2007).

T cell bound MHC class II epitope YRIMLSVHG was predicted to have the maximum score of 63.33% with HLA-DRB1*01:01 allele. Errat was used to validate the homology modeling of the allele and it was found to have score of 75.956, LG score of 1.935 and MaxSub score of 0.162 obtained using ProQ, Z-score of -5.39 obtained using ProSA and with RAMPAGE resulting in 179(94.2 %) amino acids in the favored region. Docking was done by PatchDock with score 4852 and refinement by FireDock with a global energy of -57.31. H-bond was recognized at position S6, S155, G8, and E157. An appropriately stable allele-peptide complex was accomplished during the molecular dynamic simulation interval of 10-20 ns.

It is observed that peptide YRIMLSVHG with DRB1*01:01 may prove to be the backbone in predicting design of vaccine. The peptide can be either formulated or isolated for further in-vivo and in-vitro experiments.

Financial support and sponsorship: Nil.

Conflict of Interests: There are no conflicts of interest.

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How to cite this article:

Yadav G, Rao R, Raj U, Varadwaj PK. Computational modeling and analysis of prominent T-cell epitopes for assisting in designing vaccine of ZIKA virus. J App Pharm Sci, 2017; 7 (08): 116-122.