Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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T cell receptor sequencing reveals reduced clonal breadth of T-cell responses against SARS-CoV-2 after natural infection and vaccination in allogeneic hematopoietic stem cell transplant recipients

Allogeneic hematopoietic stem cell transplantation (HSCT) recipients have a higher risk of developing severe coronavirus disease (COVID-19) and a higher mortality rate compared with the general population (Ljungman et al.[1]) potentially also as a consequence of their reduced ability to respond to vaccination (Mamez et al.[2]; Redjoul et al.[3]; Einarsdottir et al.[4]). To evaluate the magnitude and breadth of T-cell responses against SARS-CoV-2 in allogeneic HSCT recipients, we carried out high-throughput T cell receptor (TCR) repertoire profiling on cells recovered from allogeneic HSCT recipients or healthy controls (HC) after COVID-19 natural infection or messenger RNA (mRNA)-based vaccination.

Peripheral blood samples were obtained after COVID-19 infection from allogeneic HSCT recipients ($n = 11$; Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.annonc.2022.09.153) or HC ($n = 10$; Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.09.153). A total of 6 out of 11 patients were under immunosuppression for active ($n = 3$) or resolved ($n = 3$) graft-versus-host disease. T-cell receptor (TCR) beta sequencing (Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.09.153) identified SARS-CoV-2 specific T-cell clonotypes in both HC and HSCT recipients after COVID-19 infection (Figure 1A). No difference was observed in the proportion of T cells specific for SARS-CoV-2 between HSCT recipients and HC (data not shown). The diversity of the SARS-CoV-2-specific T-cell clonotypes, a measure previously shown to be inversely associated with severity of the disease (Elyanow et al.[5]), however, was significantly reduced in HSCT recipients compared with HC (Figure 1B). Enzyme-Linked ImmunoSpot (ELISpot) assay (Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.09.153) showed significantly lower numbers of interferon- γ (IFN-γ) spot forming units (SFU) after stimulation of PBMCs from HSCT recipients with peptides from both the SARS-CoV-2 spike (S) protein (Figure 1B, upper panel) and the membrane glycoprotein (M) plus the nucleocapsid phosphoprotein (N) proteins (data not shown) compared with HC. A significant positive correlation between SARS-CoV-2-specific T-cell clonotypes and IFN-γ SFU was observed (Figure 1B, upper panel). Conversely, we detected no significant difference in anti-S immunoglobulin G (IgG) titers and no correlation between antibody titers and different clonotypes (Figure 1B, middle panel). HSCT recipients displayed a less diverse TCR repertoire compared with HC as revealed by higher Simpson clonality and the Simpson clonality negatively correlated with the number of different SARS-CoV-2-specific T-cell clonotypes (Figure 1B, lower panel).

We next carried out the same analysis on samples recovered from allogeneic HSCT recipients ($n = 11$; Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.annonc.2022.09.153) or from healthy controls ($n = 10$) after vaccination with three doses of mRNA-based SARS-CoV-2 vaccines (Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.09.153). We observed a significant reduction in different S-protein-specific T-cell clonotypes in allogeneic HSCT recipients compared with HC (Figure 1C and D). ELISpot analysis revealed significantly lower numbers of IFN-γ SFU in HSCT recipients compared with HC and a slightly significant positive correlation between the ELISpot and the TCR-seq results (Figure 1D, upper panel). We observed slightly reduced anti-S titers in HSCT recipients compared with HC and a trend toward a positive correlation between S-specific clonotypes and anti-S titers (Figure 1D, middle panels). We detected a negative correlation between the Simpson clonality and the number of different S-protein-specific T-cell clonotypes after vaccination (Figure 1D).

Our results indicate that allogeneic HSCT recipients display reduced breadth of SARS-CoV-2-specific T-cell clonotypes after COVID-19 infection and vaccination. No clear correlation was detected between TCR clonal breadth and anti-S IgG titers. The clonal breadth defect was associated with increased T-cell clonality after HSCT, pointing to the reduced diversity of the TCR repertoire as a mechanism leading to impaired cellular responses against SARS-CoV-2 in HSCT recipients.

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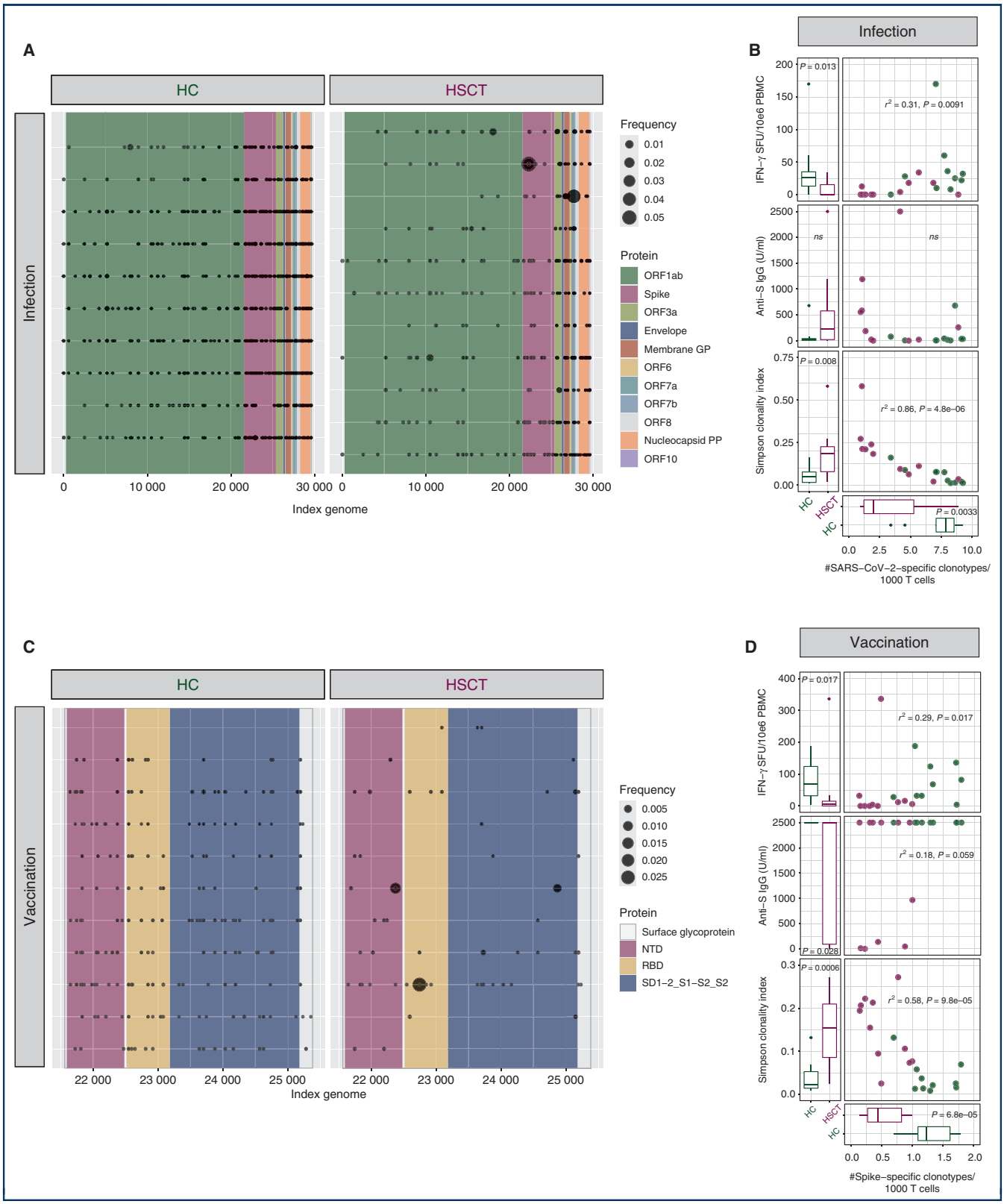

Figure 1. Reduced SARS-CoV2-specific T-cell clonotypes after COVID-19 infection and vaccination in allogeneic HSCT recipients. (A, C) SARS-CoV-2-specific T-cell clonotypes visualized based on the putative sequence of the SARS-CoV-2 genome recognized. (B, D) Scatter plots and marginal bar plots correlating and comparing the number of different SARS-CoV-2-specific T-cell clonotypes/1000 T cells, the anti-S IFN-γ SFU, the anti-S IgG titers and the Simpson clonality index in HC and HSCT. Differences between groups were assessed using the Mann—Whitney *U* test. Correlations were evaluated using a Spearman rank correlation coefficient test.
GP, glycoprotein; HC, healthy controls; HSCT, hematopoietic stem cell transplantation; IFN, interferon; IgG, immunoglobulin G; NTD, N-terminal domain; PP, phosphoprotein; RBD, receptor binding domain; SFU, spot forming units.

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DISCLOSURE

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