Immunogenic Epitope-Based Vaccine Prediction from Surface Glycoprotein of MERS-CoV by Deploying Immunoinformatics Approach

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Abstract
Middle East respiratory syndrome coronavirus (MERS-CoV) has caused a high mortality rate since its emergence in 2012 in the Middle East. Currently, no effective drug or vaccine is available for MERS-CoV. Supportive care and prevention are the only ways to manage infection. In this study, we identified an epitope-based vaccine that could be an optimal solution for the prevention of MERS-CoV infection. By deploying an immunoinformatics approach, we predicted a subunit vaccine based on the surface glycoprotein (S protein) of MERS-CoV. For this purpose, the proteome of the MERS-CoV spike protein was obtained from the NCBI GenBank database. Then, it was subjected to a check for allergenicity using the Allergen FP v.1.0 tool. The Vaxijen v.2.0 tool was used to conduct antigenicity tests for binding with major histocompatibility complex class I and II molecules. The solidity of the predicted epitope-allele docked complex was evaluated by a molecular dynamics simulation. After docking a total of eight epitopes from the MERS-CoV S protein, further analyses predicted their non-toxicity and therapeutic immunogenic properties. These epitopes have potential utility as vaccine candidates against MERS-CoV, to be validated by wet-lab testing.

Keywords Immunoinformatics · Middle East respiratory syndrome (MERS) · Antigenicity · Allergenicity · Epitope vaccine

Introduction
Middle East respiratory syndrome coronavirus (MERS-CoV) has been identified as a novel human coronavirus that poses a major threat to global public health, calling for the urgent development of effective and safe vaccines. MERS-CoV is correlated with an unusually high death rate of almost 35% (Alqahtani et al. 2018; Bermingham et al. 2012; Zaki et al. 2012). The first known infections of MERS-CoV were detected in Saudi Arabia in 2012, and the virus later spread to other countries. Worldwide, 27 countries have reported cases since 2012. In the Western Pacific Region, countries that have experienced imported cases of MERS include China, Malaysia, the Philippines, and the Republic of Korea. The importation of the virus into the Republic of Korea in 2015 led to the largest MERS outbreak outside of the Middle East. This outbreak resulted in 186 laboratory-confirmed cases and 36 deaths (Durai et al. 2015; Ki 2015).

MERS-CoV was determined to be different from all other coronavirus strains that have been found in humans, including the severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2 strains that caused the SARS (LeDuc and Barry 2004) and coronavirus disease 2019 (COVID-19) epidemics, respectively. So far, various types of vaccines targeting SARS-CoV and SARS-CoV-2 have been developed and tested in preclinical models. These include protein subunit vaccines, virus-like particle vaccines, DNA vaccines, RNA vaccines, viral vector vaccines, inactivated whole-virus vaccines, and live-attenuated virus vaccines (Anderson et al. 2020; Folegatti et al. 2020;
Jackson et al. 2020; Keech et al. 2020; Logunov et al. 2020; Mulligan et al. 2020; Sahin et al. 2020; Walsh et al. 2020; Zhu, et al. 2020a, b; Zhu, et al. 2020a, b). However, only DNA- and viral vector-based vaccine candidates have been tested in preclinical models for MERS-CoV (Modjarrad et al. 2019; Xia et al. 2020, 2021).

In recent studies, epitope-based vaccine candidates were successfully developed against SARS-CoV-2, human cytomegalovirus, Tropheryma whippelii, nervous necrosis virus, candida fungus, and dengue virus (Akhtar et al. 2021a, b, c; Sunil Krishnan et al. 2020; Jain et al. 2021; Joshi et al. 2020; Joshi and Kaushik 2020; Krishnan et al. 2021). Subunit vaccines have been clinically approved for use against pertussis, influenza, Streptococcus pneumoniae, and Haemophilus influenzae type b (Folegatti et al. 2020; Koch et al. 2020).

To our knowledge, such protein subunit vaccines are easy to produce and relatively safe and well-tolerated compared to whole-virus vaccines and viral vector vaccines. They consist of viral antigenic fragments produced by recombinant protein techniques. Thus, our study predicted epitope-based vaccine peptides that have therapeutic properties against MERS-CoV, however, experimental evaluations remain necessary to verify the exact safety and immunogenicity profile of this vaccine.

Materials and Methods

Proteomic Data Retrieval

The MERS-CoV surface glycoprotein (S protein) sequence was obtained from the National Center for Biotechnology Information (NCBI) database (http://www.ncbi.nlm.nih.gov/) using the accession ID ALW82742.1. The experimentally derived 3D structure of the MERS-CoV S protein was retrieved from the Protein Data Bank (PDB ID: 5X59).

Evaluation of Protein Physicochemical Properties

Using the online program ProtParam, the protein sequence was examined for chemical and physical characteristics such as grand average of hydropathicity (GRAVY), half-life, molecular weight, stability index, and amino acid atomic composition (Gasteiger et al. 2005).

Antigenicity Tests

The Vaxijen v.2.0 server (Doytchinova and Flower 2007; http://www.ddg-pharmfac.net/vaxijen/VaxiJen/VaxiJen.html) was used to conduct antigenicity tests. For predicting allergenicity, the protein sequence was expanded for further analysis based on Allergen FP v.1.0. (Dimitrov et al. 2013).

B-Cell Epitope Prediction

B-cell epitopes were predicted using the free web server ABCpred (Saha and Raghava 2006; http://crdd.osdd.net/raghava/abcpred/). The criteria were established at 75% specificity, and 12-residue-long epitopes were deemed sufficient to induce a protective immune response. The top results ranked from 1 to 10 were considered.

T-Cell Epitope Prediction

Epitopes of cytotoxic T lymphocytes (CTLs) are important in vaccine development. Most importantly, it saves money and time as compared to wet-lab studies. Thus, CTL epitopes of target proteins of major histocompatibility complex (MHC) classes I and II were predicted using two different internet tools, the NetMHCpan 4.1 (http://www.cbs.dtu.dk/services/NetMHCpan-4.1/) and NetMHCIIpan 4.0 servers (http://www.cbs.dtu.dk/services/NetMHCIIpan-4.0/; Reynisson et al. 2020). Because these techniques consider a large number of human leukocyte antigen (HLA) alleles during calculation, the results are highly significant. All alleles were chosen for prediction and the sequence was supplied in a simple format.

Toxicity Profiling for Selected Epitopes

After finalizing the epitopes of both MHC class I and class II alleles, the ToxinPred server (Gupta et al. 2013) was used for in silico analysis to differentiate non-toxic and toxic peptides (http://crdd.osdd.net/raghava/toxinpred/). Only non-toxic epitopes were chosen for further investigation.

Molecular Docking

The 3D structures of HLA alleles were retrieved from the Research Collaboratory for Structural Bioinformatics PDB (RCSB PDB) database (Berman 2000), and used for subsequent molecular docking purposes. The PatchDock server (Duhovny et al. 2002; Schneidman-Duhovny et al. 2005a, b) was used for conducting docking experiments (https://bioinfo3d.cs.tau.ac.il/PatchDock/php.php). Thereafter, the FireDock server (Mashiach et al. 2008) was used to screen the best-docked results based on atomic contact energy (ACE; https://bioinfo3d.cs.tau.ac.il/FireDock/php.php).
**MD Simulations**

The MDWeb tool (Hospital et al. 2012) was deployed for conducting molecular dynamics and simulation studies for obtaining the best-docked complexes (https://mmb.irbbarcelona.org/MDWeb/). Trajectory analysis produced root-mean-square deviation (RMSD) and B-Factor plots that demonstrated the integrity and stability of complexes under simulated environments.

**Results**

**Protein Evaluation**

From the protein sequence of the MERS-CoV S protein, various physicochemical properties were computed using ProtParam. AllergenFP v.1.0 results indicated that the protein had non-allergic properties as it held a higher Tanimoto similarity index of 0.84. Vaxijen v.2.0 analysis with a threshold of 0.4 revealed an antigenicity of 0.4829, indicating that the sequence was a probable antigen. Thus, we confirmed that the MERS-CoV S protein sequence can well be considered for epitope prediction. The abovementioned properties are summarized in Table 1.

**T-Cell Epitope Prediction**

T-cell epitopes were predicted from the S protein using the NetMHCpan 4.1 server for MHC Class I HLA proteins and the NetMHCIIpan 4.0 server for MHC Class II HLA proteins as both servers work efficiently based on an artificial neural network schematic framework. Tables S1 and S2 present the screened epitopes based on the binding affinity and rank generated by the NetMHC servers. Supplementary Excel Sheets 1 and 2 present the full T-cell epitopes for both MHC I and MHC II HLA allelic determinants.

**B-Cell Epitope Prediction**

The ABCpred tool was deployed for B-cell epitope prediction. B-cell epitopes bind to B-cell receptors (BCRs) and induce immune responses against MERS-CoV. Along with T-cell epitopes, B-cell epitopes are highly useful in generating immunogenicity (Table S3).

**Toxicity and Antigenicity Tests**

Allergenicity prediction using AllergenFP v.1.0 revealed that the complete S protein sequence represented a probable non-allergen. Vaxijen v.2.0 analysis of T-cell and B-cell epitopes from the MERS-CoV S protein using a threshold of 1.1 facilitated the screening of epitopes of high antigenicity, indicating that the selected protein had probable antigenic and immunogenic properties. Thus, we confirmed that the protein sequence can be considered for epitope prediction. After this analysis, the screened epitopes were analyzed using the ToxinPred tool that further confirmed their non-toxic features (Table 2).

**MHC Proteins and BCR Structure Retrieval**

All receptor structures were retrieved from the RCSB PDB database. The structural files for MHC class II HLA DRB1:0101 (PDB ID: 1AQD), MHC Class I HLA-A*0101

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**Table 1** Physicochemical properties of the MERS-CoV S protein (GenBank ID: ALW82742.1)

| Criteria                              | Value                              |
|---------------------------------------|------------------------------------|
| Number of amino acids                 | 1353                               |
| Molecular weight                      | 149,368.04                         |
| Total number of negatively charged residues (Asp + Glu) | 112                                |
| Total number of positively charged residues (Arg + Lys) | 95                                 |
| Formula                               | C_{6682}H_{10245}N_{1735}O_{2029}S_{63} |
| Total number of atoms                 | 20,754                             |
| Aliphatic index                       | 82.71                              |
| Theoretical pI                         | 5.70                               |
| Estimated half-life                    | 30 h (Mammalian reticulum-cyes, in vitro) > 20 h (yeast, in vitro) > 10 h (Escherichia coli, in vivo) |
| Grand average of hydropathicity (GRAVY)| – 0.074                           |
| Allergenicity                         | Non-allergen                       |
| Antigenicity using the VaxiJen sever  | Antigen (VaxiJen score 0.4829)     |
(PDB ID: 1W72), and BCR (PDB ID: 5IFH) were downloaded successfully.

**Molecular Docking Studies**

Molecular docking studies were conducted using the PatchDock and FireDock tools (Dina Schneidman-Duhovny et al. 2005a, b). Figure 1 presents all 11 docked complexes, of which eight complexes had suitable ACE values from −9 to −5 kcal/mol (Krishnan et al. 2021). The eight selected complexes are presented in Table 3.

The obtained results also indicated perfect binding between the ligand and receptor as presented in Fig. 2. Two B-cell epitopes, LEPRSGNHCPAG and QNCTAVGVRQQR, bound to the BCR_FAB domain during molecular docking and showed chemical interactions in visualizations with PyMOL.

Similarly, the T-cell epitopes GRGVFQNCTAVGVRQ and EGGGWLVASGSTVAM interacted with MHC class II HLA determinants (Fig. 3A and B). Additionally, the T-cell epitopes YSNITYQGLF, YIDLKEGLNYT, SYIDLKEGLNYT, and PTNFSFGVTQYEY were observed to interact with MHC class I HLA determinants (Fig. 3C–F). All such T-cell epitope interactions were observed in the binding pocket of core protein receptors using the PyMOL visualization tool.

**MD Simulations**

For epitopes interacting with the HLA allele structures, the RMSD values and atomic fluctuation per amino acid residue were acquired, allowing for ideal pair selection and confirmation. The MDWeb tool was deployed for this purpose, and RMSD and B-factor values in the appropriate range were successfully obtained (Sunil Krishnan et al. 2020). The RMSD and B-factor plots of the B-cell epitope with the lowest ACE value interacting with the BCR_FAB domain are indicated in Fig. 4.

Figures 5 and 6 present RMSD and B-factor plots, respectively, for all T-cell epitopes interacting with MHC class I and class II HLA determinants. The obtained results indicated perfect molecular stability in the docked complex in short-run simulations using the MDWeb tool.

**Discussion**

MERS-CoV and SARS-CoV-2 are emerging infectious viruses that are extremely harmful to humans. Effective immunization and protective measures against these infections are still largely undiscovered. Gaps in our understanding of these pathogens’ protective immunity pose challenges to vaccine development (Sunil Krishnan et al. 2020; Park et al. 2019).

This study aimed to use immunoinformatics approach to screen of vaccine epitopes to identify the most antigenic protein of MERS-CoV as well as the B- and T-cell epitopes that map onto this protein. The immunoinformatics method, which is based on bioinformatics breakthroughs, is a viable and necessary tool for developing vaccines against new, highly dangerous microorganisms. In this investigation, critical dominant immunogens were screened against MERS-CoV using an immunoinformatics-driven strategy.

The results revealed that the S protein was a superior antigenic protein. Indeed, all current MERS vaccination trials focus on the S protein of MERS-CoV, which facilitated the identification of the host cell DPP4 receptor and causes a strong immune response (Wang et al. 2013). After docking a total of eight epitopes from the MERS-CoV S protein,
analyses predicted that these epitopes are non-toxic and have therapeutic immunogenic properties. Two B-cell epitopes, LEPRSGNHCPAG and QNCTAVGVRQQR, bound to the BCR_FAB domain during molecular docking. Additionally, the T-cell epitopes GRGVFQNCTAVGVRQ and EGGWL-VASGSTVAM interacted with MHC class II HLA determinants. Similarly, the T-cell epitopes YSNITITYQGLF, YIDLKELGNYT, SYIDLKELGNYT, and PTNFSFG-VTQEY were observed to interact with MHC class I HLA determinants. Recent studies using a similar approach successfully identified epitope-based vaccine candidates against SARS-CoV-2, human cytomegalovirus, *Tropheryma whipplei*, nervous necrosis virus, candida fungus, and dengue virus (Akhtar et al. 2021a, b, c; Sunil Krishnan et al. 2020; Jain et al. 2021; Joshi et al. 2020; Joshi and Kaushik 2020; Krishnan et al. 2021). Thus, the identified T-cell and B-cell epitopes have therapeutic potential against the MERS virion.
Fig. 3  T-cell epitopes interacting with MHC class II receptors (A, B). A HLADRB1:0101-GRGVFQNCTAVGVRQ, B HLADRB1:0101-EGGWLVASGTVAM. T-cell epitopes interacting with MHC class I receptors (C–F). C HLA_A0101-YSNITITYQGLF, D HLA_A0101-YIDLKELGNYTY, E HLA_A0101-SYIDLKELGNYT, F HLA_A0101-PTNFSFGVTQEY
Fig. 4  RMSD plot (A) and B-factor plot (B) for the B-cell epitope with the lowest ACE value interacting with the BCR BCR_FAB-LEPRSGNHPAG
Fig. 5 RMSD plot of docked T-cell epitopes. A HLA DRB1:0101-GRGFVQNCTAVGVRQ, B HLA DRB1:0101-EGGGWLVASGTVAM, C HLA A0101-YSNITITYQGLF, D HLA A0101-YIDLKEGLNVTY, E HLA A0101-SYIDLKEGLNVTY, F HLA A0101-PTNFSGVTQEEY
Conclusions

MERS-CoV causes a severe respiratory disorder, and better vaccines need to be developed to control this pathogen. The main target of this study was to identify peptide epitopes from MERS-CoV for both T cells and B cells that have therapeutic potential. Our modern in silico study demonstrates a fast strategy for vaccine development against MERS-CoV that nevertheless requires wet-lab testing for final validation.

Fig. 6 B-factor plot of docked T-cell epitopes. A HLADRB1:0101-GRGVFQNCTAVGVRQ, B HLADRB1:0101-EGGGWLVASGSTVAM, C HLA_A0101-YSNITITYQGLF, D HLA_A0101-YIDLKELGNYTY, E HLA_A0101-SYIDLKELGNYT, F HLA_A0101-PTNFSFVTQYE
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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Research Involving Human and/or Animal Participants This article does not contain any studies with human participants or animals performed by any of the authors.

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