BIOLOGY, MEDICINE, & NATURAL PRODUCT CHEMISTRY ISSN 2089-6514 (paper)
Volume 12, Number 2, October 2023 | Pages: 525-531 | DOI: 10.14421/biomedich.2023.122.525-531 ISSN 2540-9328 (online)

In Silico B-Cell Epitope Design of Zika Virus Vaccine Using "Zika Virus Isolate Zika Virus/*H. sapiens*-Tc/Tha/2006/CVD 06-020, Complete Genome"

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Manuscript received: 03 May, 2023. Revision accepted: 30 August, 2023. Published: 15 September, 2023.

Abstract

ZIKV has been found in the cerebrospinal fluid (CSF) and brains of adults infected with viruses that manifest neurological disorders. ZIKV is a mosquito-borne single-stranded RNA virus, which belongs to the family Flaviviridae. The efforts of the scientific community have rapidly increased knowledge about this virus. However, understanding the complexities of ZIKV infection, transmission and pathogenesis remains an urgent challenge. Therefore, it is critical to study competent vectors and natural reservoirs for ZIKV, viral genetic diversity and flavivirus coinfection. Due to the great challenges to develop a ZIKV vaccine, it is still not possible to be immunized against ZIKV infection and related pathologies. The methods are nucleotide search for the Zika virus was carried out in silico, using the NCBI bioinformatics application by providing access to biomedical and genomic information. /H. sapiens-tc/THA/2006/CVD_06-020, the complete genome was then searched for FASTA, then prediction of vaccine epitope using the IEDB. The vaccine candidate peptides were analyzed for their antigenicity using VaxiJen. Proteins were classified by AllerTop to known allergenicity, then ToxinPred to predict and design toxic/non-toxic peptides. There are 30 peptide sequences are predicted to be a candidate of peptides B-cell epitope zika virus vaccine design using "zika virus isolate zika virus/H. sapiens-tc/THA/2006/CVD_06-020, complete genome".

Keywords: Vaccine; Zika Virus; B-Cell Epitope; In Silico.

Abbreviations: automatic cross covariance transformation (ACC), antibody-dependent increase (ADE), cerebrospinal fluid (CSF), congenital Zika syndrome (CZS), Ebola virus (EBOV), immune epitope database (IEDB), Middle East Respiratory Syndrome (MERS), public health emergency of international concern (PHEIC), Severe Acute Respiratory Syndrome (SARS), Spondwenivirus (SPONV), quantitative structure-activity relationship (QSAR), World Health Organization (WHO), yellow fever virus (YFV).

INTRODUCTION

The World Health Organization (WHO) has identified, warned and tracked more than 1400 epidemic events in 172 countries due to viruses that emerged between 2018 and 2018, such as influenza, Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), ebola, yellow fever, Zika, and others. Remarkably, in the last five years, WHO has declared three global health emergencies related to emerging viruses, namely SARS-CoV-2 in 2020, Ebola virus (EBOV) in 2014 (Koenig, et al., 2014; McCoy, et al., 14; Safari, et al., 2015) and Zika virus (ZIKV) in 2016.

In the context of ZIKV, WHO referred to Zika as "an extraordinary event that needed a coordinated response, constituting a public health emergency of international concern (PHEIC)", because of the description of a large outbreak of rash, with short-term and mild fever (Brazil, et al., 2016), not in all cases, and a cluster of microcephaly in newborns to infected mothers (Kleber, et al., 2016; Driggers, et al., 2016; Martines, et al., 2016). In fact, ZIKV infection carries a risk of adverse pregnancy outcomes including an increased risk of preterm delivery, fetal death and stillbirth, and congenital malformations collectively characterized as congenital Zika syndrome (CZS), including the aforementioned microcephaly, abnormal brain development, limb contractures, eye abnormalities, brain calcifications, and other neurological manifestations (Martines, et al., 2016; Dudley, et al., 2018; Leisher, et al., 2020).

ZIKV has been found in the cerebrospinal fluid (CSF) and brains of adults infected with viruses that manifest neurological disorders (Carteaux, et al., 2016; Da Silva, et al., 2017; Alves, et al., 2019). These flaviviruses cause harmful effects on the adult brain, such as GBS (Da Silva, et al., 2017; Azevedo, et al., 2016; Parra, et al.,

2016; Brito, et al., 2017; Munoz, et al., ., 2016), encephalitis (Da Silva, et al., 2017; Brito, et al., 2017; Soares, et al., 2016), meningoencephalitis (Barbi, et al., 2017; Schwartzmann, et al., 2017), acute myelitis (Da Silva, et al., 2017; Muñoz, et al., 2016; Mécharles, et al., 2016) and encephalomyelitis (Da Silva, et al., 2017; Alves, et al., 2019), among sensory polyneuropathy and other neurological complications (Nicastri, et al., 2016; Bido, et al., 2018).

ZIKV is a mosquito-borne single-stranded RNA virus, which belongs to the family Flaviviridae (genus Flavivirus) (Mayer, et al., 2017; Enfissi, et al., 2016). ZIKV is further classified on the basis of homology into Spondwenivirus (SPONV) within the Spondweni virus clade or serogroup (Kuno, et al., 2007; Haddow, et al., 2016; Brès, 1970), both viruses first characterized in Africa in 1947. and 1952 (Dick, et al., 1952; Haddow, et al., 2016), respectively. ZIKV was previously isolated from the sera of pyrexial rhesus monkeys caged in the canopy of the Zika Forest in Uganda (Dick, et al., 1952), and was discovered during a study of the vector responsible for the sylvan cycle of yellow fever virus (YFV) in Uganda (Brès, 1970). The first human infection confirmed by ZIKV occurred in Nigeria (1954) (Macnamara, et al., 1954), further cases were reported in Uganda (1962–63) and outside Africa in Central Java, Indonesia (1977) (Olson, et al., 1981). ZIKV presents three phylogenetic divisions related to East African, West African and Asian/American lineages (Lanciotti, et al., 2016; Collins, et al., 2019), constituting a single serotype (Heinz, et al., 2017). This ZIKV lineage is thought to have emerged from East Africa in the late 1800s or early 1900s (Lanciotti, et al., 2016; Gatherer, et al., 2016), with Asian lineages responsible for all ZIKV outbreaks in the Pacific. and America (WHO, 2017; Ikejezie, et al., 2017).

ZIKV is mainly transmitted to humans by infected Aedes aegypti and Aedes albopictus mosquitoes (Boyer, et al., 2018). An increase in the Aedes mosquito population has been observed in tropical developing countries (Gubler, 2011). Thus, infected mosquitoes, densely populated areas, and global commercial and tourist activities together with modern transportation constitute an efficient scenario for spreading infected mosquitoes and viruses such as ZIKV around the world (Imperato, et al., 2016), as suggested. reported with Dengue (Gubler, 2011) and as was the case with ZIKV epidemic episodes in 2007 (Duffy, et al., 2009), 2013 (Boyer, et al., 2018) and 2014-2015 (Musso, 2015), stated as PHEIC by WHO.

The efforts of the scientific community have rapidly increased knowledge about this virus. However, understanding the complexities of ZIKV infection, transmission and pathogenesis remains an urgent challenge. Therefore, it is critical to study competent vectors and natural reservoirs for ZIKV, viral genetic diversity and flavivirus coinfection (Eligio, et al., 2020), as well as potential cross-immune reactivity (i.e., challenging immune diagnosis) and increased infection immunity. (i.e., antibody-dependent increase (ADE)) (Rathore, 2020), fortunately not yet observed in humans (Terzian, et al., 2017), along with environmental factors that may have suddenly triggered the expansion of the ZIKV epidemic and worse viral pathogenesis. (Pierson, et al., 2018; Baud, et al., 2017; Rossati, 2017). Due to the great challenges to develop a ZIKV vaccine (Shan, et al., 2018; Lin, et al., 2018), it is still not possible to be immunized against ZIKV infection and related pathologies.

Based on this phenomenon, it is necessary to conduct research to examine vaccine candidates for ZIKV by conducting In Silico B-Cell Epitope Zika Virus Vaccine Design Using “Zika virus isolate Zika virus/H. sapiens-tc/THA/2006/CVD_06-020, complete genome”.

MATERIALS AND METHODS

The population in this study was the Zika virus. The sample used in this study was Zika virus isolate Zika virus/H. sapiens-tc/THA/2006/CVD_06-020, complete genome. According to Savitri (2021), the nucleotide search for the Zika virus was carried out in silico, using the NCBI bioinformatics application, the National Center for Biotechnology Information advances science and health by providing access to biomedical and genomic information. Zika virus isolate Zika virus/H. sapiens-tc/THA/2006/CVD_06-020, the complete genome was then searched for FASTA.

After obtaining FASTA, then prediction of vaccine epitope using the IEDB, which contains a catalog of experimental data on antibodies and T cell epitopes studied in humans, non-human primates, and animal species others in the context of infectious diseases, allergies, autoimmunity and transplantation was done. The IEDB also provides tools to aid in the prediction and analysis of epitopes. This study uses B Cell Epitope Prediction.

The vaccine candidate peptides were analyzed for their antigenicity using VaxiJen with the target organism of the virus. This method is based on automatic cross covariance transformation (ACC) of protein sequences into vectors of equal and uniform length. It has been applied to the study of the quantitative structure-activity relationship (QSAR) of peptides of different lengths. The main properties of amino acids are represented by the five E descriptors, which were originally derived by Venkatarajan and Braun. They described the hydrophobicity of amino acids, molecular size, tendency to form helices, relative abundance of amino acids, and tendency to strand formation. Proteins were classified by the k-nearest neighbor algorithm (kNN, k=1) based on a training set containing 2427 known allergens of different species and 2427 non-allergens.

ToxinPred is an in silico method developed to predict and design toxic/non-toxic peptides. The main data set used in this method consisted of 1805 toxic peptides (<=35 residues). One of the main features of the server is to calculate various physicochemical properties. Peptide analogues can be displayed in a sorting order based on the desired trait.

RESULTS AND DISCUSSION

Table 1. Candidate Types of Peptides B-Cell Epitope Zika Virus Vaccine Design Using "Zika Virus Isolate Zika Virus/H. sapiens-tc/THA/2006/CVD_06-020, Complete Genome".

No.	Code	Peptide
1	Peptide 1	CTTTTTGAGATTC
2	Peptide 2	ATAGATGGGGTTCAGTGGGGAAAAAAGAGGCTATGGAAATAATAAAGAAGTTCAAGAAAGATCTGG
3	Peptide 3	GCTGGATGAGGGGGTAGAA
4	Peptide 4	CTTGGGTTGTGTACG
5	Peptide 5	TTGTGTA
6	Peptide 6	TTGGGAGGTTGAT
7	Peptide 7	GCTGATGTGGGGTGCTCGGTGGAC
8	Peptide 8	TGGAAGAGAATGGAGTTCA
9	Peptide 9	GTGGAGAGG
10	Peptide 10	TGTGAGGCTGGT
11	Peptide 11	GTGAAGT
12	Peptide 12	GAGAGAGAT
13	Peptide 13	GGAAGTAAAAAAGGGGGAG
14	Peptide 14	TGTTTGGCTG
15	Peptide 15	TACGGAGAGAAAAGAGTGC
16	Peptide 16	GAGGTGGATGGA
17	Peptide 17	GGAAATTGAG
18	Peptide 18	TTGTTGTGTTCCT
19	Peptide 19	TTGCTGGTGGTGC
20	Peptide 20	GTACTT
21	Peptide 21	GTGGAGAAAAAGATGGGACAGGTGC
22	Peptide 22	TGGGGGTGGGGGGAGGCTGGGGC
23	Peptide 23	TTGTGGGAAGG
24	Peptide 24	TGGAGTT
25	Peptide 25	AGTTCAAGAAGTGAAAGGAT
26	Peptide 25	TTAAGAGTGGGGTGGACGTC
27	Peptide 27	TGGTGGGGGATTGGCTTGAAAAA
28	Peptide 28	ATGATGGGAAAAAGAGAAAAGAAACAAGGGGAATTTGGAAAGGCCAAGGGC
29	Peptide 29	ACGAGGTGGTGTTGAAGGGCTGGGATTACA
30	Peptide 30	TGGAAAGGGAGAATGGATG

Table 2. Antigenicity, Allergenicity, Toxicity, dan Mutation Position of Candidate Types of Peptides B-Cell Epitope Zika Virus Vaccine Design Using "Zika Virus Isolate Zika Virus/H. sapiens-tc/THA/2006/CVD_06-020, Complete Genome".

No.	Code	Antigenicity	Allergenicity	Toxicity	Mutation Position
1	Peptide 1	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
2	Peptide 2	Antigenic	Non-Allergenic	Non-Toxic	No Mutaion
3	Peptide 3	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
4	Peptide 4	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
5	Peptide 5	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
6	Peptide 6	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
7	Peptide 7	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
8	Peptide 8	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
9	Peptide 9	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
10	Peptide 10	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
11	Peptide 11	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
12	Peptide 12	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
13	Peptide 13	Antigenic	Non-Allergenic	Non-Toxic	No Mutation

Table 2. *Cont*.

No.	Code	Antigenicity	Allergenicity	Toxicity	Mutation Position
14	Peptide 14	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
15	Peptide 15	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
16	Peptide 16	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
17	Peptide 17	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
18	Peptide 18	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
19	Peptide 19	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
20	Peptide 20	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
21	Peptide 21	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
22	Peptide 22	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
23	Peptide 23	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
24	Peptide 24	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
25	Peptide 25	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
26	Peptide 25	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
27	Peptide 27	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
28	Peptide 28	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
29	Peptide 29	Antigenic	Non-Allergenic	Non-Toxic	No Mutation
30	Peptide 30	Antigenic	Non-Allergenic	Non-Toxic	No Mutation

Table 3. SVM Soce, Hydrophobicity, Hydropathicity, Hydrophilicity, Charge, and Molecule Weight of Candidate Types of Peptides B-Cell Epitope Zika Virus Vaccine Design Using "Zika Virus Isolate Zika Virus/H. sapiens-tc/THA/2006/CVD_06-020, Complete Genome".

No.	Code	SVM Score	Hydrophobicity	Hydropathicity	Hydrophilicity	Charge	Mol wt
1	Peptide 1	-0,84	-0,03	0,22	-0,45	0	1188,46
2	Peptide 2	-1,14	0,13	0,63	-0,33	0	3668,55
3	Peptide 3	-0,82	0,12	0,28	-0,25	0	1350,66
4	Peptide 4	-0,75	0,01	0,01	-0,33	0	1244,53
5	Peptide 5	-0,85	-0,02	-0,26	-0,3	0	607,71
6	Peptide 6	-0,67	-0,04	-0,18	-0,23	0	1008,2
7	Peptide 7	-0,78	0,06	0,19	-0,31	0	1864,34
8	Peptide 8	-0,75	0,12	0,5	-0,32	0	1422,75
9	Peptide 9	-0,73	0,14	0,06	-0,16	0	603,72
10	Peptide 10	-0,81	0,04	-0,08	-0,26	0	939,14
11	Peptide 11	-0,71	0,09	0,14	-0,26	0	533,63
12	Peptide 12	-0,71	0,16	0,54	-0,27	0	631,76
13	Peptide 13	-1,04	0,18	0,63	-0,26	0	1272,56
14	Peptide 14	-0,81	-0,02	-0,26	-0,3	0	855,03
15	Peptide 15	-0,81	0,15	0,8	-0,36	0	1394,75
16	Peptide 16	-0,74	0,13	0,1	-0,19	0	833
17	Peptide 17	-0,93	0,13	0,42	-0,28	0	732,88
18	Peptide 18	-0,44	-0,07	-0,14	-0,4	0	1204,47
19	Peptide 19	-0,81	0,01	-0,07	-0,31	0	1072,32
20	Peptide 20	-0,8	-0,01	0,3	-0,45	0	552,67
21	Peptide 21	-0,92	0,14	0,59	-0,31	0	1795,24
22	Peptide 22	-0,71	0,11	-0,09	-0,16	0	1568,94
23	Peptide 23	-0,73	0,08	-0,08	-0,2	0	805,96
24	Peptide 24	-0,68	0,03	-0,21	-0,24	0	563,66
25	Peptide 25	-0,84	0,13	0,68	-0,36	0	1507,86
26	Peptide 25	-0,81	0,08	0,26	-0,3	0	1527,89
27	Peptide 27	-0,78	0,09	0,22	-0,28	0	1725,11
28	Peptide 28	-0,93	0,16	0,8	-0,34	0	3566,47
29	Peptide 29	-0,68	0,09	0,33	-0,31	0	2274,83
30	Peptide 30	-0,91	0,14	0,36	-0,25	0	1332,62

Discussion

According to Vita, et al. (2015), the Immune Epitope Database (IEDB) website hosts epitope-specific experimental assays which mean each assay reflects antibody to the antigen or epitope being tested experimentally. Structures entered as restricted epitopes

are those that were tested in the test or were deduced as epitopes by multiple sources. In most cases, these amino acid residue sequences are more epitopecontaining regions. This means that the possible epitope can also not be limited only to a predetermined part. Epitope structures can be peptidic and non-peptidic. A peptidic epitope structure consists of linear and discontinuous amino acid sequences based on their position in the source protein. The peptidic epitope having 3D structural data is described in the presence of the residues found to be related to antibodies.

Based on the tests that have been carried out, there are 30 peptide sequences predicted to have high antigenicity values. The high value of antigenicity in a peptide sequence is a marker of ideal properties possessed by vaccines. The higher the antigenicity value, the better its ability to stimulate B cells to form specific antibodies. Allergenicity test is a step carried out to test the selected vaccine candidate whether the peptide sequence to be used can cause allergies to the body or not. The ability not to create allergies for the body is also one of the ideal properties for a vaccine product. A high value of antigenicity is one of the ideal characteristics that all vaccines should have. Allergy is the ability possessed by material to cause allergies. Non-allergen is an ideal trait that anti-viral vaccines should have. Antigenicity is the ability of an antigen to stimulate the formation of specific antibodies by B cells in the body (Rezaldi, et al., 2021).

Based on the tests that have been carried out, the 30 peptide sequences are predicted to be non-toxic to the human body. Toxicity testing at the vaccine prediction stage is important to obtain a peptide that is not toxic when administered into the human body. Only peptides with negative toxicity values can be selected for further use. In addition, this test also found the value of hydrophilicity. The higher the hydrophilicity value, the more certain the antigenic potential will be. his is following the statement of Sanchez-Trincado, et al. (2017) which states that by calculating the hydrophilicity of residues for the prediction of B cell epitope, it can be seen their antigenic potential. This is based on the assumption that the hydrophilic part is mainly located on the surface of the protein which will be directly accessible to the target antibody site.

CONCLUSIONS

There are 30 peptide sequences predicted to be a candidate of peptides B-cell epitope zika virus vaccine design using “zika virus isolate zika virus/H. sapiens-tc/THA/2006/CVD_06-020, complete genome”. This research can be continued with the immunoinformatics method for 3D visualization in order to know how compatible the peptide and epitope sequences are to be used as Zika virus vaccine candidates.

Acknowledgements: Acknowledgments are expressed in a brief; all sources of institutional, private and corporate financial support for the work must be fully acknowledged, and any potential conflicts of interest are noted.The author would like to thank the Institute for Research, Development, and Community Service (LP3M) of Kadiri University which has always provided support for writing and publications.

Authors' Contributions: Lisa Savitri designed the study. Lisa Savitri, Syntia Tanu Juwita, Ester Lianawati Antoro, Ida Septika Wulansari, and Datin An Nisa Sukmawati analyzed the data. João Gregório Freitas and Andre Mario Sequeira Alves Ornai wrote the manuscript. All authors read and approved the final version of the article.

Competing Interests: The authors declare that there are no competing interests.

Funding: The authors declare funding if any.

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