Analyzing T cell's Epitope Variance Influence of SARS-CoV-2

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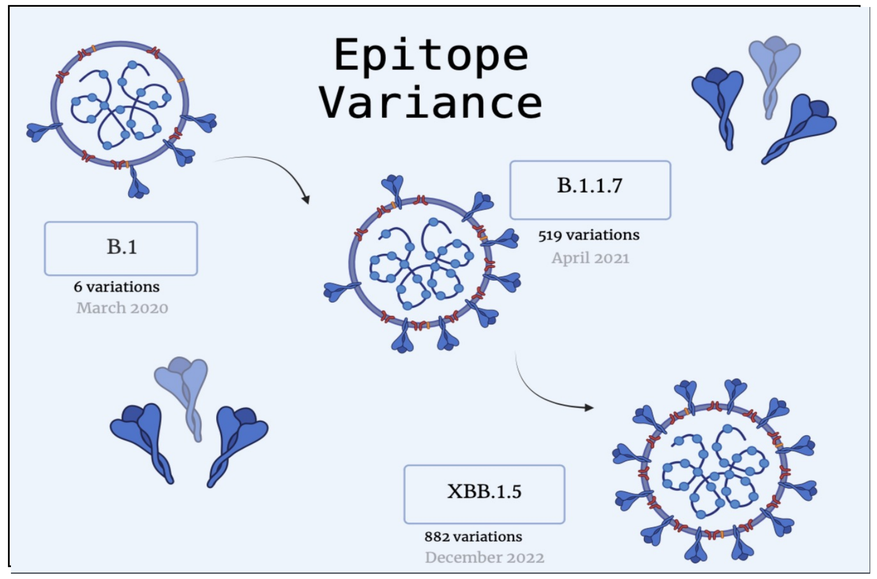
Introduction

T cell epitopes, composed of fragments of non-self or mutated proteins bound to MHC (HLA) molecules, play a crucial role in the progression and vulnerability of various diseases, such as COVID-19, the illness caused by SARS-CoV-2. For viral diseases, CD8 T cell immunity whereby epitopes bind to MHC-I (HLA-A, B, C) antigen presenting receptors, plays a major role in viral clearance, and viral epitopes recognized by CD8 T cells drive immune responses. This study explores the influence of epitopes gained, lost, and altered in predicted immunogenicity in key proteins from numerous SARS-CoV-2 variants and their potential implications for viral susceptibility, such as disease severity, and progression, which may have an impact on the immune system's ability to control the virus.

The genomic sequences of various SARS-CoV-2 variants were compared to the original Wuhan strain (INSDC accession CGA_009858895.3) using Ensembl's SARS-CoV-2 genome browser. This analysis involved a blast analysis that resulted in the generation of variant-specific cDNA sequences focusing on spike, membrane, and nucleocapsid proteins. To obtain the corresponding amino acid/protein sequences for these COVID-19 variant-specific cDNA sequences, the Expasy translate tool was utilized.

Epitope Variance



Original Data

2A

S Epitopes

Variant of Interest	Alpha		Delta					Omicron								
Comparison Variant	B.1	B.1.1.7	AY.100	AY.25	AY.3	AY.3.1	AY.44	BA.1	BA.1.1	BA.2	BA.4	BA.5	BQ.1	BQ.1.1	XBB.1	XBB.1.5
	Wuhan (NCBI: NC_045512.2)															
↓ Immunogenicity Lost	1	453	24	24	5	81	6	101	222	224	122	168	702	717	720	609
	2	37	40	40	42	38	41	97	96	103	113	114	96	138	88	131
↑ Immunogenicity Gained	1	27	3	3	4	11	4	72	80	16	18	16	20	32	37	39
	2	2	30	30	39	30	39	91	92	79	93	94	135	90	111	103

2B

M Epitopes

Variant of Interest	Alpha		Delta					Omicron								
Comparison Variant	B.1	B.1.1.7	AY.100	AY.25	AY.3	AY.3.1	AY.44	BA.1	BA.1.1	BA.2	BA.4	BA.5	BQ.1	BQ.1.1	XBB.1	XBB.1.5
	Wuhan (NCBI: NC_045512.2)															
↓ Immunogenicity Lost	0	0	0	0	0	0	0	6	2	6	7	7	6	6	6	6
	0	0	1	1	1	1	1	5	18	5	4	4	5	5	5	5
↑ Immunogenicity Gained	0	0	0	0	0	0	0	4	4	4	4	5	4	4	4	4
	0	0	1	1	1	1	1	6	7	6	6	6	6	6	6	6

2C

N Epitopes

Variant of Interest	Alpha		Delta					Omicron								
Comparison Variant	B.1	B.1.1.7	AY.100	AY.25	AY.3	AY.3.1	AY.44	BA.1	BA.1.1	BA.2	BA.4	BA.5	BQ.1	BQ.1.1	XBB.1	XBB.1.5
	Wuhan (NCBI: NC_045512.2)															
↓ Immunogenicity Lost	0	2	2	2	2	2	2	6	4	17	49	17	17	17	17	17
	0	7	3	3	3	3	3	11	8	13	16	13	13	13	13	13
↑ Immunogenicity Gained	0	1	4	4	4	4	4	5	0	0	0	0	0	0	0	0
	0		2	2	2	2	2	12	10	9	12	10	10	10	10	10

Revalidated Data

Spike

Start	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	
End	B.1	B.1.1.7	AY.100	AY.25	AY.3	AY.3.1	AY.44	BA.1	BA.1.1	BA.2	BA.4	BA.5	BQ.1	BQ.1.1	XBB.1	XBB.1.5		
Rank<-10					24	5		6	100	222			122	168	702	717	720	609	Rank<-10
Lost					40	42		41	93	96			113	114	96	138	88	131	Lost
Rank>+10					3	4		4	72	66			18	16	20	32	37	39	Rank>+10
Gained					30	39		39	91	92			93	94	135	90	111	103	Gained
Total Epitopes	*1081*	*1095*	*1084*	*1084*	*1077*	*1084*	*1077*	*1084*	*1088*	*1102*	*1098*	*1099*	*1110*	*1115*	*1109*	*1109*		

Membrane

Start	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	
End	B.1	B.1.1.7	AY.100	AY.25	AY.3	AY.3.1	AY.44	BA.1	BA.1.1	BA.2	BA.4	BA.5	BQ.1	BQ.1.1	XBB.1	XBB.1.5		
Rank<-10		0						6	2	6	7	7	6		6		Rank<-10	
Lost		0						5	18	5	4	5	5		5		Lost	
Rank>+10		0						4	4	4	5	4	4		4		Rank>+10	
Gained		0						**6**	**7**	**6**	**6**	**6**	**6**		**6**		Gained	
Total Epitopes	*237*	*237*	*237*	*237*	*237*	*237*	*237*	*236*	*241*	*236*	*236*	*236*	*237*	*237*	*236*	*236*		

Nucleocapsid

Start	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	Wuhan	
End	B.1	B.1.1.7	AY.100	AY.25	AY.3	AY.3.1	AY.44	BA.1	BA.1.1	BA.2	BA.4	BA.5	BQ.1	BQ.1.1	XBB.1	XBB.1.5		
Rank<-10		6						6	4	17	49	17	17				Rank<-10	
Lost		2						11	8	13	16	13	13				Lost	
Rank>+10		23						5	0	0	0	0	0				Rank>+10	
Gained		7						**12**	**10**	**9**	**12**	**10**	**10**				Gained	
Total Epitopes	*289*	*294*	*290*	*290*	*290*	*290*	*290*	*292*	*291*	*296*	*298*	*296*	*296*	*296*	*296*	*296*		

Results

Revalidated data closely resembled the original epitope results, verifying the accuracy of previous epitope analysis. Among the epitope data sets, the B.1 strain, closest to the original Wuhan, displayed the fewest variations in its spike (S), membrane (M), and nucleocapsid (N) components. Specifically, the B.1 epitope data, gathered in March 2020, exhibited only slight modifications in S (6 variations). Additionally, there were 2 changes in nucleotides (NT) compared to the Wuhan strain. In contrast, B.1.1.7 VOC, associated with the "Alpha" strain and sequenced 13 months after in April 2021, exhibited a substantial increase in S epitope variance (519 variations composed of 37 loss, 2 gained, and 27 increased and 453 decreased immunogenicity). Of the 27 HLA alleles analyzed, 41.4% (453/1095) B.1.1.7 S epitopes experienced a predicted decrease in immunogenicity indicating that the immune system may encounter difficulty in recognizing it. B.1.1.7 also displayed 10 and 5 NT alterations in S and N, respectively. In comparison, the XBB.1.5 VOC, representing a recombinant derivative of the "Omicron" variant collected in December 2022, demonstrated 53 NT alterations in spike, 3 NT in membrane, and 14 NT in nucleocapsid components resulting in 882, 21, and 40 epitope variations in S, M, and N respectively.

Conclusion

The progressive increase in variance observed in the S, M, and N epitopes over time may provide an explanation for the "waves" of incidence seen during the COVID pandemic. Specifically, the Spike protein displayed the most variance, suggesting that it may have a greater influence on both susceptibility and severity. The significance of differences in Spike protein epitopes lies in the fact that COVID-19 vaccines trigger a humoral immune response specifically targeting the spike protein, which may contribute to viral mutation and immune avoidance. In comparison, the minor variations observed in the nucleocapsid and membrane components, in comparison to the spike protein, imply that these highly conserved regions play a crucial role in the virus and could be potential targets for targeted therapeutic interventions or T-cell-targeted vaccines.