Immune Netw. 2022 Aug;22(4):e29
https://doi.org/10.4110/in.2022.22.e29
pISSN 1598-2629·eISSN 2092-6685

IMMUNE NETWORK

Correspondence

Omicron Subvariants, Including BA.4 and BA.5, Substantially Preserve T Cell Epitopes of Ancestral SARS-CoV-2

Kyemyung Park [1,2], **Seung Jin Choi** [3], **Eui-Cheol Shin** [1,4,*]

[1]The Center for Viral Immunology, Korea Virus Research Institute, Institute for Basic Science (IBS), Daejeon 34126, Korea
[2]Department of Biomedical Engineering, College of Information and Biotechnology, Ulsan National Institute of Science and Technology, Ulsan 44919, Korea
[3]Division of Infectious Disease, Department of Internal Medicine, Seoul National University Hospital, Seoul 03080, Korea
[4]Laboratory of Immunology and Infectious Diseases, Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 34141, Korea

Received: Jun 5, 2022
Revised: Jul 17, 2022
Accepted: Jul 27, 2022
Published online: Aug 3, 2022

***Correspondence to**
Eui-Cheol Shin
Laboratory of Immunology and Infectious Diseases, Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology (KAIST), 291 Daehak-ro, Yuseong-gu, Daejeon 34141, Korea.
Email: ecshin@kaist.ac.kr

ORCID iDs
Kyemyung Park
https://orcid.org/0000-0002-4728-5387
Seung Jin Choi
https://orcid.org/0000-0002-3842-0524
Eui-Cheol Shin
https://orcid.org/0000-0002-6308-9503

Conflict of Interest
The authors declare no potential conflicts of interest.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variants (B.1.1.529 and related) that emerged in November 2021 have spread worldwide, and are designated a variant of concern by the World Health Organization (WHO) (1). They have become the dominant strains, comprising >99% of newly deposited SARS-CoV-2 sequences in GISIAD (www.gisaid.org) as of May 16, 2022 (2). Following the emergence of B.1.1.529 (BA.1), BA.2 (often called stealth Omicron) soon became the most prevalent sublineage worldwide. Subsequent subvariants, including BA.2.9, BA.2.12.1, BA.4, and BA.5, are now rapidly dominating the circulating Omicron subvariants in originating regions, and are beginning to spread globally (2). The dominance of Omicron variants and their rapid evolution into various subvariants have raised concerns regarding the effects of the immunity elicited by natural infection or vaccination. As evolution continues, the variants' spike proteins exhibit higher affinities toward ACE2, and/or increasing capacity for evading preformed neutralizing antibodies induced by previous natural infection or vaccination (3-5). These changes are consistent with increased breakthrough infections and re-infections with Omicron variants (6,7).

However, less is known about responses of memory T cells elicited by previous natural infection or vaccination against continuously emerging Omicron subvariants. We previously reported considerable conservation of T cell epitopes that had been identified from the original SARS-CoV-2 strain (Wuhan-Hu-1) in the first reported Omicron variant (hCoV-19/South Africa/CERI-KRISP-K032284/2021) (8). Additionally, we recently demonstrated that BNT162b2-induced memory T cells respond to the Omicron spike with preserved polyfunctionality (9). Now, we have extended our previous analyses by including subsequent Omicron subvariants: BA.2, BA.2.9, BA.2.12.1, BA.4, and BA.5. In these subvariants, we examined the fractions of completely conserved T cell epitopes to provide insights into T cell responses against continuously arising Omicron subvariants.

We downloaded major histocompatibility complex (MHC) class I-restricted $CD8^+$ T cell (CD8) epitopes and MHC class II-restricted $CD4^+$ T cell (CD4) epitopes of the original SARS-CoV-2 strain (Wuhan-Hu-1) from the Immune Epitope Database (www.iedb.org) (10). We used only experimentally validated epitopes for any MHC alleles by applying the filtering option of 'positive outcome', 'T cell', and 'MHC Ligand' in 'Assay' in the database. The following analysis included epitopes with lengths of ≤11-mers for CD8, and ≤16-mers for CD4. The epitope information is presented in **Supplementary Table 1**. Among the millions of amino

IMMUNE NETWORK

Abbreviations

CD4, CD4+ T cell; CD8, CD8+ T cell; MHC, major histocompatibility complex; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Author Contributions

Conceptualization: Park K, Choi SJ, Shin EC; Data curation: Park K, Choi SJ, Shin EC; Investigation: Park K; Methodology: Park K, Choi SJ; Supervision: Shin EC; Writing - original draft: Park K, Shin EC; Writing - review & editing: Park K, Shin EC.

acid sequences of Omicron subvariants that have been uploaded to GISIAD since November 2021, we randomly sampled 100 sequences for each subvariant and finally selected the top 50 reliable sequences that carried the least number of unidentified amino acids in epitope regions. For each sequence, we quantified the percentage of conserved epitopes and calculated the median value of the percentages of conserved epitopes for each subvariant.

First, we examined CD8 epitopes (**Fig. 1A**). In all examined subvariants, the median conserved fractions were ≥85.3% for the spike protein (with 360 epitopes) (**Fig. 1A**, left), and ≥97.0% for the non-spike proteins (with 1048 epitopes) (**Fig. 1A**, center). Considering all 1408 CD8 epitopes, the subvariants exhibited median conserved fractions of 94.0%–95.1% (**Fig. 1A**, right).

We then examined CD4 epitopes (**Fig. 1B**). In all examined subvariants, the median conserved fractions were ≥73.9% for the spike protein (with 617 epitopes) (**Fig. 1B**, left), and ≥91.9% for the non-spike proteins (with 296 epitopes) (**Fig. 1B**, center). Considering all 913 CD4 epitopes, the subvariants exhibited median conserved fractions of 79.7%–84.2% (**Fig. 1A**, right).

These results illustrate that T cell epitopes of the ancestral SARS-CoV-2 are considerably preserved across major Omicron subvariants (≥94.0% for CD8 epitopes and ≥79.7% for CD4 epitopes). The extent of conservation differs depending on epitope class (higher for CD8 vs. CD4), protein (higher for non-spike vs. spike), and subvariant (higher for BA.1/BA.2/BA.2.9 vs. BA2.12.1/BA.4/BA5). The greater conservation of CD8 epitopes than CD4 epitopes is likely due to the shorter peptide length of CD8 epitopes. The reduced conservation of epitopes derived from the spike protein, compared to non-spike proteins, is consistent with the high mutation rates in the spike protein across Omicron subvariants. Among the examined Omicron subvariants, T cell epitopes were less conserved in the newest subvariants—BA.2.12.1, BA.4, and BA.5—compared to in BA.1, BA.2, and BA.2.9.

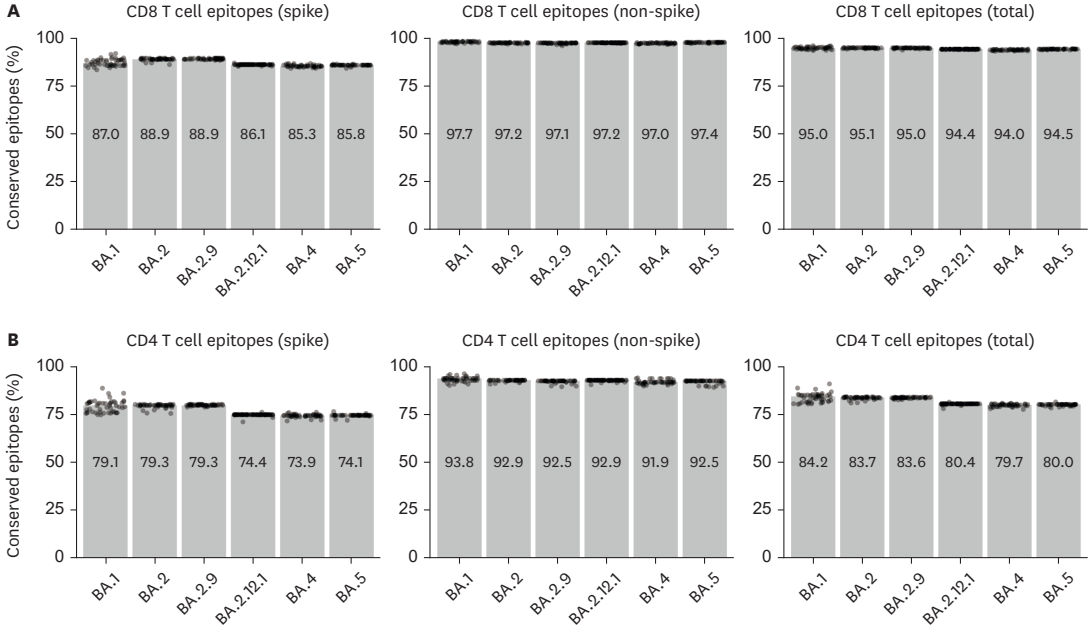

Figure 1. Fractions of conserved epitopes in Omicron subvariants. We downloaded CD8 and CD4 epitopes of the original SARS-CoV-2 from the Immune Epitope Database (www.iedb.org). We obtained 100 random sequences for each subvariant from GISIAD and selected the top 50 reliable sequences that carried the least number of unidentified amino acids in epitope regions. For each sequence, we quantified the percentage of conserved epitopes and calculated the median value of the percentages of conserved epitopes for each subvariant. Bar plots show the median conserved fractions of CD8 (A) and CD4 (B) epitopes from spike (left), non-spike (center), and total (right) proteins. Fractions from individual viral sequences are shown as points on bar plots.

https://doi.org/10.4110/in.2022.22.e29

As of July 15, 2022, BA.5-related subvariants that originated from Africa have become the most dominant in Asia and Europe (2). Although new Omicron subvariants are continuously emerging, memory T cells elicited by prior infection or vaccination likely respond against them, thereby potentially reducing disease severity under foreseeable surges of emerging Omicron subvariants.

ACKNOWLEDGEMENTS

This work was supported by the Institute for Basic Science (IBS), Republic of Korea, under project code IBS-R801-D2.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Epitope Information from the Immune Epitope Database

Click here to view

REFERENCES

1. World Health Organization. Classification of Omicron (B.1.1.529): SARS-CoV-2 variant of concern [Internet]. Available at https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern [accessed on 16 May 2022].
2. The GISAID initiative. Pandemic coronavirus causing COVID-19 [Internet]. Available at https://www.epicov.org/epi3/frontend#31b779 [accessed on 16 May 2022 and 15 July 2022].
3. Planas D, Saunders N, Maes P, Guivel-Benhassine F, Planchais C, Buchrieser J, Bolland WH, Porrot F, Staropoli I, Lemoine F, et al. Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. *Nature* 2022;602:671-675.
PUBMED | CROSSREF
4. Iketani S, Liu L, Guo Y, Liu L, Chan JF, Huang Y, Wang M, Luo Y, Yu J, Chu H, et al. Antibody evasion properties of SARS-CoV-2 Omicron sublineages. *Nature* 2022;604:553-556.
PUBMED | CROSSREF
5. Xie X, Cao Y, Yisimayi A, Jian F, Song W, Xiao T, Wang L, Du S, Wang J, Li Q, et al. BA.2.12.1, BA.4 and BA.5 escape antibodies elicited by Omicron infection. *Nature* 2022. doi: 10.1038/s41586-022-04980-y.
PUBMED | CROSSREF
6. World Health Organization. Weekly epidemiological update on COVID-19 - 11 May 2022 [Internet]. Available at https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---11-may-2022 [accessed on 16 May 2022].
7. Nyberg T, Ferguson NM, Nash SG, Webster HH, Flaxman S, Andrews N, Hinsley W, Bernal JL, Kall M, Bhatt S, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. *Lancet* 2022;399:1303-1312.
PUBMED | CROSSREF
8. Choi SJ, Kim DU, Noh JY, Kim S, Park SH, Jeong HW, Shin EC. T cell epitopes in SARS-CoV-2 proteins are substantially conserved in the Omicron variant. *Cell Mol Immunol* 2022;19:447-448.
PUBMED | CROSSREF
9. Jung MK, Jeong SD, Noh JY, Kim DU, Jung S, Song JY, Jeong HW, Park SH, Shin EC. BNT162b2-induced memory T cells respond to the Omicron variant with preserved polyfunctionality. *Nat Microbiol* 2022;7:909-917.
PUBMED | CROSSREF
10. Vita R, Mahajan S, Overton JA, Dhanda SK, Martini S, Cantrell JR, Wheeler DK, Sette A, Peters B. The Immune Epitope Database (IEDB): 2018 update. *Nucleic Acids Res* 2019;47:D339-D343.
PUBMED | CROSSREF