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LETTER TO THE EDITOR

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T cell epitopes are largely conserved in the SARS-CoV-2 Omicron subvariant (BA.1, BA.2, BA.3, and GKA)

The SARS-CoV-2 variant Omicron (B.1.1.529) was first reported in South Africa by the World Health Organization in November 2021 and the Omicron variant is now the predominant globally prevalent variant and account for almost all sequences recently reported to GISAID.[1] Choi et al.[2] discovered that most T cell epitopes are conserved in the Omicron variant by comparing amino acid sequences of T cell epitopes identified from the original SARS-CoV-2 strain (Wuhan-Hu-1) in the Omicron variant (hCoV-19/South africa/CERI-KRISP-K032284/2021). However, as of March 2022, the Omicron variant has three lineage, BA.1 (B.1.1.529.1), BA.2 (B.1.1.529.2), BA.3 (B.1.1.529.3)[3] and one recombinant of Delta (AY.4) and Omicron (BA.1) (GKA).[4,5] The dynamic change of mutation in T cell epitopes in the Omicron subvariants are still unclear. This study aimed to examine if the previously identified viral epitopes targeted by $CD4^+$ T cells and $CD8^+$ T cells are mutated in the newly described Omicron subvariants.

In this study, we randomly selected 30 full-length sequences in each Omicron subvariants (BA.1, BA.2, BA.3, and GKA) from GISAID (https://www.gisaid.org/) or NCBI (https://www.ncbi.nlm.nih.gov/sars-cov-2/) on April 1, 2021. The complete genome sequences were aligned with the Wuhan/Hu-1/2019 reference strain (NC_045512) by MAFFT (version 7.0, https://mafft.cbrc.jp/alignment/server/). The aligned genomes were then edited manually according to the reference sequence using BioEdit (version 7.2.5). In general, a total of 133, 96, 88, 86 amino acid (AA) sites were detected mutations in BA.1, BA.2, BA.3, and GKA, respectively (Figure 1A). And 45% (60/133), 59% (57/96), 64% (56/88), 73% (63/86) of these mutations were common mutations (high frequency [>90%] occurred in each variant). In this study, we used all mutations (including non-common mutations) in enrolled sequences to analyze whether it occurred in epitopes.

We examined $CD8^+$ T cell epitopes identified in three studies. In the first study, 454 MHC I-restricted $CD8^+$ T cell epitopes were identified by activation-induced marker assays.[6] 78% (121/155), 86% (133/155), 87% (135/155), 83% (128/155) of epitopes from the Spike protein and 92% (274/299), 96% (286/299), 93% (279/299), 96% (286/299) of epitopes from non-Spike protein were conserved in the BA.1, BA.2, BA.3, and GKA variant, respectively (Figure 1B). In the second study, a total of 122 $CD8^+$ T cell epitopes were identified by a systematic analysis using peptide-MHC class I complex multimers.[7] The conservation rates of $CD8^+$ T cell epitopes in the BA.1, BA.2, BA.3, and GKA variant were 93% (114/122), 88% (107/122), 91% (111/122), and 96% (117/122), respectively (Figure 1C). Nineteen dominant $CD8^+$ T cell epitopes were identified by a meta-analysis, and only BA.1 variant have mutation in these epitopes[8] (Figure 1D). In general, the majority of $CD8^+$ T cell epitopes are fully conserved both in Omicron subvariants (BA.1, BA.2, BA.3) and recombinant variant (GKA).

We also examined MHC II-restricted $CD4^+$ T cell epitopes that have been identified by Tarke et al. In the BA.1 variant, 65% (60/92) and 82% (155/188) of epitopes from the Spike and non-Spike

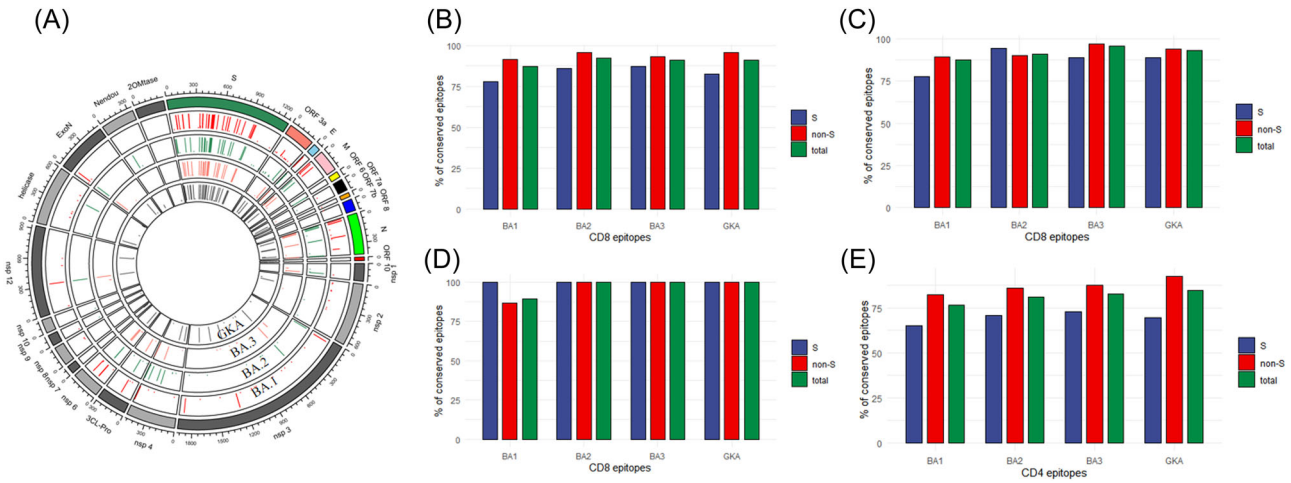

FIGURE 1 The characteristic of the SARS-CoV-2 Omicron subvariants in T cell epitopes. Genome-wide amino acid mutation rates of different subvariants of Omicron (A). Conservation rates in the $CD8^+$ T cell epitopes which were identified by Tarke et al. (B), Saini et al. (C), and Quadeer et al. (D), respectively. Conservation rates in the $CD4^+$ T cell epitopes in the Omicron subvariants (E).

protein, respectively, were conserved. In the BA.2 variants, 71% (65/92) of epitopes from Spike protein and 86% (162/188) of epitopes from the non-Spike protein were conserved. In the BA.3 variant, 73%(67/92) and 88% (165/188) of epitopes from the Spike and non-Spike protein, respectively, were conserved. And 70% (64/92) of epitopes from Spike protein and 93% (174/168) of epitopes from the non-Spike protein were conserved in the GKA variant (Figure 1E). In summary, most $CD4^+$ T cell epitopes are substantially conserved in the Omicron subvariants.

In conclusion, our study demonstrated that the majority of T cell epitopes are fully conserved in the Omicron subvariants (BA.1, BA.2, BA.3, and GKA).

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Peng Hu and Hu Li contributed to the study conception and design. Data collection were performed by Xiaoqing Liu and Zhiwei Chen. Analysis was performed by Xiaoqing Liu, Hu Li, and Zhiwei Chen. The first draft of the manuscript was written by Xiaoqing Liu, Peng Hu, Hu Li, and Zhiwei Chen revised it critically. All authors read and approved the final manuscript.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. World Health Organization. Weekly epidemiological update on COVID-19 - 5 April 2022, Edition 86; 2022.
2. Choi SJ, Kim DU, Noh JY, et al. T cell epitopes in SARS-CoV-2 proteins are substantially conserved in the Omicron variant. *Cell Mol Immunol*. 2022;19(3):447-448. doi:10.1038/s41423-022-00838-5
3. Viana R, Moyo S, Amoako DG, et al. Rapid epidemic expansion of the SARS-CoV-2 Omicron variant in southern Africa. *Nature*. 2022;603(7902):679-686. doi:10.1038/s41586-022-04411-y
4. Colson P, Fournier P-E, Delerce J, et al. Culture and identification of a "Deltamicron" SARS-CoV-2 in a three cases cluster in southern France. *J Med Virol*. 2022;94(8):3739-3749. doi:10.1101/2022.03.03.22271812
5. Bolze A, Basler T, White S, et al. Evidence for SARS-CoV-2 Delta and Omicron co-infections and recombination. 2022. doi:10.1101/2022.03.09.22272113
6. Tarke A, Sidney J, Kidd CK, et al. Comprehensive analysis of T cell immunodominance and immunoprevalence of SARS-CoV-2 epitopes in COVID-19 cases. *Cell Rep Med*. 2021;2(2):100204. doi:10.1016/j.xcrm.2021.100204
7. Saini SK, Hersby DS, Tamhane T, et al. SARS-CoV-2 genome-wide T cell epitope mapping reveals immunodominance and substantial $CD8^+$ T cell activation in COVID-19 patients. *Sci Immunol*. 2021;6(58):eabf7550. doi:10.1126/sciimmunol.abf7550
8. Quadeer AA, Ahmed SF, McKay MR. Landscape of epitopes targeted by T cells in 852 individuals recovered from COVID-19: meta-analysis, immunoprevalence, and web platform. *Cell Rep Med*. 2021;2(6):100312. doi:10.1016/j.xcrm.2021.100312