

Review

Perspectives on therapeutic neutralizing antibodies against the Novel Coronavirus SARS-CoV-2

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Abstract

A newly identified novel coronavirus (SARS-CoV-2) is causing pneumonia-associated respiratory syndrome across the world. Epidemiology, genomics, and pathogenesis of the SARS-CoV-2 show high homology with that of SARS-CoV. Current efforts are focusing on development of specific antiviral drugs. Therapeutic neutralizing antibodies (NAbs) against SARS-CoV-2 will be greatly important therapeutic agents for the treatment of coronavirus disease 2019 (COVID-19). Herein, the host immune responses against SARS-CoV discussed in this review provide implications for developing NAbs and understanding clinical interventions against SARS-CoV-2. Further, we describe the benefits, challenges and considerations of NAbs against SARS-CoV-2. Although many challenges exist, NAbs still offer a therapeutic option to control the current pandemic and the possible re-emergence of the virus in the future, and their development therefore remains a high priority.

Key words: Neutralizing antibody, SARS-CoV-2, COVID-19, severe acute respiratory syndrome

Introduction

The occurrence of coronavirus disease 2019 (COVID-19) cases in Wuhan city, Hubei province of China firstly emerged in December 2019. A newly identified novel coronavirus (SARS-CoV-2, formerly known as 2019-nCoV) is causing pneumonia-associated respiratory syndrome [1]. After analysis of genome sequences of SARS-CoV-2 samples obtained from different infected patients, SARS-CoV-2 shares high sequence identity with SARS-CoV [2]. Compared to SARS-CoV, transmitted from human-to-human of SARS-CoV-2 seems to be greater. As of February 2020, at least 25 countries reported >70,000 cases of SARS-CoV-2 infection. Patients infected with SARS-CoV-2 show typical pneumonia and severe lung damage [3]. COVID-19 can be diagnosed by either clinical CT radiography or a laboratory real time Reverse Transcription-Polymerase Chain Reaction (RT-PCR) [4]. Unfortunately, there are no specific antiviral drugs or vaccines currently. Several approaches can be suggested to control infections of SARS-CoV-2, including vaccines, monoclonal antibodies, oligonucleotides, peptides, interferon and small-

molecule drugs [5]. The antibody-mediated humoral response is crucial for preventing viral infections. A subset of these antibodies, which reduce viral infectivity by binding to the surface epitopes of viral particles and thereby blocking the entry of the virus to an infected cell, are defined as neutralizing antibodies (NAbs) [6]. NAbs elicit their protective activities in three main steps. NAbs may prevent the attachment of the virion to its receptors on targeted cells, causing aggregation of virus particles. Further, the viruses are lysed through the constant (C) region of the antibody-mediated opsonization or complement activation [7]. This review focuses on understanding immunopathogenesis of SARS-CoV-2 and addressing the benefits, challenges and considerations of neutralizing antibodies (NAbs).

Similarity of SARS-CoV-2 and SARS-CoV in antigen and receptor recognition by host

As shown in **Figure 1**, major structural proteins

of SARS-CoV-2 include the spike (S), membrane (M) and envelop (E) and nucleic capsid (N) proteins [8]. A coronavirus initiates cell fusion via attachment of the S protein with the receptor on the host cell surface. The viral nucleocapsid is delivered inside for subsequent replication. The S protein comprises two units, S1 and S2. The receptor-binding domain (RBD) within S1 directly interacts with host receptors [9]. Structural and functional analysis of the SARS-CoV-2 shows that the SARS-CoV-2 S protein binds the Angiotensin-converting enzyme 2 (ACE2) receptor on human alveolar epithelial cells [10-12], suggesting SARS-CoV-2 uses the same receptor, ACE2, as SARS-CoV. However, the SARS-CoV-2 S protein binds ACE2 with higher affinity than SARS-CoV S [13]. The high affinity of the S protein for human ACE2 may lead to the great human-to-human transmission of SARS-CoV-2. Due to the key role of the S protein, it is the main target for antibody-mediated neutralization.

Innate and adaptive responses of human to SARS-CoV-2 and SARS-CoV

The clinical spectrum of the outcome of COVID-19 is highly variable, from mild flu-like symptoms to severe pneumonia. It is critical to take insights into cellular and humoral responses in SARS-CoV-2-induced COVID-19 [14]. Elucidation of SARS-CoV-2 immunopathogenesis is useful for developing passive antibody therapy, designing vaccines, and understanding of clinical drug interventions. However, the systemic landscape of the immune responses in patients with COVID-19 is unclear. Because the clinical features and

immunopathogenesis of SARS-CoV-2 pose similarities with SARS-CoV [15], knowledge learned from SARS-CoV has important implications for understanding this new coronavirus.

Resistance to SARS-CoV infections is associated with both innate and adaptive immune responses [16]. The innate immune response to SARS-CoV has not been completely defined [17]. Some studies demonstrated that both macrophage and dendritic cell (DC) play the important roles for viral destruction and immune response induction in mucosal-associated lymphoid tissues [18]. Due to homeostasis, macrophage and DC as vehicles seemed to disseminate viruses through the efferent lymphatic system. Meanwhile, activation of DC and macrophage by SARS-CoV led to excessive pro-inflammatory cytokine responses [19]. A drastic elevation of inflammatory cytokines and chemokines was observed in the tissues and serum of SARS-CoV patients [20]. The levels of, IFN- γ , IL-1 β , IL-6, IL-12, IL-8, MCP-1 and IP-10 are generally enhanced in the early infection and subsequently reduced in the recovery stage. Uncontrolled systemic inflammation (known as cytokine storm) further resulted in illness severity. The similar symptom of cytokine storm was observed in SARS-CoV-2 infection. The inflammatory cytokines and chemokines (IL-1 β , IFN- γ , IP-10, and MCP-1), which may lead to activated T-helper-1 (Th1) cell responses, were upregulated [21,22]. However, SARS-CoV-2 patients secreted excessive IL-4 and IL-10 that may suppress inflammation via T-helper-2 (Th2) [14]. It differs from SARS-CoV infection. Further studies are necessary to elucidate innate responses in pathogenesis of SARS-CoV-2.

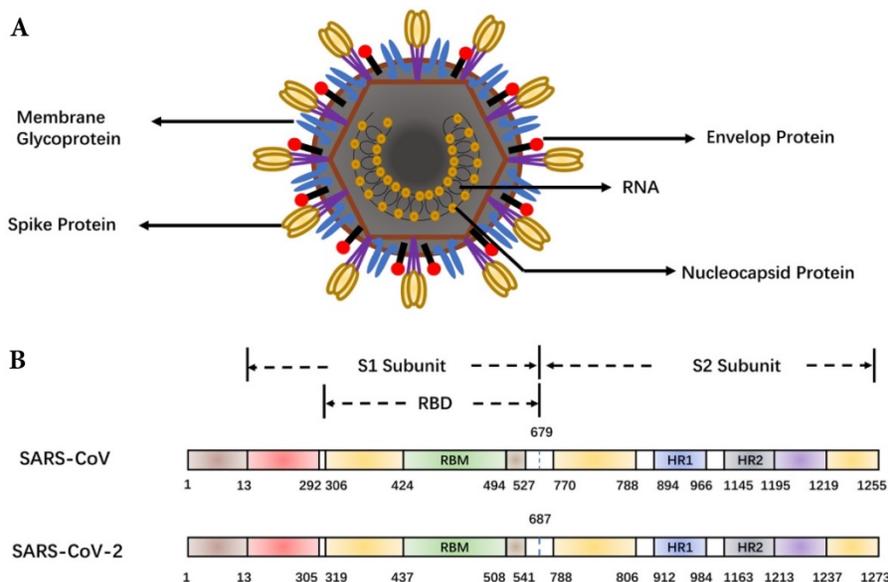


Figure 1. Schematic representation of the coronavirus and spike protein. **(A)** The coronavirus structure. The viral surface proteins (spike, envelope and membrane glycoproteins) are embedded in a lipid bilayer envelope. **(B)** Comparison of the spike (S) proteins of SARS-CoV and SARS-CoV-2. RBD, receptor-binding domain; RBM, receptor-binding motif; HR1/2, heptad repeat 1/2.

The adaptive immune response mainly consists of cellular (T cell) and humoral (B cell) responses. T cell-mediated responses in SARS-CoV infection have been well elucidated [23]. Both CD4+ and CD8+ T-cells provided broad and long-term protection. CD4+ T cells promoted the proliferation of neutralizing antibodies, whereas CD8+ T cells were responsible for the destruction of viral infected cells. Although all SARS-CoV surface proteins, including S, M, E, and N proteins were involved in T cell responses, S protein contributed to the most T-cell recognition epitopes. Overall frequency of CD8+T cell response predominates over CD4+T cell response. Lymphopenia occurred in both SARS-CoV and SARS-CoV-2 infections [14,24,25]. The reduction of CD4+ and CD8+ T cells is commonly associated with lymphopenia. It will be interesting to elucidate T-cell mediated response in SARS-CoV-2 infection that may provide important hints for the design of the vaccine composed of viral structural proteins. On the other hand, patients with SARS-CoV infection had the strong humoral immune response to SARS-CoV [26, 27]. Serum IgG, IgM, and IgA responses to SARS-CoV appeared in patients after primary SARS infection [28]. Neutralizing IgGs played a major role in the neutralization of the SARS-CoV. IgGs reached the peak in serum during the convalescent phase and diminished after recovery [29]. Memory B cells still provided the long-term protection in associated with cellular immune responses [30]. Despite markedly reducing virus replication, anti-S protein neutralizing IgGs could be associated with fatal acute lung injury through promoting IL-8/MCP-1 production and inflammatory macrophage accumulation [31]. These studies may provide important implications for observing IgG response in patients with SARS-CoV-2.

Advances in the development of neutralizing antibodies to SARS-CoV

NAbs provide important specific immune defense against viral infections in patients [32] [33,34]. Numbers of antiviral NAbs have been developed in recent years, and some are now in clinical

development. The role and importance of NAbs in protection from SARS-CoV infection has been thoroughly reviewed elsewhere [7,35-38]. Entry of SARS-CoV into the host cell is mediated by the attachment of S protein and ACE-2 receptor. The S protein is the major inducer of NAbs. Particularly, RBD within S1 unit is the most critical target for SARS-CoV NAbs [39]. Such NAbs can interrupt the interaction of RBD and its receptor ACE2. Most of NAbs have been identified to recognize RBD region [40-46]. Interestingly, some NAbs still showed to recognize epitopes on S2 unit [47], suggesting that other mechanisms could be involved in the neutralization. At last virus clearance was mediated by antibody-dependent opsonization or complement activation [7]. These NAbs against SARS-CoV are summarized in **Table 1**.

Phage display has been used to identify neutralizing human monoclonal antibodies against SARS-CoV from both naïve and immune antibody libraries. The selected antibodies, 80R [40], CR3014 [41], CR3022 [42], m396 [43], blocked the binding of S1 domain and ACE2. 80R, CR3013 and m396 showed virus neutralization and prophylaxis capability in either vitro or animal models. Although CR3022 did not showed much neutralization alone, the mixture of CR3022 and CR3014 showed neutralization of SARS-CoV in a synergistic effect due to recognition of different epitopes on RBD [42]. A method for Epstein-Barr virus (EBV) transformation of human B cells was used to isolate NAbs. Six groups of NAbs, which were divided based on differential neutralization of SARS-CoV variants, have been successfully identified from memory B cells from SARS-CoV infected patients [30]. Furthermore, transgenic mice with human immunoglobulin genes have been used to produce NAbs against SARS-CoV by antigen immunization. Two NAbs, 201 and 68, were identified from transgenic mice [44,45]. They were effective for virus prophylaxis in animal models. On the other hand, several NAbs, B1 [46], 1F8 and 5E9 [47], against epitopes on SARS-CoV S2 still showed effectiveness in neutralization.

Table 1. Neutralizing antibodies against SARS-CoV

Neutralizing antibody	Identification Method	Target Region	Animal model	Reference
80R	Phage display	S1 domain 426-492	Mouse	[40]
CR3014	Phage display	S1 domain 318-510	Ferret	[41]
CR3022	Phage display	S1 domain 318-510	NA	[42]
m396	Phage display	S protein	Mouse	[43]
B1	Phage display	S2 domain 1023-1189	NA	[46]
Group I (S132, S228.11)	EBV transformed B cells	N-terminal RBD	NA	[30]
Group II (S111.7, S224.17)	EBV transformed B cells	S1 domain 318-510	NA	[30]
Group III (S3.1, S127.6, S217.4, S222.1, S237.1)	EBV transformed B cells	S1 domain 318-510	Mouse (S.1)	[30]
Group IV (S110.4, S218.9, S223.4, S225.12, S226.10, S231.19, S232.17, S234.6)	EBV transformed B cells	S1 domain 318-510	NA	[30]
Group V (S124.5, S219.2)	EBV transformed B cells	ND	NA	[30]

Neutralizing antibody	Identification Method	Target Region	Animal model	Reference
Group VI (S109.8, S215.17, S227.14, S230.15)	EBV transformed B cells	S1 domain 318-510	Mouse	[30]
201	HuMAb-Mouse®	S1 domain 490-510	Mouse	[44, 45]
68	HuMAb-Mouse®	S1 domain 130-150	Mouse	[44, 45]
1F8	XenoMouse®	S2 domain HR1	NA	[47]
5E9	XenoMouse®	S2 domain HR2	NA	[47]

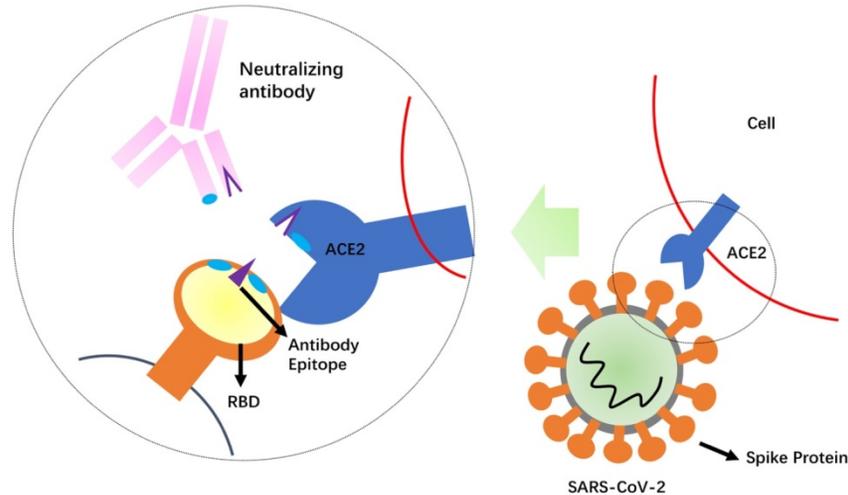


Figure 2. Schematic mechanism of the neutralizing antibodies. Competition of the neutralizing antibody with the receptor (ACE2) for binding to the receptor-binding domain (RBD) of the SARS-CoV-2 Spike protein is shown. The protruding portion (violet) of RBD is both the ACE2 receptor-binding site and the antibody epitope.

Perspectives on the development of neutralizing antibodies against SARS-CoV-2

The simplest and most direct approach to combating SARS-CoV-2 during the outbreak would be to use plasma from the convalescent patients [48]. Polyclonal NABs could be induced in some convalescent patients and will be effective in treating SARS-CoV-2 [12]. These NABs can provide passive immune responses to viral infection. Indeed, both SARS and Ebola patients received the treatment of convalescent plasma [49,50]. However, the outcomes of passive plasma therapy are unpredictable due to variability of sera in different patients.

Development of NABs against SARS-CoV-2 is a relatively rapid approach to obtain the standardized agents that control re-emergence of COVID-19 [51]. The SARS-CoV-2 S protein is likely important target for developing NABs to block binding and fusion of SARS-CoV-2 (**Figure 2**). SARS-CoV-2 seems to use the same cell entry receptor, ACE2, as the SARS-CoV because ACE2 shows binding to RBD of both SARS-CoV and SARS-CoV-2 [11]. However, a recent study demonstrates that SARS-CoV-2 S protein binds ACE2 with higher affinity than SARS-CoV (10- to 20-fold) [13], suggesting its recognition to ACE2 could be different with SARS-CoV. Although SARS-CoV-2 shows the high homology with SARS-CoV, antibody

cross-reactivity is limited between the two virus S proteins. Several published SARS-CoV NABs do not have appreciable binding to SARS-CoV-2 S protein [13,52]. A recent study shows that a SARS-CoV antibody, CR3022, binds to SARS-CoV-2 RBD [52], but its neutralization capability is uncertain. Cocktail of NABs has showed the stronger neutralization than alone in treatment of both Ebola and SARS viruses [47,53]. This finding suggests that a cocktail antibody approach for SARS-CoV-2 could be undertaken. Therefore, it will be very meaningful to generate NABs targeting different epitopes on SARS-CoV-2. Combination of several potent NABs could decrease the probability for escape virus isolates with decreased sensitivity to neutralization.

Computational simulation of antibody-antigen complexes has been used to guide the design of therapeutic antibodies [54-56]. Numbers of antibody structures (currently around 2,000 depositions) are available in the Protein Data Bank [PDB]. Based on these PDB data, the comparative model of an antibody onto the viral surface antigen can be predicted. The key residues between RBD and NABs can be identified to provide important implications for the vaccines against SARS-CoV-2. The key residues of interface between an antibody and the antigen can be optimized to produce high affinity [57]. Several recent computer docking models have been used to predict the interaction between S protein and human ACE2 [10] or antibodies [52]. The studies

revealed the important discovery that SARS-CoV-specific CR3022 antibody could cross-react to SARS-CoV-2.

Conclusion

The availability of therapeutic NABs against SARS-CoV-2 will offer benefits for the control of the current pandemic and the possible re-emergence of the virus in the future, and their development therefore remains a high priority. The efforts of NAB development will surely be an area of intense research in the coming months and even years. Currently, several strategies are used in the clinic or under development, such as viral-targeting therapeutics and host-targeting agents (such as interferons, glucocorticoids) for the treatment of COVID-19. As compared with these therapeutic strategies, NABs appear to be more specific for virions. Understanding of action mechanisms of NABs may provide valuable implications for the rapid development of antibody therapy and vaccine for SARS-CoV-2. However, the development of NAB-based therapeutics is a time-consuming and laborious process. To date, no NAB agents for either SARS-CoV or (Middle East Respiratory Syndrome Coronavirus) MERS-CoV are available in the market. Meanwhile, a note of caution is that the effect of antibody immune response in protecting against pulmonary pathogenesis of SARS-CoV is controversial [31]. Some patients who died of SARS showed the strong NAB responses and pulmonary proinflammatory accumulation, suggesting NABs could be associated with fatal acute lung injury. Therefore, it is important to take insight into humoral and cellular responses of SARS-CoV-2 when antiviral immunotherapy is developed.

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Competing Interests

The authors have declared that no competing interest exists.

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