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SARS-CoV-2 (COVID-19)-specific T cell and B cell responses in convalescent rheumatoid arthritis: Monozygotic twins pair case observation

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Abstract

Rheumatoid arthritis (RA) patients present higher risk of SARS-CoV-2 infection (COVID-19), and proper management of the disease in this population requires a better understanding of how the immune system controls the virus. We analyzed the T cell and B cell phenotypes, and their repertoire in a pair of monozygotic twins with RA mismatched for COVID-19 infection. Twin- was not infected, while Twin+ was infected and effectively controlled the infection. We found no significant changes on the αβ T cell composition, while γδ T cells and B cells presented considerable expansion of memory population in Twin+ and robust T/B cell responses to several SARS-CoV-2 peptides. T cell receptor β/γ-chain and immunoglobulin heavy chain next-generation sequencing depicted a remarkable higher diversity in Twin+ compared with Twin-, despite no significant changes being found in variable/joining family usage. Repertoire overlap analyses showed that, although being identical twins, very few clones were shared between them, indicating that COVID-19 may lead to deep changes on the immune cell repertoire in RA patients. Altogether, our results indicate that RA patients may develop robust and persistent COVID-19-specific T/B cell responses; γδ T cells and B cells may play a key role in the management of COVID-19 in RA, and the infection may lead to a profound reshaping of immune cell receptor specificities.

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing the coronavirus infection 2019 (COVID-19), has affected >200 countries with around 400 million people infected and more than six million deaths worldwide. Despite few cases progressing to severe pneumonia and around 85% of patients presenting mild symptoms or being asymptomatic,[1] the prolonged use of immunosuppressants and underlying immune system dysregulation in rheumatoid arthritis (RA) patients might make this group more susceptible to COVID-19 than the general population, with a trend to higher disease severity.[2-5] Several advances have been made on describing in detail how the immune system responds to COVID-19,[6,7] but less is known about how this is done in RA patients

specifically. Recent data have reported a robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19 in general,[8] yet little is known whether the subset of patients with RA is also able to develop protective COVID-19-specific T/B cell responses.

2 | MATERIAL AND METHODS

2.1 | Study design

Monozygotic twin brothers aged 47 were included in the study. Both were diagnosed with RA for >15 years following the American College of Rheumatology (ACR) criteria.[9] At the time of this study, they both presented the same RA activity and were being both treated with methotrexate (20 mg/week) and adalimumab (40 mg every other week). The treatment was stopped in both twins after COVID-19 diagnosis in Twin+, following ACR guidance for RA management during the pandemic.[10] Both twins were negative for rheumatoid factor (RF IgM) and anti-citrullinated protein antibodies (CCP2 IgG). The participants provided written informed consent approved by the regional ethical research board.

Peripheral blood was collected and PBMCs isolated following standard guidelines.[11] Samples were collected from both twins 3 weeks after Twin+ became fully recovered, meaning no symptoms and negative RT-PCR for COVID-19.

2.2 | COVID-19 diagnosis

RT-PCR assay was used to detect the presence of SARS-CoV-2 nucleic acid in throat swab samples using the EURORealTime SARS-CoV-2 (Euroimmun, Germany, Lübeck) kit. Serum samples were used to evaluate the titres of anti-SARS-CoV-2 IgG and IgA antibodies (Euroimmun) at Karolinska University Hospital.

2.3 | FACS

PBMCs were stained as previously described.[11] The complete list of antibodies used can be found in the table S1. Cells were acquired in CytoFLEX cytometer (Beckman Coulter), and data analyzed with Flow Jo (TreeStar).

2.4 | Functional assay

PBMCs were seeded in Human IFN-γ/IL-2 FluoroSpot Kit (Mabtech, Sweden) plates and stimulated with PepMix SARS-CoV-2 nucleoprotein (NCAP) and spike glycoprotein (SG) from JPT Peptide Technologies (Berlin, Germany) for 18h at 37°C. The SARS-CoV-2 S1 domain of spike glycoprotein (S1) and S2 domain of spike protein plus nucleoprotein (S2+N) defined peptide pool from Mabtech were also used. Phytohemagglutinin was assessed as positive control. The plate was developed and read using Mabtech Iris (Mabtech).

SARS-CoV-2-specific B cell response was assessed by using the Human IgG SARS-CoV-2 RBD FluoroSpot (Mabtech) specific to the receptor binding domain (RBD) of the S1 domain. PBMCs were firstly stimulated with R848 + IL-2 for 96h and then transferred to precoated IgG FluoroSpot plate and incubated overnight. Total IgG production was also assessed.

2.5 | Immune cell receptors next-generation sequencing

Genomic DNA was isolated from PBMCs and applied for survey-level deep sequencing of the T cell receptor β-chain (TCRB) and immunoglobulin heavy chain (IGH) employing the ImmunoSEQ platform (Adaptive Biotechnologies, Seattle, WA). For TCR γ-chain (TCRG) sequencing, γδ T cells were purified using the Anti-TCRγ/δ MicroBead Kit (Miltenyi Biotec) prior to DNA isolation. NGS data analysis was performed as previously described.[11]

3 | RESULTS

Twin+ presented several days history of cough, loss of smell and taste and fever before having confirmed COVID-19 with RT-PCR on March 4. In the following 3 weeks, he presented flu-like symptoms and was medicated at home with analgesics and antipyretic drugs until the symptoms resolved completely on March 25. Corticosteroids were not administered. During the course of his infection, Twin+ stopped RA medication and no flares or disease worsening were noticed until medications resumed. Twin- presented persistent negative RT-PCR, but also transiently stopped medication. On April 15, both twins were sampled.

COVID-19 infection is associated with an intense dysregulation of immune responses.[12,13] To assess the degree of this dysregulation in the cellular compartment, we analyzed the αβ T cell composition. Twin- and Twin+ presented no differences on $CD4^+$ and $CD8^+$ T cell composition of effector-memory (TEM), central-memory (TCM) and $HLA\text{-}DR^+CD38^+$ populations, PD1 nor CD28 expressions (Figure S1).

We then assessed changes on unconventional γδ T cell composition. Twin+ presented notable decrease in $V\delta2^+$ and increase in $V\delta1^-V\delta2^-$ populations (Figure 1A). $V\delta2^+$ T cells showed a remarkable increase in TEM in Twin+, while $V\delta1^+$ population presented an increase in both TEM/TCM populations (Figure 1B). We found a twofold increase in $V\delta1^+CD27^{low/-}CD45RO^-$ adaptive like cells,[14] high NKG2D and low PD1 expressions in γδ T cells from Twin+ (Figure 1B-C).

In order to assess the COVID-19-specific T cell response, we performed a FluoroSpot assay using several COVID-19 peptides. Twin- showed no T cell responses to any of the peptides, as observed by IFNγ (Figure 1D) and IL-2 production (Figure S2). We found no signs of cross-reactivity, even against S2 peptides, a domain with high homology to other coronaviruses.[15] Twin+ showed high responses to NCAP, SG, S1 and some response to S2+N, confirming that he had developed persistent COVID-19-specific T cell responses (Figure 1D, Figure S2).[8]

As for B cell composition, Twin+ presented higher memory and lower naïve B cells percentage than Twin- and an increase in IgD^-IgM^- B cell population (Figure 1E). Twin+ also presented lower $CD24^{hi}CD38^{hi}$ immature/transitional and $CD24^{int}CD38^{int}$ frequencies, but higher frequency of $CD24^{hi}CD38^-$, $CD24^-CD38^-$, $CD24^{hi}CD27^+$ and $CD24^-CD27^{low}$ B cell populations than Twin- (Figure 1F-G). We then performed $ELISpot^{PLUS}$ to enumerate B cells secreting IgG antibodies specific to SARS-CoV-2 RBD domain, which present the lower homology with other coronaviruses as compared to S2.[15] We observed that Twin- presented no RBD-specific B cell response, while Twin+ showed increased SFU with increasing number of cells incubated (Figure 1H) and positivity for anti-SARS-CoV-2 IgA antibodies (ratio=2.2), further confirming his infection.

Next, we evaluated the immune changes at the repertoire level of TCRB, TCRG and IGH chains. Viral infections are associated with reduced TCR/BCR diversities due to the clonal expansion of virus-specific clonotypes, resulting in skewed spectratyping. Surprisingly, we found that Twin+ presented much higher diversity for all immune cell receptors evaluated (Figure 2A) and a gaussian CDR3 spectratype distribution (Figure 2B), indicative of a healthy and diverse repertoire distribution.

Previous reports have described that identical twins present higher variable-joining (V-J) similarities than unrelated people and biased segment usage.[16] Assessing the pairing of V-J gene segments in all chains, we found that Twin+ presented several changes on V-J pairing frequencies in TCRG chain, but few changes on TCRB and IGH chains (Figure 2C). Altogether, these data indicate that, despite that there is higher TCR diversity in the COVID-19+ twin, the most used V-J family usage and pairing are still very similar.

Next, we assessed the repertoire overlap between the twins and the presence of hyperexpanded clones in Twin+ as compared to Twin-. The chain with more overlapping clonotypes was TCRG (r^2 = .306), followed by TCRB (r^2=0.0802) and IGH, that presented just a single overlapping clonotype (r^2 = 0) (Figure 2D). We then annotated the clones hyperexpanded in Twin+, which could represent the ones COVID-19-specific. We found 124 TCRB, 215 TCRG and only 1 IGH clonotype enriched in Twin+as compared to Twin- (Table S2).

VDJdb database (https://vdjdb.cdr3.net) was searched for TCRB clonotypes specific to COVID-19 epitopes and to other common pathogens, as both twins presented positive serology for CMV. We observed that both twins presented prominent presence of cytomegalovirus-specific clonotypes and to influenza A (Figure 2E). Twin- presented considerable percentage of the Epstein–Barr virus (EBV)-specific clones but not a single TCRB clonotypes specific to COVID-19, while Twin+ presented very few clones EBV-specific and 0,001% of TCRB repertoire COVID-19-specific (Figure 2E). Table S3 presents the full description of the clones.

4 | DISCUSSION

Despite that several works have shed light into COVID-19 immune response,[6,7] important questions have remained unanswered, such as how RA patients´ immune system control the infection and whether this population can develop robust COVID-19-specific adaptive cell responses. Here, we report a unique observation of immunological changes associated with COVID-19 clearance in identical twins, male and seronegative for the most used RA-associated markers.[17] We found an expansion of $V\delta2^-$ γδ T cells in Twin+, indicating that these cells might play a role on COVID-19 infection control as earlier shown for CMV.[18] In fact, the increase in $V\delta2^-$ γδ T cells was associated with clinical benefits in recovered COVID-19 patients.[19] Further studies are required to confirm our findings, including a control group of non-RA patients.

A recent report have shown that seronegative exposed donors and patients with mild or asymptomatic COVID-19 developed a robust T cell response that can mediate long-term immune protection against reinfection.[8] RA patients present several immune aberrancies that may result in ineffective generation of a protective adaptive immune response protective to COVID-19.[4,20] Additionally, the prolonged use of immunosuppressants in this population also contribute to an overall higher risk of severe infections and to a defective immune response,[4] despite some reports not showing a clear association between disease severity with some rheumatic

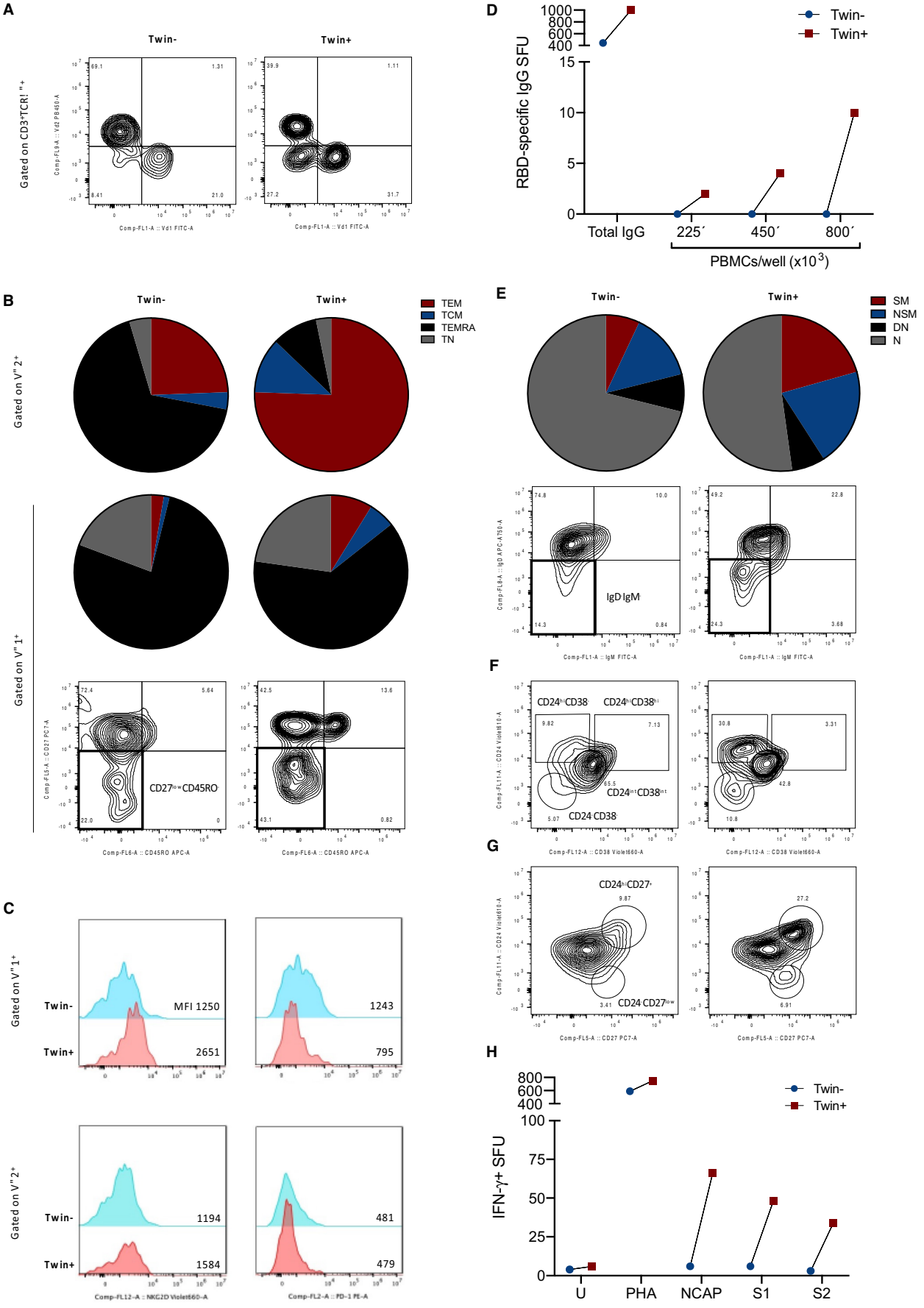
A
Twin-
Twin+
Gated on CD3+TCRγδ+
69.1
1.31
8.41
21.0
39.9
1.11
27.2
31.7
Comp-FL1-A :: Vd1 FITC-A
B
Twin-
Twin+
TEM
TCM
TEMRA
TN
Gated on Vγ2+
Gated on Vγ1+
72.4
5.64
22.0
0
42.5
13.6
43.1
0.82
CD27low CD45RO+
Comp-FL6-A :: CD45RO APC-A
C
Gated on Vγ1+
Twin-
Twin+
MFI 1250
2651
1243
795
Gated on Vγ2+
1194
1584
481
479
Comp-FL12-A :: NKG2D Violet660-A
Comp-FL2-A :: PD-1 PE-A
D
RBD-specific IgG SFU
1000
800
600
400
15
10
5
0
Twin-
Twin+
Total IgG
225´
450´
800´
PBMCs/well (x10^3)
E
Twin-
Twin+
SM
NSM
DN
N
74.8
10.0
14.3
0.84
IgD- IgM-
69.2
22.8
24.3
3.68
Comp-FL1-A :: IgM FITC-A
F
CD24hiCD38-
CD24hiCD38hi
9.82
7.13
5.5
CD24intCD38int
5.07
CD24-CD38-
30.8
3.31
42.8
10.8
Comp-FL12-A :: CD38 Violet660-A
G
CD24hiCD27+
9.87
3.41
CD24-CD27low
27.2
6.91
Comp-FL5-A :: CD27 PC7-A
H
IFN-γ+ SFU
800
600
400
100
75
50
25
0
Twin-
Twin+
U
PHA
NCAP
S1
S2

FIGURE 1 Twin+ presented COVID-19-specific T/B cell responses. A, Vδ1 and Vδ2 expression by γδ T cells. B, FACS characterization of effector-memory (TEM, $CD45RO^{+}CCR7^{-}$), central-memory (TCM, $CD45RO^{+}CCR7^{+}$), CD45RA-expressing effector-memory (TEMRA, $CD45RO^{-}CCR7^{-}$) and naïve (TN, $CD45RO^{-}CCR7^{+}$) population distribution in $V\delta1^{+}$ and $V\delta2^{+}$ cells. $V\delta1^{+}CD27^{low}CD45RO^{-}$ population is highlighted. C, NKG2D and PD1 expression (median fluorescence intensity, MFI) by $V\delta1^{+}$ and $V\delta2^{+}$ γδ T cells. D, T cell response to COVID-19 peptides measured by $IFN\gamma^{+}$ spot forming units (SFU). U, untreated; PHA, phytohemagglutinin; NCAP, nucleoprotein; S1, S1 domain of the spike glycoprotein; S2, S2 domain of the spike glycoprotein. (E) CD19+ B cell FACS characterization of switched-memory (SM, $CD27^{+}IgD^{-}$), non-switched-memory (NSM, $CD27^{+}IgD^{+}$), double-negative (DN, $CD27^{-}IgD^{-}$) and naïve (N, $CD27^{-}IgD^{+}$). $IgD^{-}IgM^{-}$ population is highlighted. (F) Distribution of $CD24^{hi}CD38^{-}$ memory, $CD24^{hi}CD38^{hi}$ immature, $CD24^{-}CD38^{-}$ memory and $CD24^{int}CD38^{int}$ naïve populations in total $CD19^{+}$ B cells. (G) Distribution of $CD24^{hi}CD27^{+}$ regulatory and $CD24^{-}CD27^{low}$ B cells. (H) B cell response to COVID-19 peptides measured by receptor binding domain (RBD)-specific IgG SFU. Total IgG was analyzed using 75.000 PBMCs

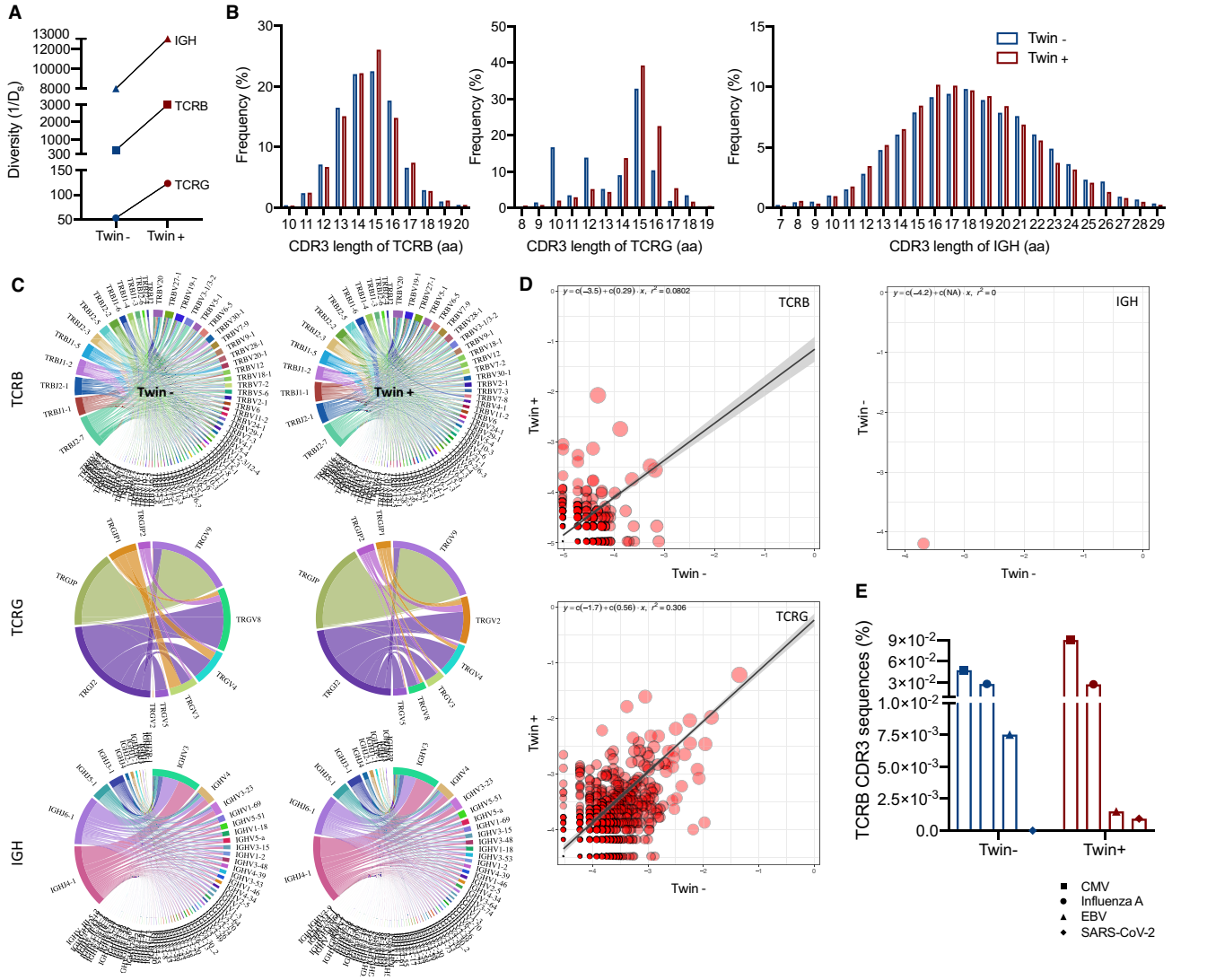

FIGURE 2 Twin+ displayed higher TCR/BCR diversity than Twin-. A, TCRB, TCRG and IGH diversity metrics measured as inverse Simpson´s index ($1/D_s$). B, TCRB (left), TCRG (middle) and IGH (right) CDR3 spectratype. Bars represent frequency of unique CDR3 sequences with different amino acid (aa) lengths. C, Variable-joining segments pairing in CDR3 sequences of TCRB (upper), TCRG (middle) and IGH (bottom) chains. Chord diagram is used for visualization, ribbons connecting segment pairs are scaled by corresponding V-J pair frequency. D, TCRB, TCRG and IGH repertoire overlap. The clonotype abundance scatter plot shows the CDR3 sequences overlap between twins. The main frame contains a scatterplot of overlapping clonotypes and a linear regression. Point size is scaled to the clonotype abundance in both samples. The axes represent log10 clonotype frequencies in each sample. R^2 represents squared Pearson's correlation coefficient. E, Percentage of TCRB CDR3 sequences specific to cytomegalovirus (CMV), influenza A, Epstein–Barr virus (EBV) and COVID-19 (SARS-CoV-2)

diseases.[21,22] In fact, a recent report has shown that the magnitude of specific responses to COVID-19 mRNA vaccine was dependent on the immunosuppressive therapy administered.[23] Our work shows that RA patients can develop robust and persistent COVID-19-specific T/B cell responses that can provide long-term immune protection. The life span of these cells in patient's circulation still requires investigation, and more data are required to understand how the immunosuppression can affect the patients´ immune cell distribution and their effect on infection susceptibility.

Despite the stochastic nature of T cell and B cell clonotypes generation, identical twins present high similarity in TCR V-gene segment usage and increased number of identical CDR3 sequences when compared to unrelated individuals.[16,24] This makes studies with twins quite valuable in autoimmune diseases and infections. Here, we report unexpected low clonotype sharing between twins, probably as a result of immune repertoire reshaping induced by COVID-19 infection. Infections trigger massive T cell expansion, leading to the skewing of the TCR repertoire due to antigen-specific T cell expansion, as observed in CMV.[11] Overall, our results indicate that a remarkable reshaping of the TCR and BCR repertoires might take place after COVID-19 infection in RA. Further investigation is required to assess whether the sequences here reported are protective to COVID-19 infection,[25] including longitudinal sampling and the assessment of a control group.

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CONFLICT OF INTEREST

The authors have no competing interests.

AUTHOR CONTRIBUTIONS

LCMA and AG performed experiments, collected and analyzed the data, wrote the paper and approved the final version of the manuscript; RSR and BM provided key/unique reagents, wrote the paper and approved the final version of the manuscript. MU provided key/unique reagents, supervised the study, wrote the paper and approved the final version of the manuscript.

ETHICS STATEMENT

The study was performed in accordance with the Declaration of Helsinki and approved by the Regional Ethical Review Board of Stockholm, Sweden.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in immuneACCESS at https://doi.org/10.21417/LCMA2022SJI.[26]

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SUPPORTING INFORMATION

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