



Review

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Seasonal coronaviruses and SARS-CoV-2: effects of preexisting immunity during the COVID-19 pandemic

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Abstract: Although the coronavirus disease 2019 (COVID-19) epidemic is still ongoing, vaccination rates are rising slowly and related treatments and drugs are being developed. At the same time, there is increasing evidence of preexisting immunity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in humans, mainly consisting of preexisting antibodies and immune cells (including T cells and B cells). The presence of these antibodies is mainly due to the seasonal prevalence of four common coronavirus types, especially OC43 and HKU1. The accumulated relevant evidence has suggested that the target of antibodies is mainly the S2 subunit of S protein, followed by evolutionary conservative regions such as the nucleocapsid (N) protein. Additionally, preexisting memory T and B cells are also present in the population. Preexisting antibodies can help the body protect against SARS-CoV-2 infection, reduce the severity of COVID-19, and rapidly increase the immune response post-infection. These multiple effects can directly affect disease progression and even the likelihood of death in certain individuals. Besides the positive effects, preexisting immunity may also have negative consequences, such as antibody-dependent enhancement (ADE) and original antigenic sin (OAS), the prevalence of which needs to be further established. In the future, more research should be focused on evaluating the role of preexisting immunity in COVID-19 outcomes, adopting appropriate policies and strategies for fighting the pandemic, and vaccine development that considers preexisting immunity.

Key words: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); Coronavirus disease 2019 (COVID-19); Preexisting immunity; Seasonal coronaviruses; Vaccine

1 Introduction

Coronavirus disease 2019 (COVID-19), caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has persisted for more than two years since December 2019, with more than six million deaths globally, seriously endangering human health and social development; the unfinished pandemic has severely influenced the production industries, altered normal life routines, and has not yet been well-controlled (Dong et al., 2020; Huang CL

et al., 2020; Wu et al., 2020; Zhou et al., 2020). Strains of novel genome mutations such as the Delta and Omicron mutants of coronavirus (CoV) directly affect its communicability, virulence, vaccine efficacy, and persistence (Kupferschmidt, 2021; Lauring and Malani, 2021). Meanwhile, the existing therapeutic drugs against COVID-19 are not effective enough (Dai and Gao, 2021). Therefore, establishing an autoimmune barrier combined with effective treatment strategies is seemingly the best strategy to fight COVID-19 (Dai and Gao, 2021).

Several studies on SARS-CoV-2 immunity have reported the occurrence of preexisting immunity against SARS-CoV-2 in the population, which includes preexisting antibodies and immune cells, especially specific memory T cells (de Vries, 2020; Grifoni et al., 2020; Ng et al., 2020; Weiskopf et al., 2020; Schulien et al., 2021). Preexisting immunity seems to greatly affect

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the spread of the virus. It alters the post-infection response to SARS-CoV-2, resulting in a variation in the degree of disease response among individuals, such as severely ill and asymptomatic patients (Sette and Crotty, 2020). In addition, it affects vaccination, and some individuals with preexisting immunity may have a better response to vaccination; moreover, it may influence the vaccination formulation and immunization policies (Sette and Crotty, 2020). The potential effects of preexisting immunity in COVID-19 patients have not been thoroughly considered. Therefore, in this review, we summarize recent studies on preexisting immunity against SARS-CoV-2, including preexisting antibodies and immune cells, and its potential impacts on disease outcomes.

2 SARS-CoV-2 and common CoVs

CoV includes the following four genera: α , β , γ , and δ (Lefkowitz et al., 2018; Shi et al., 2020). Currently known to infect humans, CoVs mainly include 229E (α genus), NL63 (α genus), human CoV (hCoV) HKU1 (β genus), OC43 (β genus), SARS-CoV (β genus), and Middle East respiratory syndrome (MERS)-CoV (β genus) (King et al., 2011; Lefkowitz et al., 2018; Shi et al., 2020). SARS-CoV-2 belongs to the β genus (Shi et al., 2020). Of these CoVs, 229E, NL63, HKU1, and OC43 mainly cause seasonal colds, which are usually accompanied by common cold symptoms but are asymptomatic in most cases (King et al., 2011; Lefkowitz et al., 2018; Shi et al., 2020). SARS-CoV, MERS-CoV, and SARS-CoV-2 can cause severe respiratory diseases and are highly contagious (Zhou et al., 2020). The CoV virion proteins are polymorphic and approximately round in shape with a diameter of 120–160 nm (King et al., 2011). Their surface contains 20-nm-sized petal-shaped projections, consisting of spike glycoprotein (S protein) trimer (King et al., 2011). CoVs have the largest RNA genome among viruses, typically ranging from 20 to 30 kb in size. The structural proteins of the virus include the S protein, M glycoprotein, membrane protein E, and nucleocapsid protein N (King et al., 2011). Angiotensin-converting enzyme 2 (ACE2) is the target cell receptor of SARS-CoV-2, which binds the S protein trimer, mediating the viral infection of the target cells (Huang Y et al., 2020). The primary role of ACE2 is to convert angiotensin I and angiotensin II into angiotensin-(1–9)

and angiotensin-(1–7), respectively (Feng et al., 2021; Jackson et al., 2022). The entry of SARS-CoV-2 into target cells needs the assistance of transmembrane serine protease 2 (TMPRSS2), and the co-expression of both proteins determines the target cells of SARS-CoV-2, which include type II pneumocytes, ileal absorptive enterocytes, and nasal goblet secretory cells (Jackson et al., 2022). The S1 subunit of the S protein contains the receptor-binding domain (RBD) that binds to ACE2, and the S2 subunit subsequently ensures that the virus is anchored to the membrane and forms endosomes entering the cells, releasing the genome, and starting the viral life cycle (Huang Y et al., 2020). Thus, both S1 and S2 subunits play an important role in the infection of target cells by SARS-CoV-2.

3 Preexisting antibodies

Several related studies, including those conducted by our research group, have shown that preexisting antibodies, mainly immunoglobulin G (IgG), can react with SARS-CoV-2 and are present in the serum of people not yet exposed to the virus.

Ng et al. (2020) collected serum samples from 151 patients before the pandemic between May 2018 and 2019, and found that samples containing antibodies actively reacted with SARS-CoV-2. In particular, cross-reactive IgG antibodies targeted the S antigens. The proportion of IgG antibodies (62%) among teenagers was significantly higher than that among adults, which may be because common CoVs tend to infect teenagers. However, virus-neutralizing antibodies, such as IgG, IgM, and IgA, were abundantly found in the sera of all 156 patients infected with SARS-CoV-2 who underwent serological conversion, whereas immunoglobulin units that predominantly responded to SARS-CoV-2 in the uninfected population were IgG, and the corresponding IgM or IgA antibody was not detected (Ng et al., 2020). As aforementioned, the S protein contains S1 and S2 subunits. Compared with the S1 fragment, the S2 evolves more conservatively in different CoVs; therefore, it has higher antibody activity with a cross-immune response to the S protein and a wider occurrence (Ng et al., 2020) (Fig. 1).

Several studies have confirmed the above results (Nguyen-Contant et al., 2020; Majdoubi et al., 2021;

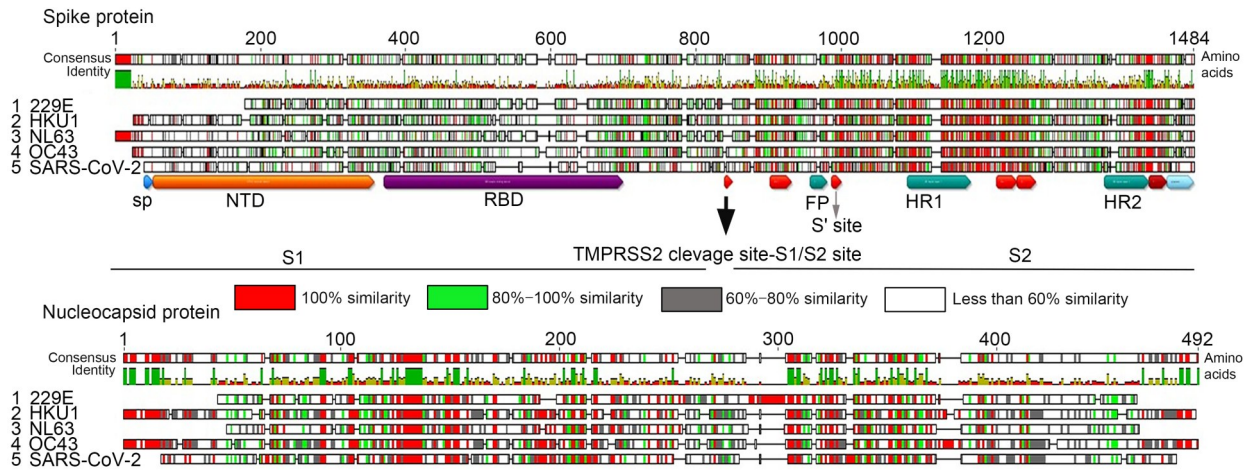


Fig. 1 Evolutionarily conserved regions of the spike (S) and nucleocapsid (N) proteins of coronaviruses. The S and N protein sequences are aligned using the Geneious 11.1.5 software (Biomatters, Auckland, NZ). The TMPRSS2 cleavage site is cleaved, resulting in the production of S1 and S2 subunits of the S protein. The red color indicates 100% similarity among the protein sequences of coronaviruses; the green, grey, and white colors indicate similarities of 80%–100%, 60%–80%, and <60%, respectively. sp: signal peptide; NTD: N-terminal domain; RBD: receptor-binding domain; FP: fusion peptide; HR: heptad repeat; TMPRSS2: transmembrane serine protease 2; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Song et al., 2021). Majdoubi et al. (2021) conducted a competition experiment to rule out nonspecific binding infections and found that antibodies interacted with the S protein of common CoV in the majority of 273 individuals not exposed to SARS-CoV-2. In addition, blood samples of infants collected at 8-month intervals before and after the outbreak revealed that antibodies can interact with common CoVs and they significantly decrease over time, which coincides with the decreased proportion of antibodies transferred from mother to offspring. It also demonstrated that approximately 90%–99% of adults have CoV-associated antibodies. Furthermore, antibodies against SARS-CoV-2 were recognised in the adult serum, including those against the S1 fragment, S2 fragment, RBD domain of the S protein, and non-structural proteins such as nonstructural protein 2 (Nsp2) and Nsp15. Some of them have shown specificity to SARS-CoV-2 (Majdoubi et al., 2021). Nguyen-Contant et al. (2020) compared samples from individuals unexposed to SARS-CoV-2 and those who recovered from COVID-19 and found IgG antibodies against CoV in the unexposed population, whose IgG response was mainly to the S2 fragment and less to the RBD domain or S1 fragment. A large number of plasma and memory B cells (MBCs) secreted IgG in response to the S1 and S2 fragments and RBD domain in patients during the recovery period. In the unexposed population, the above content was lower,

which may be less than $1/(1 \times 10^6)$ of the number of peripheral blood mononuclear cells (PBMCs).

In addition to preexisting immune activity to the S protein, the N protein has also been shown to trigger this type of immune response. First, a serum experiment conducted five years ago revealed an antigenic response in 32 (23.7%) out of 135 serum samples with SARS-CoV-2 nucleocapsid (N) protein (Mveang Nzoghe et al., 2021). Furthermore, Anderson et al. (2021) examined the serum samples collected from 2013 to 2020 before the pandemic and found that most people had common CoV-reactive antibodies before the COVID-19 pandemic. Approximately 20% of these individuals had non-neutralizing antibodies that can cross-react with the SARS-CoV-2 S and N proteins. However, N proteins were reportedly excluded from the cross-immune reaction between common cold CoVs and SARS-CoV-2 (de Assis et al., 2021). Therefore, further studies are required to verify the role of N proteins in preexisting immunity.

In addition to SARS-CoV-2, six other CoVs have been reported to infect humans, including four common cold viruses, SARS-CoV, and MERS-CoV (Millet et al., 2021). Because the number of people infected with the latter two viruses is usually small, leaving immune marks is difficult in the majority of the population; therefore, preexisting immunity after cross-immune reaction with SARS-CoV-2 is mainly caused by a common cold CoV infection. In this regard,

several research teams conducted studies to find out whether one or more CoVs include a cross-immune response to SARS-CoV-2.

In a study by Song et al. (2021), the serum samples of 36 patients with COVID-19 showed strong reactivity with the S protein but weak reactivity with the S proteins of SARS-CoV and MERS-CoV. For common CoVs, the binding abilities of HKU1 and OC43 are strong, whereas those of NL63 and 229E are weak. Nguyen-Contant et al. (2020) revealed that the cross-reactive IgG titre significantly increased in cases of novel CoV infection and strongly responded to OC43 but did not significantly respond to 229E. The cross-immune reaction between common CoV and SARS-CoV-2 is a specific reaction against the S2 fragment. This polypeptide fragment is a highly conserved segment in the evolution of CoV, and the cross-reactive antibody exists in both humans and mice (Jia et al., 2022). Furthermore, Jia et al. (2022) identified that the antigen marker 1147-sfKeeldKyFKNHT-1160, also known as P144, was associated with the production of cross-reactive antibodies through intestinal microeconomic sequencing. Six cross-reactive antibodies specific to P144 were found in mice. Additionally, the levels of preexisting antibodies were positively correlated with the titer of RBD-specific neutralizing antibodies in the population after vaccination. Thus, preexisting cross-reactive antibodies were found to be related to microbiota and they could affect the production levels of neutralizing antibodies post-vaccination (Jia et al., 2022).

The above-mentioned studies also suggested that OC43 may be the candidate occurring in common CoVs, which is involved in cross-immune responses to SARS-CoV-2.

4 Preexisting immune cells

Immune memory cells, namely memory T cells and B cells, are the most powerful cells for sustained immunity against pathogenic infections. With the assistance of memory T cells, B cells can quickly respond to an infection and produce corresponding antibodies to block pathogenic microorganisms (Netea et al., 2016). The levels of antibodies may decrease after several months, whereas some memory cells, such as memory T cells, may survive longer in the

body. SARS-CoV antibodies cannot be detected after 2–3 years; however, memory T cells are still present after 11 years (Cao et al., 2007; Ng et al., 2016; Sui et al., 2021).

For individuals unexposed to SARS-CoV-2, both memory T and B cells can react with this virus. These memory immune cells are derived from CoV cross-immunization as a result of common colds (Braun et al., 2020; Grifoni et al., 2020; Nguyen-Contant et al., 2020). In one study, the proportion of cluster of differentiation 4-positive ($CD4^+$) T cells that could react with S and other protein epitopes of COVID-19 in the unexposed population was approximately 50%, and the $CD4^+$ T cells that responded to S proteins reacted with the S2 fragment (Braun et al., 2020), a result consistent with that of IgG antibodies (Ng et al., 2020; Nguyen-Contant et al., 2020). Furthermore, $CD8^+$ T cells were also detected; however, their proportion and activity were significantly lower than those of $CD4^+$ T cells (Grifoni et al., 2020).

4.1 T cells

Grifoni et al. (2020) used bioinformatic methods to predict the antigen epitopes of a novel CoV using a database that combined the data on human leukocyte antigen class I (HLA-I) and HLA-II. All patients who recovered from COVID-19 were found to have virus-specific $CD4^+$ T cells, which comprised 50% of S protein-specific cells. In their samples unexposed to novel CoVs collected from 2015 to 2018, approximately 50% of the population had $CD4^+$ T cells that could react with the viral antigen bank. These reactive $CD4^+$ T cells were mainly S protein-specific, and M or N protein reactivity was not detected. Interestingly though, nonstructural proteins, such as Nsp4, Nsp14, and Nsp6, exhibited reactivity. However, the proportion of $CD8^+$ T cells reacting with the viral antigens was low in the unexposed populations, with approximately 4 responsive donors out of 11 (Grifoni et al., 2020).

Braun et al. (2020) established two antigen libraries, S1 and S2, corresponding to the S1 and S2 segments of the S protein, respectively, through multiple comparisons of S proteins with different CoVs. Flow cytometry tests revealed that 67% of $CD4^+$ T cells responded to S1 and 83% responded to S2, a significantly higher response than that of S1-specific T cells. Interestingly, the number of $CD4^+$ T cells reactive to S1 was extremely limited in patients with

severe disease. These researchers also found that S2-specific CD4⁺ T cells existed in approximately 24 healthy individuals (35%), although only 5.8% of them were associated with S1, a proportion slightly lower than that reported previously (50%). S1-specific IgG was not detected in healthy individuals. Subsequently, Braun et al. (2020) used S1 and S2 antigenic peptide libraries from OC43 and 229E to investigate the cross-immune response, and found more S2-reactive CD4⁺ T cells than S1-reactive ones in healthy donors.

In addition to the S protein, preexisting memory immune cells and other proteins, such as N and non-structural proteins as well as responsive memory immune cells, have been observed. During the recovery period of patients with COVID-19, 50% of the antigen clusters recognised by the virus-specific T cells were S-proteins, while non-S proteins accounted for the other 50%, indicating the significant proportion of the broad-spectrum virus-specific T cells that were specific to non-S proteins (Grifoni et al., 2020).

le Bert et al. (2020) explored the effects of the presence of memory T cells on viral protein N and the nonstructural proteins Nsp7 and Nsp13 in patients who recovered from COVID-19 as well as healthy controls. Because these two proteins are highly conserved between CoVs, approximately 100% were homologous. Moreover, Nsp7 and Nsp12 are key components of DNA/RNA polymerase activity (Knoops et al., 2008; le Bert et al., 2020). In 36 patients who recovered from COVID-19, all PBMC samples were activated by members of the N protein-peptide bank to produce interferon- γ (IFN- γ). However, only 12 patient samples with reactions in two nonstructural proteins in the peptide bank were collected (le Bert et al., 2020). Some N proteins are too short, such as 101–120- and 321–340-long fragments of amino acid residues, which can stimulate T cells in patients recovering from COVID-19 and activate T cells in patients with active COVID-19 infection. They also recorded whether related memory T cells existed in patients recovering from SARS-CoV infection. Correspondingly, 23 patients who had recovered from SARS-CoV infection 17 years before were enrolled, and their PBMC samples were collected to react with the SARS-CoV-2 peptide bank. All samples yielded positive results and could activate the N protein-peptide segment of SARS-CoV-2. However, the corresponding activation responses were not detected for Nsp7 or Nsp13. Of

the 37 PBMC samples collected from individuals unexposed to SARS-CoV-2, 19 (51.4%) reacted with the peptide bank. CD4⁺ T cells could be stimulated with 101–120-long peptide segments of the N protein in the T-cell subgroups, similar to the cellular response fragments in patients with SARS-CoV and SARS-CoV-2 infections (le Bert et al., 2020).

The long-term persistence of immune memory T cells, such as in SARS-CoV infection that can last for as long as 17 years, is an important indicator affecting the development of public prevention strategies and vaccine policies (le Bert et al., 2020).

4.2 B cells

When a preexisting antibody to SARS-COV-2 reactivity is detected, corresponding MBCs may exist. In addition, the stored virus-specific MBCs play a more influential role in the immune response against SARS-CoV-2 than reactive antibodies. Because MBCs can maintain IgG levels and quickly respond to viral infections, they can survive in the body for years or even decades. These characteristics allow MCBs to effectively function as an anti-infection strategy (le Bert et al., 2020). Nguyen-Contant et al. (2020) reported the substantial presence of plasma cells and MBCs secreted by IgG targeting S1 (including the RBD domain) and S2 in convalescent patients. Song et al. (2021) found strong antibody reactivity with the S protein in the serum of 36 patients with COVID-19 but weak reactivity with SARS-CoV and MERS-CoV. Antibodies strongly cross-reacted with the S proteins of HKU1 and OC43 in the sera of patients with COVID-19 but did not react with the proteins of NL63 or 229E (Song et al., 2021).

However, whether these antibodies are newly activated B cells against the SARS-CoV-2 infection or are evoked by existing MBCs against the common CoV remains unclear. To address this question, Song et al. (2021) isolated 20 S-protein-specific monoclonal antibodies (mAbs) from the serum of patients who recovered from COVID-19 and found that five of them showed cross-reactivity with OC43 and HKU1 S proteins but not with NL63 or 229E in α -hCoV. All cross-reactive mAbs are encoded by a variable heavy chain gene (VH) family (VH3), with somatic high-frequency mutations (SHMs), with 5.6%–10.4% by heavy (VH) chain and 3.1%–4.4% by light (VL) chain (Song et al., 2021). Subsequent biofilm interference

technology further demonstrated that the affinity of bivalent IgG and monovalent antigen-binding fragment (Fab) to HKU1 was higher than that to SARS-CoV-2. Finally, the binding ability of the antibody to the S fragment was evaluated, and cross-reactive antibodies were more inclined to bind highly conserved S2 fragments; the results were consistent with those of previous study (Song et al., 2021). However, genes with SARS-CoV-2-specific mAbs have lower nucleic acid SHMs (VH, 0%–11.6% (median=0.7%); VL, 0%–4.2% (median=1.3%)) (Song et al., 2021).

The above findings suggest the possibility that the source of cross-antibody production for SARS-CoV-2 response may be preexisting MBCs. Moreover, the activity against common CoV was stronger than that against SARS-CoV-2, suggesting that this immune event may result from the antibody-dependent enhancement (ADE).

5 Protective effects of preexisting immunity

A recent study by Kaplonek et al. (2021) on the relationship between preexisting antibodies and patients with different severities COVID-19 demonstrated a significant result. Two-hundred and seventeen hospitalized patients were observed for 0–12 d and divided into three groups based on disease severity and outcomes: moderate symptom, severe symptom, and death groups (corresponding to ≤ 4 , 6–7, and 8 points, respectively, based on the World Health Organization (WHO) evaluation criteria) (Kaplonek et al., 2021). It was found that RBD-, S-, S2-, N-specific IgG1 and S2-specific IgM, IgG1, IgA1 were significantly deficient in the blood of patients in the death group when compared with the other two groups during the acute phase of infection (3–9 d), further showing a reduced binding ability to Fc gamma receptor (Fc γ R). The binding force of Fc γ R was found to be correlated with neutralizing antibodies, which clearly disappeared in the death group, whereas high coordination was observed in critically viable patients. The results indicated that patients with severe COVID-19 who survived experienced a highly coordinated and rapid humoral immune response at an early disease stage (during the onset of symptoms), as compared with patients with severe COVID-19 who deceased. Subsequent statistical analyses established the efficient and selective enrichment of S2-specific Fc

receptor-binding antibodies among survivors, of which S2-specific IgG4 was particularly prominent, whereas a more balanced distribution of distinct antibody features was observed in the moderate symptom and death groups. The subsequent analysis of common CoV cross-immune responses was performed, and Kaplonek et al. (2021) found that RBD-specific IgM and IgG1 levels of OC43 in patients with early symptom onset were significantly higher in the asymptomatic and severe symptom groups than in the death group. Simultaneously, the RBD-specific IgM and IgG1 levels were significantly higher in survivors with severe COVID-19 than in the moderate symptom group, suggesting that survival in patients with severe COVID-19 may be related to the enrichment of OC43-specific immunity at the early disease stage. The analysis of paired nested linear mixed models revealed that IgM, IgG3, IgA, and Fc γ R3A of OC43 were correlated with disease severity. Furthermore, the associated immunity to OC43 in patients directly affects the overall response to SARS-CoV-2 antigens. The specific immune response to the S2 subunit and non-S protein exerts a protective effect on SARS-CoV-2 infection and can potentially eliminate SARS-CoV-2 in asymptomatic infections. Therefore, the above study suggests that the S2-specific immune response to common CoV contributes to early immune evolution, and the class switch of antibodies occurs at the early stage of infection, an important manifestation of pre-stored immune memory. Unlike RBD antibodies that directly neutralize the virus, S2-specific antibodies may protect various pathways, including early recognition of the virus and later involvement in the virus clearance. Thus, S2-specific pre-stored immunity plays a significant role in functional humoral immunity at the early stage of immune responses (Kaplonek et al., 2021).

A different study supported the same idea. Pre-existing T-cell immunity against OC43 and 229E was associated with a higher number of S1- and S2-specific T cells in SARS-CoV-2 in the blood of convalescent COVID-19 patients, which was beneficial to the development of SARS-CoV-2-specific cellular immunity and outcomes (Bonifacius et al., 2021). In addition to the S protein, the N protein also showed cross-reactive preexisting immunity. Ortega et al. (2021) demonstrated cross-reactivity between the OC43N protein and SARS-CoV-2. They found a positive correlation between preexisting antibodies

to the N protein and antibody titres of SARS-CoV-2, and showed the protective effects of cross-reactive antibodies resulting from common CoV infection. Therefore, the clearance of and defense against SARS-CoV-2 by preexisting antibodies or immune cells as well as the function and mechanism of human immune protection require further research. In addition, the highly conserved nature of S2 is potentially beneficial for vaccine development and antibody research.

Furthermore, a patient may also be asymptomatic owing to preexisting antibodies. Ortega et al. (2021) found that the levels of antibodies against common CoVs were higher in asymptomatic patients, especially antibodies against OC43. Similar results were found for the blood of patients recovering from COVID-19 (Nguyen-Contant et al., 2020), suggesting that these preexisting common CoV reactive antibodies exert a protective effect on humans. However, patient's response to infection with SARS-CoV-2 shows variation; patients may have severe, mild, or few-to-no symptoms. However, the extent of cross-reactivity between common CoVs and SARS-CoV-2 remains to be determined.

6 Conclusions and perspectives

Despite the small sample size and insufficient data from the above-mentioned studies, the presence of preexisting antibodies and immune memory cells effective against SARS-CoV-2 in the population cannot be ignored. According to the existing reports, common CoVs, especially OC43 and HKU1, infect humans and produce antibodies and memory T/B cells that can cross-react with SARS-CoV-2. The preexisting antibodies and cells mainly include IgG, memory T cells, and MBCs. The target proteins of preexisting immunity are S protein, N protein, and even nonstructural proteins that are highly conserved between different CoVs. The conserved region of the S protein is mainly the S2 subunit. Thus, it can be seen that preexisting immunity plays a crucial role in COVID-19, reducing the disease severity and enhancing the immune response induced by SARS-CoV-2 infection.

The worldwide H1N1 pandemic (also known as swine flu) in 2009 was an event similar to the ongoing COVID-19 pandemic (Greenbaum et al., 2009;

Wilkinson et al., 2012; Sridhar et al., 2013). It lasted for a year, with tens of millions to approximately 100 million infections and more than 200 000 deaths. Several scholars agreed that preexisting internal immunity was an important factor that ended the pandemic (Greenbaum et al., 2009; Wilkinson et al., 2012; Sridhar et al., 2013). The H1N1 strain is a recombination of the North American and Eurasian H1N1 swine flu strains that jump the species burden and become zoonotic. Owing to the prevalence of other influenza viruses, preexisting immunity resulting from the presence of MBCs (31%) and T cells (69%) in humans (whether CD4⁺ T or CD8⁺ T cells; the evidence is inconsistent) reduced the disease severity in patients with H1N1 infection (Greenbaum et al., 2009; Wilkinson et al., 2012; Sridhar et al., 2013). These findings lead to the suspicion that, in the case of COVID-19, we may have underestimated the capacity of preexisting immunity. Numerous studies have focused on antibody titers and their persistence when investigating the efficacy and protective ability of vaccines; however, memory T cells may be more significant players in immune resistance against viral infection. For example, a study from Singapore reported that SARS-CoV-associated memory T cells remained in the human body for 17 years (le Bert et al., 2020). Nevertheless, the functional analysis of memory T cells is challenging, and more studies should be devoted to the formulation of public policies and development of vaccination programs (Doshi, 2020).

At present, inactivated viral particles and the S protein or its messenger RNA (mRNA) are the main strategy of vaccines for COVID-19, and the available data suggest that such vaccines can induce effective human immune responses to SARS-CoV-2. However, the question of which one of these, or other alternative vaccine design strategies that have encouraging results, could enable B and T cells to harbor longer memory and B cells to produce higher antibody titers with improved efficacy, remains to be validated.

The above-mentioned studies mainly focused on the positive effects of preexisting antibodies. Meanwhile, the potential negative effects of these antibodies, such as ADE and original antigenic sin (OAS), cannot be ignored (Fierz and Walz, 2020). To this end, the relationship between ADE and COVID-19 has been assessed (Lee et al., 2020). However, recent reports demonstrated that, although similar phenomena have been observed in mice, stronger evidence is required

to confirm whether ADE and original antigenic sin can affect vaccination and human resistance against the virus (Lapp et al., 2021; Vashishtha, 2021).

The COVID-19 pandemic caused by SARS-CoV-2 infection is projected to continue for a certain length of time, which is difficult to predict in the foreseeable future. Moreover, a repeated outbreak is also possible (Kissler et al., 2020). However, it can be assumed that SARS-CoV-2 transmission will eventually be blocked by the establishment of a specific immune barrier through vaccination, which can be continuously developed for broader immunity in human populations. Meanwhile, preexisting immunity prompts us to consider the potential effects of new vaccine designs or strategies against SARS-CoV-2 and other viruses, for some of the immune memories can last for years and exert protective functions.

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Author contributions

Gang WANG, Ze XIANG, Wei WANG, and Zhi CHEN were responsible for data collection and article writing. Zhi CHEN was responsible for conceptualization and manuscript revision. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Gang WANG, Ze XIANG, Wei WANG, and Zhi CHEN declare that they have no conflict of interest.

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References

- Anderson EM, Goodwin EC, Verma A, et al., 2021. Seasonal human coronavirus antibodies are boosted upon SARS-CoV-2 infection but not associated with protection. *Cell*, 184(7):1858-1864.e10.
<https://doi.org/10.1016/j.cell.2021.02.010>
- Bonifacius A, Tischer-Zimmermann S, Dragon AC, et al., 2021. COVID-19 immune signatures reveal stable antiviral T cell function despite declining humoral responses. *Immunity*, 54(2):340-354.e6.
<https://doi.org/10.1016/j.immuni.2021.01.008>
- Braun J, Loyal L, Frensch M, et al., 2020. SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19. *Nature*, 587(7833):270-274.
<https://doi.org/10.1038/s41586-020-2598-9>
- Cao WC, Liu W, Zhang PH, et al., 2007. Disappearance of antibodies to SARS-associated coronavirus after recovery. *N Engl J Med*, 357(11):1162-1163.
<https://doi.org/10.1056/NEJMc070348>
- Dai LP, Gao GF, 2021. Viral targets for vaccines against COVID-19. *Nat Rev Immunol*, 21(2):73-82.
<https://doi.org/10.1038/s41577-020-00480-0>
- de Assis RR, Jain A, Nakajima R, et al., 2021. Analysis of SARS-CoV-2 antibodies in COVID-19 convalescent blood using a coronavirus antigen microarray. *Nat Commun*, 12:6.
<https://doi.org/10.1038/s41467-020-20095-2>
- de Vries RD, 2020. SARS-CoV-2-specific T-cells in unexposed humans: presence of cross-reactive memory cells does not equal protective immunity. *Signal Transduct Tar Ther*, 5:224.
<https://doi.org/10.1038/s41392-020-00338-w>
- Dong ES, Du HR, Gardner L, 2020. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis*, 20(5):533-534.
[https://doi.org/10.1016/S1473-3099\(20\)30120-1](https://doi.org/10.1016/S1473-3099(20)30120-1)
- Doshi P, 2020. Covid-19: do many people have pre-existing immunity? *BMJ*, 370:m3563.
<https://doi.org/10.1136/bmj.m3563>
- Feng BH, Zhang D, Wang Q, et al., 2021. Effects of angiotensin II receptor blocker usage on viral load, antibody dynamics, and transcriptional characteristics among COVID-19 patients with hypertension. *J Zhejiang Univ-Sci B (Biomed & Biotechnol)*, 22(4):330-340.
<https://doi.org/10.1631/jzus.B2000730>
- Fierz W, Walz B, 2020. Antibody dependent enhancement due to original antigenic sin and the development of SARS. *Front Immunol*, 11:1120.
<https://doi.org/10.3389/fimmu.2020.01120>
- Greenbaum JA, Kotturi MF, Kim Y, et al., 2009. Pre-existing immunity against swine-origin H1N1 influenza viruses in the general human population. *Proc Natl Acad Sci USA*, 106(48):20365-20370.
<https://doi.org/10.1073/pnas.0911580106>
- Grifoni A, Weiskopf D, Ramirez SI, et al., 2020. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. *Cell*, 181(7):1489-1501.e15.
<https://doi.org/10.1016/j.cell.2020.05.015>
- Huang CL, Wang YM, Li XW, et al., 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, 395(10223):497-506.
[https://doi.org/10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5)
- Huang Y, Yang C, Xu XF, et al., 2020. Structural and functional properties of SARS-CoV-2 spike protein: potential antiviral drug development for COVID-19. *Acta Pharmacol Sin*, 41(9):1141-1149.

- <https://doi.org/10.1038/s41401-020-0485-4>
- Jackson CB, Farzan M, Chen B, et al., 2022. Mechanisms of SARS-CoV-2 entry into cells. *Nat Rev Mol Cell Biol*, 23(1):3-20.
<https://doi.org/10.1038/s41580-021-00418-x>
- Jia LQ, Weng SF, Wu J, et al., 2022. Pre-existing antibodies targeting a linear epitope on SARS-CoV-2 S2 cross-reacted with commensal gut bacteria and shaped vaccine induced immunity. *medRxiv*, preprint.
<https://doi.org/10.1101/2021.07.13.21260404>
- Kaplonek P, Wang CQ, Bartsch Y, et al., 2021. Early cross-coronavirus reactive signatures of protective humoral immunity against COVID-19. *bioRxiv*, preprint.
<https://doi.org/10.1101/2021.05.11.443609>
- King AMQ, Adams MJ, Carstens EB, et al., 2011. Virus Taxonomy. Ninth Report of the International Committee on Taxonomy of Viruses. Elsevier, St. Louis, p.770-783.
- Kissler SM, Tedijanto C, Goldstein E, et al., 2020. Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. *Science*, 368(6493):860-868.
<https://doi.org/10.1126/science.abb5793>
- Knoops K, Kikkert M, van den Worm SHE, et al., 2008. SARS-coronavirus replication is supported by a reticulo-vesicular network of modified endoplasmic reticulum. *PLoS Biol*, 6(9):e226.
<https://doi.org/10.1371/journal.pbio.0060226>
- Kupferschmidt K, 2021. New coronavirus variants could cause more reinfections, require updated vaccines. Science COVID-19 Report. <https://www.science.org/content/article/new-coronavirus-variants-could-cause-more-reinfections-require-updated-vaccines> [accessed on Jan. 15, 2021].
- Lapp SA, Edara VV, Lu A, et al., 2021. Original antigenic sin responses to *Betacoronavirus* spike proteins are observed in a mouse model, but are not apparent in children following SARS-CoV-2 infection. *PLoS ONE*, 16(8):e0256482.
<https://doi.org/10.1371/journal.pone.0256482>
- Lauring AS, Malani PN, 2021. Variants of SARS-CoV-2. *JAMA*, 326(9):880-880.
<https://doi.org/10.1001/jama.2021.14181>
- le Bert N, Tan AT, Kunasegaran K, et al., 2020. SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. *Nature*, 584(7821):457-462.
<https://doi.org/10.1038/s41586-020-2550-z>
- Lee WS, Wheatley AK, Kent SJ, et al., 2020. Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies. *Nat Microbiol*, 5(10):1185-1191.
<https://doi.org/10.1038/s41564-020-00789-5>
- Lefkowitz EJ, Dempsey DM, Hendrickson RC, et al., 2018. Virus taxonomy: the database of the International Committee on Taxonomy of Viruses (ICTV). *Nucl Acids Res*, 46(D1):D708-D717.
<https://doi.org/10.1093/nar/gkx932>
- Majdoubi A, Michalski C, O'Connell SE, et al., 2021. A majority of uninfected adults show preexisting antibody reactivity against SARS-CoV-2. *JCI Insight*, 6(8):e146316.
<https://doi.org/10.1172/jci.insight.146316>
- Millet JK, Jaimes JA, Whittaker GR, 2021. Molecular diversity of coronavirus host cell entry receptors. *FEMS Microbiol Rev*, 45(3):fuaa057.
<https://doi.org/10.1093/femsre/fuaa057>
- Mveang Nzoghe A, Essone PN, Leboueny M, et al., 2021. Evidence and implications of pre-existing humoral cross-reactive immunity to SARS-CoV-2. *Immun, Inflamm Dis*, 9(1):128-133.
<https://doi.org/10.1002/iid3.367>
- Netea MG, Joosten LAB, Latz E, et al., 2016. Trained immunity: a program of innate immune memory in health and disease. *Science*, 352(6284):aaf1098.
<https://doi.org/10.1126/science.aaf1098>
- Ng KW, Faulkner N, Cornish GH, et al., 2020. Preexisting and de novo humoral immunity to SARS-CoV-2 in humans. *Science*, 370(6522):1339-1343.
<https://doi.org/10.1126/science.abe1107>
- Ng OW, Chia A, Tan AT, et al., 2016. Memory T cell responses targeting the SARS coronavirus persist up to 11 years post-infection. *Vaccine*, 34(17):2008-2014.
<https://doi.org/10.1016/j.vaccine.2016.02.063>
- Nguyen-Contant P, Embong AK, Kanagaiah P, et al., 2020. S protein-reactive IgG and memory B cell production after human SARS-CoV-2 infection includes broad reactivity to the S2 subunit. *mBio*, 11(5):e01991-20.
<https://doi.org/10.1128/mBio.01991-20>
- Ortega N, Ribes M, Vidal M, et al., 2021. Seven-month kinetics of SARS-CoV-2 antibodies and role of pre-existing antibodies to human coronaviruses. *Nat Commun*, 12:4740.
<https://doi.org/10.1038/s41467-021-24979-9>
- Schulien I, Kemming J, Oberhardt V, et al., 2021. Characterization of pre-existing and induced SARS-CoV-2-specific CD8⁺ T cells. *Nat Med*, 27(1):78-85.
<https://doi.org/10.1038/s41591-020-01143-2>
- Sette A, Crotty S, 2020. Pre-existing immunity to SARS-CoV-2: the knowns and unknowns. *Nat Rev Immunol*, 20(8):457-458.
<https://doi.org/10.1038/s41577-020-0389-z>
- Shi Y, Wang G, Cai XP, et al., 2020. An overview of COVID-19. *J Zhejiang Univ-Sci B (Biomed & Biotechnol)*, 21(5):343-360.
<https://doi.org/10.1631/jzus.B2000083>
- Song G, He WT, Callaghan S, et al., 2021. Cross-reactive serum and memory B-cell responses to spike protein in SARS-CoV-2 and endemic coronavirus infection. *Nat Commun*, 12:2938.
<https://doi.org/10.1038/s41467-021-23074-3>
- Sridhar S, Begom S, Bermingham A, et al., 2013. Cellular immune correlates of protection against symptomatic pandemic influenza. *Nat Med*, 19(10):1305-1312.
<https://doi.org/10.1038/nm.3350>
- Sui ZW, Dai XH, Lu QB, et al., 2021. Viral dynamics and antibody responses in people with asymptomatic SARS-CoV-2 infection. *Signal Transduct Tar Ther*, 6:181.
<https://doi.org/10.1038/s41392-021-00596-2>

- Vashishtha VM, 2021. Is 'original antigenic sin' complicating Indian vaccination drive against Covid-19? *Hum Vacc Immunother*, 17(10):3314-3315.
<https://doi.org/10.1080/21645515.2021.1945904>
- Weiskopf D, Schmitz KS, Raadsen MP, et al., 2020. Phenotype and kinetics of SARS-CoV-2-specific T cells in COVID-19 patients with acute respiratory distress syndrome. *Sci Immunol*, 5(48):eabd2071.
<https://doi.org/10.1126/sciimmunol.abd2071>
- Wilkinson TM, Li CKF, Chui CSC, et al., 2012. Preexisting influenza-specific CD4⁺ T cells correlate with disease protection against influenza challenge in humans. *Nat Med*, 18(2):274-280.
<https://doi.org/10.1038/nm.2612>
- Wu F, Zhao S, Yu B, et al., 2020. A new coronavirus associated with human respiratory disease in China. *Nature*, 579(7798):265-269.
<https://doi.org/10.1038/s41586-020-2008-3>
- Zhou P, Yang XL, Wang XG, et al., 2020. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, 579(7798):270-273.
<https://doi.org/10.1038/s41586-020-2012-7>