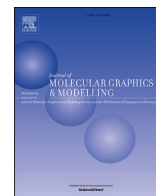Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Epitope mimicry analysis of SARS-COV-2 surface proteins and human lung proteins

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ABSTRACT

Background: Autoimmune response after the infection of SARS-COV-2 is evident as more cases of Guillain Barre syndrome and Kawasaki disease are diagnosed. In this study, we aim to investigate a possible mechanism of autoimmune lung injury.

Methods: We extracted the peptide sequences of surface proteins of the SARS-COV-2 from the NCBI data protein. We used Blastp to assess the homologous sequences between the human proteins in the UNI-PROT database that are associated with respiratory distress. Then, we filtered the homologous sequences to those selectively expressed in the lung and homologous to surface viral proteins. We then assessed the epitope sequences for MHC-I and MHC-II using recommended settings and reference MHC in the IEDB database.

Results: Homeobox protein 2.1 (NKX2-1) and ATP-binding cassette sub-family A member 3 (ABCA3) showed homologous sequence to both surface glycoproteins and envelope proteins. The HLA-DR and HLA-DQ had a similar binding pattern to ABCA3 as surface glycoproteins and envelope proteins, respectively. Other HLA molecules that had a similar binding pattern to SARS-COV-2 as human proteins were HLA-A and HLA-DP.

Conclusion: Our study indicates that there is a possible autoimmune mechanism underlying the acute respiratory distress syndrome in SARS-COV-2.

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1. Introduction

The recent coronavirus pandemic (SARS-COV-2) has caused worldwide distress and confusion over its pathogenesis especially that it had a significant difference to its precedent coronaviruses, MERS and SARS [1].

There is a lack of evidence regarding how the immune system reacts to SARS-COV-2. Once any virus enters the body, the antigenic peptides are presented on MHC I and MHC II which T cells recognize to initiate the immune response to the virus [2]. Based on SARS and MERS studies, the HLA polymorphism increases the susceptibility to the disease and its complications [3]. For instance, HLA-B*4601, HLA-B*0703, HLA-DR B1*1202, and HLA-Cw*0801 increased the susceptibility whereas the HLA-DR0301, HLA-Cw1502, and HLA-A*0201 alleles decreased the risk of infection [3–5].

For humoral response, IgG and IgM were detected in the patients of SARS-COV-2 but IgM disappeared after 12 weeks [1]. For cellular immunity, there was decreased CD4$^+$ and CD8$^+$ which persisted even with increased levels of HLA-DR and CD-38 [2,5].

This is not the first time SARS-COV-2 was associated with different autoimmune diseases e.g. Guillain Barre syndrome and Kawasaki disease. In Northern Italy, patients developed Guillain-Barré syndrome after 5–10 days after infection [6]. Many cases were diagnosed as Guillain Barre syndrome in China, United States, and Iran [7–9]. For Kawasaki disease, many countries reported an increased incidence of the disease after the COVID-19 infection [10]. Although the immunopathogenesis of autoimmune diseases is still vague, it provides insight into a possible mechanism for COVID-19 immunopathogenesis. The in-silico approach can be used to determine a possible autoimmune mechanism through the molecular mimicry analysis [11].

Molecular mimicry has been investigated in different viral and bacterial pathogens as a cause of different clinical diseases [11]. It is the structural similarity between the host proteins and the

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pathogens causing cross-reacting immune response against the host proteins. This was proved in many diseases in which immune response appeared during or after the infection [11–13].

In the current study, we hypothesize that the SARS-COV-2 induces an autoimmune response that may be a fulminant response causing multiorgan failure. We investigated the molecular mimicry between human proteins and SARS-COV-2 proteins and investigated whether the homologous peptides will create a cross-reacting antibody against these human proteins.

2. Methods

2.1. SARS-COV-2 surface protein sequences

In this study, we extracted SARS-COV-2 surface proteins sequence from the NCBI virus database (Ref Seq ID: NC_045512) [14]. The extracted surface protein sequences were membrane glycoproteins, envelope proteins, and surface glycoprotein. In addition, we performed a systematic search in PubMed, Scopus, ISI web of science and Google Scholar using search terms ("COVID-19" OR "SARS-COV-2" OR "2019-nCoV" OR "Coronavirus Disease-19") AND ("autoimmune" OR "Autoantibodies" OR "Autoantibody"). We included any reported proteins that cause an autoimmune response in COVID-19 patients.

2.1.1. Proteins involved in acute respiratory distress syndrome

We extracted the proteins involved in respiratory distress using the Uniprot database by using search terms "Respiratory distress" and "Respiratory failure" [15]. We refined our research to the reviewed proteins and those expressed in *Homo sapiens*.

2.2. Homology search

The Blastp program (https://blast.ncbi.nlm.nih.gov/Blast.cgi) was used to find homologous sequences between the identified human proteins to SARS-COV-2 proteins [16,17]. The search was limited to *Homo sapiens* (taxid: 9606) and those in the UniProtKB/Swiss-Prot database. We used the default BLASTp algorithm parameters [17]. After carefully revising the homologous sequence, homologous proteins were filtered through the Human Protein Atlas (http://www.proteinatlas.org) to only keep the proteins selectively expressed in the lung [18].

2.3. Prediction of potential T cell epitopes

The homologous sequences were investigated for the ability to function as T cell epitopes. First, the homologous viral proteins and human proteins were analyzed using the IEDB analysis tools (http://www.iedb.org) to detect both MHC-I and MHC-II epitopes [19]. Then, we checked if the homologous sequences detected by the BLASTp can function as an epitope for T cells or not.

We used the IEDB recommended models and parameters. For HLA selection, the HLA allele reference set was selected for both MHC-I and MHC-II [19]. We filtered the binding epitopes based on those who exhibited a low percentile rank, which indicated a good binding capacity. We then selected the homologous peptides that had a low percentile rank and high homology to human proteins.

2.4. Peptide-MHC docking

Peptide-MHC docking was performed using the GalaxyPepDock server (http://galaxy.seoklab.org/) to compare the binding patterns of MHC molecules to corresponding homologous sequences [20]. We chose this server because it allows the docking of the peptide to a 3D protein structure. Unlike other services, it does not need the

3D structure of the peptide. So, the docking will not depend on the prediction error of the homologous peptide structure. The docking of the Galaxy pepdock depends on searching a similar protein-peptide interaction in the database of experimentally determined structures. If similar peptide-protein interactions are found, this template is used to refine the docking. The server reports the top 10 possible docking conformations based on the similarity to the template. Unfortunately, no docking scores were reported. In addition, based on the interaction similarity between the template and predicted docked model, GalaxyPepDock determines the important amino acid residues that are essential for the binding of HLA molecule to different epitopes.

To compare the binding of SARS-COV-2 and human peptides to HLA of the predicted docked models, the docked models were analyzed using UCSF Chimera 1.14 [21] and LigPLOT+ [22]. We used Root Mean Square Deviation (RMSD) to compare the affinity of binding of SARS-COV-2 and human peptides to HLA. In simple words, RMSD is considered an expression of the distance between the docked peptide and HLA molecule; the less the RMSD, the stronger the docking. It is used to compare the docked conformation to a reference model. In this study, we considered the human HLA interaction as the reference model and we compared the binding of SARS-COV-2 peptide to HLA molecule to the human model.

We used the crystal structure of HLA-DRB1 (HLA-DRB1 in complex with Type II collagen peptide), HLA-A (HIV RT-derived peptide complexed to HLA-A), HLA-DQ (HLA-TCR complex), and HLA-DP (MHC TCR peptide complex) obtained from the Protein Data Bank database (PDB ID: 6BIN, 3RL1, 6PX6, and 4P57) [23]. These crystal structures were modified to remove any bound ligands and make the groove available to dock with SARS-COV-2 and human proteins using UCSF-Chimera 1.14 [21].

3. Results

3.1. Homology with human proteins

Seven human proteins showed homology to surface glycoproteins and only three proteins showed homology to envelop proteins Supplementary Table 1. Two proteins were selectively expressed in the lung: Homeobox protein 2.1 (*NKX2-1*) and ATP-binding cassette sub-family A member 3 (*ABCA3*); these proteins were associated with respiratory failure. The surface glycoproteins and envelope proteins were homologous to *ABCA3*; however, *NKX2-1* was only homologous to surface glycoproteins. The homologous sequences for *NKX2-1* were from 17:67 and 241:257 corresponding to 241:288 and 667:683 of the surface glycoproteins, respectively. For *ABCA3*, the homologous peptides were from 309 to 340 and 283 to 328 corresponding to 20−61 and 1179:1235 of the envelope glycoproteins.

3.2. Homologous sequences acting as T-cells epitope inducing an immune response

The resulting MHC-I and MHC-II epitopes of SARS-COV-2 for both the envelope and surface glycoproteins were ranked based on the percentile rank (the lower the percentile, the greater the binding) and epitopes that exhibited the highest homology to the homologous human proteins' sequences were selected. Most selected epitopes were among the top five epitopes based on the percentile ranking. For NKX2-1, there were three homologous peptides with surface glycoprotein epitopes that showed high binding with MHC-I and MHC-II (Table 1). For ABCA3, there were two homologous peptides with surface glycoprotein and envelope proteins epitopes that showed high binding with MHC-I and MHC-II (Table 1).

Table 1
The viral epitopes for MHC-I and MHC-II and the corresponding homologous human proteins.

COVID-19 protein	Human protein	HLA	Potential COVID-19 epitope	Corresponding human epitope	Percentile rank
Surface glycoproteins	NKX2-1	HLA-A*26:01	WTAGAAAYY	LGAPLAAYR	0.11 (2nd)
		HLA-A*68:01,	QTQTNSPRR	QAQQQSPRR	1.53 (3rd)
		HLA-DQA1*05:01/DQB1*03:01	SSGWTAGAAAYYVGY	GGGLGAPLAAYRQGQ	0.94 (1st)
		HLA-DRB1*04:01	GICASYQTQTNSPRR	GCPQQQQAQQQSPRR	5.30 (1st)
	ABCA3	HLA-A*02:03	FIAGLIAIV	FLFLLIAAS	0.16 (10th)
		HLA-DQA1*05:01/DQB1*03:01	GFIAGLIAIVMVTIM	FFLFLLIAASFMTLL	1.60 (5th)
Envelope proteins	ABCA3	HLA-A*02:01	FLLFFLFLLI	FLAFVVFLLV	0.15 (2nd)
		HLA-DPA1*03:01/DPB1*04:02	FLAFVVFLLVTLAIL	FLLFFLFLLIAASFM	0.06 (1st)

3.3. Molecular docking for the comparison between the binding of human NKX2-1 and SARS-COV-2 surface glycoproteins to MHC-I and MHC-II

The docking between the homologous peptide of SARS-COV2 (WTAGAAAYY) and human protein (LGAPLAAYR) linked to HLA-A revealed an RMSD of 1.22 A°. Out of all hydrogen bonds stabilizing the binding of the peptide to HLA groove, both peptides shared the same glutamate and tyrosine at the 152nd and 159th position, respectively, in the HLA-A molecule (Fig. 1A). For the second-highest binding homologous sequences (surface glycoproteins

[QTQTNSPRR] and NKX2-1 [QAQQQSPRR]), these homologous peptides were considered to be better than the first one because they had a lower RMSD of 1.08 A°. The docked peptides shared the hydrogen bonds between the tyrosine residues at the 7th and 157th position in HLA and the glutamine residue at the 275th position on the SARS-COV-2 peptides. In addition, Threonine at the 80th position in the HLA molecule to Arginine at the 283rd position in the human and SARS-COV-2 proteins. Both ABCA3 and surface glycoproteins epitopes also shared binding to the Glutamate at the 152nd position of HLA-A molecules (Fig. 1B).

For HLA-DR, the difference between the binding of human and
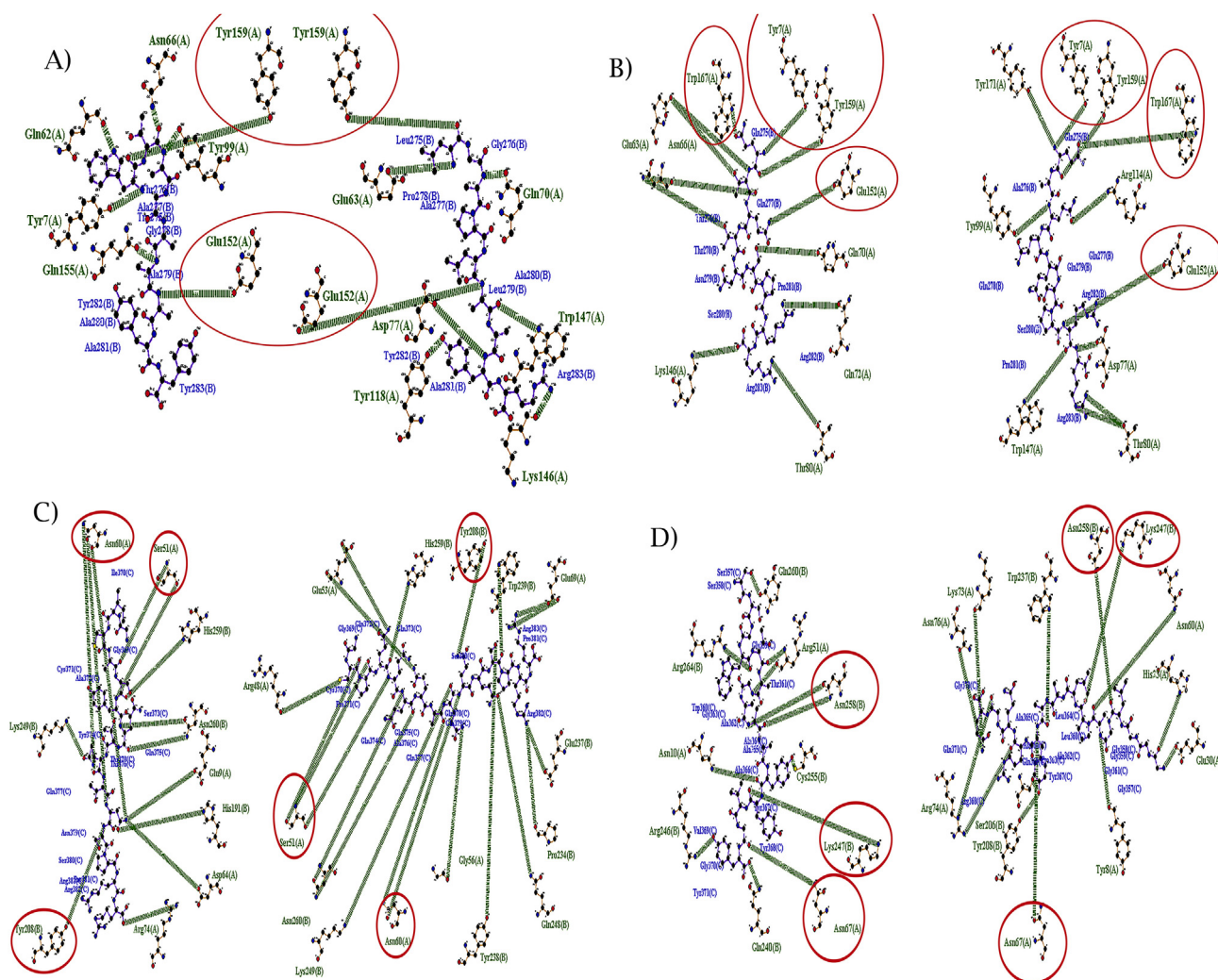
Fig. 1. The hydrogen bonds (green color) between the HLA-A (A and B) and HLA-DR (C and D) amino acids and homologous peptides: surface glycoproteins (left) and NKX2.1 (right). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

SARS-COV-2 to HLA-DR was 1.29A°. *NKX2-1* and *SARS-COV-2* surface glycoproteins shared the hydrogen bonds between residues in the HLA-DR molecule as serine 51, asparagine 60, and tyrosine 208 (Fig. 1C). For HLA-DQ, the docking between the SARS-COV2 homologous peptide and human protein to HLA-A revealed an RMSD of 1.20 A°. Both peptides shared the same asparagine 67, 258, and lysine 247 binding residues to the HLA-A molecules (Fig. 1D).

3.4. Molecular docking for a comparison between the binding of human ABCA3 and SARS-COV-2 surface glycoproteins to MHC-I and MHC-II

For HLA-A, the RMSD between the docked homologous human and SARS-COV-2 protein was 1.34A°. Both peptides were found to bind to asparagine 66, glutamine 70, tyrosine 99, and aspartate 77 residues in the HLA molecule by through hydrogen bonds. For HLA-DQ, the binding of the SARS-COV-2 peptide was similar to the corresponding homologous protein, ABCA3, with an RMSD of 0.72 A°. Both homologous peptides shared hydrogen bonds between leucine 362 in the peptides and asparagine 60 in the HLA-DQ molecules. In addition, they shared hydrogen binding to arginine 74 and asparagine 258 in the HLA-DQ molecules (Fig. 2).

3.5. Molecular docking for a comparison between the binding of ABCA3 and SARS-COV-2 envelope proteins to MHC-I and MHC-II

For HLA-A, the RMSD between the binding of SARS-COV-2 and ABCA3 homologous peptides was between 1.340 A°. Leucine 283 in SARS-COV-2 and the human ABCA3 homologous peptide bound to the tryptophan 147 in HLA-A through hydrogen bonds. No other amino acids in the HLA-A molecule bound via hydrogen bonds to homologous peptides (Fig. 3). For HLA-DP, there were minimal differences between the binding of SARS-COV-2 and ABCA3 homologous peptides (RMSD = 0.868). Both homologous peptides were bound to the HLA-DP molecules through Glycine 184 (Fig. 4).

4. Discussion

This study suggests that the molecular mimicry between SARS-COV-2, NKX2-1, and ABCA3 may explain the immunopathogenesis of the disease. Our results indicate that the SARS-COV-2 envelope proteins and surface glycoproteins share antigenic MHC-I and MHC-II epitopes with NKX2-1 and ABCA3.

The most interesting result was the homologous peptides between *ABCA3* and both envelope proteins and surface glycoproteins. *ABCA3* is a protein that consisted of 1704 residues and is selectively expressed in the lung [24,25]. It belongs to the family of ABC transporter that is responsible for the transport of molecules through the lipid bilayer of the lung [24]. It was detected in the plasma membrane of alveolar cells and the limiting membrane of the lamellar bodies [25,26]. The alveolar cells II are responsible for the secretion of surfactant which is important for protection against lung collapse [24,27]. That is why mutations in the ABCA3 gene caused respiratory distress and interstitial pneumonia [28]. In this study, the homologous peptides between the ABCA3 and both envelope proteins and surface glycoproteins peptides acted also as antigenic epitopes for HLA-A*02:03, HLA-DQA1*05:01/DQB1*03:01, HLA-DPA1*03:01/DPB1*04:02, HLA-A*02:01. The binding between the molecules was similar in pattern and hydrogen bonds. We believe that the antibodies produced against surface proteins cross-react against ABCA3 proteins causing alveolar collapse and respiratory failure based on other studies that found that functional defect in the protein resulted in respiratory failure [29]. Furthermore, the specific HLA that cross-reacts with these epitopes might explain why specific populations are more susceptible to respiratory failure and death while other patients are symptomless. That was observed in different viral infections where specific HLA polymorphisms were associated with the severity of the disease [30–32]. In addition, a study revealed that the Taiwanese general population with HLA-B* 4601 had more susceptibility to ARDS after SARS infection compared to the Taiwanese indigenous population who do not have this HLA allele [3]. Another small study found that SARS patients admitted to ICU have HLA-B46 compared to those who have not [33]. However, there are still no clinical studies in SARS-COV-2 that support our study. Based on our study, the binding strength of SARS-COV-2 to HLA is more powerful than human epitopes based on RMSD values. In addition, based on the docking models, more hydrogen bonds were stabilizing the SARS-COV-2 peptide than human peptides.

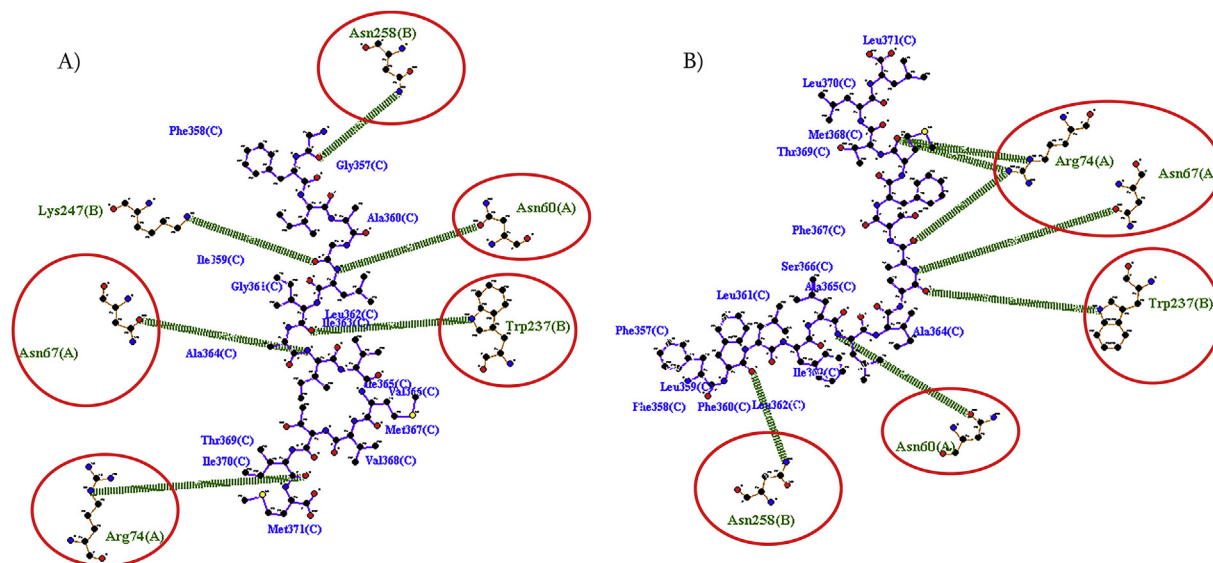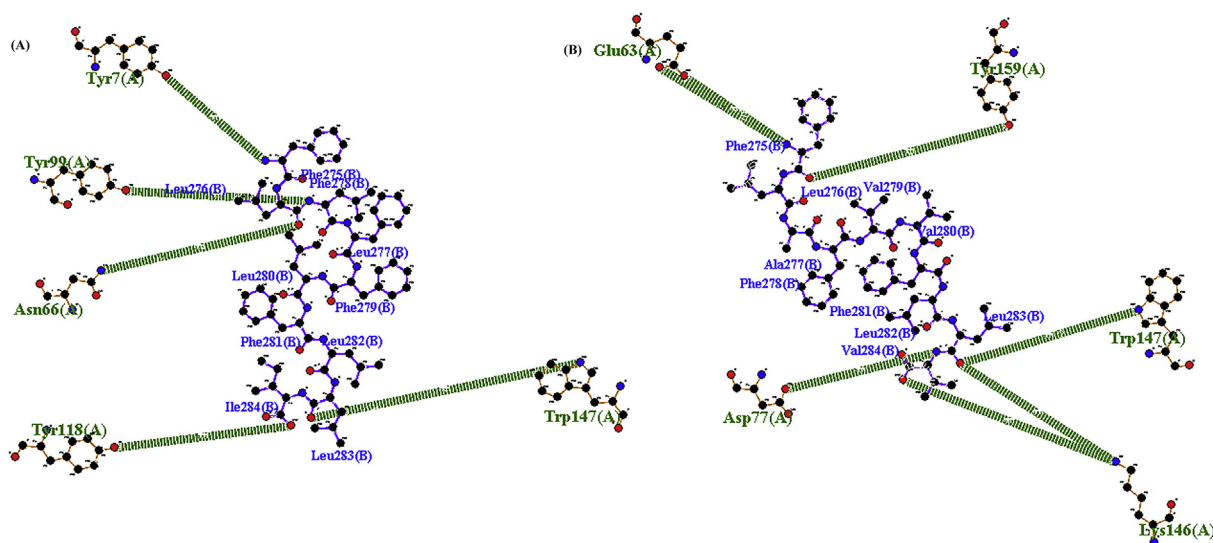We also recommend that further clinical trials should assess the

Fig. 2. The hydrogen bonds (green color) between the HLA-A (A) and HLA-DR (B) amino acids and homologous peptides: surface glycoproteins (left) and ABCA3 (right). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Fig. 3. The hydrogen bonds (green color) between the HLA-A amino acids and homologous peptides: envelope proteins (left) and ABCA3 (right). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
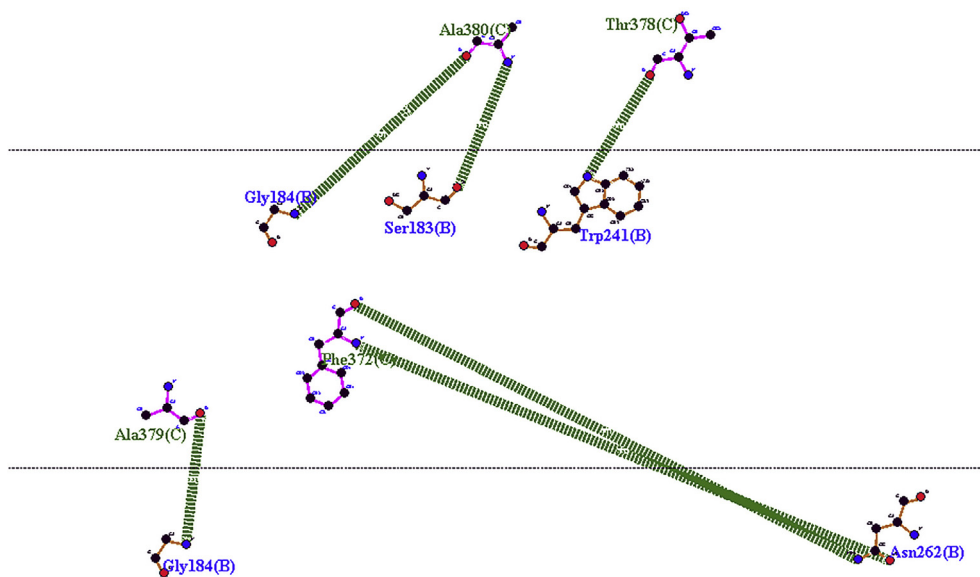
Fig. 4. The hydrogen bonds (green color) between the HLA-DP amino acids and homologous peptides: envelope proteins (left) and ABCA3 (right). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

effect of drugs potentiating the effect of ABCA3 like the cystic fibrosis transmembrane conductance regulator e.g. ivacaftor and genistein [34].

Another interesting result is the homologous peptides between *NKX2-1* and surface glycoproteins. NK2 homeobox 1 is a transcription factor that is expressed in the early development of the lung and thyroid gland [35]. It is also involved in the synthesis of the surfactant proteins A, B, and C [35]. Furthermore, it was found that it regulates the expression of ABCA3 proteins, thus, *NKX2-1* is required for the normal structure of surfactant which is important for the alveolar function and lowering the alveoli surface tension [27]. Furthermore, the surfactant is considered as the innate immunity in the lung as well as antibacterial properties [27]. The *NKX2-1* defects have a wide variety of respiratory symptoms including respiratory distress, pneumonia, asthma, recurrent

pneumothorax, lung fibrosis, or respiratory insufficiency [36,37]. These symptoms are similar to those developed by SARS-COV-2 that was reported by a recent Chinese cohort [38]. The symptoms may be evident since birth or appear at an older age [36]. In the current study, we found that surface glycoproteins share antigenic epitopes with SARS-COV-2 causing an autoimmune response that may cause respiratory symptoms similar to mutation of *NKX2-1*. The antigenic epitopes were linked to HLA-A*26:01, HLA-DQA1*05:01/DQB1*03:01, HLA-A*68:01, HLA-DRB1*04:01. Again, this might explain why specific populations get severe symptoms.

5. Limitation

The findings in this study must be supported through further experimental and clinical studies.

6. Conclusion

The envelope and surface glycoproteins have high similarity to ABCA3 protein which is important for the prevention of alveolar collapse and respiratory failure. Both share antigenic epitopes to HLA-A*02:03, HLA-DQA1*05:01/DQB1*03:01, HLA-DPA1*03:01/DPB1*04:02, HLA-A*02:01 which indicates the high risk of respiratory failure in population with these MHC polymorphisms. Another striking homology was between the Surface glycoproteins and NKX2-1 which explains how the SARS-COV-2 causes acute respiratory failure.

Funding

None.

Author contribution

Formulation of the idea: Sara Morsy and Ahmed Morsy.
Analysis: Sara Morsy.
Writing: Sara Morsy and Ahmed Morsy.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmgm.2021.107836.

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