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What do we know about the antibody responses to SARS-CoV-2?

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\textbf{ARTICLE INFO}

\textbf{Keywords:}

SARS-CoV-2, Humoral response, Seroconversion, Convalescent plasma

\textbf{ABSTRACT}

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide causing a pandemic with millions of infected people and deaths. Currently, the scientific community is working hard to develop a specific vaccine or treatment. However, since antibody production is an important part of the adaptive immune response, to develop vaccines and therapies, we must understand the antibody response to SARS-CoV-2 infection. In this work, we summarize the most important findings of antibody-mediated immunity against SARS-CoV-2 and highlight its role in the efficient use of plasma from convalescent patients and the direct application of antibodies as treatment.

1. Introduction

The pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) continues to affect much of the world (Lagunas-Rangel and Chávez-Valencia, 2020). Despite all the research that has been done, there are still many unanswered questions about how the human body responds to SARS-CoV-2 infection. Among them, one that is important to answer in order to develop vaccines, new drugs, and use plasma from convalescent patients is how antibody-mediated immunity against this infectious agent develops.

Overall, SARS-CoV-2 virus has four well-identified structural proteins which are: the spike (S) glycoprotein, the small envelope (E) glycoprotein, the membrane (M) glycoprotein, and the nucleocapsid (N) protein (Fig. 1A). S protein is divided into 2 subunits called S1 and S2 and forms homotrimers that protrude from the viral surface. Remarkably, S protein mediates viral entry into the host cell by first binding to the angiotensin-converting enzyme 2 (ACE2) receptor through the receptor binding domain (RBD) that is part of the S1 subunit and then with the S2 subunit it fuses the viral and host membranes. Meanwhile, N protein binds to the virus RNA and participates in processes related to the viral replication cycle and the response of the infected cell. M protein stabilize the complex between protein N and viral RNA and promotes completion of the viral assembly. Finally, E protein plays a role in the production and maturation of the virus (Astuti and Ysrafi, 2020). Each of these proteins is capable of arousing an immune response that leads to the production of antibodies, to a greater or lesser degree. Although, those that stand out are protein S due to its role in viral entry, and protein N for its high concentration that facilitates its detection (Petherick, 2020).

In this work, we summarize the most important findings of antibody-mediated immunity against SARS-CoV-2 and highlight its participation in the efficient use of plasma from convalescent patients and the direct application of antibodies as treatment.

2. Antibody responses to SARS-CoV-2

Antibodies can help stop viral infection by different mechanisms that include neutralizing the virus by recognizing epitopes on its surface, blocking entry or fusion of the virus into the host cell, as well as improving the activity of other immune components such as complement, phagocytes and natural killer cells (Fig. 1B). Currently, it is known from some studies that serum viral antibodies increase only slightly in the early stage of the disease (first 4 days after the onset of symptoms) and, therefore, in few patients these are detectable (making diagnosis difficult by detecting antibodies). Subsequently, COVID-19 patients show a gradual increase in virus-specific IgG and IgM levels until the third week after the onset of symptoms, and then IgM levels begin to decrease, while IgG levels continue increasing, keeping anti-trimerized IgG S titers stable for approximately three months. IgM often peaks earlier than IgG. Virus-specific IgA has also been observed in COVID-19 patients with behavior similar to IgM, but peaking until day 20 after infection. IgG levels usually reach a peak by day 30 and then decline slowly, but remain detectable for months to years after infection. IgE levels are also elevated in COVID-19 patients and can persist for many months after infection.

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https://doi.org/10.1016/j.imbio.2021.152054

Received 18 May 2020; Received in revised form 1 December 2020; Accepted 11 January 2021

Available online 23 January 2021

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onset of symptoms (Iyer et al., 2020; Liu et al., 2020b; Long et al., 2020; Padoan et al., 2020; Wajnberg et al., 2020; Xiao et al., 2020). Apparently, antibody levels increase rapidly between days 7 to 10 after the symptoms onset and peak at days 17 to 19, with both antibodies being detectable beyond day 30 where IgG levels also start to drop (Long et al., 2020; To et al., 2020; Zeng et al., 2020c). Interestingly, SARS-CoV-2 infection also results in secretion of IgG, IgA and IgM in saliva against protein S and the RBD region, where only the IgG response persists up to three months after the onset of symptoms and it correlates well with serum titers (Isho et al., 2020). Although IgM levels contributed the most to the prediction of a recent infection in the early phase of the disease, IgG responses were the most predictive of infection 8 or more days after the onset of symptoms (Iyer et al., 2020). The concentration of antibodies in the serum of the patients has shown a negative correlation with the levels of viral RNA, which tells us that, in effect, they collaborate to neutralize and eliminate the virus (Fig. 1C) (Du et al., 2020; Zhang et al., 2020b). Additionally, low antibody levels at discharge increase the risk of redetectable viral RNA (Li et al., 2020).

While some articles report higher antibody responses in more severe cases, others do not. Some studies (Crawford et al., 2020; Qu et al., 2020; Seow et al., 2020; To et al., 2020) reported that in the first two weeks after symptom onset, severely ill patients had higher IgG levels than
patients with moderate disease. Indeed, this can be explained since the high viral load in severe cases could activate extra follicular B cells and cause the production of antibodies earlier (Yongchen et al., 2020).

Another study (Liu et al., 2020b) did not observe changes in the early phase, but until 15 days after the onset of symptoms, and another study (Wu et al., 2020a) found higher levels of IgG against protein S and N in patients without severe symptoms. Also, an earlier IgM response that also decreased more rapidly has been mentioned, and higher IgM and IgG levels in severe cases (Iyer et al., 2020; Long et al., 2020; Zeng et al., 2020c). Mucosal IgA has also been mentioned to have higher levels in severe patients (Cervia et al., 2020).

Approximately 97% of patients have showed seroconversion within 20 days after the onset of symptoms and the remaining 3% did not show seroconversion, where day 12 was the median day for IgG, IgM and IgA seroconversion (Iyer et al., 2020; Long et al., 2020; Zhao et al., 2020). In approximately half of the population, seroconversion against protein S, RBD, and protein N occurs simultaneously (Seow et al., 2020). Some asymptomatic patients also did not develop seroconversion presumably due to the low level of viral load (Lee et al., 2020; Yongchen et al., 2020). Interestingly, seroconversion has occurred in three different ways: synchronous seroconversion of both immunoglobulins (47.8%), IgM seroconversion later than that of IgG (40.5%), and IgM seroconversion earlier than that of IgG (11.6%) (Long et al., 2020; To et al., 2020). Most patients had earlier IgG and IgM seropositivity for anti-RBD than anti-N, and in both cases the IgG concentrations correlated better with the microneutralization assays than the IgM concentrations (To et al., 2020). Antibody responses to other virus proteins have been lower in patient serum (Ni et al., 2020).

SARS-CoV-2 N protein–directed antibodies have shown a cross reaction with the SARS-CoV N protein, as well as antibodies directed to the SARS-CoV 2 S and S1 proteins and the SARS-CoV counterparts (Long et al., 2020; Okba et al., 2020), but no cross reactivity has been detected between the SARS-CoV-2 RBD protein and the SARS-CoV RBD (Ju et al., 2020b, 2020a). This can be explained because the SARS-CoV-2 N protein shares 90.52% identity with SARS-CoV N protein, while the SARS-CoV-2 S protein shares a 76.42%, and where S1 subunit is less conserved (64%) than the S2 (90%). SARS-CoV-2 RBD region has 74% identity with the SARS-CoV counterpart, but the identity of the residues that have shown direct contact with the ACE2 receptor drops to 50% (Jaimes et al., 2020; Xu et al., 2020).

The competitive ability of ACE2 has correlated well with the neutralizing activities of the antibodies, although the antibodies analyzed so far have recognized epitopes in S1, both for the RBD region and for the N-terminal domain (NTD), and for S2, especially of the IgG class (Ju et al., 2020b; Liu et al., 2020a). Antibodies directed against the RBD region can prevent interaction with the ACE2 receptor, destabilize prefusion or restrict the conformational change of the S protein, in all cases preventing the entry of the virus, while for antibodies directed against NTD and S2 is unknown the mechanism of action (Gavor et al., 2020). Notably, antibodies identified in convalescent patients showed that only those targeting the RBD site with a dissociation constant (Kd) smaller or closer to that of ACE2/RBD showed potent neutralization effects against pseudoviruses and true SARS-CoV-2 virions (Cao et al., 2020). Despite the strong humoral response against the N protein, these antibodies have not been shown to be neutralizing for the virus, and also have a shorter half-life (Addetta et al., 2020; Grandjean et al., 2020; Wu et al., 2020).

Notably, it has been mentioned that the percentage of B cells and plasmablasts is higher in COVID-19 patients and increases with the severity of the disease (Marcos-Jiménez et al., 2020). RBD-specific B cells have been reported to vary from person to person among COVID-19 patients, but on average they represent approximately 0.005–0.065% of the total B cell population and 0.023–0.329% among memory sub-populations. Antibodies in COVID-19 patients are derived from broad and diverse families of antibody heavy and light chains and even in the same patient, the pattern of antibodies changed over time, only interdigitating between them, suggesting that patients develop different antibodies during SARS-CoV-2 infection, and these are related during the early stages of the disease. IgVH 3–30 was overrepresented and three clones were significantly enriched in these samples: antibodies with heavy-chain variable regions belonging to the VH1-2*06, VH3-48*02, and VH3-9*01 families, together with the corresponding light-chain kappa (Igk) belonging to 2–40*01/2D-40*01, 3–20*01, and light-chain lambda (Igl) to 2–14*02 with the respective joining segment kappa 4 (Jk4), Jk5 and joining segment lambda 1 (Jl1). This group of antibodies had a longer CDR3 length than other antibodies less present in the serum and were enriched with tyrosine residues in this region, indicating possible areas to establish hydrogen bonds and hydrophobic interactions with the surrounding residues. VH1-2*06 and VH3-9*01 showed a tendency to increase over time, while VH3-48*02, which has smallest CDR3 region of these three, to decrease (Ju et al., 2020b, 2020a). The mean number of nucleotide mutations in the V genes for IGH and IGL was lower than in antibodies from individuals with chronic infections and similar to antibodies in individuals with primary circulating malaria or from non-antigen-enriched circulating IgG memory cells (Robbiani et al., 2020). Anti-N and anti-RBD IgG are mainly of the IgG1 isotype, and some patients presented the IgG3 isotype (Cao et al., 2020; Ni et al., 2020). Low reactivity was also detected for IgG2 and IgG4 (Amanat et al., 2020). In particular, for SARS-CoV-2 neutralizing antibodies, similar levels of somatic hypermutation were identified, regardless of the isolation time (Kreer et al., 2020).

It is not clear whether convalescent patients are at risk of “relapse” or “reinfection”, or how long protection lasts after infection. It has been seen that the presence of neutralizing antibodies from a previous infection was associated with protection against reinfection (Addetta et al., 2020), but at the same time, there have been cases where it is considered that there was reinfection (Vrieze, 2020). Experiments with Rhesus monkeys showed that infection with SARS-CoV-2 protects against reinfections in subsequent exposures, at least for short times, where the concentration of specific antibodies produced against the virus was much faster and higher in the re-exposure (Bao et al., 2020). Some studies reported that neutralizing antibody titers decrease 60 days after the onset of symptoms to reach a stable plateau and in some patients the decrease is quite drastic, but still appears to be sufficient to provide protection against SARS-CoV-2 (Crawford et al., 2020; Seow et al., 2020).

Although still in controversy, it is thought that IgG against SARS-CoV-2 can be transferred through the placenta from mother to fetus, but it is only identifiable in neonates for about 50 days and then disappears (Gao et al., 2020). IgM was also detected in infants, but it was not identified if it was due to any damage to the placenta, or if the virus crossed the placenta and the baby produced the antibodies, or if the antibodies were actually transferred from mother to child (Zeng et al., 2020a). This presence is also mentioned in other reports, disappearing 28 days after delivery (Cavalieri et al., 2020). Additionally, breast milk has also shown IgG and IgA antibodies against SARS-CoV-2 (Ong et al., 2020).

3. Antibodies as treatment

Because there are currently no vaccines or drugs that can be used specifically for the treatment of patients with COVID-19, treatment with the plasma of convalescent patients has emerged as a therapeutic option (Fig. 1B). Convalescent plasma treatment is a passive administration of recovered patients, which contains antibodies against the SARS-CoV-2, to treat critically ill people (Tanne, 2020). Currently, the effectiveness of convalescent plasma is still unclear and there is insufficient data from well-controlled, adequately powered, randomized clinical trials to
recommend either for or against its use for the treatment of COVID-19. Convalescent COVID-19 patients, who recovered from moderate illness, had detectable IgM and IgG levels (Duan et al., 2020; Shen et al., 2020; Zeng et al., 2020b; Zhang et al., 2020a, 2020b). It has been reported that plasma-treated patients significantly dropped the virus load within the first 12 days after transfusion and improved its clinical characteristics. Gradually virus-specific IgG and IgM levels and their neutralizing activities increased in patients, which remained high for more than 7 days (Duan et al., 2020; Shen et al., 2020; Zhang et al., 2020a). IgG against protein S and the RBD region increased within 3 days after transfusion, with no apparent changes for IgA against protein N (Li et al., 2020). In some cases it is mentioned that the use of convalescent plasma was effective in very severe cases (Duan et al., 2020; Ye et al., 2020) and also had detectable IgM and IgG levels (Duan et al., 2020; Shen et al., 2020; b)

- Based on full-length IgG (although there are also therapies based on IgG). In clinical trials, the vast majority of these correspond to monoclonal anti-SARS-CoV-2 antibodies. These antibodies are mainly obtained by selecting neutralizing antibodies from patients infected with SARS-CoV (Pinto et al., 2020). Likewise, an antibody cocktail with one antibody against the RBD region and the other against the NTD region has been shown to be effective in Rhesus monkeys and golden hamsters in reducing viral load and virus-induced pathological sequelae (Baum et al., 2020). Several candidate antibodies are currently in clinical trials, the vast majority of these correspond to monoclonal antibody designs, single domain antibody, polyclonal antibodies, with fusion protein or other variants (Yang et al., 2020). To optimize the results and the pharmacokinetics, modifications have been made in some antibodies which include the selective change of isotype and the modifications of the Fc region through the substitution of different glycans or amino acids (Hussen et al., 2020).

4. Conclusion

We want to highlight that many of the results presented in this work are preliminary, contain very small patient samples, or require more trials to be conclusive. In this way, we want to highlight the importance of studying antibody-mediated immunity against SARS-CoV-2 and leave some questions that we hope can be answered soon: What factors intervene so that a person does not carry out seroconversion? Is a lasting memory immunity generated after infection with SARS-CoV-2? Does the transfer of antibodies from the mother prevent infection of the fetus? What is the optimal time to apply the plasma of convalescent patients in critically ill patients? What is the optimal concentration of neutralizing antibodies that must be in the plasma to be efficient? What precautionary strategies should be implemented for the safe administration of convalescent plasma therapy to mitigate the risk of SARS-CoV-2 transmission?

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

FALR is recipient of a doctoral scholarship (application number 2018-000012-01NACF-07226) from the National Council of Science and Technology, CONACyT.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmbo.2021.152054.

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