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ORIGINAL ARTICLE

Immunoinformatics prediction of potential immunodominant epitopes from human coronaviruses and association with autoimmunity

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Abstract

Cross-reactivity between different human coronaviruses (HCoVs) might contribute to COVID-19 outcomes. Here, we aimed to predict conserved peptides among different HCoVs that could elicit cross-reacting B cell and T cell responses. Three hundred fifty-one full-genome sequences of HCoVs, including SARS-CoV-2 (51), SARS-CoV-1 (50), MERS-CoV (50), and common cold species OC43 (50), NL63 (50), 229E (50), and HKU1 (50) were downloaded aligned using Geneious Prime 20.20. Identification of epitopes in the conserved regions of HCoVs was carried out using the Immune Epitope Database (IEDB) to predict B- and T-cell epitopes. Further, we identified sequences that bind multiple common MHC and modeled the three-dimensional structures of the protein regions. The search yielded 73 linear and 35 discontinuous epitopes. A total of 16 B-cell and 19 T-cell epitopes were predicted through a comprehensive bioinformatic screening of conserved regions derived from HCoVs. The 16 potentially cross-reactive B-cell epitopes included 12 human proteins and four viral proteins among the linear epitopes. Likewise, we identified 19 potentially cross-reactive T-cell epitopes covering viral proteins. Interestingly, two conserved regions: LSFVSLAICFVIEQF (NSP2) and VVHSVNSLVSSMEVQSL (spike), contained several matches that were described epitopes for SARS-CoV. Most of the predicted B cells were buried within the SARS-CoV-2 protein regions' functional domains, whereas T-cell stretched close to the functional domains. Additionally, most SARS-CoV-2 predicted peptides (80%) bound to different HLA types associated with autoimmune diseases. We identified a set of potential B cell and T cell epitopes derived from the HCoVs that could contribute to different diseases manifestation, including autoimmune disorders.

Keywords Immunoinformatics · Coronavirus · B cell · T cell · Cross-reactivity · Auto-immune disease

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative pathogen of the coronavirus disease 2019 (COVID-19) pandemic, is a member of the family Coronaviridae (Lai et al. 2020). This single-stranded, positive-sense beta coronavirus is closely related to other lethal members of the human coronaviruses, including severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) (Pal et al. 2020). The genome of SARS-CoV-2 shares 79% and 50% sequence similarity to SARS-CoV-1 and MERS, respectively (Kiyotani et al. 2020). SARS-CoV-2 consists of four main protein components: spike (S), membrane (M), envelope (E), and nucleocapsid (N) (Satarker and Nampoothiri 2020). In addition to the high sequence similarity between SARS-CoV-1 and SARS-CoV-2, both follow the same viral entry mechanism by binding to the host's angiotensin-converting enzyme 2 (ACE2) receptors using S protein specifically (Davidson et al. 2020). Nevertheless, the antigenic epitopes of SARS-CoV-2 are poorly understood, with little information on which parts of SARS-CoV-2 trigger immune response.

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Given the high homology between SARS-CoV-2 and other coronaviruses, there is a high possibility of conserved antigenic epitopes (Grifoni et al. 2020a). Therefore, previous exposure to MERS, SARS, or seasonal human coronaviruses (i.e., 229E, NL63, OC43, and HKU1) may contribute to modulating immunity against SARS-CoV-2 infection, particularly B and T cell immune responses.

Notably, the antigenic burden from viral epitopes that do not induce protection could lead to adverse events, including autoimmune reactions or viral-induced enhanced diseases illness (Smatti et al. 2018; Yarmarkovich et al. 2020).

Since the start of the COVID-19 pandemic, multiple reports highlighted the possible relationship between SARS-CoV-2 infection and the autoimmunity. Several cases of autoimmunity have been reported following COVID-19, such as Kawasaki-like multisystem inflammatory syndrome in children (MIS-C), Guillain-Barré syndrome (GBS), autoimmune hemolytic anemia (AIHA), and systemic lupus erythematosus (Paul et al. 2020; Liu et al. 2021). Additionally, evidence suggested that some autoimmunity medications could have therapeutic effect in patients with severe COVID-19 (Esmaeilzadeh and Elahi 2021). It has been speculated that SARS-CoV-2 can disturb self-tolerance and induce autoimmunity mainly through the production of cross-reactive antibodies. Specifically, viral antigens that are structurally similar to self-antigens could activate B and T cells and lead to a cross-reactive response against both self- and non-self-antigens, a mechanism known as "molecular mimicry" (Kim et al. 2006). These antigens are known as mimotopes: pathogen's epitopes that mimic self-antigens, such as self B-cell epitopes and self T-cell epitopes (MHC) (Paul et al. 2020). As a consequence of exposing the immune system to these antigens, the immune tolerance can be disrupted, leading to the production of cross-reactive autoantibodies.

Antigenic mimicry between different viral and human proteins has been reported in large number of viral infections, such as herpes simplex virus (HSV)-induced stromal keratitis (Zhao et al. 1998), viral-induced diabetes (Coppieters et al. 2012), autoimmune myocarditis mediated by Coxsackie virus infection (Gauntt et al. 1995), Theiler's murine encephalomyelitis virus-induced demyelinating disease (TMEV-IDD) (Croxford et al. 2002), and several others (Getts et al. 2013). Similarity, in SARS-CoV-2, some epitopes were found to exhibit cross-reactivity with host antigens (Liu et al. 2021; Annand et al. 2020). Moreover, autoantibodies have been detected in patients with COVID-19. We had previously shown that strong and moderate antinuclear antibodies (ANA) levels are present in ICU COVID-19 compared to non-ICU cases (Fakhroo et al. 2021). Other reports have also shown the presence of ANA, anticytoplasmic neutrophil antibodies (ANCA), and antiantiphospholipid (APL) antibodies in COVID-19 patients (Pascolini et al. 2021). Importantly, the presence of autoantibodies was correlated with poorer COVID-19 prognosis.

Despite the currently available data, there is a critical need to understand the molecular basis of autoimmunity in SARS-CoV-2 infection, as well as the role of cross-reactive B and T cell responses in shaping SARS-CoV-2 outcomes. Here, we identified candidate conserved immune epitopes across the whole genome of different human coronaviruses through an immunoinformatics-based approach and propose the potential cross-reactive epitopes that elicit or attribute different diseases manifestation, especially autoimmune disorders.

Methods

Data retrieval and sequence alignment

A total of 351 full-length full-genome sequenced of human coronaviruses (including SARS-CoV-2 (Nguyen et al. 2020), SARS-CoV-1 (50), MERS-CoV (50), and common cold species OC43 (50), NL63 (50), 229E (50), HKU1 (50) were downloaded from Virus Pathogen Database and Analysis Resource (ViPR) (maximum length = 29,900 bp) and aligned using Geneious Prime 20.20 (https://www.geneious.com). All the sequences were aligned using the Clustal Omega 1.2.2. using Ktuple-distance matrix calculated using with cluster size 1000 iterations. Conserved protein fragments were identified using BioEdit with the following criteria: minimum length of 8 to 23 amino acids with 100% similarity (Olvera et al. 2020). We screened a discontinuous epitope containing one gap consistent with a previously published study (Olvera et al. 2020).

Prediction of potential B cell epitopes

Identification of epitopes in the conserved regions of human coronaviruses, including SARS-CoV-2, SARS-CoV-1, MERS-CoV, OC43, NL63, 229E, and HKU1, were carried out in the Immune-Epitope-Database And Analysis-Resource (IEDB) (Peters et al. 2005). The search criteria were as follows: "linear peptide; blast option: 90%; host: homo sapiens; any MHC restriction; positive assays only; all assays; any disease" (Olvera et al. 2020). Kolaskar and Tongaonkar antigenicity scale was used to predict the antigenicity score, and Bepipred linear epitope prediction 2.0 was used to predict antibody epitope prediction (Jepersen et al. 2017).

Prediction of potential T cell epitopes

To identify T cell epitopes in the conserved regions of human coronaviruses, including SARS-CoV-2, SARS-CoV-1, MERS-CoV, OC43, NL63, 229E, and HKU1, the Immune-Epitope-Database And Analysis-Resource (IEDB) was used (Peters et al. 2005). To identify the smallest peptide (MHC peptide) in an antigen that has the potential to generate immunogenicity and activate T-cell response, we used TepiTool (Paul et al. 2016), available at IEDB (Fleri et al. 2017). For predicting MHC class-I epitopes, the parameter for selecting predicted peptides was set as equal or less than 500 median inhibitory concentrations (IC50), while for MHC class-II epitope prediction, the same parameter was set to equal or less than 1000 nM IC50 (Paul et al. 2013; Wang et al. 2008). The prediction method used for this analysis was IEDB-recommended, Consensus, and NetMHCpan (version 2.8). Following the prediction of HLA alleles, we explored the clinical significance of these HLA alleles in previously reported studies as well as in the Genome-Wide Association Studies (GWAS) catalog. Additionally, the overall allelic frequencies of the identified HLA types were extracted from The Allele Frequency Net Database (2020).

Structural analysis of predicted epitopes

SWISS-MODEL server was used to generate a homology model of the protein structure to visualize the conserved epitopes in ORF1ab, spike, and ORF3a using NCBI Reference Sequence: YP_009725298.1 (Waterhouse et al. 2018). The surface confrontations of the potential functional domains and the positions of forecast predicted epitopes in their bound conformations were built using Pymol (DeLano 2002).

Results

Identification of conserved protein sequences across different coronaviruses

We evaluated the presence of protein fragments that are conserved across a wide range of members of the coronavirus family; the full-length consensus open reading frame from SARS-CoV-2 was aligned with other coronavirus sequences. The protein sequences of SARS-CoV-2 shared 108 conserved regions (ranging from 8 to 23 amino acids) that were also found in other coronaviruses, including SARS-CoV-1, MERS-CoV, OC43, NL63, 229E, and HKU1 in the sequence alignment. The search yielded 73 linear epitopes and 35 discontinuous epitopes. Among the linear epitopes, we observed amino acid sequence identity result confirmed a high similarity in ORF1ab which encodes 16 non-structural proteins (NSPs; 68.4%, 50/73), followed by the spike (29%, 21/73) and ORF3a that encodes ORF3 accessory protein (2.6%, 2/73) (Supplementary Tables 1 and 2). Of note, according to our search criteria, we noticed discontinuous epitopes only in the ORF1ab region.

Prediction of potential B-cell epitopes in the conserved regions

We next identified potential B cell epitopes in these conserved regions. We searched the IEDB for described B-cell epitopes similar (> 90% sequence identity) to the conserved peptides present in the SARS-CoV-2 consensus sequence. The IEDB analysis search yielded a total of 16 B-cell epitopes, out of which four epitopes were identified for other viruses, and the rest were similar to human epitopes (Table 1). The similar epitopes for other viruses, such as epitope LHRVEERCLLLP (NSP1), was found to be derived for enteroviruses (VP1), TLSLNELLISKLNDNVKRQLYG (spike region) was found to be derived for influenza virus H1N1 (HA), and epitope HNLLSLCRLQLLCFL (spike region) was found to be derived for human herpesvirus 4 (BMRF1). In addition, the majority of epitopes (9ofthe16) were similar to human ones. Similarity to human proteins included serine/threonine-protein kinase PLK4, exosome component 10, and protein-glutamine gamma-glutamyltransferase 2 (Table 1) (Serwas et al. 2019; Baharlooi et al. 2020). We also detected one conserved epitope ESATVLLII located at SARS-CoV-2 exonuclease, similar for parasite *Plasmodium falciparum* (ORF). Concerning antigenicity among the B cell epitopes, epitope HNLLSLCRLQLLCFL showed the highest score of 1.170 compared to other B-cell epitopes. The potential identified B-cell epitopes are represented in Figs. 1 and 2.

Prediction of potential T-cell epitopes in SARS-CoV-2

Similarly, we utilized the IEDB server to search for potential T cell epitopes in these conserved regions. We looked for peptides with 90% or more similarity to the conserved peptides present in CoVs. The search yielded a total of 19 T cell epitopes that were found to be similar from other viruses. Interestingly, two conserved epitopes: LSFVSLAICFVIEQF (NSP2) and VVHSVNSLVSSMEVQSL (spike region), contained several matches to epitopes of SARS-CoV (Table 2). Other similar epitopes were found to be similar to the following organisms (> 90% sequence identity); human coronavirus: 9, West Nile virus (genome polyprotein): 2, alpha papillomavirus 9 (regulatory protein E2): 2, influenza virus H1N1 (HA): 2, and human beta herpesvirus 6B (capsid protein): 6. Of note, the T-cell epitopes identified were not restricted only to the spike protein; instead, it was distributed

Table 1 B-cell epitopes predicted via IEDB analysis resource are shown along with their starting positions and antigenicity scores

S. no	Consensus sequence	Protein	Start position	Number of epitopes (blast > 90%)	Antigenicity score	Epitopes			
						SARS-CoV	Homo sapiens (Protein)	Other viruses (protein)	Other microorganisms (protein)
1	QETSNSSLFC	NSP1	315	2	1.002	-	Human (serine/threonine-protein kinase PLK4)	-	-
2	LHRVEERCLLLP	NSP1	801	1	1.085		–	Enteroviruses (VP1)	-
3	VYLEDKFDLL	Helicase	16,793	2	1.027	-	Human (Exosome Component 10)	-	-
4	ESATVLLII	nsp14A2-exonuclease	18,459	3	1.138	-	-	-	Plasmodium falciparum (ORF)
5	TLSLNELLISKLNDNVKRQLYG	Spike glycoprotein	23,587	1	1.035	-	-	H1N1 (HA)	-
6	HNLLSLCRLQLLCFL	Spike glycoprotein	25,133	3	1.170	-	-	Human herpesvirus 4 (BMRF1)	-
7	FLWIKIRVGQSAEFI	ORF3a	25,749	4	1.042	-	Human (Protein-glutamine gamma-glutamyltransferase 2)	-	-

across the whole SARS-CoV-2 proteins, including NSP2, RdRp, and ORF3a. Concerning immunogenicity among the T-cell epitopes, epitope NCPRAIAARQIEPA showed the highest score of 0.43328 compared to other T-cell epitopes (Table 2). The potential T-cell epitopes identified are represented in Figs. 1 and 2.

Structural analysis of B cell and T cell epitopes SARS-CoV-2 protein

Structural analysis of the predicted B cell and T cell epitopes was mapped on SARS-CoV-2 protein structure highlighted with functional domains (Figs. 1 and 2). Based on the NSP1 structure, both B/T cells epitopes ($n=2$) were buried within the functional domain (3–809 AA). Likewise, the conserved B cell epitope identified at exonuclease and ORF3a mapped within the respective functional domains located at 18,351–18,650 AA and 25,555 to 25,751 AA (Fig. 2). Besides, those epitopes lying close to the functional domains were mostly T cell epitopes. More specifically, the T cell epitope in the NSP2 region, RdRp, and spike stretched close to the functional domains located at 1253–1310 AA, 15,675–15,879 AA, and 23,326 to 23,559 AA, respectively (Figs. 1 and 2). Only one B cell epitope in the helicase region mapped far from the functional domain located at 12,953 to 13,765.

Binding of SARS-CoV-2 conserved peptides to HLA alleles

Human leukocyte antigen (HLA) plays a major role in initiating cellular immune responses. Therefore, it is important to investigate the peptides that can bind to HLA alleles and elicit a strong immune response. The 12 conserved epitopes, which were identified as B or T cells epitopes were further analyzed for the binding ability to HLA using IEDB EpiTool. Considering that all sequences were less than 15 AA in length, and HLA II prediction requires peptides of at least 15 AA, the analysis was only performed for HLA class I types. Moreover, we investigated the diseases associated with each predicted HLA type. As shown in Table 3, the resultant peptides were predicted to bind to different HLA types (A, B, and C), with the most enriched binding observed with HLA-A. Notably, the majority of SARS-CoV-2 predicted peptides (80%) bind to different HLA types associated with autoimmune diseases and/or hyper-inflammatory conditions, such as multiple sclerosis (MS), ankylosing spondylitis, polyglandular autoimmune syndrome (PGA), systemic lupus erythematosus (SLE), type 1 diabetes (T1D, autoimmune vitiligo, etc. The binding affinity (IC50) ranges from 5.63 to 498.29 (i.e., high to low affinity) (Table 3). In addition to autoimmune conditions, 70% of SARS-CoV-2 predicted peptides bind to HLA

Table 2 T-cell epitopes predicted via IEDB analysis resource are shown along with their starting positions and immunogenicity scores

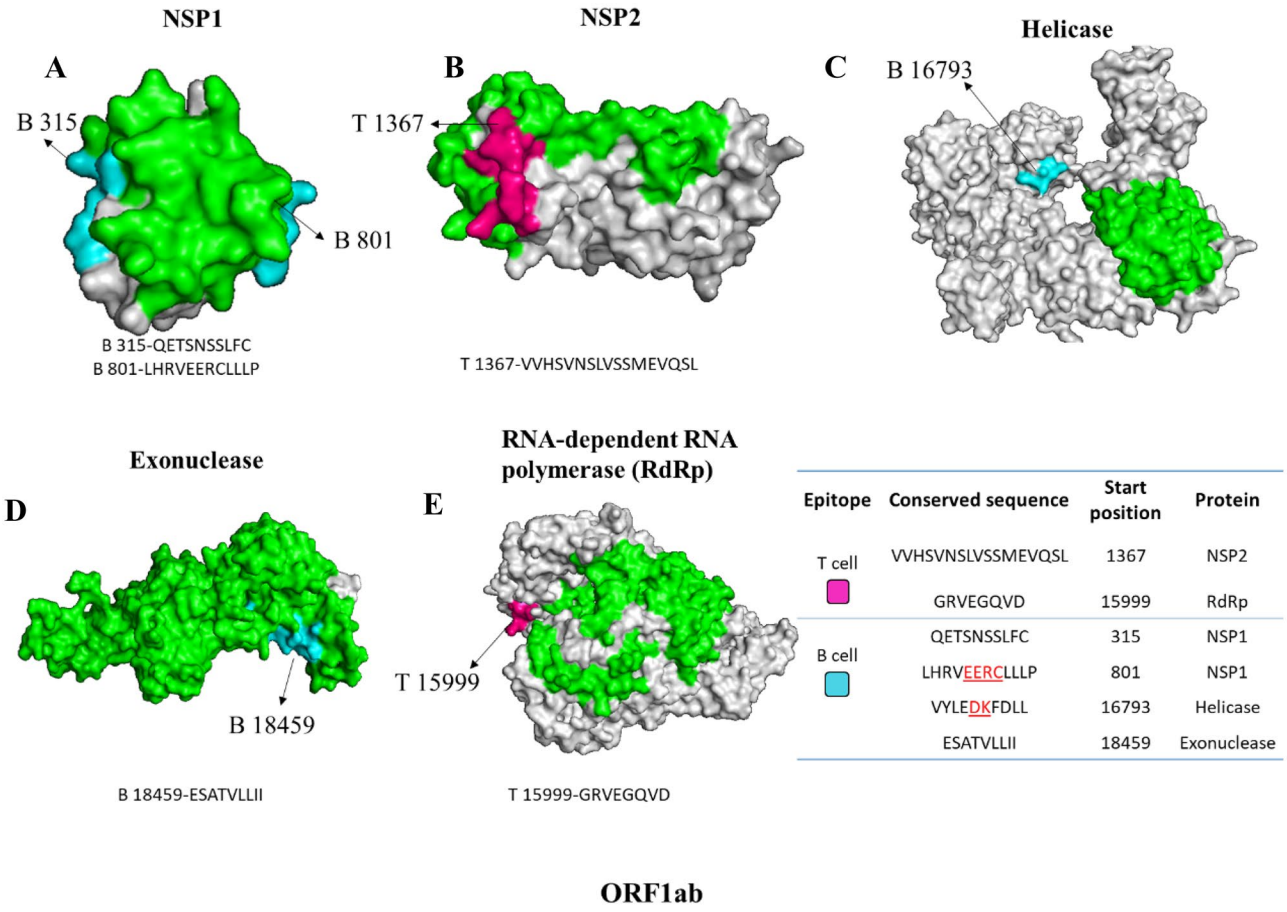
S. no	Consensus sequence	Protein	Start position	Number of epitopes (blast > 90%)	Immunogenicity score	Epitopes			
						SARS-CoV	Homo sapiens Protein	Other viruses (protein)	Other microorganisms (protein)
1	VVHSVNSLVSSMEVQSL	NSP2	1367	4	−0.80503	SARS	-	West Nile virus (genome polyprotein)	-
2	GRVEGQVD	RNA-dependent RNA polymerase	15,999	2	0.07295	-	-	Alpha papillomavirus 9 (regulatory protein E2)	-
3	LSFVSLAICFVIEQF	Spike glycoprotein	23,555	7	0.31914	HKU1 (orf1ab), OC43 (RNA-dependent RNA polymerase), 229E (orf1ab polyprotein), NL63 (orf1ab polyprotein), SARS-CoV2 (orf1ab polyprotein), SARS-CoV1 (orf1ab polyprotein)	-		-
4	TLSLNELLISKLNDNVKRQLYG	Spike glycoprotein	23,587	4	−0.47852	-	-	H1N1 (HA), human herpesvirus 6B (capsid protein)	-
5	NCPRAIAARQIEPA	ORF3a	25,562	2	0.43328	-	-	Human betaherpesvirus 6B (capsid protein)	-

types associated with other viral infections, including HIV-1 and chickenpox susceptibility, and 40% bind to HLA alleles associated with drug-induced illnesses (Table 3). In parallel, IEDB EpiTool analysis was also performed to predict the binding of all identified 73 linear epitopes to HLA class I molecules (Supplementary Table 3). According to Fig. 3, 68.49% of conserved SARS-CoV-2 peptides (50/73) were shown to bind to HLA-A, B, and C alleles.

Discussion

In spite of the high sequence homology between different coronaviruses, little is known about the conserved epitopes and their impact on modulating the host response to infection. Additionally, it is important to understand the role of conserved T and B cell epitopes between SARS-CoV-2 and other coronaviruses in disease protection or pathogenesis. Several recent studies evidenced the relationship between SARS-CoV-2 and autoimmune conditions; yet, the molecular mechanisms are largely unknown. Through bioinformatics screening of a total of 351 full-length human coronaviruses genome sequences, here, we report a number of cross-reactive B- and T-cell epitopes that could modulate the immune response and mainly lead to autoimmunity.

Our analysis resulted in the identification of 108 conserved regions (73linear, 35discontinuous) among different coronaviruses, of which, 16 were B-cell and 19 T-cell immunogenic epitopes, that could be implicated in cross-reactivity and/or autoimmunity. Interestingly, these epitopes were not limited to the spike protein only, as they were identified in both structural and non-structural SARS-CoV-2 proteins. Among the predicted B-cell epitopes, four were potentially cross-reactive with different viruses, such as human herpesvirus 4 and H1N1. This suggests that preexisting immunity to other viruses may contribute to the immune response against SARS-CoV-2, ranging from providing protection to enhanced disease illness. In addition to viruses' cross-reactivity, some of the B-cell epitopes are homologous to that of human proteins (blast > 90%), including serine/threonine-protein kinase PLK4 (QETSNSSLFC), exosome component 10 (VYLEDKFDLL), and protein-glutamine

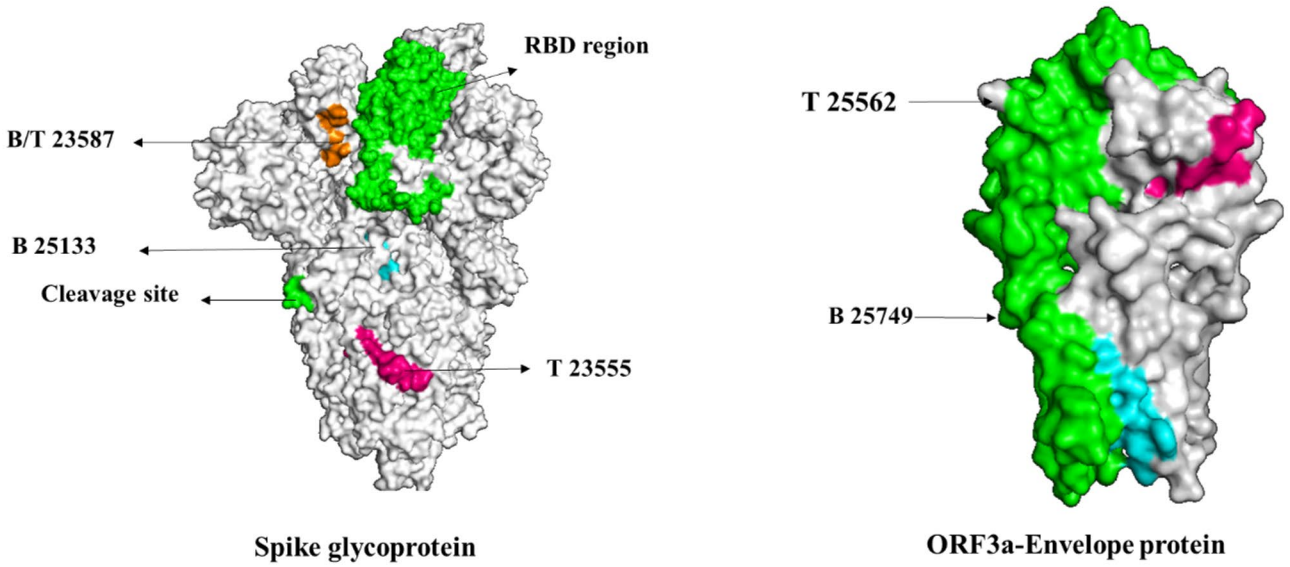


Epitope	Conserved sequence	Start position	Protein
T cell	VVHSVNSLVSSMEVQSL	1367	NSP2
	GRVEGQVD	15999	RdRp
B cell	QETSNSSLFC	315	NSP1
	LHRVEERCLLLP	801	NSP1
	VYLEDKFDLL	16793	Helicase
	ESATVLLII	18459	Exonuclease

Fig. 1 Schematic of modeled SARS-CoV-2 ORF1ab CoV-2 protein regions highlighted B cell (cyan) and T cell epitopes (pink) represented as surface structure (gray). Potential functional domains are mapped as green color. Pymol was utilized to visualize the positions of forecast epitopes on the 3D structure. **A** NSP1 region representing predicted B-cell epitopes (cyan) located at position 315 and 801. **B** NSP2 region representing predicted T cell epitope (pink) at position 1367. **C** Helicase region representing predicted B cell epitope (cyan) at position 16,793. **D** Exonuclease region denotes predicted B-cell epitope (cyan) at position 18,459. **E** RDRP region denotes T cell epitopes (pink) at position 15,999. The table to the right denotes list of predicted B cell and T cell epitopes and their start position. Residues underlined and colored in red denotes specific residues that are predicted to elicit antibody response by using Bepipred linear epitope prediction 2.0

gamma-glutamyltransferase 2 (FLWIKIRVGQSAEFI). This could partially explain the autoimmunity disorders seen in COVID-19 patients as a result of molecular mimicry. Due to the similarity between viral and host antigens, the immune response fails to recognize self from non-self-antigens (Rodríguez et al. 2020). A recent study has identified shared antigenic epitopes between human molecular chaperons and SARS-CoV-2, with a potential role of inducing autoimmunity against endothelial cells using molecular mimicry (Marino et al. 2020). Similarly, it has been proposed that brainstem-related respiratory failure in COVID-19 patients may take place as a result of molecular mimicry between SARS-CoV-2 and neuronal proteins (Lucchese and Flöel 2020). In fact, sequence homology has been identified between three SARS-CoV-2 amino acid sequences (GSQASS, LNEVAK, and SAAEAS) and three proteins, specifically DAB1, AIFM, and SURF1 that are part of the respiratory pacemaker in the brainstem (preBötC). Therefore, immunological responses against DAB1, AIFM, and SURF1 may potentially contribute to neurological-related respiratory complications observed in COVID-19 (Lucchese and Flöel 2020). Several other studies have also reported potential cross-reactivity between SARS-CoV-2 and the human proteome, suggesting the possibility that SARS-CoV-2 could induce cross-reactivity with host autoantigens and lead to various clinical manifestations and autoimmune diseases (Venkatakrishnan et al. 2020; Kanduc 2020).

In terms of T-cell immunity, 9 out of 19 conserved SARS-CoV T cell epitopes were matching T cell epitopes in repose to other viruses, indicating that these regions are immunogenic in humans, supporting that some degree of



Epitope	Conserved sequence	Start position	Protein
B/T cell	TLSLNELLISKLNDNVKRQLYG	23587	Spike
T cell	LSFVSLAICFVIEQF	23555	Spike
	NCPRAIAARQIEPA	25562	ORF3a
B cell	HNLLSLCRLQLLCFL	25133	Spike
	FLWIKIRVGQSAEFI	25749	ORF3a

Fig. 2 Schematic of modeled SARS-CoV-2 spike and ORF3 proteins (gray) highlighted B cell (cyan) and T cell epitopes (pink) represented as surface structure (gray). Potential receptor-binding region (RBD) and cleavage site are mapped as green color. Pymol was utilized to visualize the positions of forecast epitopes on the 3D structure. **A** The 3D structure denotes site of both B cell and T cell in SARS-CoV-2 spike protein trimer at position 23,587 (orange color), site of B cell epitopes predicted in SARS-CoV-2 spike protein trimer at position 25,133 (cyan), and site of T cell epitopes predicted in SARS-CoV-2 spike protein trimer at position 23,555 (pink). The table below the spike protein denotes list of predicted B cell and T cell epitopes and their start position. Residues underlined and colored in red denotes specific residues that are predicted to elicit antibody response by using Bepipred linear epitope prediction 2.0. **B** The 3D structure denotes site of B cell epitope (cyan) predicted in ORF3a-envelope protein at position 25,749 and site of T cell epitopes (pink) predicted at position 25,562. Bepipred Linear Epitope Prediction 2.0 tool was used to predict antibody epitopes (red color) in the B cell epitopes. The table below the spike protein denotes list of predicted B cell and T cell epitopes and their start position. Residues underlined and colored in red denotes specific residues that are predicted to elicit antibody response by using Bepipred linear epitope prediction 2.0

cross-reactivity among coronavirus can be expected (Grifoni et al. 2020b; Braun et al. 2020). Pre-COVID-19 pandemic data analysis indicated that most individuals have hCoV-reactive antibodies, upon which 20% showed antibodies that were cross-reactive with SARS-CoV-2 spike and nucleocapsid proteins (2020). In spite of the non-neutralizing and unprotective nature of these antibodies, they were boosted upon SARS-CoV-2 infection (Anderson et al. 2020). Thereby, this reinforces the possibility of cross-reactivity between different coronaviruses, particularly in terms of memory B-cell immunity and antibody production.

The IEDB analysis revealed SARS-CoV-2 68.49% of conserved SARS-CoV-2 peptides (50/73) were shown to bind to HLA class I molecules (HLA A, B, and C) with variable affinity, possibly inducing CD8 + and CD4 + T-cell responses (Anderson et al. 2020). The majority of HLA types were associated with autoimmune diseases and hyper-inflammatory conditions, such as MS, ankylosing spondylitis, PGA, SLE, T1D, and autoimmune vitiligo. This, again, highlights the potential association between COVID-19 and autoimmunity. The development of autoimmune condition following SARS-CoV-2 infection has been reported in multiple studies. For instance, cold agglutinin syndrome (CAS) and autoimmune hemolytic anemia have been linked to COVID-19 (Jensen et al. 2020; Patil et al. 2020). Moreover, a case of systemic lupus erythematosus has been reported to

Table 3 Predicted SARS-CoV-2 conserved peptides binding to HLA-A, HLA-B, and HLA-C gene alleles using IEDB EpiTool are shown along with the diseases associated with each HLA type

No	Consensus peptide	Peptide start	Peptide end	Predicted peptide	Affinity (IC50)	Allele	Allele frequency	Genome-wide associations trait	Reported diseases
1	QETSNSSLFC	1	9	QETSNSSLF	460.08	HLA-B*18:01	0.03814	-	Subacute thyroiditis Type 1 diabetes
		1	9	QETSNSSLF	252.35	HLA-B*40:01	0.04177	-	Ankylosing spondylitis
		1	9	QETSNSSLF	44.62	HLA-B*44:02	0.05243	Susceptibility to chickenpox	Multiple sclerosis (MS)
		1	9	QETSNSSLF	56.39	HLA-B*44:03	0.04972	-	Stevens-Johnson syndrome with severe ocular surface complications
2	LHRVEERCLLLP	2	10	HRVEERCLL	270.41	HLA-B*27:05	0.02240	Drug-induced agranulocytosis HIV-1 infection Drug-induced agranulocytosis	Autoimmune spondyloarthropathies
		2	10	HRVEERCLL	143.39	HLA-B*39:01	0.01011	Drug induced agranulocytosis	Drug-induced agranulocytosis Type 1 diabetes
		2	10	HRVEERCLL	450.46	HLA-C*06:02	0.08359	Drug-induced liver injury Set-point viral load in HIV-1 infection	Chronic/recurrent tonsillitis Psoriasis Celiac disease
		2	10	HRVEERCLL	468.52	HLA-C*07:01	0.12235	HIV-1 infection Neuromyelitis optica Beta-2 microglubulin plasma levels	-
		3	11	RVEERCLLL	498.29	HLA-C*15:02	0.02997	-	-
3	VYLEDKFDLL	2	10	YLEDKFDLL	24.63	HLA-A*02:01	0.19256	Beta-2 microglubulin plasma levels Susceptibility to chickenpox	Polyglandular autoimmune (PGA) syndrome Drug-induced maculopapular exanthema Autoimmune vitiligo Ankylosing spondylitis Multiple sclerosis

Table 3 (continued)

No	Consensus peptide	Peptide start	Peptide end	Predicted peptide	Affinity (IC50)	Allele	Allele frequency	Genome-wide associations trait	Reported diseases
		2	10	YLEDKFDLL	40.7	HLA-A*02:06	0.01365	-	Juvenile idiopathic arthritis Stevens-Johnson syndrome
		1	9	VYLEDKFDL	179.6	HLA-A*23:01		-	
		1	9	VYLEDKFDL	331.25	HLA-A*24:02	0.10000	-	Buerger's disease Type 1 diabetes Systemic lupus erythematosus (SLE)
		2	10	YLEDKFDLL	91.61	HLA-C*05:01	0.05914	Susceptibility to chickenpox	
		2	10	YLEDKFDLL	338.53	HLA-C*08:02	-	HIV-1 infection	Lassa virus infection
		1	9	VYLEDKFDL	251.74	HLA-C*14:02	0.01949	-	
		2	10	YLEDKFDLL	199.46	HLA-C*17:01	0.01958	-	
4	ESATVLLII	1	9	ESATVLLII	42.42	HLA-A*68:02	0.01941	-	Drug-induced maculopapular exanthema HIV-specific CD8 + T-cell responses
5	TLSLNELLISKLNDNVKRQLYG	8	16	LISKLNDNV	420.32	HLA-A*02:06	0.01365	-	Juvenile idiopathic arthritis Stevens-Johnson syndrome
		3	11	SLNELLISK	33.53	HLA-A*03:01	0.09323	Beta-2 microglubulin plasma levels	Maculopapular eruption (MPE)
		3	11	SLNELLISK	19.38	HLA-A*11:01	0.07281	Frontal fibrosing alopecia	HIV Epstein-Barr Hepatitis B
		3	11	SLNELLISK	415.33	HLA-A*30:01	0.02466	-	Hepatitis C
		9	17	ISKLNDNVK	137.84	HLA-A*30:01	0.02466	-	Takayasu arteritis (TA)
		8	16	LISKLNDNV	428.46	HLA-A*68:02	0.01941		Drug-induced maculopapular exanthema HIV-specific CD8 + T-cell responses

Table 3 (continued)

No	Consensus peptide	Peptide start	Peptide end	Predicted peptide	Affinity (IC50)	Allele	Allele frequency	Genome-wide associations trait	Reported diseases
6	HNLLSLCRLQLLCFL	3	11	LLSLCRLQL	201.47	HLA-A*02:01	0.19256	Beta-2 microglubulin plasma levels Susceptibility to chickenpox	Polyglandular autoimmune (PGA) syndrome Drug-induced maculopapular exanthema Autoimmune vitiligo Ankylosing spondylitis Multiple sclerosis
		4	12	LSLCRLQLL	405.03	HLA-B*08:01	0.06554	Primary sclerosing cholangitis Neuromyelitis optica Drug-induced agranulocytosis Beta-2 microglobulin plasma levels HIV-1 infection	Early-onset myasthenia gravis
		7	15	CRLQLLCFL	48.97	HLA-B*27:05		Drug-induced agranulocytosis HIV-1 infection Drug-induced agranulocytosis	Autoimmune spondyloarthropathies
		4	12	LSLCRLQLL	402.51	HLA-B*58:01	0.02326	-	Cutaneous adverse reactions (SCAR) Drug-induced severe cutaneous adverse drug reactions
		4	12	LSLCRLQLL	151.81	HLA-C*15:02	0.02997	-	-
		4	12	LSLCRLQLL	87.28	HLA-C*16:01	0.04129	-	-
7	FLWIKIRVGQSAEFI	5	13	KIRVGQSAE	414.73	HLA-A*30:01	0.02466	-	Takayasu arteritis (TA)
		6	14	IRVGQSAEF	213.2	HLA-C*07:02	0.12441	Drug-induced liver injury HIV-1 infection	-
8	VVHSVNSLVSSMEVQSL	4	12	SVNSLVSSM	280.83	HLA-A*26:01	0.03199	-	Behçet's disease Idiopathic hypoparathyroidism
		1	9	VVHSVNSLV	318.74	HLA-A*30:01	0.02466	-	Takayasu arteritis (TA)

Table 3 (continued)

No	Consensus peptide	Peptide start	Peptide end	Predicted peptide	Affinity (IC50)	Allele	Allele frequency	Genome-wide associations trait	Reported diseases
		1	9	VVHSVNSLV	49.79	HLA-A*68:02	0.01941	-	Drug-induced maculopapular exanthema HIV-specific CD8 + T-cell responses
		6	14	NSLVSSMEV	241.13	HLA-A*68:02	0.01941	-	Drug-induced maculopapular exanthema HIV-specific CD8 + T-cell responses
		4	12	SVNSLVSSM	88.71	HLA-B*15:01	0.03966	Beta-2 microglubulin plasma levels	COVID-19 Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) Skin hypersensitivity reactions
		4	12	SVNSLVSSM	187.89	HLA-B*15:02		-	Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)
		4	12	SVNSLVSSM	61.06	HLA-B*15:25	0.00156	-	-
		4	12	SVNSLVSSM	254.3	HLA-C*02:02	-	HIV-1 infection	Multiple myeloma (MM)
		4	12	SVNSLVSSM	254.3	HLA-C*02:09	-	-	-
		9	17	VSSMEVQSL	205.47	HLA-C*03:02	0.01493	-	-
		4	12	SVNSLVSSM	38.8	HLA-C*03:02	0.01493	-	-
		9	17	VSSMEVQSL	76.86	HLA-C*03:03	0.04178	Beta-2 microglubulin plasma levels	Multiple myeloma (MM)
		4	12	SVNSLVSSM	139.82	HLA-C*03:03	0.04178	Beta-2 microglubulin plasma levels	Multiple myeloma (MM)
		9	17	VSSMEVQSL	76.86	HLA-C*03:04	0.06755	Beta-2 microglubulin plasma levels	
		4	12	SVNSLVSSM	139.82	HLA-C*03:04	0.06755	Beta-2 microglubulin plasma levels	
		4	12	SVNSLVSSM	123.67	HLA-C*12:02	0.01678	HIV-1 infection	Late-onset type of psoriasis

Table 3 (continued)

No	Consensus peptide	Peptide start	Peptide end	Predicted peptide	Affinity (IC50)	Allele	Allele frequency	Genome-wide associations trait	Reported diseases
		9	17	VSSMEVQSL	339.4	HLA-C*12:03	0.03938		Ulcerative colitis Psoriasis
		4	12	SVNSLVSSM	78.19	HLA-C*12:03	0.03938	-	Ulcerative colitis Psoriasis
		6	14	NSLVSSMEV	351.23	HLA-C*12:03	0.03938	-	Ulcerative colitis Psoriasis
		4	12	SVNSLVSSM	189.06	HLA-C*14:02	0.01949	-	-
		1	9	VVHSVNSLV	362.97	HLA-C*15:02	-	-	-
		6	14	NSLVSSMEV	225.79	HLA-C*15:02	-	-	-
		9	17	VSSMEVQSL	38.25	HLA-C*16:01	-	-	-
		4	12	SVNSLVSSM	106.27	HLA-C*16:01	-	-	-
		6	14	NSLVSSMEV	126.16	HLA-C*16:01	-	-	-
9	LSFVSLAICFVIEQF	3	11	FVSLAICFV	12.69	HLA-A*02:01	0.19256	Beta-2 microglubulin plasma levels Susceptibility to chickenpox	Polyglandular autoimmune (PGA) syndrome Drug-induced maculopapular exanthema Autoimmune vitiligo Ankylosing spondylitis Multiple sclerosis
		4	12	VSLAICFVI	337.73	HLA-A*02:06	0.01365	-	Juvenile idiopathic arthritis Stevens-Johnson syndrome
		3	11	FVSLAICFV	5.63	HLA-A*02:06	0.01365	-	Juvenile idiopathic arthritis Stevens-Johnson syndrome
		2	10	SFVSLAICF	108.65	HLA-A*23:01		-	
		2	10	SFVSLAICF	469.32	HLA-A*24:02	0.10000	-	Buerger's disease Type 1 diabetes Systemic lupus erythematosus (SLE)
		2	10	SFVSLAICF	320.76	HLA-A*29:02	0.02847	Birdshot chorioretinopathy	Inflammatory eye disease maculopapular eruption (MPE)

Table 3 (continued)

No	Consensus peptide	Peptide start	Peptide end	Predicted peptide	Affinity (IC50)	Allele	Allele frequency	Genome-wide associations trait	Reported diseases
		4	12	VSLAICFVI	480.58	HLA-A*32:01	0.02784	-	Drug reaction with eosinophilia and systemic symptoms (DRESS)
		3	11	FVSLAICFV	8.46	HLA-A*68:02	0.01941	-	Drug-induced maculopapular exanthema HIV-specific CD8 + T-cell responses
		4	12	VSLAICFVI	482.12	HLA-B*57:01		Drug-induced liver injury HIV-1 infection Beta-2 microglobulin plasma levels	Hypersensitivity reaction
		4	12	VSLAICFVI	105.44	HLA-B*58:01		-	Cutaneous adverse reactions (SCAR) Drug-indued severe cutaneous adverse drug reactions
		3	11	FVSLAICFV	474.22	HLA-C*12:02	0.01678	-	Ulcerative colitis Psoriasis
		3	11	FVSLAICFV	210.96	HLA-C*12:03	0.03938	-	Ulcerative colitis Psoriasis
		2	10	SFVSLAICF	114.45	HLA-C*14:02	0.01949	-	-
11	NCPRAIAARQIEPA	1	9	NCPRAIAAR	461	HLA-A*33:03	0.02965	-	Drug-induced liver injury Stevens-Johnson Syndrome or epidermal necrolysis Persistent HBV infection

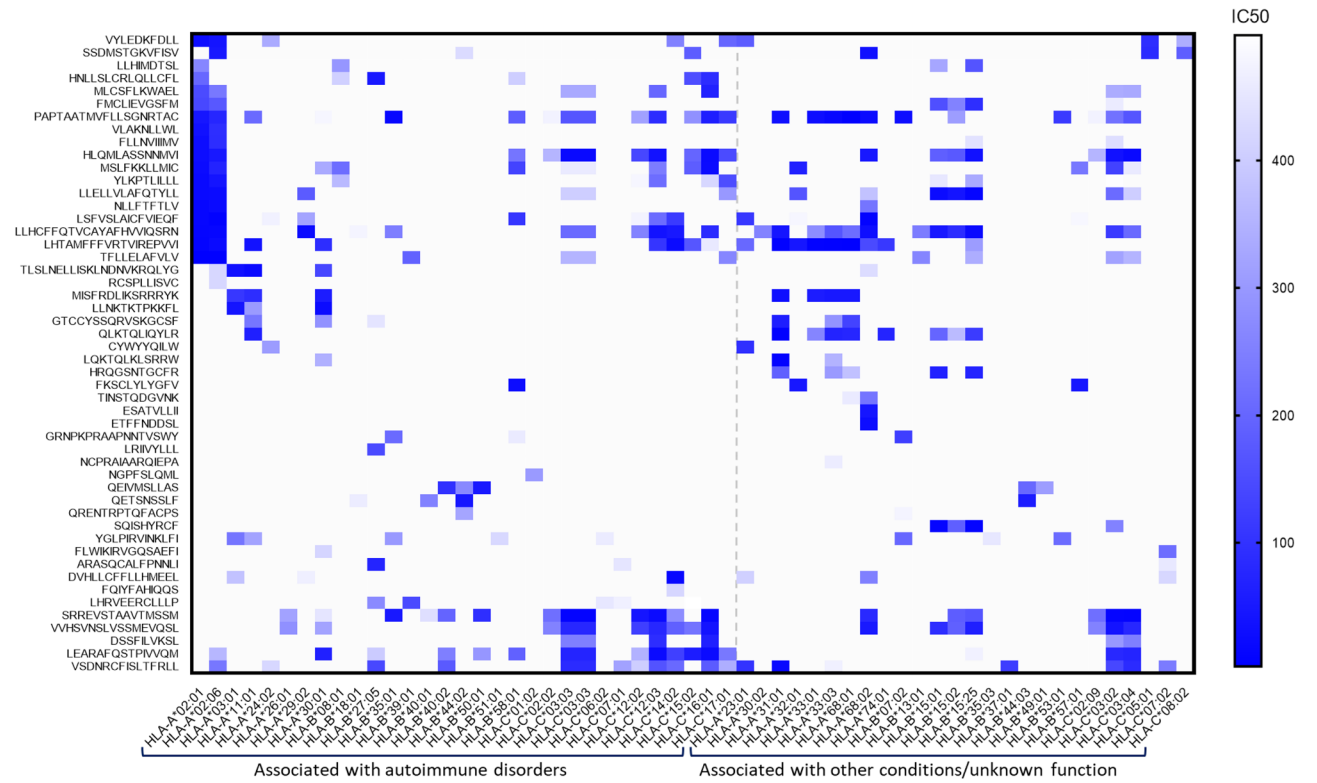


Fig. 3 Heat map plot sowing the binding of 50 conserved SARS-CoV-2 epitopes to HLA different variants. IEDB EpiTool analysis was performed for all 73 identified linear epitopes to predict binding to HLA class I molecules, out of which, 50 epitopes bind to HLA-A, B, and C gene variants. Each row indicates an epitope's sequence, and each column indicates a different HLA variant. The color gradient for each cell of the heatmap plot represents the affinity, which inversely correlates with the IC50 value

be induced by SARS-CoV-2 infection (Shayestehpour and Zamani 2020). Guillain-Barré syndrome (GBS), another autoimmune disorder, has been also associated with SARS-CoV-2 infection (Finsterer et al. 2021). Most importantly, this area of research is still growing and more COVID-19 associated autoimmune diseases might be identified in future studies.

Previous studies have linked autoimmune conditions to other viruses. An interaction has been observed between anti-EBV (Epstein-Barr Virus) antibodies and HLA-DRB1*15 increasing the risk for MS (Sundqvist et al. 2012). Additionally, a strong connection has been established between HLA-DRB1*1301 (a marker for pediatric autoimmune hepatitis) and protracted forms of HAV (hepatitis A virus) infection (Fainboim et al. 2001). In terms of SARS-CoV-2, the immunogenic symptoms observed in COVID-19 patients are relatively similar to those observed in autoimmune conditions (Rodríguez et al. 2020). One of these main immunological impacts is the cytokine storm; which was shown to be the leading cause of death in COVID-19 through inducing acute respiratory distress syndrome (ARDS) (Rodríguez et al. 2020). Recent studies suggested a correlation between COVID-19 and an autoimmune conditions in kids, known as Kawasaki disease (Galeotti and Bayry 2020). A proposed mechanism (hypothesis) involves the role of TNF-α (Amirfakhryan 2020). Since children who are susceptible to KD exhibit genetically downregulated ACE2 receptor, SARS-CoV-2 infection will further downregulate ACE2 expression by TNF-α, leading to Kawasaki-like disease (Amirfakhryan 2020). Interestingly, 70% of SARS-CoV-2 predicted peptides bind to HLA types associated with other viral infections (e.g., HIV-1 and chickenpox susceptibility). This raises the questions of whether people previously exposed to either virus could have CD8 + and CD4 + T-cell responses against SARS-CoV-2. In addition, HLA polymorphism has been associated with several infectious diseases including COVID-19. An in silico study identified that HLA-B*46:01 variant accounts for susceptibility to COVID-19, whereas HLA-B*15:03 could provide cross-protective T-cell-based immunity against COVID-19 (Nguyen et al. 2020). In another study, HLA-A*01:01 variant was associated with high-risk groups of COVID-19,

while HLA-A*02:01 and HLA-A*03:01 were mainly found in the low-risk groups (Shkurnikov et al. 2020). According to our analysis, some of SARS-CoV-2 conserved epitopes were likely to bind to HLA-A*02:01 and HLA-A*03:01 molecules (i.e., protective variants), which may result in a potential protective role against COVID-19. However, none of the identified SARS-CoV-2 epitopes was shown to bind to HLA risk variants. Although our predictions were based on IEDB's HLA reference set that cover almost all populations, one of the limitations is that South American population is underestimated in the IEDB's database. Requena et al. have presented an updated datasets reporting HLA frequencies of South American populations and reported the identification of several novel candidate epitopes on SARS-CoV-2 proteins for South America specifically (Requena et al. 2020).

According to the structural analysis, the majority of the conserved T and B cell epitopes lay within the functional domain of SARS-CoV-2 proteins. In particular, B and T cell epitopes are localized in close proximity to the receptor-binding domain (RBD) of the spike protein. Since the B-cell epitope is right beneath the functional domain embedded inside the spike, this may trigger the production of protective antibodies that may potentially hinder or induce an allosteric effect on ACE2 binding (Galeotti and Bayry 2020). Similarly, B-cell epitopes were localized within the functional domains of NSP1, exonuclease, and ORF3, potentially inducing a similar antibody effect interfering with the viral proteins' function. On the other hand, the T-cell epitopes were found within the functional domain of NSP1, NSP2, RdRp, and spike (i.e., common in both structural and non-structural SARS-CoV-2 proteins). During response, viral infection, the CD4 +, and CD8 + T cell responses are induced against both structural and non-structural viral proteins (Nguyen et al. 2020). Also, the fact that these epitopes are conserved among different viruses suggests that T and B cell responses provide a broad protection. Although the limited data on the relationship between human coronavirus epitope abundance and immune response, previous reports on vaccinia virus data showed that early peptide antigens could generate CD8 + T-cell responses in contrast to antibody and CD4 + T-cell responses which targets later mRNA expression (Nguyen et al. 2020; Sette et al. 2009). In addition, the induction of memory T and B cells is plausible due to previous coronavirus infection leading to long-term protection against SARS-CoV-2 (Shkurnikov et al. 2020). Specifically, T follicular helper cells (TFH) may induce the production of neutralizing antibodies from memory B cells that can rapidly recognize and block the virus (Shkurnikov et al. 2020). However, this data emphasizes the importance of conducting further studies that experimentally look into the immunogenic effect of these identified conserved epitopes.

Conclusion

In summary, this study presents the identification of highly conserved epitopes among seasonal and zoonotic coronavirus, with their potential implication on development of autoimmune conditions. The description of these conserved target peptides and of the matching cross-reactive epitopes will aid in understanding SARS-CoV-2 pathogenesis and complications. However, these initial results are based on immunoinformatic prediction, and hence, it will be particularly encouraging to measure functional antibodies and immunogenic effect in multiple animal models.

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Declarations

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References

Amirfakhryan H (2020) Kawasaki-like disease in children with COVID-19: A hypothesis Med Hypotheses 143:110117

Anand P, Puranik A, Aravamudan M, Venkatakrishnan AJ, Soundararajan V (2020) SARS-CoV-2 strategically mimics proteolytic activation of human ENaC. Elife 9

Anderson EM, Goodwin EC, Verma A, Arevalo CP, Bolton MJ, Weirick ME et al (2020) Seasonal human coronavirus antibodies are boosted upon SARS-CoV-2 infection but not associated with protection. MedRxiv 11(06):20227215

Baharlooi H, Azimi M, Salehi Z, Izad M (2020) Mesenchymal stem cell-derived exosomes: a promising therapeutic ace card to address autoimmune diseases. Int J Stem Cells 13(1):13–23

Braun J, Loyal L, Frentsch M, Wendisch D, Georg P, Kurth F et al (2020) Presence of SARS-CoV-2-reactive T cells in COVID-19 patients and healthy donors. MedRxiv 04(17):20061440

Coppieters KT, Wiberg A, von Herrath MG (2012) Viral infections and molecular mimicry in type 1 diabetes. APMIS 120(12):941–949
Croxford JL, Olson JK, Miller SD (2002) Epitope spreading and molecular mimicry as triggers of autoimmunity in the Theiler's virus-induced demyelinating disease model of multiple sclerosis. Autoimmun Rev 1(5):251–260
Davidson AM, Wysocki J, Batlle D (2020) Interaction of SARS-CoV-2 and other coronavirus with ACE (angiotensin-converting enzyme)-2 as their main receptor. Hypertension 76(5):1339–1349
DeLano WL (2002) Pymol: An open-source molecular graphics tool. CCP4 Newslett Protein Crystallograph 40(1):82–92
Esmaeilzadeh A, Elahi R (2021) Immunobiology and immunotherapy of COVID-19: a clinically updated overview. J Cell Physiol 236(4):2519–2543
Fainboim L, Cañero Velasco MC, Marcos CY, Ciocca M, Roy A, Theiler G et al (2001) Protracted, but not acute, hepatitis A virus infection is strongly associated with HLA-DRB1*1301, a marker for pediatric autoimmune hepatitis. Hepatology 33(6):1512–1517
Fakhroo AD, Nasarallah GK, Khan T, Cyprian FS, Ali FA, Ata MMA et al (2021) Detection of autoimmune antibodies in severe but not in moderate or asymptomatic COVID-19 patients. MedRxiv 03(02):21252438
Finsterer J, Scorza FA, Fiorini AC (2021) SARS-CoV-2-associated Guillain-Barre syndrome in 62 patients. Eur J Neurol 28(1):e10–e12
Fleri W, Paul S, Dhanda SK, Mahajan S, Xu X, Peters B et al (2017) The immune epitope database and analysis resource in epitope discovery and synthetic vaccine design. Front Immunol 8:278
Galeotti C, Bayry J (2020) Autoimmune and inflammatory diseases following COVID-19. Nat Rev Rheumatol 16(8):413–414
Gauntt CJ, Arizpe HM, Higdon AL, Wood HJ, Bowers DF, Rozek MM et al (1995) Molecular mimicry, anti-coxsackievirus B3 neutralizing monoclonal antibodies, and myocarditis. J Immunol 154(6):2983–2995
Getts DR, Chastain EM, Terry RL, Miller SD (2013) Virus infection, antiviral immunity, and autoimmunity. Immunol Rev 255(1):197–209
Grifoni A, Sidney J, Zhang Y, Scheuermann RH, Peters B, Sette A (2020a) A sequence homology and bioinformatic approach can predict candidate targets for immune responses to SARS-CoV-2. Cell Host Microbe 27(4):671–80.e2
Grifoni A, Weiskopf D, Ramirez SI, Mateus J, Dan JM, Moderbacher CR et al (2020b) Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. Cell 181(7):1489–501.e15
Gonzalez-Galarza Faviel F, McCabe A, Santos Eduardo J Md, Jones J, Takeshita L, Ortega-Rivera Nestor D et al (2019) Allele frequency net database (AFND) 2020 update: gold-standard data classification, open access genotype data and new query tools. Nucleic Acids Res 48(D1):D783-D8
https://www.geneious.com
Jensen CE, Wilson S, Thombare A, Weiss S, Ma A (2020) Cold agglutinin syndrome as a complication of COVID-19 in two cases. Clin Infect Pract 7:100041
Jespersen MC, Peters B, Nielsen M, Marcatili P (2017) BepiPred-2.0: improving sequence-based B-cell epitope prediction using conformational epitopes. Nucleic Acids Res 45(W1):W24–W9
Kanduc D (2020) From anti-SARS-CoV-2 immune responses to COVID-19 via molecular mimicry. Antibodies (Basel) 9(3)
Kim B, Kaistha SD, Rouse BT (2006) Viruses and autoimmunity. Autoimmunity 39(1):71–77
Kiyotani K, Toyoshima Y, Nemoto K, Nakamura Y (2020) Bioinformatic prediction of potential T cell epitopes for SARS-Cov-2. J Hum Genet 65(7):569–575
Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR (2020) Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. Internatl J Antimicro Agents 55(3):105924
Liu Y, Sawalha AH, Lu Q (2021) COVID-19 and autoimmune diseases. Curr Opin Rheumatol 33(2):155–162
Lucchese G, Flöel A (2020) Molecular mimicry between SARS-CoV-2 and respiratory pacemaker neurons. Autoimmun Rev 19(7):102556
Marino Gammazza A, Légaré S, Lo Bosco G, Fucarino A, Angileri F, Conway de Macario E et al (2020) Human molecular chaperones share with SARS-CoV-2 antigenic epitopes potentially capable of eliciting autoimmunity against endothelial cells: possible role of molecular mimicry in COVID-19. Cell Stress Chaperones 25(5):737–741
Nguyen A, David JK, Maden SK, Wood MA, Weeder BR, Nellore A et al (2020) Human leukocyte antigen susceptibility map for severe acute respiratory syndrome coronavirus 2. J Virol 94(13):e00510-e520
Olvera A, Noguera-Julian M, Kilpelainen A, Romero-Martín L, Prado JG, Brander C (2020) SARS-CoV-2 consensus-sequence and matching overlapping peptides design for COVID19 immune studies and vaccine development. Vaccines 8(3)
Olvera A, Noguera-Julian M, Kilpelainen A, Romero-Martín L, Prado JG, Brander C (2020) SARS-CoV-2 consensus-sequence and matching overlapping peptides design for COVID19 immune studies and vaccine development. Vaccines 8(3):444
Pal M, Berhanu G, Desalegn C, Kandi V (2020) Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2): an update. Cureus 12(3):e7423-e
Pascolini S, Vannini A, Deleonardi G, Ciordinik M, Sensoli A, Carletti I et al (2021) COVID-19 and immunological dysregulation: can autoantibodies be useful? Clin Transl Sci 14(2):502–508
Patil NR, Herc ES, Girgis M (2020) Cold agglutinin disease and autoimmune hemolytic anemia with pulmonary embolism as a presentation of COVID-19 infection. Hematol Oncol Stem Cell Ther
Paul S, Weiskopf D, Angelo MA, Sidney J, Peters B, Sette A (2013) HLA class I alleles are associated with peptide-binding repertoires of different size, affinity, and immunogenicity. J Immunol 191(12):5831–5839
Paul S, Sidney J, Sette A, Peters B (2016) TepiTool: a pipeline for computational prediction of T cell epitope candidates. Current Proto Immunol 114(1):18.9. 1-.9. 24
Paul P, Mosites E, Laws RL, Scobie H, Slayton RB, Clarke KEN (2020) Modeling the frequency and number of persons to test to detect and control COVID-19 outbreaks in congregate settings. BioRxiv 11(20):391011
Peters B, Sidney J, Bourne P, Bui H-H, Buus S, Doh G et al (2005) The immune epitope database and analysis resource: from vision to blueprint. PLoS Biol 3(3):e91
Requena D, Médico A, Chacón RD, Ramírez M, Marín-Sánchez O (2020) Identification of novel candidate epitopes on SARS-CoV-2 proteins for South America: a review of HLA frequencies by country. Front Immunol 11:2008
Rodríguez Y, Novelli L, Rojas M, De Santis M, Acosta-Ampudia Y, Monsalve DM et al (2020) Autoinflammatory and autoimmune conditions at the crossroad of COVID-19. J Autoimmun 114:102506
Satarker S, Nampoothiri M (2020) Structural proteins in severe acute respiratory syndrome coronavirus-2. Arch Med Res 51(6):482–491
Sette A, Grey H, Oseroff C, Peters B, Moutaftsi M, Crotty S et al (2009) Definition of epitopes and antigens recognized by vaccinia specific immune responses: their conservation in variola virus sequences, and use as a model system to study complex pathogens. Vaccine 27(Suppl 6):G21–G26
Serwas NK, Hoeger B, Ardy RC, Stulz SV, Sui Z, Memaran N et al (2019) Human DEF6 deficiency underlies an immunodeficiency syndrome with systemic autoimmunity and aberrant CTLA-4 homeostasis. Nat Commun 10(1):3106

Shayestehpour M, Zamani B (2020) The first case of systemic lupus erythematosus (SLE) triggered by COVID-19 infection. Eur Rev Med Pharmacol Sci 24(22):11474

Shkurnikov M, Nersisyan S, Jankevic T, Galatenko A, Gordeev I, Vechorko V et al (2020) Association of HLA class I genotypes with age at death of COVID-19 patients. MedRxiv 11(19):20234567

Smatti MK, Al Thani AA, Yassine HM (2018) Viral-induced enhanced disease illness. Front Microbiol 9:2991

Sundqvist E, Sundström P, Lindén M, Hedström AK, Aloisi F, Hillert J et al (2012) Epstein-Barr virus and multiple sclerosis: interaction with HLA. Genes Immun 13(1):14–20

Venkatakrishnan AJ, Kayal N, Anand P, Badley AD, Church GM, Soundararajan V (2020) Benchmarking evolutionary tinkering underlying human-viral molecular mimicry shows multiple host pulmonary-arterial peptides mimicked by SARS-CoV-2. Cell Death Discov 6:96

Wang P, Sidney J, Dow C, Mothé B, Sette A, Peters B (2008) A systematic assessment of MHC class II peptide binding predictions and evaluation of a consensus approach. PLoS Comput Biol 4(4):e1000048

Waterhouse A, Bertoni M, Bienert S, Studer G, Tauriello G, Gumienny R et al (2018) SWISS-MODEL: homology modelling of protein structures and complexes. Nucleic Acids Res 46(W1):W296-w303

Yarmarkovich M, Warrington JM, Farrel A, Maris JM (2020) Identification of SARS-CoV-2 vaccine epitopes predicted to induce long-term population-scale immunity. Cell Rep Med 1(3):100036

Zhao ZS, Granucci F, Yeh L, Schaffer PA, Cantor H (1998) Molecular mimicry by herpes simplex virus-type 1: autoimmune disease after viral infection. Science 279(5355):1344–1347