Research Square

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Phenotypes and Functions of Dendritic Cells in SARS-CoV-2 Vaccine-derived Humoral Immunity

An Cui
National Medical Center for Infectious Diseases, Fudan University
Anni Li
National Medical Center for Infectious Diseases, Fudan University
Wei Hu
National Medical Center for Infectious Diseases, Fudan University
Chao Wang
Huashan Hospital
Dian Zhang
Huashan Hospital
Jia Tang
National Medical Center for Infectious Diseases, Fudan University
Xiangyu Qin
National Medical Center for Infectious Diseases, Fudan University
Junwei Qian
Huashan Hospital
Abolaihaiti Maimaitimin
Huashan Hospital
Jingwen Ai
National Medical Center for Infectious Diseases, Fudan University
Wenhong Zhang
National Medical Center for Infectious Diseases, Fudan University
Mingquan Chen (mingquanchen@fudan.edu.cn)
National Medical Center for Infectious Diseases, Fudan University

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Abstract

DCs regulate humoral immunity against SARS-CoV-2 by regulating CD4 + T cell activation, but the relations between DC phenotypes and functions and anti-RBD antibodies are unclear. We conducted this observational study in Huashan Hospital using a third 6.5U BBIBP-CorV or 25 μg ZF2001 administered at an interval of 4 to 8 months following the previous two doses in healthy adults. anti-RBD response and neutralizing titers against SARS-CoV-2 and VOCs were examined. DC maturation markers and pattern recognition receptors and cytokines produced by DC were measured, and DC function was tested in mixed lymphocyte reaction(MLR). Mean anti-RBD Ab and IgG rose from 22.08 and 9.17 on D0 to 4704.18 and 798.11 on D14(BAU/ml). Meanwhile, the surrogate virus neutralization test(sVNT) elevated from 17.15 on D0 to 2538.83 on D14. The expression of DC maturation markers on D3 and MLR were negatively correlated to sVNT, anti-RBD antibody, and IgG titers on D14(Spearman r=-0.558~-0.326) and D28(Spearman r=-0.615~-0.397), but positively correlated to IgG/Ab ratio(Spearman r = 0.249 ~ 0.509). DC function in activating T cells was also negatively related to anti-RBD antibody titer on D28(r=-0.532~-0.453, p = 0.015 ~ 0.035), and positively correlated with the proportion of anti-RBD IgG in Ab(r = 0.490 ~ 0.561, p = 0.010 ~ 0.032). DC-SIGN level showed a relation to antibody titer and IgG proportion opposite to DC maturation and function and was negatively related to the level of IL-10 produced by DCs. Our research suggested that DCs controlled CD4 + T cells in differentiating into regular T cells, and DC-SIGN might restrain T regular cells by suppressing IL-10 production of DC in anti-SARS-CoV-2 vaccination.

1. Introduction

The severe acute respiratory syndrome-coronavirus-2(SARS-CoV-2) has infected more than 3 hundred million people infected, with more than 5 million deaths because of coronavirus disease-2019(COVID-19) [36]. Global health is under a great threat of pandemics around the world.

Vaccines are the most effective weapons against infectious diseases. Nowadays several types of SARS-CoV-2 vaccines have been used broadly around the world against the spread of the virus in individuals with different conditions and have shown comparable capacity in priming a great titer of antigen-specific immunoglobulins[18, 35, 37, 43, 14, 2, 27, 12, 1]. However, vaccination has not completely ceased the pandemic, breakthrough infections occurred frequently after immunization with various vaccines[25]. One of the most important reasons is that the immune condition varies among individuals, as vaccines could not trigger enough cellular or humoral immunity in immunocompromised people[38, 28, 23, 4, 8]. Several studies have already revealed that antibody(Ab) titer is significantly correlated with the efficacy of vaccines, even in protecting against variants of concern(VOC)[11, 16, 6]. However, the key immune factors affecting the anti-S immunoglobulin titer have not been illuminated. It is important to understand the underline immune mechanism and reveal the immunologic difference among individuals.

Dendritic cells(DC) are the most important antigen-presenting cells(APC) with the most effective capacity in antigen presentation and the ability to activate naive T cells[5]. T cells primed by DCs will differentiate

into CD8 + T cells, CD4 + T helpers including Th1, Th2, Th17, T follicular helper(Tfh), etc, and T regulatory cells(Treg), which all depend on the help that DCs provide to naïve T cells [5]. When viruses intrude, DCs recognize them via different pattern recognition receptors(PRR) to combine with pathogen-associated molecular patterns(PAMP) and internalize them via endocytosis or macropinocytosis. After that, activated DCs present antigens via peptide - major histocompatibility complex(MHC)-I OR -II to naïve T cells. At the same time, several costimulating signals and cytokines provided by DCs help T cells mature and differentiate. DCs express B7-1(CD80), B7-2(CD86), OX40L, and inducible costimulatory(ICOS) ligand(ICOSL) and produce IL-6 and other cytokines, which prime differentiation towards Tfh[5, 39]. As is known, Tfh is the key helper in the germinal center(GC) development, as multiple mechanisms in Tfh- GC B interaction guarantee B cells maturation, affinity choosing, and differentiation towards plasmacytes or memory B cells[33, 34]. Accordingly, DCs appear in the role of a sentinel and a forerunner of vaccine-induced humoral immunity.

There have been several pieces of research revealing changes in the function and relocation of DC during SARS-CoV-2 infection. They showed that Toll-like receptors (TLR)3 and 7/8 were the PRRs of DCs and macrophages in recognizing virus nucleic acids and triggering inflammation[7]. Besides, TLR2 and 4 were shown to bond viral proteins such as spike protein(S) and envelop protein(E) and induce inflammation via nuclear factor kappa light chain enhancer of activated B cells (NF-κB)-dependent and independent pathways[42, 31, 22, 41]. S protein, as a hyper-glycosylated protein, can also be recognized by other PRRs such as C-type lectin receptors(CLR)[26, 3]. Dendritic cell-specific intercellular adhesion molecule-3 grabbing non-integrin(DC-SIGN), a CLR expressed specifically on several myeloid cells, has been revealed to bond S protein. This reaction can not only induce inflammation within multiple immune cells but also engage DCs in the trans-infection of SARS-CoV-2[32]. Moreover, It was demonstrated that DC-SIGN could recognize HIV-I glycoprotein gp120 and facilitate the antigen presentation to T cells[13], such a mechanism has not been found in SARS-CoV-2 infection. Until now, little is known about the phenotype and function of DCs in the priming of humoral immunity after the vaccination against SARS-CoV-2.

Here, we delivered an observational clinical study, to build a bridge between phenotypes and functions of DCs and the titer of anti-SARS-CoV-2 Ab after the third vaccine(inactivated or subunit) injection.

2. Methods

2.1 Participants

Individuals vaccinated with a second dose of an inactivated SARS-CoV-2 vaccine 4 to 8 months before the beginning of the study were recruited into the trial. Participants were randomly divided into two groups injected with either 6.5U of inactivated SARS-CoV-2 vaccine (BBIBP-CorV) or 25 μg of protein subunit vaccine (ZF2001). Serum anti-RBD immunoglobulin titer was evaluated on days 0, 14, and 28, along with neutralization tests on days 0, 3, 14, and 28. PBMCs were collected on days 0, 3, and 28 and induced to differentiate into DCs to evaluate the phenotypes. Cytokines level in the serum of participants and the supernatant of DCs were measured at the same time. The function of DCs collected and

differentiated on day 28 were evaluated in mixed lymphocyte reaction(MLR). The study protocol and informed consent form were approved by Huashan Hospital Ethics Committees (Ethical number: KY2021-749). This study is registered at ClinicalTrials.gov, NCT05095298.

2.2 Monocyte-derived DC culture and stimulation

On days 0, 3, and 28, 10ml of peripheral blood was collected from each participant with an Ethylene Diamine Tetraacetic Acid(EDTA) anticoagulation tube Serum was separated in centrifugation from peripheral blood and was stored in -80℃. Peripheral blood mononuclear cells(PBMC) were separated using Ficoll density-gradient centrifugation. Monocytes were separated from PBMCs using immunomagnetic anti-CD14 beads according to the manufacturer's instructions(Miltenyi). Monocytes were cultured in RPMI 1640(Gibco) plus 10% fetal bovine serum (Gibco) with 1000U/ml recombinant human(rh) granulocyte-macrophage colony stimulation factor(GM-CSF) and 500U/ml interleukin(IL)-4 for 5 days to differentiated into monocyte-derived DCs(mo-DC). The medium was half-exchanged with the replenishment of these cytokines every two days. The fully differentiated mo-DCs were then stimulated with 100ng/ml tumor necrosis factor(TNF)-α for 2 days and were collected for the surface biomarkers tests or DC function analysis. Supernatant on days 5 and 7 of the mo-DC culture was collected for tests of the titers of cytokines.

2.3 Anti-SARS-CoV-2 Ab titers and surrogate virus neutralization tests

Blood samples were taken from participants for serology tests on days 0, 14, and 28 after the boosting vaccination. Plasma sVNT titer was determined by using a SARS-CoV-2 Neutralizing Ab detection kit (PerkinElmer SuperFlex Anti-SARS-CoV-2 Neutralizing Ab Kit, SDX-57042). The anti-RBD Ab and IgG were measured by PerkinElmer SuperFlex Anti-SARS-CoV-2 Ab Kit and SuperFlex Anti-SARS-CoV-2 IgG Kit according to the manufactory brochures.

To measure the neutralizing titer, the signals were converted to a surrogate virus neutralization test(sVNT) titer using a reference standard curve plotted with kit-suppled reagents. The sVNT titer was determined by the reciprocal of the last dilution that resulted in > 50% reduction of chemiluminescence signal. The concentration of the anti-SARS-CoV-2 Ab or IgG of the samples was correlated with the luminous intensity. The Ab assay was analyzed in its original scale, and results were then converted to the WHO international standard units using the conversion factors supplied by the laboratory.

2.4 Flow cytometry analysis

Expression of surface markers was analyzed by flow cytometry using conjugated monoclonal mouse antihuman Ab: allophycocyanin(APC) anti-TLR4, fluorescein isothiocyanate(FITC) anti-TLR2, Peridinin-Chlorophyll-Protein Complex(PerCP)-Cy5.5 anti-human leukocyte antigen(HLA)-DR, Brilliant Violet(BV)-421 anti-C-C chemokine receptor(CCR)-7, Phycoerythrin(PE) anti-DC-SIGN, and BV605 anti-CD86. Flow cytometry analysis was performed on FACSCalibur(BD Biosciences) instruments and analyzed using FlowJo software(Tree Star Inc.).

2.5 DC function analysis

CD4 + T cells were separated using anti-CD14 immunomagnetic beads from the PBMC of individuals other than those recruited in this study. MLR test was delivered as was described before[24]. DCs cultured for 7 days were treated with 50 mg/L mitomycin C(MMC) at 37°C for 45 min, washed 3 times with PBS, and suspended in complete RPMI 1640 medium, and the cell concentration was adjusted to be 5×10^5/ml. DCs were added in 96-well round-bottom plates at 5×10^3/well, 1×10^4/well, and 5×10^4/well, respectively. DCs from unvaccinated participants were used as the blank control group. Meanwhile, 2×10^5 T cells from the same blank control participants were added per well, with a final volume of 200 μl/well, thus the ratios of amounts of DCs and $CD4^+$T cells were controlled to be 1:40, 1:8, and 1:4, respectively. The whole mixed cells were cultured for 96h at 37°C. After the end of the culture, the supernatant was collected and stored at -20°C for examination. CCK8 solution was added to each well with a volume of 10μL. The plates were for 1 to 4 h and then the absorbance at 450 nm was tested using a microplate reader. CCK8 test was used to test T cell proliferation. The absorbance was read at 450 nm using a plate reader.

2.6 ELISA

Culture supernatants of DCs were tested for IL-2, IL-6, IL-10, IL-12, IL-27, interferon(IFN)-α, and IFN-β. MLR supernatants were tested for IL-4 and IL-21. All cytokine titers were analyzed using commercial ELISA kits(MEIMIAN) according to the manufacturers' instructions. The absorbance was read at 450 nm using an ELISA plate reader.

2.7 Statistical analysis

Mann-Whitney U test, Student's t-test or one-way ANOVA test was used for continuous variables and Pearson χ^2 test or Fisher's exact test for categorical variables to assess the statistical significance between groups and subgroups. Relations between Ab levels, DC phenotypes and functions, and cytokine titers were established using Pearson relation(equal variance assumed) or Spearman(equal variance not assumed) and linear regression analysis. Hypothesis testing was two-sided and P values of less than 0.05 were considered to be significant. R project(version 4.1.2) and Graphpad Prism (version 9.0) were used for statistical analysis.

3. Results

3.1 Participants characteristics

Between August 24th and August 28th, 2021, 20 volunteers were recruited in this study. The demographical information and types of the second vaccine of these participants are shown in Table 1. The medium age of the participants was 28.00 years(IQR 26.75–32.25). Thirteen(65%) participants were male. Seven(35%) were injected with recombinant vaccines.

Table 1
Participants and vaccine types

No	Gender	Age	Vaccine Type
1	F	30	Recombinated
2	M	51	Inactivated
3	M	27	Inactivated
4	F	33	Inactivated
5	M	34	Inactivated
6	F	25	Inactivated
7	M	42	Recombinated
8	F	24	Recombinated
9	F	29	Inactivated
10	M	44	Recombinated
11	M	28	Inactivated
12	M	32	Recombinated
13	M	24	Inactivated
14	M	26	Inactivated
15	M	28	Recombinated
16	M	27	Recombinated
17	F	25	Inactivated
18	M	27	Inactivated
19	M	30	Inactivated
20	F	27	Inactivated

3.2 Ab titers and sVNT

The anti-RBD Ab level rose from 22.08(95%CI 6.91–37.25) on day 0 to 4704.18(95%CI 2316.35–7092.00) on day 14 and persisted at 4111.57(95%CI 2097.55-6125.58) BAU/ml on D28. The according anti-RBD IgG titer was 9.17(95%CI 2.76–15.57), 798.11(95%CI 588.76-1007.46), and 767.26(95%CI 579.41-955.11) BAU/ml on days 0, 14, and 28, respectively. Geometric means of sVNT level were 17.15(95%CI 9.55–30.78) on D0, 12.88(95%CI 5.96–27.87) on D3, and increased to 2538.83(95%CI 1472.94-4376.08) on D14 and 3961.52(95%CI 2480.30-5494.23) on days 0, 3, 14, and 28(Fig. 1).

3.3 Surface markers of DCs

Surface markers(CD86, CCR7, HLA-DR, TLR2, TLR4, and DC-SIGN) expressed on DCs are shown in Fig. 2A. The levels of CD86, CCR7, and TLR2 were significantly lower on days 3 and 28 than on day 0($p < 0.001$). HLA-DR showed higher levels of expression on days 3 and 28($p < 0.001$). TLR4 and DC-SIGN expression reached the peak on day 3($p < 0.01$).

Pearson relation or Spearman relation analysis were used in finding the correlations between DC surface markers and anti-RBD Ab titers. We found that the D3 markers of DC maturation CCR7 and CD86 were negatively correlated with anti-RBD IgG and antibody titers but positively correlated with IgG/Ab ratio on D14 and D28. On the contrary, DC-SIGN and TLR4, PRRs of S protein, were positively correlated with anti-RBD IgG and antibody, but negatively correlated with IgG/Ab ratio(Fig. 2B). Among these correlations, only CCR7 and the anti-RBD IgG level($r=-0.559$, $p = 0.027$) and IgG/Ab ratio($r = 0.509$, $p = 0.046$) on D14, anti-RBD Ab($r=-0.615$, $p = 0.013$) and IgG($r=-0.515$, $p = 0.044$) levels on D28, CD86 and anti-RBD IgG($r=-0.522$, $p = 0.040$), and DC-SIGN level and IgG/Ab ratio($r=-0.626$,$p = 0.011$) showed statistical significance (Fig. 2C).

3.4 Cytokines produced by DCs

The culture supernatants of DCs before and 48 hours after TNF-α stimulation were examined for the levels of cytokines as was listed above using ELISA tests. The production levels of these cytokines were defined as the gap between the levels of these two time points. Production levels of these cytokines on D0 and D3 were exhibited in Fig. 3A and showed no significant difference except IL-10, which was lower on D3 than D0($P < 0.0001$).

When considering the relationship between these cytokines and anti-RBD antibodies, we found that IL-6 on D3 was positively correlated with anti-RBD Ab on D14($r = 0.535$, $p = 0.035$) and D28($r = 0.515$, $p = 0.044$). Besides, IL-27 expressed by DCs on D3 was negatively related to sVNT on D3($r=-0.611$, $p = 0.013$). Meanwhile, the IFN-β expression level on D3 was correlated with the anti-RBD IgG/Ab rate on D28($r = 0.536$, $p = 0.034$)(Fig. 3B and C). In a rough glance, IL-6 showed mild to moderate positive correlations with anti-RBD antibodies on D14 and D28($r = 0.303 \sim 0.535$)(Fig. 3B).

We also managed to search for the correlations among levels of different cytokines and found a moderate positive correlation between levels of IL-2 and IFN-β($r = 0.534$, $p = 0.035$). Negative correlations were found between IL-2 and IL-10($r=-0.523$, $p = 0.040$) and between IL-27 and IFN-β($r=-0.701$, $p = 0.003$) (Fig. 3D and E).

When searching for the relationship between DC surface markers and levels of the cytokines produced by DCs, we found only IL-10 level showed to be significantly negatively correlated with DC-SIGN + DC ratio($r=-0.671$, $p = 0.006$)(Fig. 3F and G).

3.5 DCs function in priming T cells activation

CD4$^+$T cell viability triggered by DCs of every well was defined as below.

$$V = \frac{OD450\left(CD4^+T + DC + CCK8\right) - OD450(CCK8)}{OD450\left(CD4^+T + CCK8\right) - OD450(CCK8)}$$

The ability of DCs in priming CD4$^+$T cells to produce cytokines IL-4 and IL-21 was defined as:

$$R(IL\text{-}4ORIL\text{-}21) = \frac{Titer\left(CD4^+T + DC\right) - Titer\left(CD4^+T\right)}{Titer\left(CD4^+T\right)}$$

Cell viability and the cytokines IL-4 and IL-21 production showed no difference among CD4$^+$T cultured with different amounts of DCs(Figure A).

We analyzed the relation between MLR results and anti-RBD antibodies and sVNT and found that CD4$^+$T cell viability primed by DCs in different concentrations (1:40, 1:8, and 1:4) were all negatively related to anti-RBD antibody titer on D28(r=-0.532~-0.453, p = 0.015 ~ 0.035), and were positively correlated with the proportion of anti-RBD IgG in Ab(r = 0.490 ~ 0.561, p = 0.010 ~ 0.032). Besides, cell viability primed by the high level of DCs(1:4) was positively correlated with sVNT(r=-0.451, p = 0.035). A similar relationship was found between sVNT and IL-4 production triggered by the low amount of DCs(1:40)(r=-0.514, p = 0.019). However, IL-4 primed by a high concentration of DC showed to be positively correlated with IgG/Ab ratio. No relation was found between the IL-21 production and anti-RBD immunoglobulin or sVNT(Fig. 4B and C).

When considering the relationship of surface markers of DCs and DC function in priming CD4$^+$T cells, we found that no but DC-SIGN level was correlated with IL-4 positively(r = 0.521, p = 0.034), and IL-21 production, negatively(r=-0.504, p = 0.041), triggered by a low amount of DC only(Fig. 4D and E).

4. Discussion

Vaccines are the most effective weapon against viral infections. However, in the era of SARS-CoV-2 vaccines being used widely, pandemic COVID-19 is persistently threatening the world's public health[36]. One of the most important reasons is the heterogeneous response to vaccination among different individuals.

In our study, we found a peak of anti-RBD antibody and IgG and sVNT on D14. After that, the titers of antibody and IgG of most participants showed a slight decline, while others showed to persist or even rise on D28. The heterogeneity of humoral immunity against COVID-19 after vaccination was obvious among different individuals.

DCs are the first line in recognition of foreign antigens and are the bridge between innate and adaptive immunity, so the phenotype and function of DCs are related to humoral immunity intention beyond doubt. In our research, surprisingly, the levels of maturation markers of DCs were negatively related to antibody titers against SARS-CoV-2 RBD but positively correlated with IgG/Ab ratio. Besides, we found a similar influence of DC functions in triggering CD4 + T cells activation on the humoral immunity. In other words, more mature DCs, and more functional DCs in the activation of T cells, could trigger lower levels of anti-RBD antibodies, but a higher proportion of IgG. It seemed that the maturation of DCs would improve antibody or B cell receptor(BCR) class switch recombination(CSR).

T follicular cells play an important role in the maintenance and regulation of GC reaction. Tfh serves as the center in the initiation of GC and provides a special circumstance for the competition of GC B cells and the maturation of BCR affinity[20]. DCs present antigen with major histocompatibility complex(MHC)-II and provide multiple types of help in priming Tfh differentiation including ICOSL, OX40L, and IL-6[39]. Here we found that the level of IL-6 produced by DCs was negatively correlated with CSR level, while positively related to anti-RBD antibody titers. Besides, in MLR tests, IL-4 and IL-21 levels, the specific cytokines that Tfhs produce to regulate GC B cells activation and maturation, were not demonstrated to have a relationship with antibody levels. It reminded us to rethink the direction of CD4 + T cell differentiation evoked by DCs in SARS-CoV-2 vaccination.

Meanwhile, there are several types of regular cells in germinal centers that play the regulatory role in GC B cells activation and differentiation. Tfr, as has been reported to serve as a regulatory cell specifically resident in the lymph follicle, has been shown to play a critical but ambiguous role in regulating GC reaction[15] at different stages. It was demonstrated that Tfr could control the intensity of GC[17], arrest the production of autoantibodies[10], and cease the GC reaction at the end[19]. It has been shown that in the immunity against SARS-CoV-2 S protein, Tfr reduced the level of antibody, but lifted the somatic hypermutation(SHM) of BCR in GC B cells and the maturation and affinity of BCR. It was hypothesized that Tfr provided a high SHM threshold for GC B activation[9]. There is no evidence of whether Tfr or Treg can control BCR or Ig CSR, and it is known that CSR related gene mutation occurs before GC generation[40, 30], but some research showed that the maturation and choosing among different categories of immunoglobulins happened in GC reaction in the same way as SHM competition[40], so it is reasonable for us to suppose the role of Tfr in the Ig class switching and competing. Our discovery that the maturation of DCs, as well as the function of DCs in activating CD4 + T cells, decreased antibody titers, and increased IgG ratio, let us suspect that DCs might control CD4 + T cells to differentiate into T regular cells(Treg or Tfr) rather than Tfh.

Upon vaccination, PRRs serve the distinguish between DCs and viral proteins or adjuvant substances. Several PRRs on DCs, including TLR2[22, 42, 29], TLR4[41, 21], and DC-SIGN[3, 32], have already been demonstrated to bind SARS-CoV-2 proteins. Here we dramatically found that DC-SIGN might give rise to antibody levels but suppress IgG/Ab ratio, which was opposite to DC maturation and function. Besides, no statistically significant correlations were found between DC markers and cytokines, except the negative one between DC-SIGN and IL-10, a cytokine that controlled regular T cells differentiation. This

evoked our hypothesis that DC-SIGN could suppress IL-10 expression of DCs, and thus negatively control Treg or Tfr differentiation or proliferation.

In summary, our research explored the relationships among DC PRRs and maturation status, DC functions in triggering CD4 + T cell differentiation, and anti-SARS-CoV-2 humoral immunity, and demonstrated that mature DC might control T cells to differentiate towards Treg or Tfr, therefore reducing the level of antibody titers but lifting IgG proportion. DC-SIGN, as a PRR recognizing and binding S protein, might suppress IL-10 expressed by DCs and thereafter regulate Treg or Tfr activation.

5. Conclusions

Our study indicates that DCs controlled CD4 + T cells in differentiating into regular T cells, and DC-SIGN might restrain T regular cells by suppressing IL-10 production of DC in anti-SARS-CoV-2 vaccination.

Declarations

6. Author Contributions

MC, WZ designed the research. AC, AL, XQ, WH, CW, DZ, JT, JQ, AM, and JA performed the research and analyzed the data. AC wrote the manuscript. All authors contributed to the article and approved the submitted version.

7. Conflict of Interest

None of the authors has any potential financial conflict of interest related to this manuscript.

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Figures

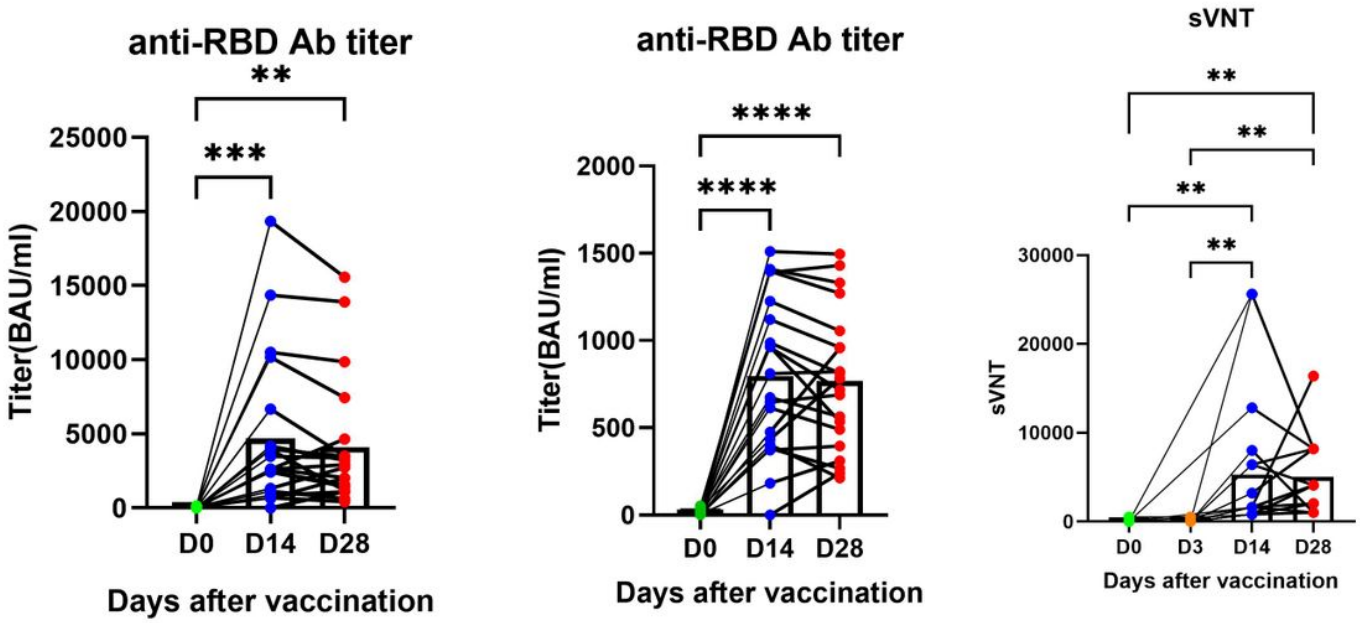

Figure 1

Humoral immune responses after the third-dose vaccination evaluated by anti-RBD Ab titer(BAU/ml), anti-RBD IgG titer(BAU/ml), and sVNT(IU/mL).

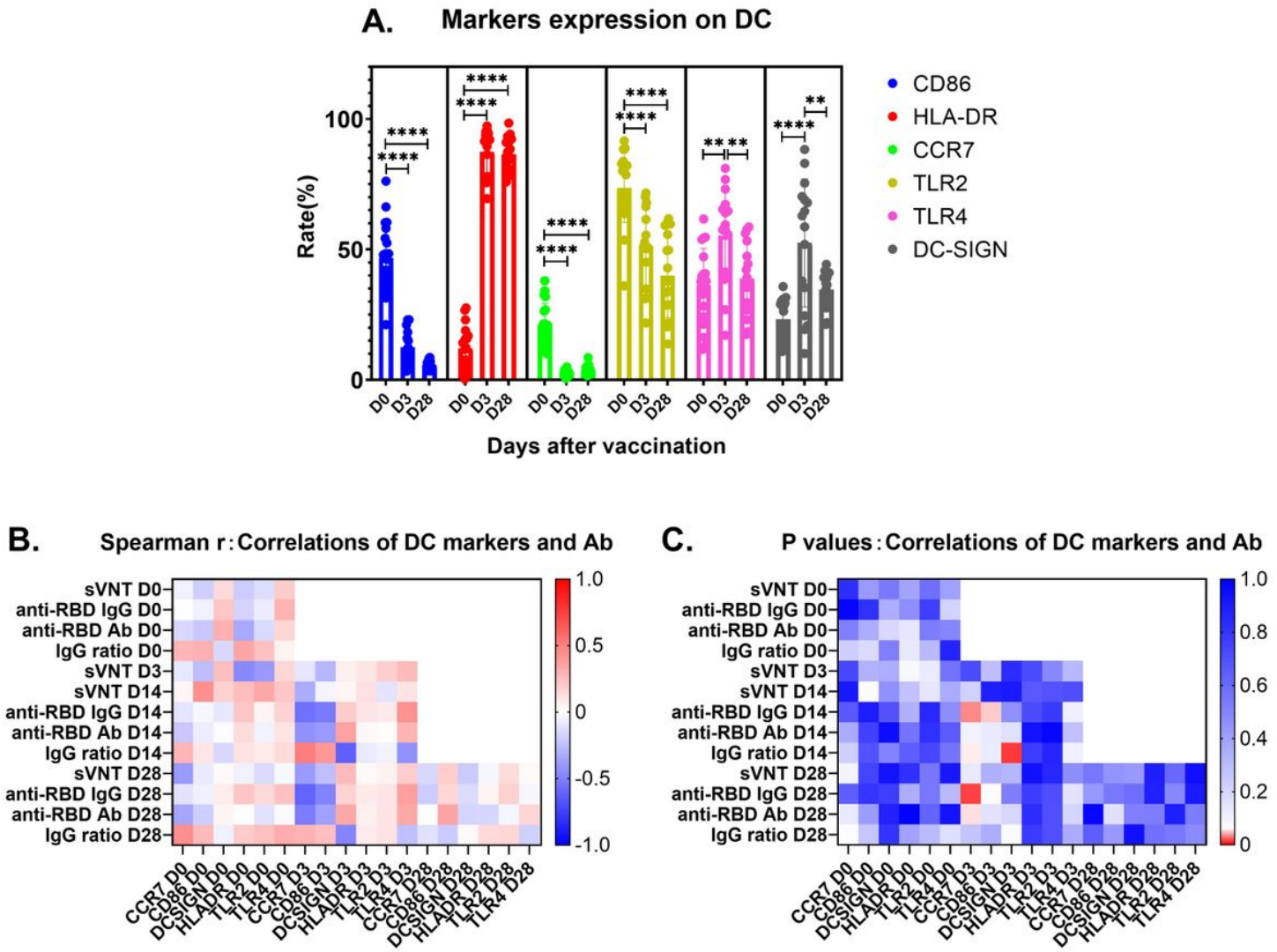

Figure 2

Relations between DC surface markers and humoral immunity. A. Expressions of DC markers measured as the positive rate of each marker. B. Heat map of the Spearman r measuring the relationship between DC markers and humoral immunity against SARS-CoV-2 with the color red(>0) or blue(<0). C. Heat map of P levels on Spearman tests measuring the relationship between DC markers and humoral immunity with the color blue(>0.05) or red(<0.05).

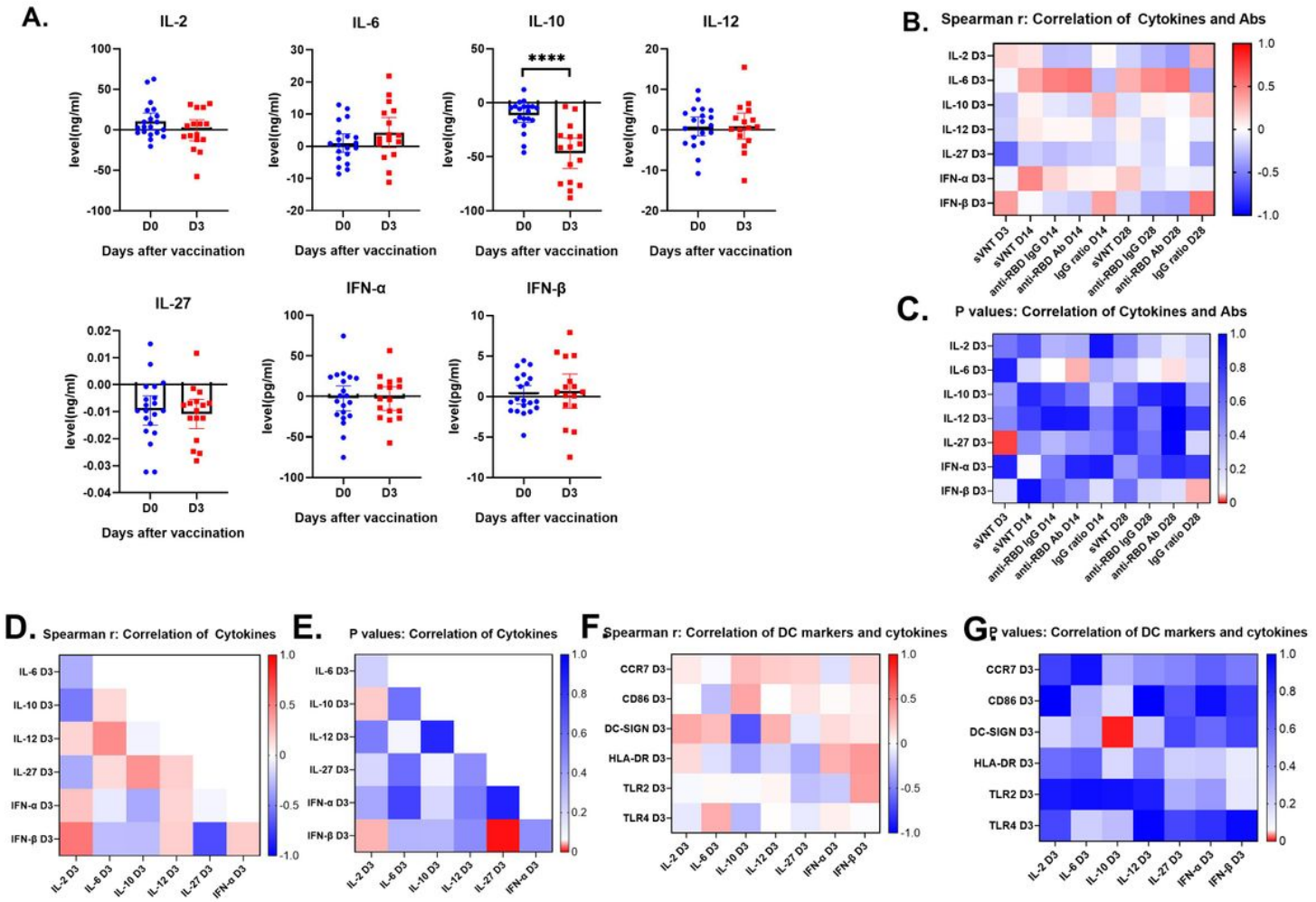

Figure 3

Relations between cytokines produced by DCs and humoral immunity. A. Levels of cytokines produced by DCs. B. Heat map of the Spearman r measuring the relationship between DC production of cytokines and humoral immunity with the color red(>0) or blue(<0). C. Heat map of P levels on Spearman tests measuring the relationship between DC production of cytokines and humoral immunity with the color blue(>0.05) or red(<0.05). D. Heat map of the Spearman r measuring the relationship among different cytokines with the color red(>0) or blue(<0). E. Heat map of P levels on Spearman tests measuring the relationship among different cytokines with the color blue(>0.05) or red(<0.05). F. Heat map of the Spearman r measuring the relationship between DC production of cytokines and DC markers with the color red(>0) or blue(<0). G. Heat map of P levels on Spearman tests measuring the relationship between DC production of cytokines and DC markers with the color blue(>0.05) or red(<0.05).

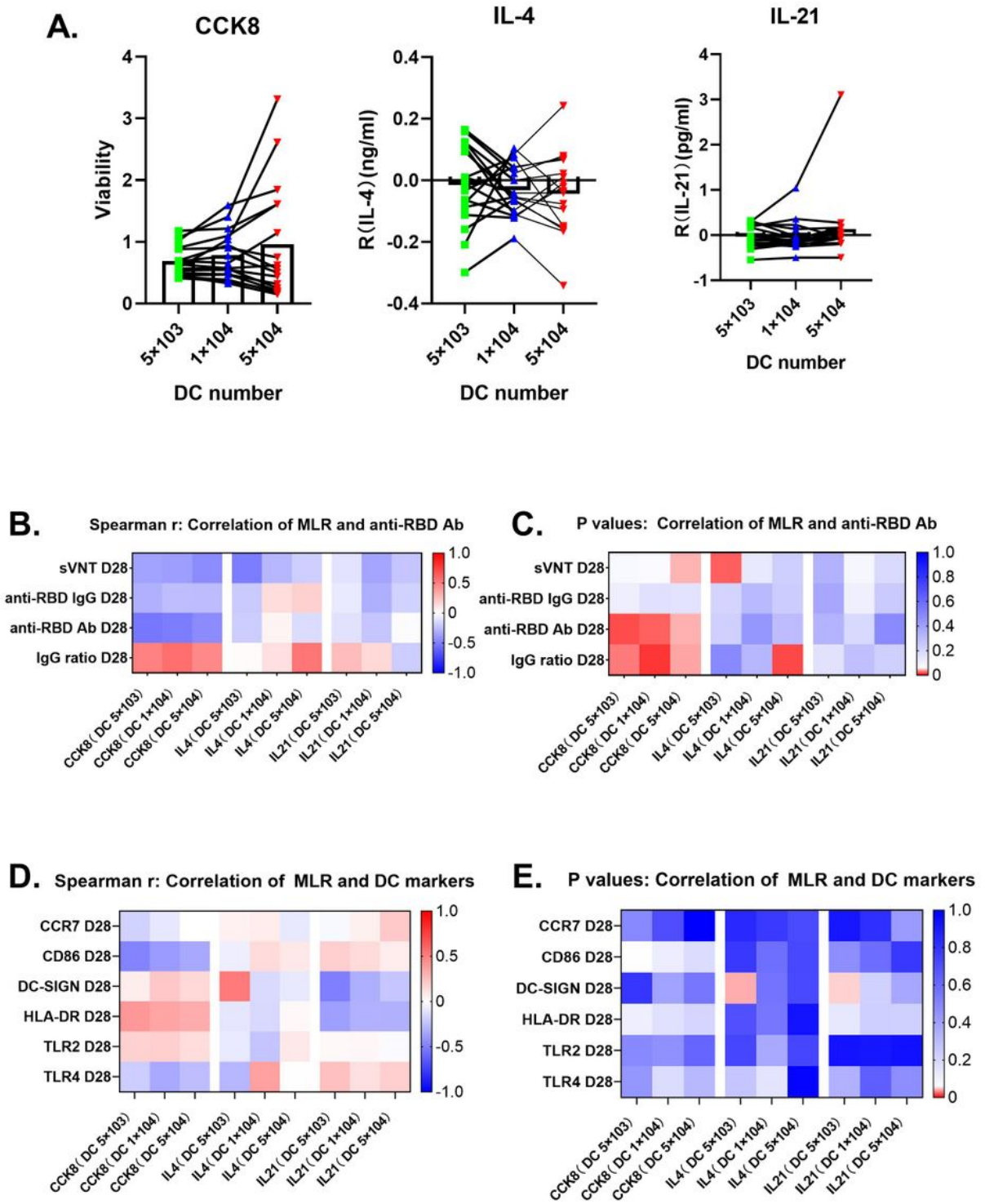

Figure 4

Relations between MLR and humoral immunity. A. Cell viability of, and IL-4 and IL-21 produced by CD4+T cells activated by different concentrates of DC. B. Heat map of the Spearman r measuring the relationship between MLR and humoral immunity with the color red(>0) or blue(<0). C. Heat map of P levels on Spearman tests measuring the relationship between MLR and humoral immunity with the color blue(>0.05) or red(<0.05). D. Heat map of the Spearman r measuring the relationship between MLR and

DC markers with the color red(>0) or blue(<0). E. Heat map of P levels on Spearman tests measuring the relationship between MLR and DC markers with the color blue(>0.05) or red(<0.05).