IgG from patients with mild or severe COVID-19 reduces the frequency and modulates the function of peripheral mucosal-associated invariant T cells in PBMCs from healthy individuals

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Abstract. Lower levels of peripheral mucosal-associated invariant T (MAIT) cells have been observed in the peripheral blood of patients with severe coronavirus disease 2019 (COVID-19). Following on from previous research into the effect of the IgG repertoire on human lymphocytes, the present study aimed to evaluate if immunoglobulin G (IgG) antibodies obtained from patients with mild or severe COVID-19 contribute to these effects on MAIT cells. Culture experiments were performed using healthy human peripheral blood mononuclear cells (PBMCs) and different repertoires of IgG obtained from patients with COVID-19 as a mild or severe disease and compared with mock, healthy control or therapeutic IgG conditions. The results indicate that the IgG repertoire induced during the development of mild and severe COVID-19 has, *per se*, the *in vitro* potential to reduce the frequency of MAIT cells and the production of IFN-γ by the MAIT cell population in PBMCs from healthy individuals. In conclusion, the results of the present study indicate that IgG in patients with severe COVID-19 may participate in the reduction of peripheral MAIT cell frequency and hinder the antiviral activity of these cells.

Introduction

In 2020 a study reported a decline in peripheral mucosal-associated invariant T (MAIT) cells in patients with active Coronavirus disease 2019 (COVID-19) (1). The same study indicated significant MAIT cell enrichment and IL-17 production in the airways with normalized levels of MAIT cells in the convalescent phase, indicating that these cells are engaged in the immune response against severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and may be involved in COVID-19 immunopathogenesis. A year later, it was demonstrated that altered MAIT cell functions could contribute to the severity of COVID-19 and that the therapeutic manipulation of MAIT cells may prevent disease aggravation (2). More recently, another study indicated that severe COVID-19 is associated with a reduced frequency of peripheral MAIT cells in convalescent individuals (3). However, this issue has not been adequately explored, and the possible role of an induced immunoglobulin G (IgG)-mediated immune response has not been evaluated. The present research group has been investigating the role of the IgG repertoire in the induction, regulation and modulation of the development of human diseases, and has proposed the 'hooks without bait' hypothesis (4). In this research program, evidence has been found to indicate that the human naturally produced or induced IgG repertoire, obtained from different immune backgrounds, can mediate some functional and phenotypic modulations of healthy human thymic and peripheral T and B cells, including $CD4^+$, $CD8^+$ and γδ T-cell receptor $(\gamma\delta\ TCR)^+$ T cells, and that the modulation profile may be associated with the development or control of atopic (5-12) or infectious diseases (13). These approaches may contribute to the development of immune signatures associated with the development or severity of several diseases. Based on those evidence, the present study aimed to evaluate if the development of mild or severe COVID-19 induces the establishment of an IgG repertoire that can, at some point, be involved in the development of a disease-related immune phenotype.

Materials and methods

Samples. Blood samples from the Central Laboratory Division of the Clinics Hospital of the Faculty of Medicine of the University of São Paulo (São Paulo, Brazil) were used. Serum samples were isolated and kept at -20˚C until used for IgG purification. As an inclusion criterion, the diagnosis of

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COVID-19 was confirmed via the detection of SARS-CoV-2 RNA by reverse transcription-polymerase chain reaction. Patients aged >75 years and those who did not test positive for SARS-CoV-2 were excluded from the study. As IgG donor controls, 40 samples from healthy individuals [17 males and 23 females; age (mean ± SE): 28.5±2,3 years] collected prior to the COVID-19 pandemic from March to July 2019 were used.

The cohort of 79 patients infected with COVID-19 included 39 males and 40 females. Patients were categorized based on the World Health Organization classification of 2020 (https://apps.who.int/iris/handle/10665/332196): Hospitalized patients who did not receive oxygen therapy or who received oxygen by a mask or nasal cannula were considered to be mild cases (n=39); patients admitted under non-invasive ventilation or high-flow oxygen were considered severe cases (n=40); and patients admitted under invasive ventilation without or with additional support for another organ, for example, extracorporeal membrane oxygenation or replacement therapy, were considered critical cases. In the present study severe and critical cases were evaluated together and termed as severe. The samples from patients with COVID-19 were obtained from May to July 2020.

Blood samples from 10 volunteers (2 males and 8 females) were collected in EDTA and used for the isolation of peripheral blood mononuclear cells (PBMCs) on the day of collection. As an inclusion criterion, it was confirmed that these volunteers had not tested positive for SARS-CoV-2 and had no clinical or laboratory COVID-19 diagnosis history. The samples were obtained from PBMCs donors from February to May 2022 and PBMCs were isolated by via centrifugation in a density gradient using Ficoll-Paque (GE Healthcare Bio Science) at 540 x g for 20 min at 21˚C. Detailed information about the patients with COVID-19 and the PBMC donors is presented in Tables SI and SII, respectively. The Ethics Committee at the School of Medicine at the University of São Paulo approved the study [Certificado de Apresentação de Apreciação Ética (CAAE): 63361622.7.0000.0068 and 70823623.0.0000.0068], and written consent was obtained from all participants.

IgG purification. IgG was purified from pooled serum using a Melon™ Gel IgG Spin Purification Kit (Thermo Fisher Scientific, Inc.) in accordance with the manufacturer's protocol. Purified IgG was collected, sterilized using 0.20-μm filters (Corning Life Sciences), and stored at -80˚C for use in cell culture experiments. IgG concentrations were determined using Coomassie Protein Assay Reagent (Pierce; Thermo Fisher Scientific, Inc.) in accordance with the manufacturer's instructions. The purity of the IgG, as evaluated by SDS-PAGE, was >95%. All pools were evaluated for the presence of IgA, IgM and IgE antibodies, all of which were undetectable.

Cell culture and flow cytometry. Suspensions of PBMCs were washed and resuspended in RPMI-1640 medium containing 10% FetalClone™ III (FC-III; HyClone; Cytiva). Using a Neubauer chamber, an aliquot of the cell suspension was diluted in trypan blue (Sigma-Aldrich; Merck KGaA) to evaluate the cell viability and number. Then, $1x10^6$ viable PBMCs were placed in each well of a 96-well culture plate (Costar; Corning, Inc.) and cultured with 100 μg/ml IgG purified from the pooled serum samples of patients with mild or severe COVID-19 in RPMI-1640 medium containing 10% FC-III. As controls, the mock condition (absence of IgG), the addition of 100 μg/ml therapeutic intravenous IgG (IVIg; Baxter International Inc.) or the addition of IgG purified from the serum of healthy controls were used. The culture plates were incubated for 3 days at 37˚C in 5% CO_2, and 1 μg/ml brefeldin A (Sigma-Aldrich; Merck KGaA) was added in the last 12 h for intracellular staining. Cell staining was performed and cell labeling was evaluated via flow cytometry. For cell viability analysis, the cells were incubated with LIVE/DEAD™ (PE-Texas red) fluorescent reagent (Thermo Fisher Scientific, Inc.). All extracellular and intracellular analyses were performed using viable cells.

To perform extracellular staining, PBMCs were transferred to test tubes, and 1 μg each antibody was added to the cells, with the exception of the unlabelled tubes. The samples were then incubated for 30 min at 4˚C while protected from light. After that, 500 μl PBS solution was added, and the tubes were centrifuged at 400 x g for 5 min at 21˚C. The supernatant was discarded by inverting each tube. Then, PBS was added, followed by fixation in 200 μl 1% formaldehyde for ≥10 min at 8˚C. The PBMCs were then incubated with mouse anti-human CD3 (BV421; cat. no. 555412), CD19 (FITC; cat. no. 555412), CD14 (PerCP-Cy5.5; cat. no. 562692), CD45 (PeCy7; cat. no. 557748), CD161 (BV510; cat. no. 563212), CD4 (BV605 cat. no. 562658), CD8 (APC-Cy7; cat. no. 557834), γδTCR (FITC; cat. no. 347903) and Vα7.2 (PE; cat. no. 566739) or isotype control antibodies (BD Pharmingen; BD Biosciences) for 20 min at 8˚C.

To perform intracellular labeling, tubes containing PBMCs were centrifuged at 400 x g for 5 min at 21˚C, the supernatant was discarded, and 1 μg each antibody was added to the cells, with the exception of the unlabelled tubes. Then, 100 μl PBS containing 0.05% saponin permeabilization reagent was added, and the tubes were stored at 4˚C for 30 min while protected from light. After centrifugation at 400 x g for 5 min at 21˚C, the supernatant was discarded by inverting each tube, and the cells were resuspended in 300 μl PBS solution. The PBMCs were then incubated with mouse anti-human IFN-γ (APC; cat. no. 551385) and IL-17 (Alexa 700; cat. no. 560613) or isotype control conjugated with the corresponding fluorochromes for 20 min at 8˚C (BD Pharmingen; BD Biosciences).

Using an LSRII Fortessa™ flow cytometer (BD Biosciences), 500,000 events per PBMC sample were acquired in the lymphocyte quadrant, as determined by their relative size/granularity. Compensation was performed using adsorbed microspheres (CompBeads; BD Biosciences) treated with the antibodies used for extra- and intracellular staining. Cell gating was based on the specific isotype control values as well as the fluorochrome minus 1 setting. $CD45^{high}CD14^{-}CD19^{-}CD3^{+}CD161^{+}V\alpha7.2^{+}$ live lymphocytes were considered MAIT cells (Fig. S1). The frequencies of $\gamma\delta TCR^{+}CD3^{+}$, $CD4^{+}CD8^{-}$, $CD8^{+}CD4^{-}$ and $CD19^{+}CD8^{-}CD4^{-}$ live lymphocytes were also determined to evaluate the frequency of γδT, $CD4^{+}$ T, $CD8^{+}$ T and B cells, respectively. Data analysis was performed using FlowJo software (Version 10.8; Tree Star, Inc.), and only the extra- and intracellular staining of viable cells was analyzed.

Statistical analysis. Statistical analysis was performed using GraphPad Prism 5.0 (GraphPad Software; Dotmatics). *In vitro* data were obtained from 6 separate experiments with 1 or 2 samples. $P \leq 0.05$ was considered to indicate a statistically

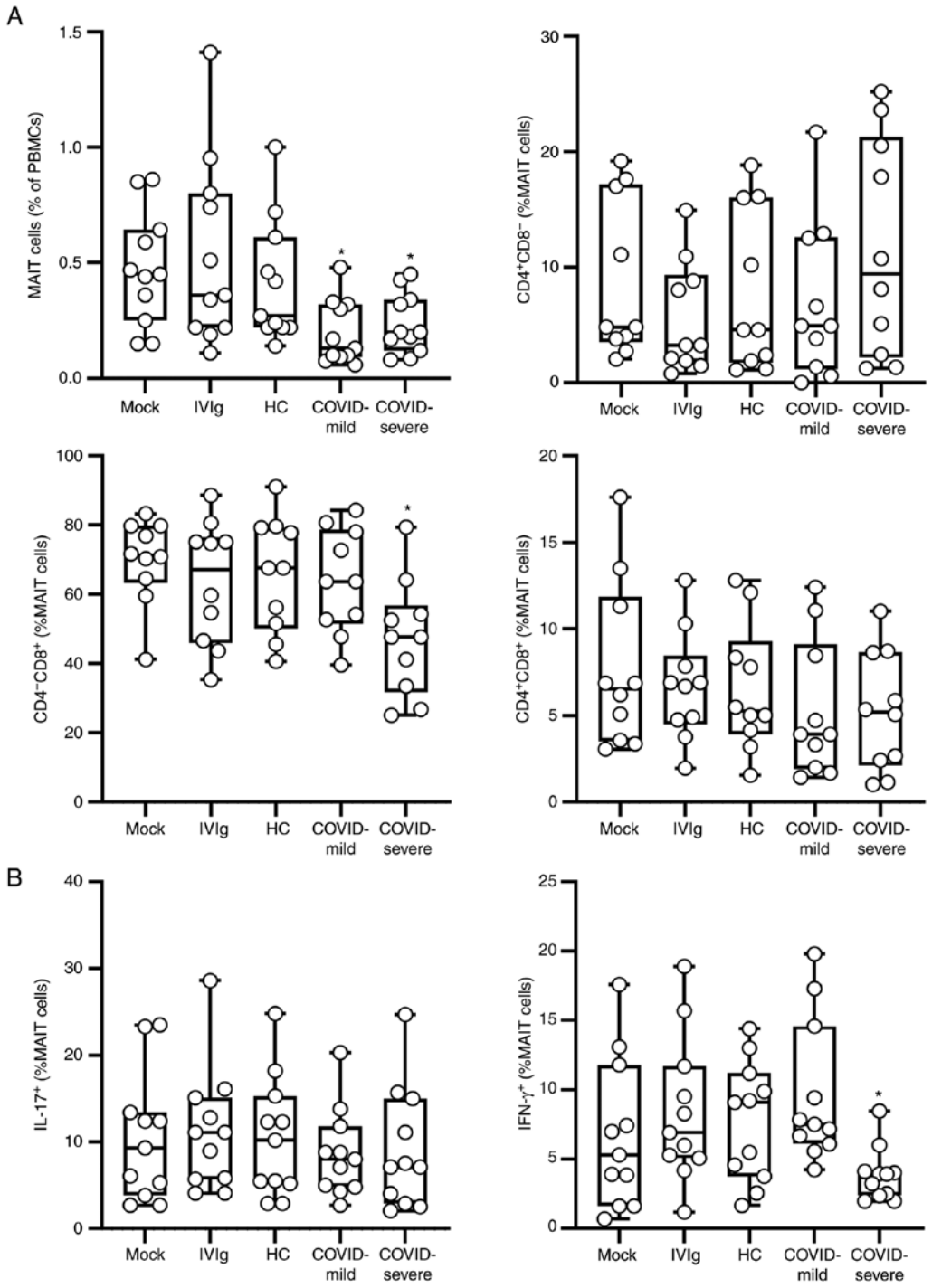

Figure 1. Frequency, phenotype and intracellular cytokine production of cultured MAIT cells. PBMCs from healthy individuals (n=10) were cultured with 100 μg/ml purified IgG from patients with mild COVID-19 (n=39) or severe COVID-19 (n=40) for 3 days. The controls were mock treated in the absence of IgG, treated with IVIg or treated with IgG from HCs (n=40) obtained prior to the COVID-19 pandemic. After culture, PBMCs were evaluated for the (A) frequency extracellular expression of CD4 and CD8 co-receptors and (B) intracellular production of IL-17 and IFN-γ. *P≤0.05 compared with control conditions. MAIT, mucosal-associated invariant T; PBMCs, peripheral blood mononuclear cells; IgG, immunoglobulin G; COVID, coronavirus disease 2019; IVIg, intravenous immunoglobulin IgG for therapeutic use; HC, healthy control.

difference, as assessed by one-way ANOVA using Tukey's post hoc test for multiple comparisons among all groups.

Results

The frequency of MAIT cells (Fig. S1) was first identified and evaluation of the results revealed that purified IgG obtained from mild and severe cases of COVID-19 reduced the frequency of these cells compared with the frequency under control conditions (Fig. 1A). When evaluating the expression of co-receptors, it was observed that purified IgG obtained from severe COVID-19 cases reduced the frequency of $CD4^{-}CD8^{+}$ MAIT cells compared with that of the controls. No difference in the frequency of the phenotypes $CD4^{+}CD8^{-}$ or $CD4^{+}CD8^{+}$ was observed when all culture conditions were compared. When the intracellular production of cytokines was evaluated,

it was observed that IgG from patients with mild or severe COVID-19 did not influence the intracellular production of IL-17 in MAIT cells. It was also observed that IgG from severe cases of COVID-19 reduced the frequency of IFN-γ-producing MAIT cells compared with that of the controls, while mild COVID-19 IgG had no effect (Figs. 1B and S2). Finally, whether the experimental conditions influenced the frequency of important peripheral human lymphocyte populations was evaluated, but none of the evaluated conditions influenced the frequency of γδT, $CD4^+$ T, $CD8^+$ T and B cells (Figs. S3-5).

Discussion

It was recently reported that downregulated levels of peripheral MAIT cells were observed in the peripheral blood of patients who had recovered from severe COVID-19[3], corroborating previous and recent observations in the literature (1,2). The results of the present study indicate that the IgG repertoire induced during the development of mild and severe COVID-19 has, *per se*, the *in vitro* potential to reduce the frequency of the MAIT cell population in healthy individuals. It has also been demonstrated that peripheral lymphopenia could be related to COVID-19 disease severity and mortality (14,15). However, this phenomenon is potentially associated with several aspects of COVID-19 development, including intense cytokine production at the primary site of infection, and may differentially encompass the peripheral populations of lymphocytes, an aspect that continues to be investigated and in which MAIT cells may have a role. Furthermore, lymphopenia has been described in patients infected with various viruses from different families, indicating that the possible mechanisms engaged in this process are not specific to individual viral families and may include the host antibody response (16), a mechanism that remains vague. Combining those pieces of evidence, it may be hypothesized that the reduced frequency of peripheral MAIT cells is due to the high levels of circulating COVID-19-induced IgG, a major characteristic of the convalescent period, corroborating the results of other researchers (3). However, the results obtained in the present study did not indicate differences in the MAIT cell reduction intensity between mild or severe IgG, possibly because the experimental protocols did not fully reproduce *in vivo* conditions. These differences may include aspects such as the concentration of IgG, which may differ between conditions, and the inclusion criteria for each COVID-19 group, which also differ between studies.

The ability of MAIT cells to produce IL-17 and modulate inflammatory responses has been known for over a decade (17). In the present study, whether this major functional parameter was influenced by IgG obtained from patients with different COVID-19 severity was evaluated, but no influence was observed.

When evaluating the intracellular production of cytokines, it was observed that the production of IFN-γ by MAIT cells was reduced by the IgG of patients with severe COVID-19 and not by that of patients with mild COVID-19. IFN-γ-producing MAIT cells have been associated with the control of bacterial infections (18), and their production is related to the $CD8^+$ MAIT cell phenotype and cytotoxic activity (19). The IgG from patients with severe COVID-19 reduced the frequency of $CD4^-CD8^+$ and IFN-γ-producing MAIT cells, indicating a reduction in the antiviral activity mediated by these cells. This observation substantiates the development of more severe disease development. It also corroborates previous evidence about MAIT cells in COVID-19 by indicating that the total frequency of MAIT cells is reduced and may specifically affect certain MAIT cell subpopulations. However, the role of $CD8^+$ MAIT cells in COVID-19 severity is under investigation, and its precise role requires elucidation.

Unfortunately, the approaches used in the present study were limited and did not elucidate the possible mechanisms that may mediate the IgG-induced reduction of peripheral MAIT cells; however, from some similar approaches used in other studies, some possibilities may be suggested. It was recently demonstrated in a similar protocol using purified IgG *in vitro* that IgG directly interacts with the membrane of another unconventional T-cell population with a limited diversity of clonal receptors, namely γδT cells (12). The induction of apoptosis was not evaluated in the present study, but it may be considered as a possible mechanism for the reduction in MAIT cell frequency since single-cell transcriptomic profiling has already indicated that cell death is a main cause of the reduction in MAIT cell frequency during severe COVID-19 (20). The biological relevance of a reduced frequency of peripheral MAIT cells in the development of protective immunity against SARS-Cov-2 requires elucidation. However, it was recently demonstrated that MAIT cells might contribute to T-cell responses, including the priming of T follicular helper cells, and the induction of humoral immunity (21).

In conclusion, the findings of the present study indicate the potential of a severe COVID-19-induced IgG response to mediate a reduction in the frequency of peripheral MAIT cells, particularly that of IFN-γ-producing MAIT cells. This unprecedented observation contributes to elucidation of the mechanism by which this peripheral MAIT cell reduction may occur in patients with severe COVID-19. Finally, it is suggested that future investigations should focus on understanding the COVID-19-induced IgG repertoire as a mediator of immune alterations in severe and critical cases.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

NRM and BOF performed *in vitro* experiments. IGF and DTAR selected the patients and collected blood samples. MNS collaborated with the design of the study and writing the manuscript. JRV designed the study, wrote the manuscript, and coordinated the activities of the other authors. JRV, NRM and BOF confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the School of Medicine at the University of São Paulo (CAAE: 63361622.7.0000.0068 and 70823623.0.0000.0068).

Patient consent for publication

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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