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In-silico Immunomodelling of SARS-CoV-2

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ABSTRACT

Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-sense single-strand RNA virus belonging to the *Coronaviridae* family, responsible for coronavirus infectious disease 2019 (COVID-19) with the rapid transmission. This study aimed to characterize and compare SARS-CoV-2 and SARS-CoV major viral proteins and predict antigen proteasomal cleavage patterns, MHC class I processing and presentation, and B T-cell and anti-inflammatory epitopes. **Methods:** The amino acid sequences of spike surface (S) glycoprotein, membrane (M) glycoprotein, envelop (E) protein, and nucleocapsid (N) phosphoprotein was obtained from NCBI. The sequences were aligned by MEGA 7.0 and modeled by SWISS-MODEL. The proteasomal cleavage pattern, MHC class I processing, and T-cell epitopes were predicted via IEDB analysis and EPISOFT. The B-cell epitopes were predicted by BepiPred 2.0. Also, the prediction of anti-inflammatory epitopes was performed by AntiInflam. **Results:** Two major antigen proteins, S glycoprotein and M glycoprotein of SARS-CoV-2, respectively, showed 26.57% and 20.59% less efficiency in proteasomal cleavage and presentation to MHC class I, comparing SARS-CoV. There were fewer B-cell predicted epitopes in SARS-CoV-2, comparing SARS-CoV. The anti-inflammatory properties of SARS-CoV-2 S glycoprotein and N protein were higher than SARS-CoV**. Conclusion:** It seems that the evolution of SARS-CoV-2 is on the way to reducing antigen-presenting to MHC class I and escaping cellular immunity. Moreover, the predicted hotspot epitopes potentially can be used to induce adaptive cellular immunity against SARS-CoV-2. Besides, SARS-CoV-2 appears to be less immunopathogenic than SARS-CoV due to its higher anti-inflammatory proteins.

INTRODUCTION

At the moment, the pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [responsible for coronavirus infectious disease of 2019 (COVID-19)] is a considerable challenge facing infectious medicine [1]. This positive-sense single-strand RNA virus, a member of the *Coronaviridae* family, has high invasion power and rapid transmission rate via droplets and aerosols. SARS-CoV-2 has more than 123 million confirmed cases and more than 2.7 million mortality worldwide, as of Jan. 2021 [https://covid19.who.int] [2].

Cellular immunity plays the primary role in the inhibition of viral infections. Antigen-presenting cells (APCs) with antigen proteasomal cleavage presents digested peptides to T helper lymphocytes via MHC class I [3]. Also, the humoral immune system plays a role in adaptive immunity against viruses [4]. Unlike conventional coronaviruses, e.g., SARS-CoV, the SARS-CoV-2 shows more intensity in transmission and immune response failure.

Bioinformatics has provided valuable tools to simulate the evolution mechanism of SARS-CoV-2. Sequencing of the SARS-CoV-2 genome in the early days of the COVID-19 pandemic has enabled scientists to predict the probable protein and nucleoprotein structures of SARS-CoV-2 for proteomics-based therapeutic and prophylaxis approaches. SARS-CoV-2 might have evolved in antigen presentation to the adaptive immune system in the way of surviving and escaping the immune system. This evolution may be responsible for the alteration of the presented antigen [5].

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In this study, we analyzed the protein homology, proteasomal cleavage pattern, major histocompatibility complex (MHC) class I presentation, and B- and T-cells epitopes of SARS-CoV and SARS-CoV-2 for spike (S) surface glycoprotein, membrane (M) glycoprotein, envelop (E) protein and nucleocapsid (N) phosphoprotein with different bioinformatics tools.

MATERIALS AND METHODS

Proteome Sequences and Alignment. The amino acid sequences of S glycoprotein, M glycoprotein, E protein, and N phosphoprotein in SARS-CoV (Acc. No. NC004718) and SARS-CoV-2 (Acc. No. MT106053) were retrieved from the "Nucleotide" Genbank database. The open reading frame of S glycoprotein, M glycoprotein, E protein, and N phosphoprotein was aligned by MEGA ver.7.

***In-silico* Characterization of Viral Proteins**. After approval of the difference in SARS-CoV and SARS-CoV-2 proteomic sequence, the proteins mentioned were characterized via SWISS-MODEL (Swiss Institute of Bioinformatics, Biozentrum) [6-9]. The comparative 3D structures, table of comparison with Non-redundant set of PBD structure (adjusted by normalized QMEAN4 score and residual size), and Ramachandran plots were plotted to estimate the individual protein structure model variation between SARS-CoV and SARS-CoV-2 viral proteins.

Prediction of Proteasomal Cleavage Pattern and T Cell-Related Potential Epitope. For prediction of proteasomal cleavage and MHC class I processing of viral antigens, the MHC class I binding predictions was made on 2/26/2020 using the IEDB analysis tool [10], which combines predictions from ANN aka NetMHC (4.0) [11-13], SMM [14], and Comblib [15] [https://www.iedb.org/]. The results were categorized by 9-meric peptides as the -digestion pattern. HLA allele reference set of IEDB server was used as the most frequent alleles for prediction. For each 9-meric peptide, Proteasome Score, Transporter Associated with Antigen Processing (TAP) Score, MHC Score, Processing Score, Total Score, and MHC-IC50 (nM) (Inhibitory Concentration 50) were reported. Then, all results were sorted by "Total Score. Top-ten 9-meric peptides were inserted into EPISOPT (Epitope Vaccine Optimization server). EPISOPT (http://bio.med.ucm.es/episopt.html) predicts epitope HLA I (MHC class I) binding profiles and population protection computes (PPC). It also identifies minimal sets of epitopes that reach a target PPC for 5 distinct user-selected ethnic groups [16]. The EPISOPT results report PPC score and MHC class I binding profile. The statistical analysis was performed by EXCEL ver.2019. The efficiency was calculated as follow:

$$Efficiency\ of\ proteosomal\ cleavage = \frac{total\ score\ of\ SARSCoV - total\ score\ of\ SARSCoV2}{total\ score\ of\ SARSCoV} \times 100$$

Prediction of B Cell-Related Potential Epitope. Continuous B-Cell epitope predictions were made by BepiPred-2.0 (http://www.cbs.dtu.dk/services/BepiPred/). "The BepiPred-2.0 server predicts the linear B-cell epitopes from a protein sequence, using a Random Forest algorithm trained on epitopes and non-epitope amino acids determined from crystal structures [17].

Prediction of Anti-inflammatory Peptides. We used the AntiInFlam server [metagenomics.iiserb.ac.in/antiinflam] to predict the ant-inflammatory property of 9-meric epitopes of S glycoprotein, M glycoprotein, E protein, and N phosphoprotein proteins (from step 2.3) in SARS-CoV and SARS-CoV-2. Prediction of the anti-inflammatory epitopes allows the users to predict the anti-inflammatory nature of the multiple variants of the query peptide (substitution of each amino acid of the peptide with other amino acids), and thus, helps assess the position-specific effects of each amino acid in modulating the anti-inflammatory activity of the peptide.

RESULTS

Minor Differences in Protein Homology of SARS-CoV and SARS-CoV-2. There were minor differences within the structure of homologous S glycoprotein, M glycoprotein, E protein, and N phosphoprotein of SARS-CoV and SARS-CoV-2 (Fig. 1). The filled 3D-structures showed different exposure patterns, implying that SARS-CoV-2 viral protein sequences directly affect 3D-structure and surface exposure patterns, which leads to different behavioral patterns compared to SARS-CoV. Minor differences in Ramachandran plots dots confirm minor (but not major) homologous structural variations in SARS-CoV and SARS-CoV-2. Additionally, the comparison of modeled proteins with a non-redundant PBD structure set (Fig. 1b) confirmed the comparative results.

Difference in Proteasomal Cleavage Pattern and MHC Class I Presentation of T-cells Epitopes of SARS-CoV-2 and SARS-CoV. The IEDB analysis showed variations in the proteasomal cleavage pattern of 9-meric peptides of SARS-CoV-2 and SARS-CoV. The top-ten 9-meric peptides of each viral protein were compared via the "total score" index. The S glycoprotein of SARS-CoV-2 exhibited 26.57% less efficiency in antigen proteasomal cleavage and presentation to MHC class I, compared to SARS-CoV S glycoprotein. The other giant surface-exposed protein, the SARS-CoV-2 M protein, had 20.59% less efficiency in proteasomal and presentation to MHC class I than SARS-CoV M glycoprotein (Table 1).

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Unlike the above proteins, the E protein and N phosphoprotein of SARS-CoV-2 and SARS-CoV showed a different pattern in antigen proteasomal cleavage and presentation to MHC class I. There was a 0.08% more efficiency in the cleavage of the E protein of SARS-CoV and its presentation to MHC class I than SARS-CoV-2. Also, proteasomal cleavage and MHC class I presentation of N phosphoprotein of SARS-CoV were 15.19% more efficient than SARS-CoV-2.

According to our results, “LTDEMIAQY” (total score: 1.71, PPC: 0.0423), “CVADYSVLY” (total score: 1.16, PPC: 0.2654) and “TSNQVAVLY” (total score: 0.94, PPC: 0.2724) were top-three major 9-meric presented peptides in S glycoprotein of SARS-CoV-2. In addition, “ATSRTLSYY” (total score: 0.92, PPC: 0.0159) and “YANRNRFLY” (total score: 0.51, PPC: 0.0140) were the top-two hotspot 9-meric presented peptides in M glycoprotein of SARS-CoV-2.

Difference in B-cells Epitopes of SARS-CoV-2 and SARS-CoV. The results of the prediction of potential B-cells epitopes via BepiPred V2.0 showed that S glycoprotein and M glycoprotein of SARS-CoV-2 contained higher-potent B-cell epitopes than SARS-CoV, while E protein and N phosphoprotein of SARS-CoV contained higher-potent B-cell epitopes than SARS-CoV-2 (Fig. 2). Also, SWISS-MODEL structure prediction results approved that the predicted epitopes had surface exposure.

Differences in Anti-inflammatory Properties of SARS-CoV-2 and SARS-COV Epitopes. Scanning of four major viral proteins in SARS-CoV-2 and SARS-COV, *i.e.*, S glycoprotein, M glycoprotein, E protein, and N phosphoprotein proteins, showed that the 9-meric epitopes of SARS-CoV-2 had higher anti-inflammatory properties in S glycoprotein (264 *9*-meric epitopes in SARS-CoV-2, comparing the 77 *9*-meric epitopes in SARS-CoV) and N phosphoprotein (224 *9*-meric epitopes in SARS-CoV-2, comparing 54 *9*-meric epitopes in SARS-CoV). Despite the two above proteins, analysis of the anti-inflammatory property of the 9-meric M glycoprotein epitopes in SARS-CoV-2 and SARS-CoV showed that this protein has a slightly more anti-inflammatory property in SARS-CoV (29 *9*-meric anti-inflammatory epitopes), comparing SARS-CoV-2 (23 *9*-meric anti-inflammatory epitopes). The E protein analysis in these two viruses also showed the same result (7 *9*-meric anti-inflammatory epitopes) (Table 2).

DISCUSSION

SARS-CoV-2, responsible for coronavirus infectious disease 2019 (COVID-19), has evolved to a higher transmission potential than SARS-CoV. Bioinformatic tools have equipped us to realize the molecular evolution pattern of SARS-CoV-2.

After the virus enters the host body, the antigen-presenting cells (APCs) capture them and start the proteasomal cleavage process of viral proteins. After antigen digestion, 9-meric peptides are presented to T-cytotoxic lymphocytes in the cellular immunity system via major histocompatibility complex (MHC) class I. Cellular immunity leads to the elimination of infected cells from the host body. A different viral protein digestion pattern leads to different MHC class I presentations and different immune responses to viruses. Spike (S) surface glycoprotein, membrane (M) glycoprotein, envelop (E) protein, and nucleocapsid (N) phosphoprotein are major structural proteins in SARS-CoV-2. Our results authenticate a difference in proteasomal cleavage pattern of S glycoprotein, M glycoprotein, E protein, and N phosphoprotein in SARS-CoV-2 comparing to SARS-CoV. The results showed that two major antigen proteins of SARS-CoV-2, S glycoprotein and M glycoprotein, had 26.57% and 20.59% fewer efficiency in antigen proteasomal cleavage and presentation to MHC class I, respectively, comparing to SARS-CoV. Thus, the cellular immune system is more powerless in the elimination of SARS-CoV-2 in comparison with SARS-CoV.

Our results show a minor structural difference in row alignment of S glycoprotein, M glycoprotein, E protein, and N phosphoprotein. Also, SWISS-MODEL results revealed that the minor difference in row homology leads to minor changes in the 3D structure of these viral proteins. On the other hand, various studies established the role of humoral immunity against viral infections [18]. Thus, SARS-CoV-2 may have evolved to escape from the humoral immune system. The exposed B-cell epitopes of SARS-CoV-2 were predicted by BepiPred and compared to SARS-CoV. The results showed that S glycoprotein and M glycoprotein (most exposed proteins) of SARS-CoV contain much more potent epitopes. So, it seems that the humoral immune system is probably more involved in response to SARS-CoV than SARS-CoV-2.

IEDB results predicted "LTDEMIAQY" 9-meric as the highest scored cleaved peptide (total score: 1.71). "LTDEMIAQY" binds to different MHC class I alleles (A0207, B1508, B1516, B3801, B5702, and B5801) CPP 0423. Thus, we suggest that the "LTDEMIAQY" linear peptide can potentially be used as a peptide antigen vaccine to induce cellular immunity prophylaxis. Subsequent research can be conducted on in-vitro stimulation of T-helper lymphocytes by "LTDEMIAQY" peptide or generation of induced "LTDEMIAQY" presenting cells. In a study, the potent epitopes for E protein of SARS-CoV-2 were investigated computationally to develop a multivalent vaccine against COVID-19.

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Table 1. Prediction of proteasomal cleavage pattern, MHC class I processing, and T cell-related potential epitope.

Predicted Peptide			Proteasome Score	TAP Score	MHC Score	Processing Score	Total Score	MHC IC50	PPC	MHC class I binding profile
Spike Surface Glycoprotein	SARS-CoV	LTDDMIAAY	1.38	1.21	-0.63	2.59	1.95	4.3	0.2532	B1516 B5801 C0702
		ASSEVAVLY	1.47	1.41	-1.64	2.88	1.24	43.5	0.0056	B1516 B1517
		CVADYSVLY	1.48	1.38	-1.74	2.86	1.12	54.5	0.2654	A1101 A6801 B1508 B1517 C0702
		TSSMRGVYY	1.45	1.27	-2.09	2.71	0.63	122.1	0.0000	-
		STGNYNYKY	1.51	1.22	-2.11	2.73	0.62	128.9	0.2756	A1101 A6801 B1516 C0702
		ATSTGNYNY	1.38	1.26	-2.11	2.64	0.54	128.1	0.0000	B1516
		TQDLFLPFY	1.52	1.24	-2.39	2.76	0.37	242.9	0.0193	A0301 B2701
		HTSSMRGVY	1.37	1.2	-2.33	2.57	0.23	215.7	0.0000	B1516
		KTSVDCNMY	1.3	1.37	-2.8	2.67	-0.12	623.8	0.0028	B1517 B2702
		RVDFCGKGY	1.36	1.4	-2.9	2.77	-0.13	791.3	0.0470	A1101 B1508
		Mean ± STDEV	1.42± 0.07	1.30± 0.08	-2.07± 0.65	2.79± 0.10	0.64± 0.64	235.51±264.24	0.0869± 0.12	
	SARS-CoV-2	LTDEMIAQY	1.21	1.21	-0.72	2.42	1.71	5.2	0.0423	A0207 B1508 B1516 B3801 B5702 B5801
		CVADYSVLY	1.51	1.38	-1.74	2.89	1.16	54.5	0.2654	A1101 A6801 B1508 B1517 C0702
		TSNQVAVLY	1.47	1.3	-1.83	2.77	0.94	68.1	0.2724	A1101 B1508 B1516 B5701 C0702
		WTAGAAAYY	1.24	1.24	-1.6	2.48	0.88	40.1	0.0195	A0202 A0205 A6802 B1508 B3801
		SANNCTFEY	1.18	1.3	-2.13	2.48	0.35	134.2	0.0682	A1101 B1508 B5801
		CNDPFLGVY	1.5	1.06	-2.22	2.56	0.34	166	0.0140	B1508 B1516 B3801 B5702
		RVDFCGKGY	1.36	1.4	-2.9	2.77	-0.13	791.3	0.0470	A1101 B1508
		NIDGYFKIY	1.47	1.31	-2.94	2.78	-0.16	874.3	0.1291	A0207 A0301 B1508
		KTSVDCTMY	1.26	1.31	-2.73	2.57	-0.16	538.7	0.0028	B1517 B2702
		NSFTRGVYY	1.45	1.36	-2.98	2.8	-0.18	953.3	0.0000	B1508 B1516
		Mean ± STDEV	1.36± 0.13	1.29± 0.10	-2.18± 0.73	2.65± 0.17	0.47± 0.67	362.57± 384.39	0.0860 ± 0.10	
Membrane Glycoprotein	SARS-CoV	GTDSGFAAY	1.26	1.13	-0.91	2.38	1.47	8.2	0.0159	A0207 B1508 B5801
		YSNRNRFLY	1.18	1.3	-1.25	2.49	1.24	17.7	0.0167	B1517 B4402
		ATSRTLSYY	1.26	1.34	-1.68	2.6	0.92	48.2	0.0159	B5801
		VATSRTLSY	1.34	1.31	-2.98	2.65	-0.33	946	0.0040	B1502 B1508 C0102
		IVGLMWLSY	1.41	1.27	-3.17	2.68	-0.49	1472	0.0000	B1502
		WIMLLQFAY	1.37	1.41	-3.61	2.78	-0.83	4085.3	0.0159	A0203 A6802
		ACFVLAAVY	1.69	1.41	-4.24	3.1	-1.13	17265.1	0.0054	B1508 B1517 B2702
		SGFAAYNRY	1.65	1.17	-4	2.81	-1.19	10050.5	0.0359	A0301 B1517 B2701 B2702 B4402
		WLSYFVASF	1.38	1.11	-3.99	2.49	-1.5	9708.7	0.0225	A0202 A0203 A6802
		YNRYRIGNY	1.36	1.28	-4.18	2.64	-1.54	15044.6	0.0000	-
		Mean ± STDEV	1.39± 0.16	1.27± 0.11	-3.00± 1.27	2.66± 0.20	-0.34 ± 1.14	5864.63± 6629.1	0.0132± 0.01	
	SARS-CoV-2	ATSRTLSYY	1.26	1.34	-1.68	2.6	0.92	48.2	0.0159	B5801
		YANRNRFLY	1.18	1.31	-1.98	2.49	0.51	95.6	0.0140	B4402
		LVGLMWLSY	1.55	1.26	-3.08	2.81	-0.27	1199.7	0.0000	-
		AGDSGFAAY	1.24	1.16	-2.72	2.4	-0.32	525.6	0.0000	B1508
		VATSRTLSY	1.34	1.31	-2.98	2.65	-0.33	946	0.0040	B1502 B1508 C0102
		WICLLQFAY	1.45	1.32	-3.39	2.77	-0.63	2476.4	0.0000	-
		YSRYRIGNY	1.36	1.37	-3.5	2.73	-0.77	3140.6	0.0000	B1516
		SSDNIALLV	0.95	0.12	-1.94	1.07	-0.87	86.6	0.0000	B1516 B3909
		ACFVLAAVY	1.69	1.41	-4.24	3.1	-1.13	17265.1	0.0054	B1508 B1517 B2702
		SGFAAYSRY	1.53	1.17	-3.93	2.69	-1.23	8435.9	0.0386	A0301 B1508 B1517 B2701 B2702 B4402
		Mean ± STDEV	1.35± 0.21	1.18± 0.38	-2.94± 0.87	2.53± 0.55	-0.41± 0.68	3421.97± 5485.1	0.0078± 0.01	

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Envelope Protein	**SARS-CoV**	LTALRLCAY	1.42	1.27	-2.09	2.69	0.6	123.3	0.0000	-
		VSLVKPTVY	1.37	1.38	-3.5	2.75	-0.75	3168	0.0028	B1517
		LVKPTVYVY	1.51	1.35	-3.83	2.86	-0.97	6797.8	0.2790	A1101 A6801 B1502 B1508 B1516 C0702
		NSVLLFLAF	1.3	1.19	-4.03	2.49	-1.54	10687.4	0.0855	C0304
		LIVNSVLLF	1.15	1.2	-4.08	2.35	-1.73	11893.9	0.0159	B5801
		LLFLAFVVF	1.53	1.18	-4.53	2.71	-1.82	34097.3	0.0587	A2402 B1502
		IVNSVLLFL	1.66	0.47	-3.96	2.12	-1.83	9047.2	0.3429	A0201 A0202 A0203 A0206 A0214 A6802
		SSEGVPDLL	1.36	0.46	-3.78	1.82	-1.96	5976	0.0394	B1509 B3801 B39011
		FVVFLLVTL	2	0.54	-4.53	2.54	-1.99	33863.9	0.3382	A0201 A0202 A0203 A0205 A0206 A0214
		FLAFVVFLL	1.45	0.41	-4.06	1.86	-2.2	11445.5	0.3565	A0201 A0202 A0203 A0205 A0206 A0209 A0214 A6802 B4402
		Mean ± STDEV	1.47± 0.23	0.94± 0.41	-3.84± 0.69	2.42± 0.37	-1.42± 0.84	12710.03± 11806.1	0.1519± 0.16	
	SARS-CoV-2	LTALRLCAY	1.42	1.27	-1.91	2.69	0.78	80.87	0.0000	-
		VSLVKPSFY	1.19	1.38	-3.35	2.58	-0.77	2216.49	0.0000	-
		LVKPSFYVY	1.51	1.35	-3.9	2.86	-1.03	7860.43	0.2790	A1101 A6801 B1502 B1508 B1516 C0702
		NSVLLFLAF	1.3	1.19	-3.77	2.49	-1.28	5869.13	0.0855	C0304
		LLFLAFVVF	1.53	1.18	-4.36	2.71	-1.65	22695.78	0.0587	A2402 B1502
		LIVNSVLLF	1.15	1.2	-4.03	2.35	-1.68	10757.62	0.0159	B5801
		NVSLVKPSF	1.43	1.19	-4.37	2.62	-1.75	23699.6	0.0000	-
		FVVFLLVTL	2	0.54	-4.39	2.54	-1.86	24747.82	0.3382	A0201 A0202 A0203 A0205 A0206 A0214
		IVNSVLLFL	1.66	0.47	-4.01	2.12	-1.89	10301.97	0.3429	A0201 A0202 A0203 A0206 A0214 A6802
		NSSRVPDLL	1.34	0.47	-3.76	1.81	-1.95	5805.97	0.0000	-
		Mean ± STDEV	1.45± 0.25	1.02± 0.37	-3.78± 0.74	2.48± 0.31	-1.31± 0.83	11403.57± 9101.46	0.1120± 0.15	
Nucleocapsid Phosphoprotein	**SARS-CoV**	LSPRWYFYY	1.07	1.21	-1.85	2.28	0.44	70.4	0.0000	-
		ELSPRWYFY	1.58	1.23	-2.89	2.81	-0.08	784.1	0.0394	A0206 B1513 B4402
		LLNKHIDAY	1.31	1.24	-3.04	2.55	-0.49	1103.5	0.1342	A0301 B1502 B1508 B5701 B5702
		GTTLPKGFY	1.48	1.15	-3.16	2.62	-0.53	1438.7	0.0000	A6802
		GPDDQIGYY	1.24	1.01	-3.37	2.25	-1.12	2327.8	0.0080	B3801
		KLDDKDPQF	1.68	1.08	-3.93	2.76	-1.17	8515.8	0.0213	A0203 B3801 B5702
		TPSGTWLTY	1.53	1.15	-3.88	2.67	-1.2	7522	0.2782	B0702 B1502 B1508 B3501 B5301 B5401
		FAPSASAFF	1.3	1.05	-3.93	2.35	-1.57	8448.7	0.0000	C0102
		SGPDDQIGY	1.37	1.23	-4.25	2.61	-1.65	17944.5	0.2136	B5701 C0702
		QKRTATKQY	1.55	1.38	-4.63	2.92	-1.7	42422.1	0.1706	C0702
		Mean ± STDEV	1.41± 0.19	1.17± 0.11	-3.49± 0.82	2.58± 0.23	-0.91± 0.72	9057.76± 12957.26	0.0865± 0.10	
	SARS-CoV-2	LSPRWYFYY	1.07	1.22	-1.85	2.3	0.45	70.4	0.0000	-
		DLSPRWYFY	1.58	1.18	-3.11	2.76	-0.35	1298.9	0.1215	A0206 A6801 A6802 B1513 B4402
		LLNKHIDAY	1.31	1.24	-3.04	2.55	-0.49	1103.5	0.1342	A0301 B1502 B1508 B5701 B5702
		GTTLPKGFY	1.48	1.15	-3.16	2.62	-0.53	1438.7	0.0000	A6802
		SSPDDQIGY	1.37	1.36	-3.32	2.74	-0.58	2066.5	0.2207	B1517 B5701 C0702
		SPDDQIGYY	1.24	1.11	-3.07	2.35	-0.73	1185.9	0.0080	B3801
		TPSGTWLTY	1.52	1.15	-3.88	2.67	-1.21	7522	0.2782	B0702 B1502 B1508 B3501 B5301 B5401
		KLDDKDPNF	1.58	1.08	-3.96	2.66	-1.31	9202.3	0.0000	A0203 B5702
		FAPSASAFF	1.3	1.05	-3.93	2.35	-1.57	8448.7	0.0000	C0102
		MKDLSPRWY	1.31	1.28	-4.19	2.58	-1.61	15499.3	0.0000	-
		Mean ± STDEV	1.38± 0.16	1.18± 0.09	-3.35± 0.68	2.56± 0.17	-0.79± 0.64	4783.62± 5106.69	0.0763± 0.11	

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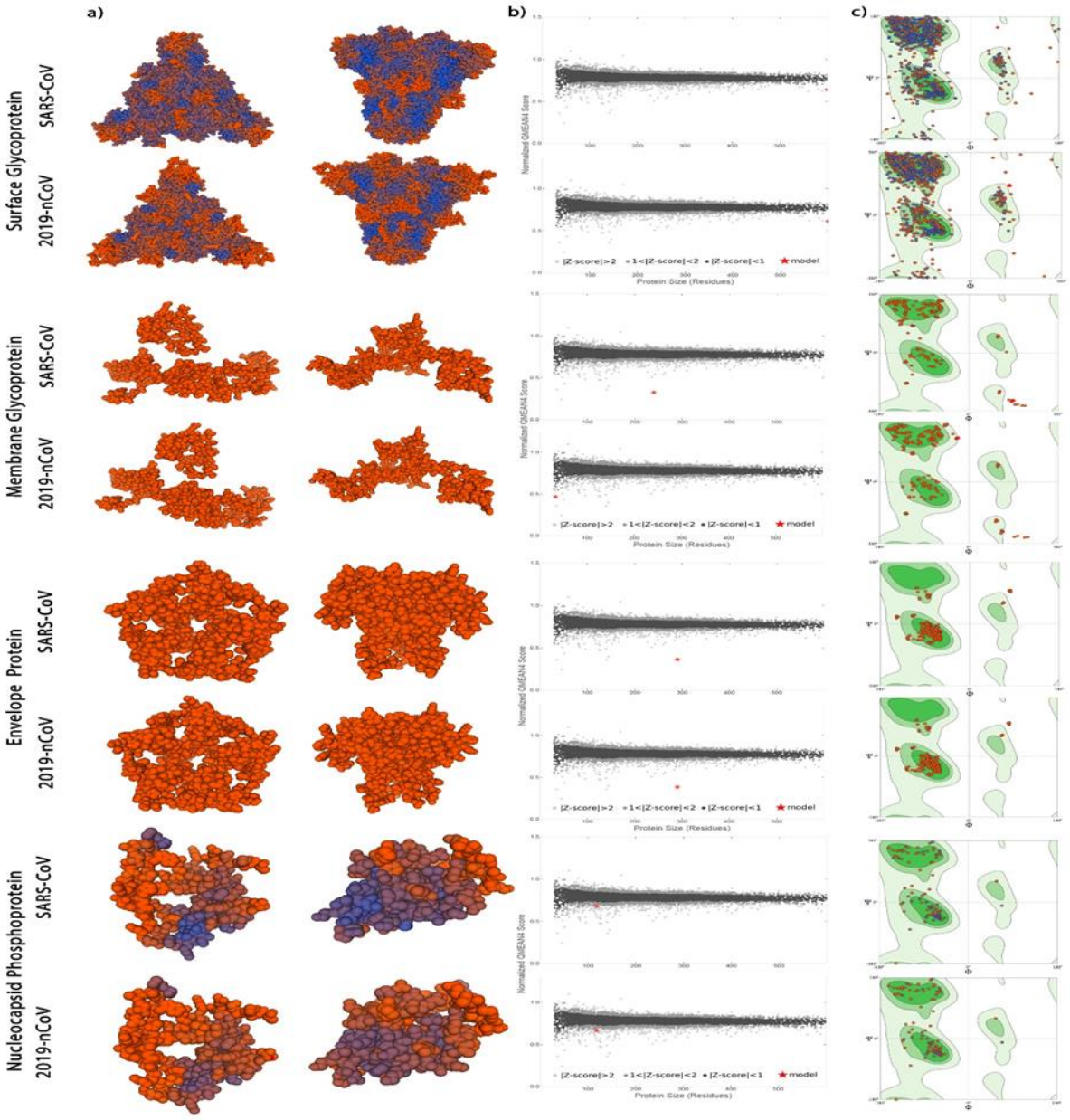

Fig. 1. SWISS-MODEL characterization of surface glycoprotein, membrane glycoprotein, envelop protein, and nucleocapsid phosphoprotein of SARS-CoV-2 and SARS-CoV. a) The top-view and side-view of filled 3D structures, **b)** table of comparison with a non-redundant set of PBD structures (adjusted by normalized QMEAN4 score and residual size), and **c)** Ramachandran plots of SARS-CoV-2 and SARS-CoV proteins.

The cytokine-secretion prediction showed that the "SFVSEETGT" is a potent epitope for the secretion of IL4. The "NVSLVKPSFYVYSRVK" was also introduced as the IL4, IL10, and INFγ inducer [19]. Further studies are required to predict the cytokine-secretion pattern by in-silico pattern.

Control of the immune system's inflammatory response to these two viruses is of great importance in controlling the complications since the pathogenesis caused by these two viruses is immune-mediated. According to the analysis results of the anti-inflammatory properties of 9-meric epitopes on the four main proteins of SARS-CoV-2 and SARS-CoV, the former appears to be more pathogenic than SARS-CoV due to its higher anti-inflammatory proteins and better triggering of the inflammatory response of the immune system.

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Table 2. Prediction of anti-inflammatory peptides.

	SARS-CoV		SARS-CoV-2	
	Epitope	**Score Prediction**	**Epitope**	**Score Prediction**
Surface Glycoprotein	DILSRLDKV	4.54	TKCTLKSFT	4.75
	ILSRLDKVE	4.54	DILSRLDKV	4.54
	LGFIAGLIA	4.47	ILSRLDKVE	4.54
	GFIAGLIAI	4.47	VFNATRFAS	4.49
	FIAGLIAIV	4.47	LGFIAGLIA	4.47
	IAGLIAIVM	4.47	GFIAGLIAI	4.47
	AGLIAIVMV	4.47	FIAGLIAIV	4.47
	LSRLDKVEA	4.33	IAGLIAIVM	4.47
	RLITGRLQS	4.27	AGLIAIVMV	4.47
	ESLIDLQEL	3.33	LSRLDKVEA	4.33
	Mean ± STDEV	4.34 ± 0.36	Mean ± STDEV	4.50 ± 0.10
Membrane Glycoprotein	PLRGTIVTR	3.64	YRIGNYKLN	2.87
	YRIGNYKLN	2.87	RIGNYKLNT	2.87
	RIGNYKLNT	2.87	IGNYKLNTD	2.52
	IGNYKLNTD	2.52	GNYKLNTDH	2.52
	GNYKLNTDH	2.52	NYKLNTDHS	2.52
	NYKLNTDHA	2.52	GTILTRPLL	2.38
	NILLNVPLR	2.21	TILTRPLLE	2.38
	ILLNVPLRG	2.21	ILTRPLLES	2.38
	LLNVPLRGT	2.21	LTRPLLESE	2.38
	LNVPLRGTI	2.21	TRPLLESEL	2.38
	Mean ± STDEV	2.58 ± 0.45	Mean ± STDEV	2.52 ± 0.20
Nucleocapsid Phosphoprotein	TNSGPDDQI	3.50	DLSPRWYFY	2.88
	NSGPDDQIG	3.50	LSPRWYFYY	2.88
	VPINTNSGP	2.88	GYYRRATRR	2.69
	PINTNSGPD	2.88	YYRRATRRI	2.69
	INTNSGPDD	2.88	YRRATRRIR	2.69
	NTNSGPDDQ	2.88	RRATRRIRG	2.69
	ELSPRWYFY	2.88	RATRRIRGG	2.69
	LSPRWYFYY	2.88	ATRRIRGGD	2.69
	GYYRRATRR	2.69	GQTVTKKSA	2.60
	YYRRATRRV	2.69	QTVTKKSAA	2.60
	Mean ± STDEV	2.97 ± 0.29	Mean ± STDEV	2.71 ± 0.10
Envelope Protein	LAILTALRL	2.42	LAILTALRL	2.42
	AILTALRLC	2.42	AILTALRLC	2.42
	ILTALRLCA	2.42	ILTALRLCA	2.42
	LTALRLCAY	2.42	LTALRLCAY	2.42
	TALRLCAYC	2.42	TALRLCAYC	2.42
	ALRLCAYCC	2.42	ALRLCAYCC	2.42
	LRLCAYCCN	2.42	LRLCAYCCN	2.42
	Mean ± STDEV	2.42 ± 0.00	Mean ± STDEV	2.42 ± 0.00

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Fig. 2. Difference in B-cells Epitopes of SARS-CoV-2 and SARS-CoV in surface glycoprotein, membrane glycoprotein, envelop protein, and nucleocapsid phosphoprotein via BepiPred. The epitope threshold was 0.64. All predicted epitopes contained a coiled structure and exposed surface.

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We declare that there is no Acknowledgment.

CONFLICT OF INTEREST

We declare that there is no conflict of interest associated with this manuscript.

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