Discordant antibody and T cell responses to the SARS-CoV-2 Omicron variant in COVID-19 mRNA vaccine recipient

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Running title: Antibody and T cell responses to Omicron

Abstract

We compared antibody and T cell responses against the SARS-CoV-2 vaccine strain spike protein to responses against the Omicron variant in 15 mRNA vaccine recipients. While these individuals had significantly lower levels of antibodies that inhibited Omicron spike protein binding to ACE2, there was no difference in T cell responses.

Keywords: COVID-19; SARS-CoV-2; Omicron; antibodies; T cells

Introduction

The Omicron variant was first reported in November 2021 by scientists in South Africa. The variant contains more than 50 mutations, including 33 in the spike protein, and studies show that this results in evasion of vaccine-elicited neutralizing antibodies [1]. However, less is known about how these mutations impact the T cell response to the virus. We compared antibody and T cell responses to the vaccine strain and Omicron variant spike proteins in 15 mRNA vaccine recipients (VRs). Our data may partially explain the clinical outcomes seen in VRs with breakthrough Omicron variant infection.

Methods

We obtained blood from 15 VRs (7 men, 8 women) after informed consent was obtained. The study was approved by the Johns Hopkins University institutional review board. Eleven VRs received the Pfizer-BioNTech (BNT162b2) vaccine with a homologous booster, one VR received BNT162b2 followed by the Moderna (mRNA-1273) vaccine, and one VR received mRNA-1273 followed by a homologous booster vaccine. The other two VRs received two doses of BNT162b2 without a booster vaccine.

Twelve of the VRs were 21-30 years old, one was 41 to 50 years old and two were 51 to 60 years old. Informed consent was obtained from all study participants. Peripheral blood mononuclear cells (PBMCs) were isolated from whole blood using Ficoll centrifugation. mRNA for the nucleocapsid protein is not included in vaccines so natural infection was ruled out by screening for T cell responses to a pool of 57 nucleocapsid peptides at a concentration of 10 ug/ml (BEI, Manassas, VA). To measure the ability of participant plasma to inhibit ACE2 binding to spike proteins from the vaccine strain and multiple VOCs, we used the Meso Scale Discoveries pseudoneutralization/ACE2 inhibition assay (Rockville, Maryland, USA). The percent inhibition of ACE2 binding measured with this assay correlates well with the results of culture-based neutralization assays [2]. The assay was performed with plasma diluted at 1:100 as previously described [2]. We determined cellular immunity to the SARS-CoV-2 spike protein by

performing an interferon-γ (IFN-γ) Elispot assay with unfractionated PBMCs as previously described [3]. The assay was also performed with CD8+ T cell–depleted PBMCs to determine the relative contribution of CD4+ T cells and CD8+ T cells to the total T cell response. CD8+ T cells were removed by positive selection with CD8 MicroBeads (Miltenyi Biotec, Gaithersburg Maryland). This process typically removes > 90% of CD8+ T cells as determined by flow cytometry. To compare recognition of spike proteins from the vaccine strain and the Omicron variant, we stimulated PBMCs with overlapping spike peptide pools from both viruses at a concentration of 1 μg/mL (JPT, Berlin, Germany). Both spike peptide pools were made up of 315 peptides that were mostly 15 amino acids long with an overlap of 11 amino acids. Statistical comparisons were done using GraphPad Prism 9.2.0. Comparisons were made with One-way ANOVA with Geisser-Greenhouse correction Dunnet's multiple comparison test was done, with individual variances computed for each comparison. P value < 0.05 was considered significant.

Results

VR plasma contained significantly lower levels of antibodies that inhibited the binding of ACE2 to spike proteins from the Alpha, Beta, Delta, and Omicron variants than to the vaccine strain spike protein. ACE2 binding to the Omicron spike protein was least inhibited by the VR plasma. (Figure 1A).

In contrast, the VRs made robust T cell responses to peptide pools from both vaccine strain and Omicron spike proteins (Figure 1B). Interestingly, depletion of CD8+ T cells did not result in a significant decrease in the total T cell response to both sets of spike peptides, implying that CD4+ T cells were the major producers of IFN-g in the assay (Figure 1C). There was a strong correlation between T cell responses to spike peptides from the vaccine strain and from the omicron variant, with both total (Figure 1D) and CD8 depleted T cells (Figure 1E), suggesting cross recognition of epitopes in both proteins. None of the VRs had T cell responses to nucleocapsid peptides, supporting the absence of prior infection.

Discussion

In this study, we extended the results of previous studies on the ability of vaccine generated antibodies to block ACE-2 binding by comparing antibody and T cell responses in mRNA vaccine recipients. We found lower inhibition of binding of ACE2 to the Omicron spike protein versus vaccine strain, consistent with prior studies [1]. Despite discordant antibody responses, T cells from the vaccine recipients made comparably robust responses to overlapping peptides from vaccine and Omicron proteins. While prior studies have concluded that T cells induced by infection [4] and vaccination demonstrate recognition of prior variants [3, 5] and Omicron [6-9], we extend these findings by comparing these responses to functional antibody responses in the same individuals. We confirm T cell cross recognition of the Omicron variant and extend the findings by directly comparing these responses to functional antibody responses in the same individuals. Similar results have been recently reported by two other groups [10, 11]. Despite the large number of mutations present in the Omicron variant, the correlation between T cell responses to the vaccine strain and Omicron variant spike proteins supports cross recognition of epitopes. This lack of significant T cell escape by Omicron and prior variants is most likely due to the fact that mRNA vaccines induce broad T cell responses that target many different epitopes in the spike protein [3, 5, 9, 12]. These broad mRNA vaccine-elicited T cell responses will likely be effective against future variants of concern that evade antibody responses.

NOTES

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Figure legend

Antibody and T cell responses to vaccine strain and Omicron variant spike proteins. The level of antibodies that inhibit ACE2 binding to spike are shown for the vaccine strain, and different variants of concern (A). The number of SFU per million cells generated in response to stimulation with vaccine strain or Omicron variant spike peptides or nucleocapsid peptides (S2N) is shown for unfractionated PBMCs (B) and CD8-depleted PBMCs (C). Horizontal bars represent the median value. The frequency of SFU per million cells generated in response to stimulation with the vaccine strain spike peptides is compared to the frequency of SFU per million cells generated in response to Omicron variant spike peptides for PBMCs (D) and CD8-depleted PBMCs (E). The hexagon and square represent two VRs who received 2 vaccine shots but not a booster. The triangle represents the VR who received 3 mRNA 1273 shots and the diamond represents the VR who received 2 BNT162b vaccines and an mRNA 1273 booster 0.1234 (ns), 0.0332 (∗), 0.0021 (∗∗), 0.0002 (∗∗∗), <0.0001 (∗∗∗∗). Abbreviations: IFN-γ, interferon-γ; ns, nonsignificant; PBMC, peripheral blood mononuclear cell; SFU, spot forming units.

Figure 1

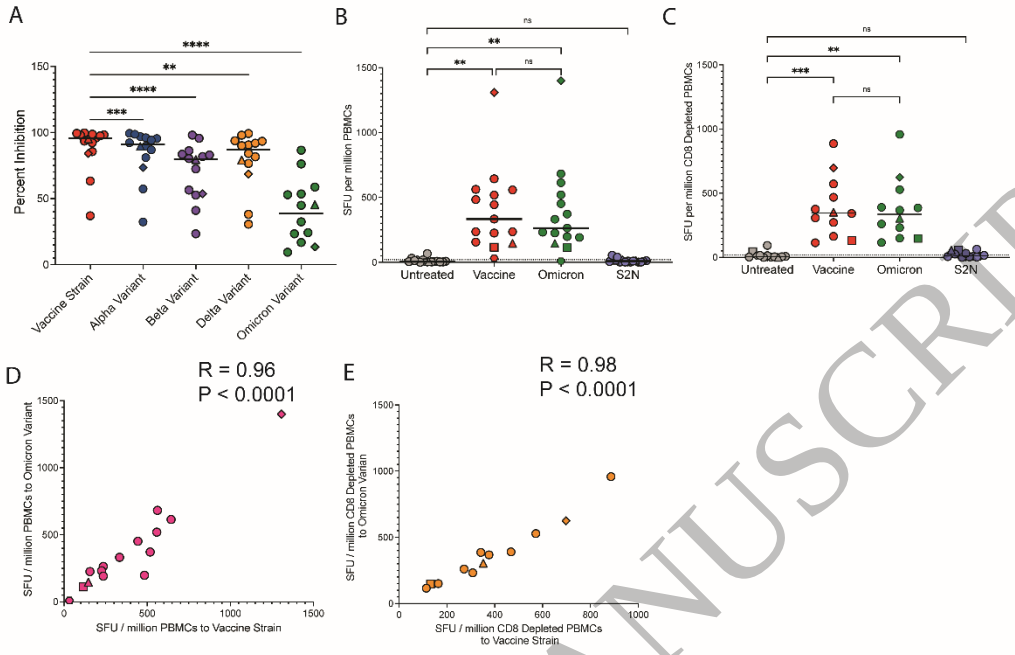

Figure 1
165x214 mm (0.2 x DPI)