Short Communication

Identification of SARS-CoV RBD-targeting monoclonal antibodies with cross-reactive or neutralizing activity against SARS-CoV-2

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ABSTRACT

SARS-CoV-2-caused COVID-19 cases are growing globally, calling for developing effective therapeutics to control the current pandemic. SARS-CoV-2 and SARS-CoV recognize angiotensin-converting enzyme 2 (ACE2) receptor via the receptor-binding domain (RBD). Here, we identified six SARS-CoV RBD-specific neutralizing monoclonal antibodies (nAbs) that cross-reacted with SARS-CoV-2 RBD, two of which, 18F3 and 7B11, neutralized SARS-CoV-2 infection. 18F3 recognized conserved epitopes on SARS-CoV and SARS-CoV-2 RBDs, whereas 7B11 recognized epitopes on SARS-CoV RBD not fully conserved in SARS-CoV-2 RBD. The 18F3-recognizing epitopes on RBD did not overlap with the ACE2-binding sites, whereas those recognized by 7B11 were close to the ACE2-binding sites, explaining why 7B11 could, but 18F3 could not, block SARS-CoV or SARS-CoV-2 RBD binding to ACE2 receptor. Our study provides an alternative approach to prevent SARS-CoV-2 infection using anti-SARS-CoV nAbs.

1. Introduction

The coronavirus disease 2019 (COVID-19) caused by a novel coronavirus 2019-nCoV, which is also known as severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2) (Gorbalenya et al., 2020) or human coronavirus 2019 (HCoV-2019) (Jiang et al., 2020c), has infected more than 3.2 million people globally, including more than 229,000 deaths (case fatality rate 7%), in Africa, Americas, Eastern Mediterranean, Europe, South-East Asia, and Western Pacific, as of May 02, 2020 (WHO, 2020). Different from SARS-CoV and Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV), two other highly pathogenic human coronaviruses (CoVs) causing global epidemics in 2003, or continuous human infections (Zhong et al., 2003; Zaki et al., 2012; Du et al., 2009), SARS-CoV-2 has superior human-to-human transmission with rapid spread in humans (Zhu et al., 2020). Currently, no vaccines or therapeutics are available to prevent and treat SARS-CoV-2-associated human infections, calling for immediate efforts to develop effective countermeasures to control COVID-19 (Jiang et al., 2020a; Jiang, 2020).

The CoV spike (S) protein plays critical roles in viral infection and pathogenesis. It consists of two subunits: S1 subunit binds cells expressing viral r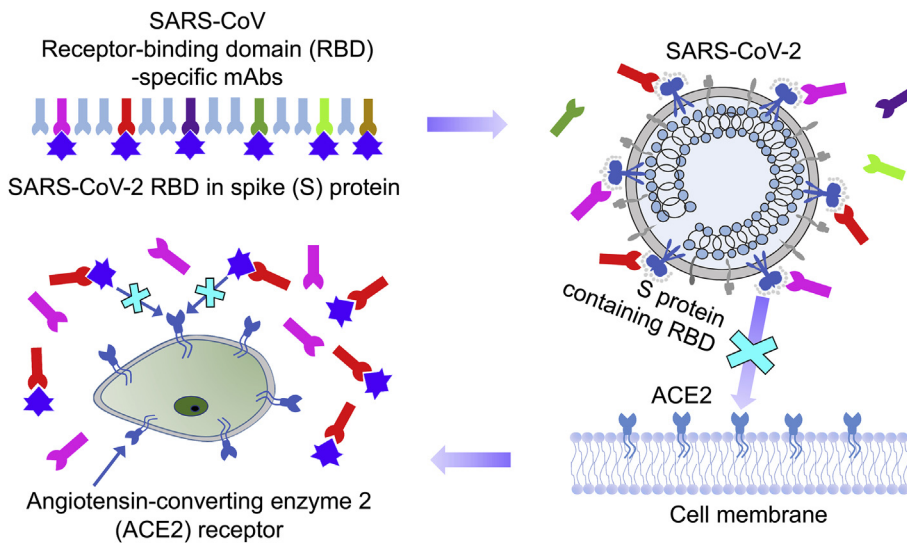eceptor through the receptor-binding domain (RBD), whereas S2 subunit mediates fusion between the virus and cell membrane (Liu et al., 2004; Du et al., 2009; Lu et al., 2014). Similar to SARS-CoV, SARS-CoV-2 recognizes angiotensin-converting enzyme 2 (ACE2) as its cellular receptor, and its RBD (residues 331–524) shares about 70% sequence identity with SARS-CoV RBD (Zhou et al., 2020). SARS-CoV S protein RBD is an important vaccine and therapeutic target, and it induces potent neutralizing antibodies against divergent strains of SARS-CoV infection (Du et al., 2009; Liu et al., 2004; He et al., 2004).

We previously developed a number of SARS-CoV RBD-specific mouse monoclonal antibodies (mAbs) (He et al., 2005, 2006a, 2006b, 2006c). In this study, we detected their cross-reactivity with a SARS-CoV-2 RBD protein, as well as their cross-neutralizing activity against SARS-CoV-2 S protein-mediated viral entry. We found that six mAbs cross-reacted with SARS-CoV-2 RBD, two of which could neutralize SARS-CoV-2 pseudovirus infection in human ACE2 (hACE2)-expressing 293T cells (hACE2/293T), and one of which blocked the binding between SARS-CoV-2 RBD and ACE2 receptor. The cross-reactivity of these mAbs with SARS-CoV-2 RBD, their cross-neutralization against SARS-CoV-2 pseudovirus infection, and their inhibition to block the SARS-CoV-2 RBD-ACE2 binding were illustrated in Fig. 1. We also identified the potential epitopes on the RBD of SARS-CoV recognized by these two mAbs. Our study provides the possibility of treating SARS-

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CoV-2 infection using SARS-CoV RBD-targeting neutralizing mAbs (nAbs).

2. Materials and methods

2.1. Construction, expression and purification of recombinant RBD proteins

The construction, expression and purification of recombinant SARS-CoV RBD wild type (WT) and its mutant proteins, as well as SARS-CoV-2 protein, were performed as previously described (Tai et al., 2017, 2020; Du et al., 2016). Briefly, genes encoding residues 318–510 of SARS-CoV S protein and residues 331–524 of SARS-CoV-2 S protein were respectively amplified by PCR using codon-optimized SARS-CoV S protein (GenBank accession no. **AY278488.2**), or SARS-CoV-2 S protein (GenBank accession no. **QHR63250.1**), as the template, and fused into pFUSE-hIgG1-Fc2 vector (hereinafter named Fc, InvivoGen, San Diego, CA). SARS-CoV RBD mutants were constructed based on SARS-CoV RBD WT plasmid using the Multi Site-directed Mutagenesis Kit (Agilent Technologies, Santa Clara, CA). Recombinant SARS-CoV RBD, SARS-CoV-2 RBD, or SARS-CoV RBD mutant proteins (containing a C-terminal Fc tag) were expressed in 293T cells, secreted into cell culture supernatants, and purified using protein A affinity chromatography (GE Healthcare, Marlborough, MA).

2.2. ELISA

ELISA was performed to detect the reactivity of SARS-CoV RBD-specific mAbs with SARS-CoV RBD, or cross-reactivity with SARS-CoV-2 RBD protein (Tai et al., 2017, 2020). Sera from mice immunized with SARS-CoV RBD protein and a MERS-CoV RBD-specific mAb (Tai et al., 2020; Du et al., 2016) were used as controls. Briefly, ELISA plates were precoated with respective RBD proteins (1 μg/ml) overnight at 4 °C, which were blocked with 2% fat-free milk in PBST for 2 h at 37 °C. SARS-CoV RBD-specific mouse mAbs (10 and 1 μg/ml) were added to the plates and incubated for 2 h at 37 °C. After washes, the plates were further incubated with horseradish peroxidase (HRP)-conjugated anti-mouse IgG antibody (Fab specific, 1:3,000, Thermo Fisher Scientific) for 1 h at 37 °C. Substrate 3,3′,5,5′-Tetramethylbenzidine (TMB) (Sigma, St. Louis, MO) was added to the plates, and the reactions were stopped by addition of H_2SO_4 (1N). The absorbance at 450 nm (A450) was measured using an ELISA plate reader (Tecan, San Jose, CA).

Mapping of epitopes of the selected SARS-CoV RBD-specific mAbs on SARS-CoV RBD was performed using a protocol similar to that described above, except for coating of the ELISA plates with respective SARS-CoV RBD WT and mutant proteins (1 μg/ml), followed by the

addition of mAbs at serial dilutions for detection.
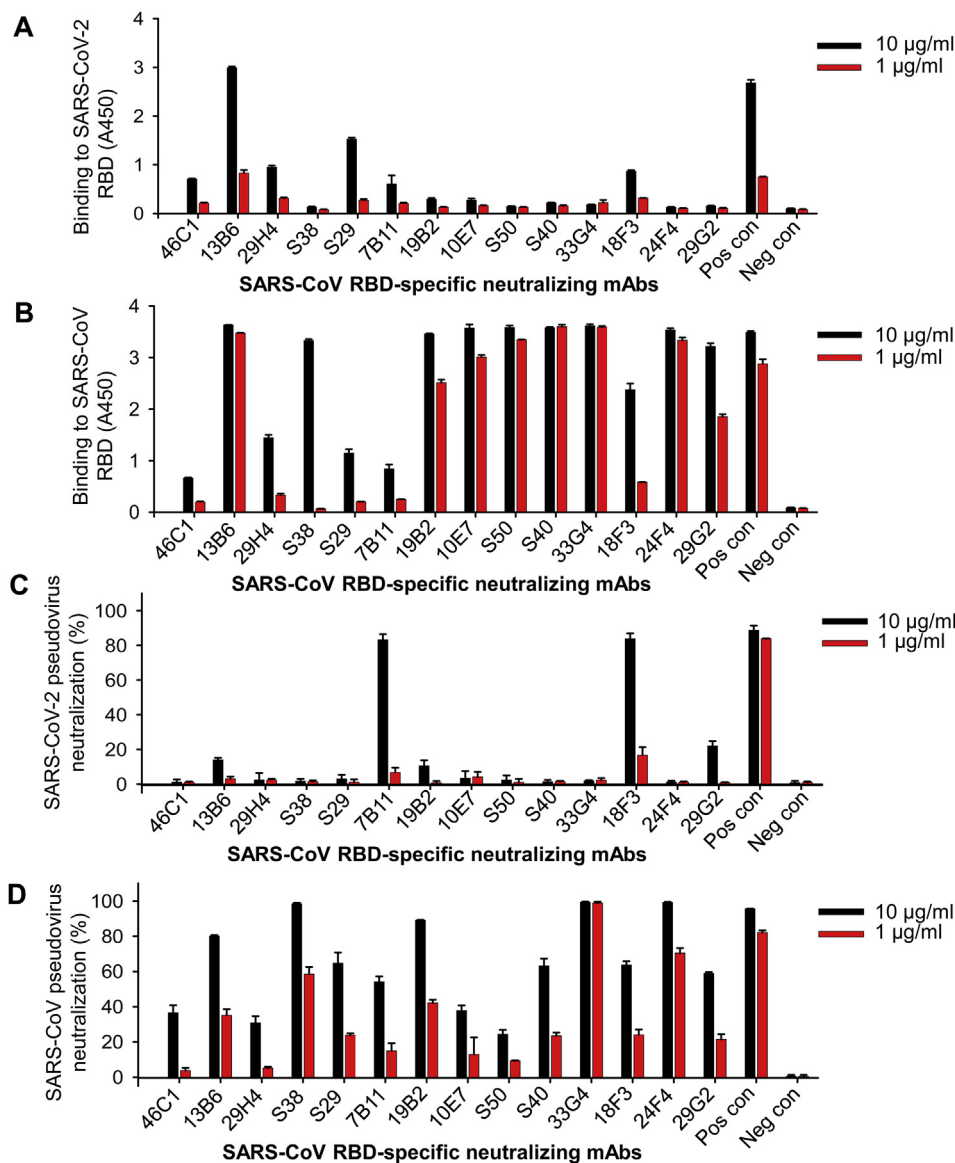
2.3. Pseudovirus neutralization assay

A pseudovirus neutralization assay was performed to detect the neutralizing activity of SARS-CoV RBD-specific mAbs against SARS-CoV infection, or their cross-neutralizing activity against SARS-CoV-2 infection. SARS-CoV RBD-immunized mouse sera and a MERS-CoV RBD-specific mAb were used as controls (Tai et al., 2020; Du et al., 2016). Briefly, SARS-CoV and SARS-CoV-2 pseudoviruses were first generated as previously described (Tai et al., 2020). 293T cells were cotransfected with a plasmid encoding SARS-CoV or SARS-CoV-2 S protein and a plasmid expressing Env-defective, luciferase-expressing HIV-1 genome (pNL4-3. luc.RE), using the calcium phosphate method. The culture medium was replaced with fresh Dulbecco's Modified Eagle's Medium (DMEM) 8 h later, and pseudovirus-containing supernatants were collected 72 h later for single-cycle infection in 293T cells expressing SARS-CoV or SARS-CoV-2 receptor human ACE2 (hACE2/293T). A pseudovirus neutralization assay was then performed by incubating SARS-CoV or SARS-CoV-2 pseudovirus with SARS-CoV RBD-specific mAbs (10 and 1 μg/ml) for 1 h at 37 °C and then adding the mixture into cells. Fresh medium was added 24 h later, and the cells were lysed in cell lysis buffer (Promega, Madison, WI) 72 h after infection. Luciferase substrate (Promega) was added to the lysed cell supernatants, which were detected for relative luciferase activity using the Infinite 200 PRO Luminator (Tecan). The percent (%) pseudovirus neutralization was calculated.

2.4. Flow cytometry analysis

Flow cytometry analysis was performed to detect the inhibitory activity of SARS-CoV RBD-specific nAbs on the binding of SARS-CoV or SARS-CoV-2 RBD protein to hACE2/293T-expressing cells (Tai et al., 2020). Briefly, SARS-CoV RBD or SARS-CoV-2 RBD (2 μg/ml) protein containing a C-terminal hFc was incubated with the mAb (10 or 1 μg/ml) for 30 min at room temperature, and then the mixture was added to the cells for another 30 min at room temperature. Human IgG-Fc protein was added as negative control. The cells were further incubated with FITC-labeled goat anti-human IgG-Fc antibody (1:500; Thermo Fisher Scientific) for 30 min and then processed for flow cytometry analysis.

3. Results

We initially performed an ELISA to detect the cross-reactivity of 14

SARS-CoV RBD-targeting mAbs against SARS-CoV-2 RBD protein containing residues 331–524 of S antigen fused with a C-terminal Fc of human IgG1 (Tai et al., 2020). A SARS-CoV RBD containing residues 318–510 of S protein fused with a C-terminal human Fc (Tai et al., 2020) was used as comparison. Six mAbs, including 46C1, 13B6, 29H4, S29, 7B11, and 18F3, bound SARS-CoV-2 RBD in a dose-dependent manner, with higher binding affinity at 10 μg/ml (Fig. 2A). In contrast, all these mAbs could bind SARS-CoV RBD protein, and most had strong binding affinity at 10 and 1 μg/ml (Fig. 2B). These data suggest that SARS-CoV RBD-specific mAbs could cross-react with SARS-CoV-2 RBD.

We then investigated the potential of these six anti-SARS-CoV RBD mAbs in cross-neutralizing SARS-CoV-2, or neutralizing SARS-CoV, infection in hACE2/293T cells using a pseudovirus neutralizing assay expressing S protein of SARS-CoV-2 or SARS-CoV. Among the mAbs tested, 7B11 and 18F3 could neutralize SARS-CoV-2 pseudovirus infection with about 80% neutralization at 10 μg/ml (Fig. 2C). However, all these mAbs neutralized SARS-CoV pseudovirus infection, most of which had > 50% neutralizing ability at 10 μg/ml, and a few reached > 50% neutralization at 1 μg/ml (Fig. 2D). Notably, several mAbs, such as S28, 33G4, and 24F4, had potent neutralizing activity against SARS-CoV pseudovirus, but failed to neutralize SARS-CoV-2 infection, even at 10 μg/ml (Fig. 2C and D), suggesting that these mAbs

may recognize epitopes on the RBD of SARS-CoV different from those of SARS-CoV-2 RBD. Therefore, we identified two SARS-CoV RBD-targeting nAbs with proven cross-neutralizing ability against SARS-CoV-2 S protein-mediated viral entry.

We further detected the epitopes on SARS-CoV RBD potentially recognized by the two cross-neutralizing mAbs, 7B11 and 18F3, and included two non-cross-neutralizing mAbs, 13B6 and 33G4, as controls. We have previously shown that 13B6 may recognize epitopes at residues R441 and D454 of SARS-CoV RBD (He et al., 2006a). Here, we constructed a series of SARS-CoV RBD mutant proteins based on the interaction between the RBD and viral receptor (Li et al., 2005), and performed an ELISA to test binding ability of the above mAbs to these mutant proteins. Compared with the binding to SARS-CoV RBD wild type (WT) protein, neither 13B6 nor 18F3 bound to the RBD containing D392 and V394 mutations. Moreover, 13B6 did not bind to the RBD containing D414 and F416 mutations, and 7B11 did not bind to the RBD containing I428 and A430 mutations or the RBD containing K439 mutation (Fig. 3). In addition, 13B6 showed reduced binding to the RBDs containing V369/A371, A371/K373, or Y481 mutations (Fig. 3). This line of evidence suggests that the above residues were the epitopes recognized by respective mAbs, among which residues D392 and V394 in SARS-CoV RBD were conserved neutralizing epitopes corresponding
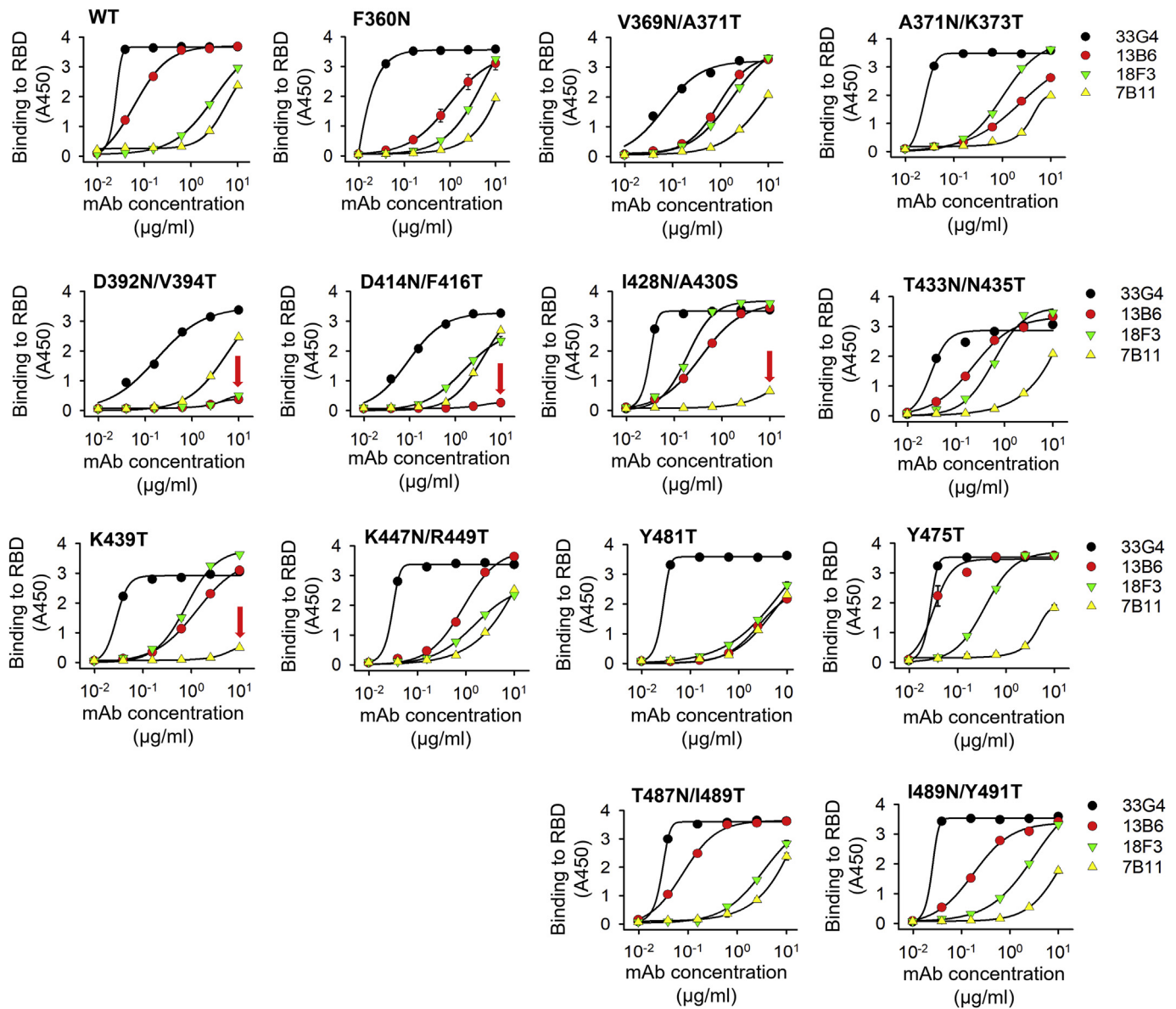
Fig. 3. Identification of epitopes of SARS-CoV RBD-targeting nAbs by ELISA. The two (18F3 and 7B11) SARS-CoV RBD-specific nAbs with cross-neutralizing activity against SARS-CoV-2 were detected for their potential recognition of epitopes on SARS-CoV RBD. SARS-CoV RBD-targeting nAbs (33G4 and 13B6) without cross-neutralizing activity were included as controls. The plates were coated with SARS-CoV RBD wild type (WT) or each mutant protein (1 μg/ml), and the mAbs at serial dilutions were added for binding. Arrows represent mAbs that did not bind to mutant proteins at the indicated amino acid residues on SARS-CoV RBD, which are epitopes recognized by the mAbs tested. The data are presented as mean A450 ± s. e. m. (n = 2). The experiments were repeated once and obtained similar results.

to residues D405 and V407 in SARS-CoV-2 RBD, and residues I428, A430, and K439 in SARS-CoV RBD were neutralizing epitopes not fully conserved in SARS-CoV-2 RBD (Fig. 4A).

We performed a flow cytometry analysis to detect whether the two identified SARS-CoV RBD-specific mAbs, 7B11 and 18F3, with cross-neutralizing activity inhibited SARS-CoV or SARS-CoV-2 RBD binding to the respective ACE2 receptor in 293T cells expressing hACE2 (hACE2/293T). We included 13B6 and 33G4 mAbs without cross-neutralizing activity as controls. Different from 7B11, which blocked the binding between both SARS-CoV and SARS-CoV-2 RBDs to their respective ACE2 receptor, the results revealed that 13B6 and 18F3 could not block such binding (Fig. 4B and C). This might be due to that most or all epitopes recognized by 13B6 or 18F3 did not overlap with the ACE2 binding sites on SARS-CoV or SARS-CoV-2 RBD (Li et al., 2005; Yan et al., 2020), while most epitopes recognized by 7B11 were very close to the ACE2 binding sites (Fig. 4A). In addition, control mAb 33G4 only blocked SARS-CoV RBD, but not SARS-CoV-2 RBD, binding to the

ACE2 receptor (Fig. 4B and C), partially explaining why this mAb did not neutralize SARS-CoV-2 infection.

4. Discussion

Development of efficacious neutralizing antibodies against SARS-CoV-2 is a key approach to prevent and treat continuous spread of COVID-19 (Jiang et al., 2020b). We and others have shown that SARS-CoV S1 or RBD-immunized animal sera or SARS-CoV-infected convalescent human sera may cross-react with SARS-CoV-2 and/or cross-neutralize its infection (Tai et al., 2020; Hoffmann et al., 2020; Tian et al., 2020).

In this study, we detected 14 SARS-CoV RBD-specific nAbs and tested their cross-reactivity with SARS-CoV-2 RBD and cross-neutralizing ability against SARS-CoV-2 infection. Six of these mAbs cross-reacted with SARS-CoV-2 RBD protein, two of which could cross-neutralize SARS-CoV-2 S protein-mediated pseudovirus entry into its

A

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SARS-CoV-2 331  NITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFT  393
SARS-CoV   318  NITNLCPFGEVFNATKFPSVYAWERKKISNCVADYSVLYNSTFFSTFKCYGVSATKLNDLCFS  380
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SARS-CoV-2 394  NVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYNYLYRLF  456
SARS-CoV   381  NVYADSFVVKGDDVRQIAPGQTGVIADYNYKLPDDFMGCVLAWNTRNIDATSTGNYNYKYRYL  443
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SARS-CoV-2 457  RKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH  519
SARS-CoV   444  RHGKLRPFERDISNVPFSPDGKPCTP-PALNCYWPLNDYGFYTTTGIGYQPYRVVVLSFELLN  505
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SARS-CoV-2 520  APATV  524
SARS-CoV   506  APATV  510
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B

C
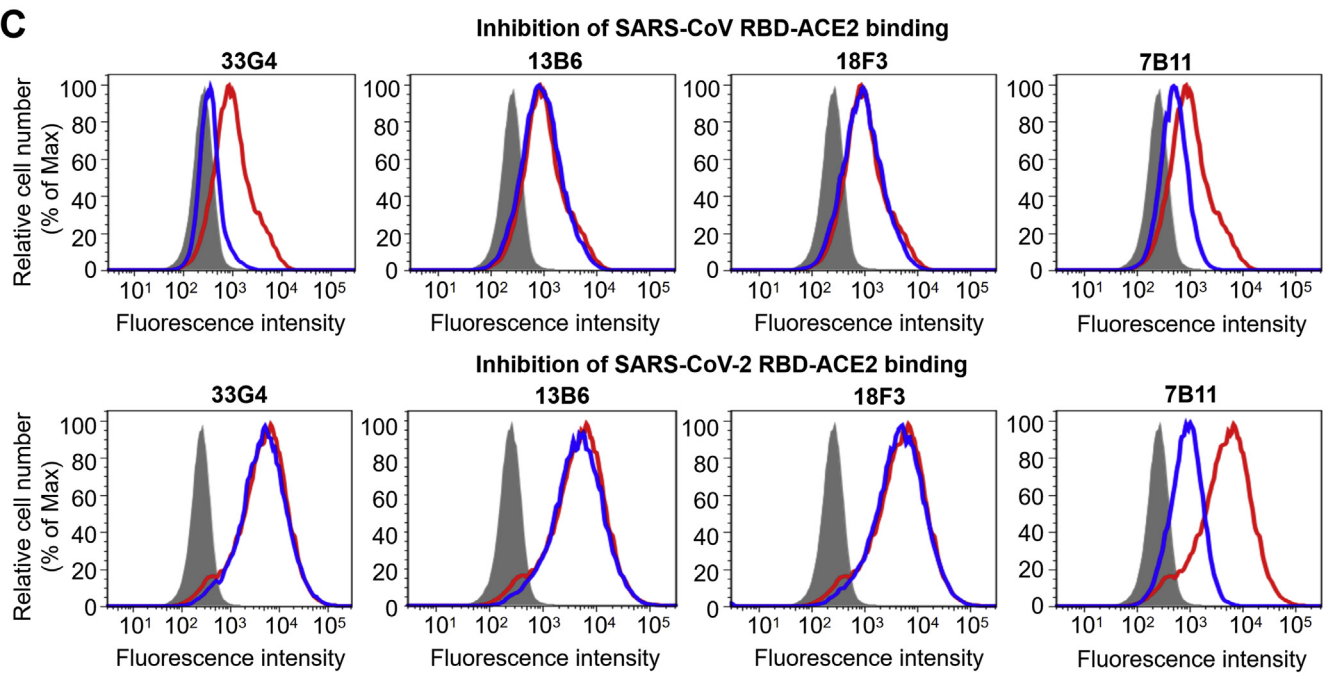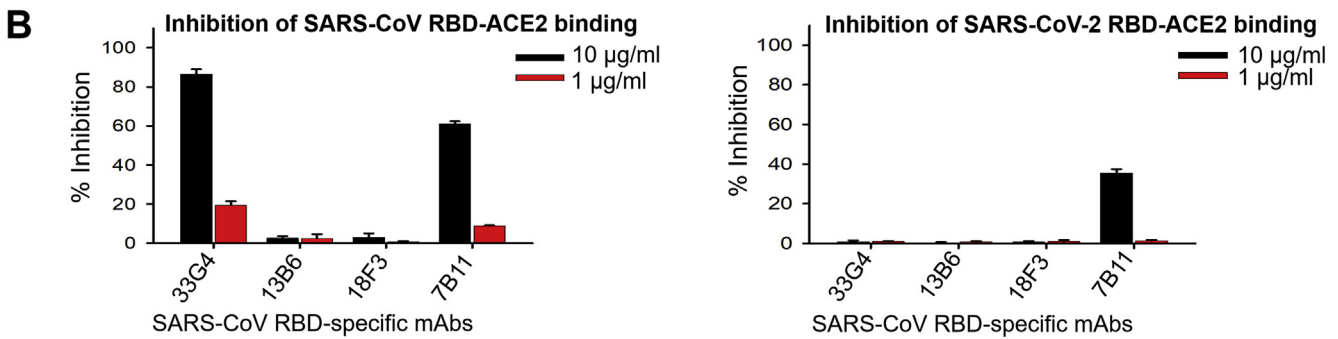
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hACE2 receptor-expressing cells, albeit with relatively low neutralizing activity. In contrast, other anti-SARS-CoV RBD nAbs, such as 33G4, with potent neutralizing activity against SARS-CoV pseudovirus infection in hACE2-expressing cells, did not react with SARS-CoV-2 RBD and could not neutralize SARS-CoV-2 pseudovirus infection. In addition, 13B6 mAb, which bound strongly to SARS-CoV-2 RBD, failed to neutralize SARS-CoV-2 infection.

Our results are consistent with previous studies, showing that SARS-CoV RBD-specific potent neutralizing human mAbs (CR3014 and m396) could target ACE2-binding sites, but failed to bind SARS-CoV-2 S protein RBD (Tian et al., 2020). Moreover, the two cross-neutralizing mAbs, 18F3 and 7B11, respectively recognized two conserved, as well

Fig. 4. Mapping of epitopes of SARS-CoV RBD-specific mAbs on SARS-CoV or SARS-CoV-2 RBD and their inhibition to the binding of SARS-CoV or SARS-CoV-2 RBD to ACE2 receptor. (A) Amino acid alignment of SARS-CoV RBD (residues 318–510) and SARS-CoV-2 RBD (residues 331–524) in S proteins and mapping of epitopes recognized by SARS-CoV RBD-specific nAbs with (18F3 and 7B11) and without (13B6) cross-neutralizing activity against SARS-CoV-2 infection. The alignment was performed using Clustal Omega. The identified mAb epitopes on SARS-CoV RBD and the residues corresponding to SARS-CoV-2 RBD were labeled in red with respective mAbs shown underneath. Letters in cyan represent receptor ACE2-binding residues and their locations in SARS-CoV or SARS-CoV-2 RBD (Li et al., 2005; Yan et al., 2020). (B) Inhibition of SARS-CoV RBD-specific mAbs for the binding of SARS-CoV or SARS-CoV-2 RBD to ACE2 receptor by flow cytometry analysis. Percent (%) inhibition was calculated based on the relative fluorescence intensity with or without respective mAbs at 10 and 1 μg/ml, respectively. SARS-CoV or SARS-CoV-2 RBD (2 μg/ml) was used for the binding to hACE2/293T cells. The data are expressed as mean inhibition (%) ± s. e.m. (n = 3). The experiments were repeated twice and obtained similar results. (C) Representative flow cytometry images of SARS-CoV RBD-specific mAbs (10 μg/ml) in inhibition of the binding between SARS-CoV or SARS-CoV-2 RBD and ACE2 receptor. The binding of SARS-CoV or SARS-CoV-2 RBD (2 μg/ml) to hACE2/293T cells is shown in red line, and the blockage of this binding by mAbs (33G4, 13B6, 18F3, and 7B11) is shown in blue line. hIgG-Fc protein (background control) was shown in gray shade.

as several non-conserved, neutralizing epitopes on the RBDs of SARS-CoV and SARS-CoV-2. While 18F3 could not block the binding between RBD and ACE2 receptor, 7B11 did block this binding, indicating that they recognized epitopes different from, or close to, the receptor binding sites on the RBDs.

Notably, 7B11 had a relatively higher neutralizing activity against SARS-CoV-2 infection than that against SARS-CoV infection, whereas its ability to inhibit the SARS-CoV-2 RBD-ACE2 binding was relatively lower than that to inhibit the SARS-CoV RBD-ACE2 binding, partially because that the neutralizing activity of nAbs could not always be positively correlated with the inhibition of their binding to the receptor. Other reasons might be due to that the binding between SARS-CoV-2 RBD and ACE2 receptor was much stronger than that between SARS-CoV RBD and ACE2 (Tai et al., 2020), potentially resulting in the reduced inhibition.

Overall, our study demonstrates an alternative approach to prevent and treat SARS-CoV-2 infection using currently available SARS-CoV nAbs. It also provides an important basis to rapidly design and develop effective SARS-CoV-2-specific nAbs based on the viral RBD.

Contributors

L.D. designed the study. W.T., Z.X. and H.Y. performed the experiments and analyzed the data. S.J. and L.D. wrote and revised the manuscript. All authors approved the final version of the manuscript.

Funding

Declaration of competing interest

The authors declare no competing interests.

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