Received: 31 May 2020 | Revised: 13 November 2020 | Accepted: 5 December 2020

DOI: 10.1111/1348-0421.12866

ORIGINAL ARTICLE

Microbiology and Immunology WILEY

Prediction of putative epitope-based vaccine against all corona virus strains for the Chinese population: Approach toward development of vaccine

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Abstract

Currently, the whole world is facing the coronavirus disease-19 pandemic. As of now, approximately 0.15 million people around the globe are infected with the novel coronavirus. In the last decade, two strains of the coronavirus family, severe acute respiratory syndrome-related coronavirus and Middle East respiratory syndrome coronavirus, also resulted in epidemics in south Asian and the Middle Eastern countries with high mortality rate. This scenario demands the development of a putative vaccine which may provide immunity against all current and new evolving coronavirus strains. In this study, we designed an epitope-based vaccine using an immunoinformatic approach. This vaccine may protect against all coronavirus strains. The vaccine is developed by considering the geographical distribution of coronavirus strains and host genetics (Chinese population). Nine experimentally validated epitopes sequences from coronavirus strains were used to derive the variants considering the conservancy in all strains. Further, the binding affinities of all derived variants were checked with most abundant *human leukocyte antigen* alleles in the Chinese population. Three major histocompatibility complex (MHC) Class I epitopes from spike glycoprotein and nucleoprotein showed sufficient binding while one MHC Class II epitope from spike glycoprotein was found to be an effective binder. A cocktail of these epitopes gave more than 95% population coverage in the Chinese population. Moreover, molecular dynamics simulation supported the aforementioned predictions. Further, in vivo studies are needed to confirm the immunogenic potential of these vaccines.

KEYWORDS

Chinese population, COVID-19, epitope-based vaccines, epitopes, human leukocyte antigen *HLA*, MHC-I, MHC-II, SARS-CoV-2

Hina Batool and Sana Batool contributed equally to this study.

1 | INTRODUCTION

Coronaviruses are positive-sense RNA and belong to the family *Coronaviridae*. This family includes *alpha, beta, gamma*, and *delta coronaviruses*.[1] To date, two strains from *alphacoronaviruses* (HCoV-NL63 and HCoV-229E) and four from *betacoronaviruses* (severe acute respiratory syndrome-related coronavirus [SARS-CoV], Middle East respiratory syndrome coronavirus [MERS-CoV], HCoV-HKU1, and HCoV-OC43) are known to cause respiratory tract illness in humans.[2] Of these six human pathogens, the epidemics of SARS-CoV in 2003 and MERS-CoV in 2012 were responsible for mortality rates of 10% and 37%, respectively.[3] Recently, in December 2019, multiple cases of pneumonia in Wuhan, Hubei, China, were linked to a novel strain of *betacoronavirus*. Based on its homology with SARS-CoV, the WHO has named this novel coronavirus "SARS-CoV-2." The outbreak of SARS-CoV-2 and its rapid prevalence demand the development of a vaccine.[4] In the past, multiple treatments were proposed for the control of SARS and MERS outbreaks. Ribavirin and Interferon proved useful against MERS-CoV.[5] These drugs are, however, associated with substantial adverse effects such as hemolysis and, therefore, are not as effective.[6] An epitope-based vaccine may be an excellent option to control viral epidemics. These vaccines may elicit a potent immune response with fewer side effects. However, the synthesis of an epitope-based vaccine requires detailed insights about the amino acid sequence of the immunogenic proteins.[7]

Computational tools have gained considerable attention in the field of immunology as they help predict putative epitopes from the pathogenic proteins.[8,9]

This study is designed to identify the putative epitopes from conserved portions of the spike glycoprotein (S) and nucleoprotein (N) of seven human coronaviruses (HCoV-NL63, HCoV-229E, SARS-CoV, MERS-CoV, HCoV-HKU1, HCoV-OC43, and SARS-CoV-2) followed by the assessment of binding affinities with the human leukocyte antigen (*HLA*) alleles from the Chinese population. Finally, the interactions between peptide fragments and the *HLA* alleles were confirmed using molecular docking analysis, which marked the peptide fragments, that may help in designing the future vaccine for SARS-CoV-2. These epitopes, therefore, are likely to reduce the mortality and morbidity associated with SARS-CoV-2 infections.

2 | MATERIALS AND METHODS

2.1 | Selection of epitopes and their associated consensus variants

In the first step, experimentally validated MHC Class I and Class II epitopes, reported from the different proteins of human coronavirus, were retrieved from the Immune Epitope Database (IEDB).[10] The amino acid sequences of these viral proteins were aligned using the Viral Pathogen Resource (ViPR) Database.[11] The alignment results were submitted to the WebLogo 3 software based on which web logos and percentage conservancy of these epitopes, in different strains of coronavirus, were assessed.[12] In addition to the original epitope sequence, the peptide variants were derived and considered for the analysis.

2.2 | Assessment of antigenic and allergenic nature of selected peptide fragments

The antigenic and nonallergenic nature of all selected epitopes was estimated using VaxiJen and AllerTOP, respectively. VaxiJen differentiates antigenic epitopes from nonantigens based on their physicochemical properties, whereas AllerTOP uses the auto-cross covariance method to distinguish between allergens and nonallergens.[13,14]

2.3 | Retrieval of highly prevalent *HLA* alleles of the Chinese population

Class I and Class II *HLA* alleles of the Chinese population were retrieved using Online Allele Frequency Net Database (AFND) at allele frequency threshold of 4.[15]

2.4 | Assessment of the binding affinities of epitopes and their consensus variants with *HLA* alleles

MHC-I and MHC-II binding prediction tools calculated the binding affinities of selected epitopes and their consensus variants with the Chinese-specific *HLA* alleles. The MHC-I binding prediction tool works on the artificial neural network (ANN) algorithm, whereas the MHC-II binding prediction tool works on the netMHCIIpan algorithm. These two algorithms display binding affinities in terms of half maximal inhibitory concentration (IC_{50}) nM units. IC_{50} values less than 50 nM indicate high binding affinities of epitopes with *HLA* alleles, those in between 50 and 500 nM indicate intermediate affinities, and values in the range of 500–5000 nM indicate low affinities of epitopes for the *HLA* alleles.[16,17]

2.5 | Population coverage

After the screening of epitopes and their consensus variants having a significant affinity with Chinese *HLA*

TABLE 1 Experimentally validated nine MHC-1 and MHC-II epitopes retrieved from the IEDB

Details	Epitope	Antigen	Organism	References	Assays
MHC-I epitopes					
17382	FPREGVFVF	Spike glycoprotein	Severe acute respiratory syndrome-related coronavirus	[5]	13
14829	EVMPVSMAK	Spike glycoprotein	Severe acute respiratory syndrome-related coronavirus	[4]	17
16156	FIAGLIAIV	Spike glycoprotein	Severe acute respiratory syndrome-related coronavirus	[4]	16
17385	FPRGQGVPI	Nucleoprotein	Severe acute respiratory syndrome-related coronavirus	[4]	10
33105	KQYNVTQAF	Nucleoprotein	Severe acute respiratory syndrome-related coronavirus	[4]	10
33667	KTFPPTEPK	Nucleoprotein	Severe acute respiratory syndrome-related coronavirus	[4]	12
MHC-II epitopes					
32340	KMKELSPRWYFYYLG	Nucleoprotein	Severe acute respiratory syndrome-related coronavirus	[2]	2
61554	STDLIKNQCVNFNFN	Spike glycoprotein	Severe acute respiratory syndrome-related coronavirus	[2]	2
61598	STFFSTFKCYGVSATKL	Spike glycoprotein	Severe acute respiratory syndrome-related coronavirus	[2]	4

Abbreviation: IEDB: Immune Epitope Database.

alleles, the next step was the estimation of population coverage of these peptides using the IEDB population coverage tool.[18]

2.6 | Docking of selected vaccine targets with prevalent Chinese *HLA* alleles

Herein, we also performed molecular docking as a way to confirm appropriate binding of selected epitopes with Chinese *HLA* alleles. For this purpose, the 3D structures of highly prevalent *HLA* allele (*HLA*-02-01) of the Chinese population were downloaded from the PDB database (PDB ID 6NCA). The 3D structures of all potent peptides were predicted using the PEP-FOLD3 server.[19] The peptide fragments were docked with the *HLA* allele using the PatchDock server, followed by the evaluations of binding affinities in terms of atomic contact energies (ACEs) values. The low ACE values were considered to be an indication of high binding affinity.[20]

2.7 | Molecular dynamics simulations

MD simulations were performed using NAMD software through the QwikMD interface plugin in VMD using the peptides and MHC-1-docked complexes. Then, 1 ns equilibration and 5 ns production phase MD simulations were carried out at 315 K to check the stability of docked complexes.[21] The analysis of MD simulations was performed using VMD software.[22] The frames of the production trajectories were aligned relative to the center-of-mass coordinates and the root-mean-square deviation (RMSD) was calculated with the initial equilibrated structures as the reference.

3 | RESULTS

3.1 | Selection of epitopes and their consensus variants

A total of nine peptide fragments, among which six peptides belong to MHC-I and three to MHC-II, were retrieved from the IEDB. As all these epitopes belong to the spike glycoprotein and nucleoprotein of coronavirus (Table 1), the multiple sequence alignment files of these two proteins were downloaded from the ViPR database, followed by the designing of web logos from WebLogo 3 (Table S1). Based on these web logos, the conservancy of selected epitopes in all strains of human coronaviruses was assessed, and consensus variants were derived. This leads to the inclusion of a total of 130 Class I and 127 Class II variants in the analysis (Table S2).

3.2 | Assessment of antigenic and allergenic nature of peptide fragments

VaxiJen and AllerTOP help in the screening of immunogenic and nonallergenic epitopes, respectively. Among all variants, 36 Class I and 49 Class II epitopes were allergenic and, therefore, excluded from the analysis. Likewise, 46 Class I and 8 Class II epitopes were found to be nonantigenic. Thus, at the end of this step, 61 Class I and 72 Class II epitopes were shortlisted for further analysis (Figure 1).

3.3 | Retrieval of highly prevalent *HLA* alleles of the Chinese population

AFND resulted in the extraction of 67 MHC-I and 48 MHC-II *HLA* alleles from all Chinese population groups.

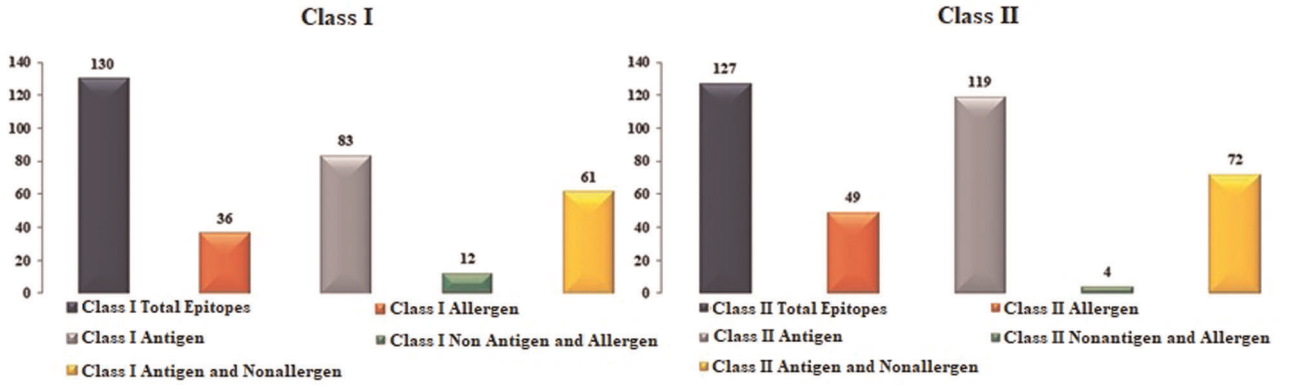

FIGURE 1 Epitope statistics: number of antigenic, nonantigenic, allergenic, and nonallergenic epitopes obtained from MHC Class I and Class II epitopes. A total of 61 MHC Class I epitopes were antigenic and nonallergenic. Similarly, 72 MHC Class II epitopes were marked as antigenic and nonallergenic. In both cases, only these selected epitopes were considered further [Color figure can be viewed at wileyonlinelibrary.com]

In MHC-I, 17 alleles belong to *HLA*-A, 31 to *HLA*-B, and 19 to *HLA*-C. Likewise, 17 alleles from MHC-II belong to *DQB*1 and 31 to the *DRB*1. The frequencies of these alleles are listed in Table S3.

3.4 | Assessment of binding predictions of class I and class II epitopes with *HLA* alleles

Of all selected antigenic and nonallergenic epitopes, 36 MHC-I and 58 MHC-II epitopes have IC_{50} values in the range of 50–500 nM. All 94 epitopes have moderate binding affinities with the *HLA* alleles. Moreover, 60 MHC-I and 7 MHC-II epitopes have IC_{50} values less than 50 nM, indicating that these peptides have strong binding affinities with the *HLA* alleles (Tables S4 and S5).

3.5 | Population coverage analysis

For population coverage analysis, four epitope sequences (3 from Class I and 1 from Class II), showing restriction to the broad range of Chinese *HLA* alleles, were selected. All these epitopes show 95.62% population coverage for most of the Chinese-specific *HLA* alleles (Tables 2 and S6).

3.6 | Molecular docking and MD simulations

HLA-02-01 is a most frequent *HLA* allele in the Chinese population. The 3D structure of the allele was downloaded from the protein databank and used in the molecular docking analysis. PEP-FOLD3 predicted the 3D structures of MHC-I epitopes only. Two epitopes (YVMPVSMAK and VVMPVSMAL) showed strong binding affinities with *HLA*-02-01 by demonstrating low ACE values of −114.79 and −215.71, respectively (Supporting Information Figure S2). These epitopes belong to the spike protein of coronaviruses. The third epitope (RQYNVTQAF) demonstrated −100 kJ/mole ACE value, indicating weak interaction as compared with two previously discussed epitopes (Figure 2 and S3). It is worth noting that these results are also consistent with MHC-I and MHC-II binding predictors. The epitope-2 showed the least IC_{50} value

TABLE 2 The selected epitopes for vaccine development

S. no.	Epitope	Sequence	MHC class	Protein
1	Epitope-1	YVMPVSMAK	MHC-I	Spike glycoprotein
2	Epitope-2	VVMPVSMAL	MHC-I	Spike glycoprotein
3	Epitope-3	RQYNVTQAF	MHC-I	Nucleoprotein
4	Epitope-4	SFDLIKNQCVNFNFN	MHC-II	Spike glycoprotein

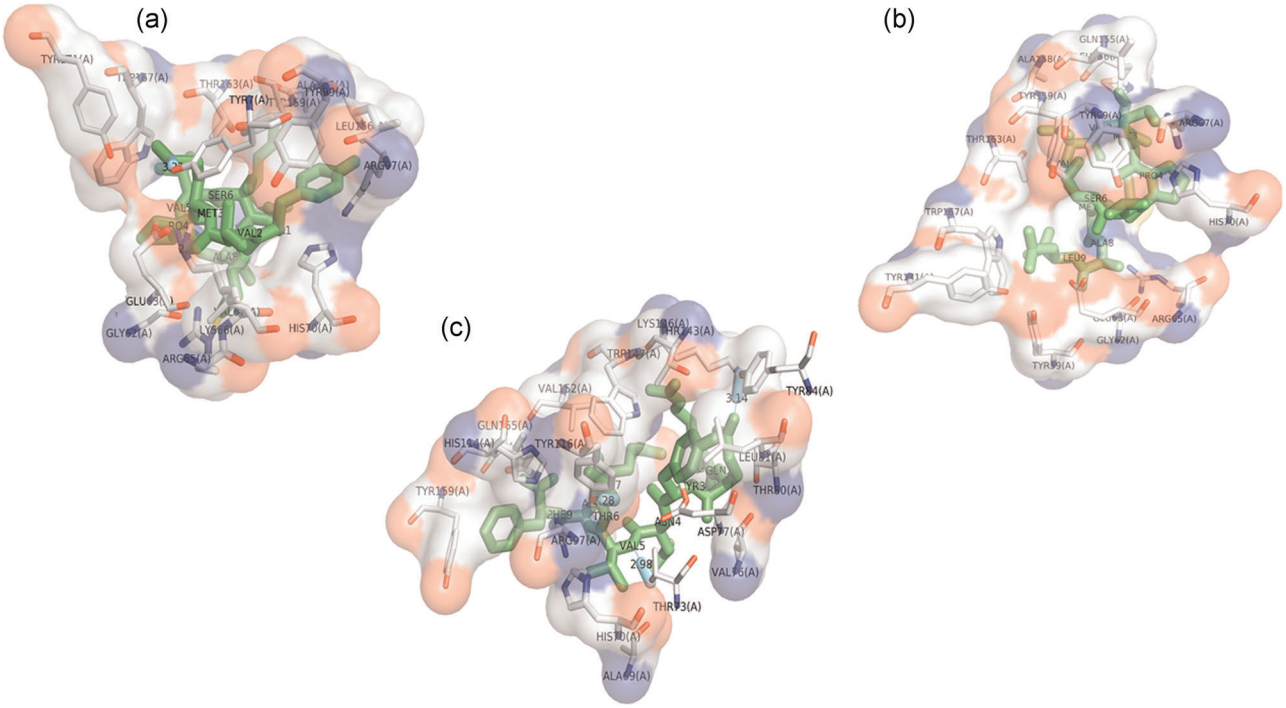

FIGURE 2 The orientation of MHC-I residues making interactions with epitopes (green) in 3D conformation. (a) The binding of epitope-1 with MHC-I protein. The amino acids residues are making hydrophobic and hydrogen interaction with the epitopes. (b) The binding of epitope-2 with MHC-I protein. The amino acids residues of MHC-I are making hydrophobic interaction with the epitopes. (c) The binding of Epitope 3 with MHC-I protein. The hydrophobic interactions are involved in the binding of the epitope with the molecule [Color figure can be viewed at wileyonlinelibrary.com]

(36.6), indicating the strong binding affinity with *HLA*. Furthermore, 5 ns production phase MD simulation was performed to validate the docking data. Interestingly, MD simulation data also supported the efficacy of the final peptide cocktail as a vaccine against novel coronavirus (Supporting Information Figure S4).

4 | DISCUSSION

Since December 2019, the world is under the continuous threat of a new strain of betacoronavirus, SARS-CoV-2. After its initial identification from Wuhan, China, this virus has spread across the globe and has become one of the major health concerns worldwide.[23] Currently, there is no reliable treatment option available to curtail viral progression probably because of the lack of potential information on the pathogenic mechanism of SARS-CoV-2 and on specific immune responses against this virus. The present study employs the immunoinformatics strategies to identify the potentially antigenic and nonallergenic epitopes from the SARS-CoV-2. As the epitopes are displayed on the surface of antigen-presenting cells (APCs) in complex with the MHC molecules, after the identification of epitopes, assessing their binding affinities with the prevalent *HLA* alleles of the particular population are also essential.[24] In the recent past, a few studies based on computational vaccine designing have been conducted.[25-28] These studies, however, have not considered conservancy of identified epitopes in different strains of the virus. The allergenic nature of these epitopes was also not mentioned. Moreover, the structural insights into the attachment of these epitopes with *HLA* alleles were also not evaluated through docking. It is now evident that the genomic sequences of this virus isolated from different population groups are different; therefore, one of the promising approaches is to align the pathogenic proteins of all strains of human coronaviruses for epitope mapping.[29]

Herein, we present an approach to highlight peptides that could counteract the novel coronavirus by eliciting $CD4^+$ and $CD8^+$ T-cell responses. This study focused on the experimentally validated and highly promising MHC-I and MHC-II epitopes from the IEDB. Most of these epitopes belong to spike glycoprotein and nucleoproteins. In this study, the conserved epitopes and their consensus variants are suggested as the vaccine candidates because these epitopes can recognize diverse members of the betacoronaviruses, and therefore may be ideal for controlling the future infections caused by the new viruses of this family. From all selected epitopes and their consensus variants, only four peptides (three class I and one class II) were selected.

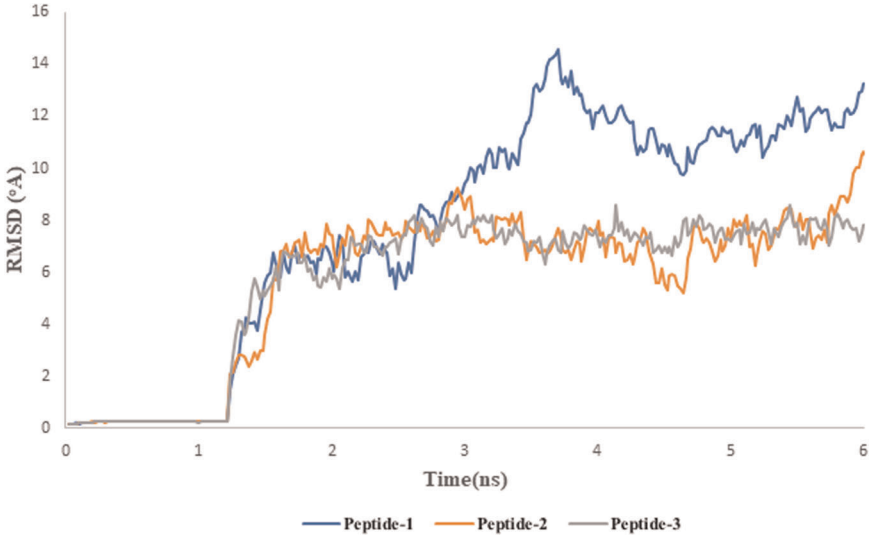

FIGURE 3 RMSD values of 5 ns MD simulations. Epitope 2 and Epitope 3 have smaller fluctuations in the RMSD, which become stable after 1.5 ns, whereas epitope 1 has comparatively larger variations in RMSD which take a longer time span to normalize. MD, molecular dynamics; RMSD, root-mean-square deviation [Color figure can be viewed at wileyonlinelibrary.com]

Three of these peptides belong to Spike glycoprotein with YVMPVSMAK and VVMPVSMAL are part of the receptor-binding domain while the third epitope SFDLIKNQCVNFNFN is adjacent to it. Similarly, the fourth epitope RQYNVTQAF is the part of the nucleoprotein, which is required for viral replication (Figure 3). As the four epitopes identified in this study are part of functionally important regions of the viral proteins, the cocktail of these epitopes would play an important role to control the propagation of this family of viruses in the Chinese population. Moreover, the molecular docking analysis revealed the significant binding affinities with Chinese-specific HLA alleles and MD simulations analysis marked the minimum fluctuations in RMSD values. (Supporting Information Figure S4).[30]

5 | CONCLUSIONS

From the beginning of the 21st century, the world is facing coronavirus epidemics, including SARS-CoV, MERS-CoV, and the current COVID-19. The origin of these epidemics is from China, which, therefore, demands considerable attention to design vaccine(s) which may be suitable against all coronaviruses strains. In this study, we presented four epitopes from the conserved regions of all human coronaviruses as the ideal candidates to provide broader immunity to the Chinese population.

ACKNOWLEDGMENTS

Authors are thankful for the online available open access databases which are used in this study. The research was self-supported by the authors.

DISCLOSURE

The authors declare that there are no conflict of interests and being an *in silico* study there is no need for informed consent in this regard.

ETHICAL STATEMENT

This study is a computational work so humans or animal were not used during this study. Therefore, there is no need for ethical approval.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Batool H, Batool S, Mahmood MS, et al. Prediction of putative epitope-based vaccine against all corona virus strains for the Chinese population: Approach toward development of vaccine. *Microbiology and Immunology*. 2021;65:154–160. https://doi.org/10.1111/mim.12866