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Perspective

Realization of humoral immunity against SARS-CoV-2 infections

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The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a major ongoing challenge to global health. After being infected by SARS-CoV-2, a specific humoral immune response may be rapidly induced in the host to restrain the viral infection via the production of neutralizing antibodies (NAbs), which are also useful for preventing reinfection [1,2]. However, there is a lack of comprehensive understanding of the mechanisms underlying SARS-CoV-2 specific humoral immunity and alterations in immunoglobulin M (IgM) and G (IgG) levels in humans during viral infection. In this perspective, we have summarized several characteristics of the humoral immune response against SARS-CoV-2 infection and its potentially critical role in vaccine development. Additionally, we have discussed the antibody-dependent enhancement (ADE) phenomenon in antibody immunotherapy, the current status of vaccine development, and public health strategies aimed at ending the global COVID-19 pandemic.

Since the novel coronavirus SARS-CoV-2 was reported as the causative agent of COVID-19 in December 2019, the subsequent spread of SARS-CoV-2 has led to the COVID-19 pandemic. SARS-CoV-2 continues to considerably impact human health and life expectancy and endangers the global economy and socio-economic stability. The gold standard technique used to confirm early SARS-CoV-2 infection is reverse transcription polymerase chain reaction (RT-PCR)-based viral nucleic acid testing. However, previous studies conducted by our colleagues and other researchers indicate that virus-specific antibody detection for COVID-19 may be used as a complement to viral RNA detection for the diagnosis of suspected cases with negative RT-PCR results and/or for surveying asymptomatic infection in close contacts [3]. For the emerging virus, the characteristics and specific detailed mechanisms of how protective humoral immunity is developed in COVID-19 patients are not clearly defined. Herein, we compared the characterization of SARS-CoV-2-specific antibody responses in the COVID-19 patients conducted in different studies worldwide and further discussed the critical roles of specific anti-viral humoral immunity in virus clearance and vaccine development.

1. Kinetics of SARS-CoV-2-specific humoral immunity

The human immune system counters and eliminates invasive foreign pathogens with the assistance of innate immunity and adaptive immunity. Upon SARS-CoV-2 infection, specific humoral immunity, which is mainly characterized by elicitation of specific antibody responses in human B cells, may play a critical role in the effective removal of the highly transmissible coronavirus (Fig. 1). Under stimulation by SARS-CoV-2 antigens, B cells from the germinal center can proliferate and differentiate into plasma cells, which then produce and secrete specific antibodies to control virus replication. Meanwhile, the virions may also directly modulate host-specific immunity by infecting immune cells expressing the virus-specific receptor angiotensin converting enzyme 2 (ACE2).

Specific antibodies against SARS-CoV in most convalescent patients can exist for more than 2 years, and their NAbs have been reported to exist for 2 years in a few recovered patients. Our understanding of the kinetics and detailed mechanism of establishing human-specific humoral immunity against SARS-CoV-2 is limited in COVID-19 patients, despite active studies being conducted on the virus. Multiple studies have reported on the kinetics of SARS-CoV-2-specific antibody responses in the patients with COVID-19 (Table 1). Our recent study showed that the titers of serum-specific IgM and IgG antibodies increased at the same stage and, in some clinical cases, serum IgG or IgA reactions preceded those of serum IgM [3]. The levels of the serum specific IgM antibody increased on day 9 after the onset of symptoms in these COVID-19 patients, while the serum IgG levels increased on day 11. Subsequently, we further found that asymptomatic patients with SARS-CoV-2 infection exhibited a weaker serum-specific IgG antibody response [1], suggesting that there is necessity to determine the duration of SARS-CoV-2-specific antibody responses. Collectively, the dynamic trends of viral-specific antibody levels provide us with important information reflecting the changes of the SARS-CoV-2-specific humoral immunity.

The humoral immune response helps restrain the SARS-CoV-2 infection mainly through virus-specific NAb production. NAb titers may increase over time in parallel with the increase in levels of specific IgG antibodies against SARS-CoV-2 [4]. Our previous work demonstrated that SARS-CoV-2-specific NAb titers increased 2–3 weeks after symptom onset and titers peaked at 33 days. NAb titers in most patients decreased gradually over a 3-month study period, with a median decrease of 34.8%. Therefore, it is important to better understand the kinetics of viral-specific antibody responses including NAb production in SARS-CoV-2 infection and recovery phases.

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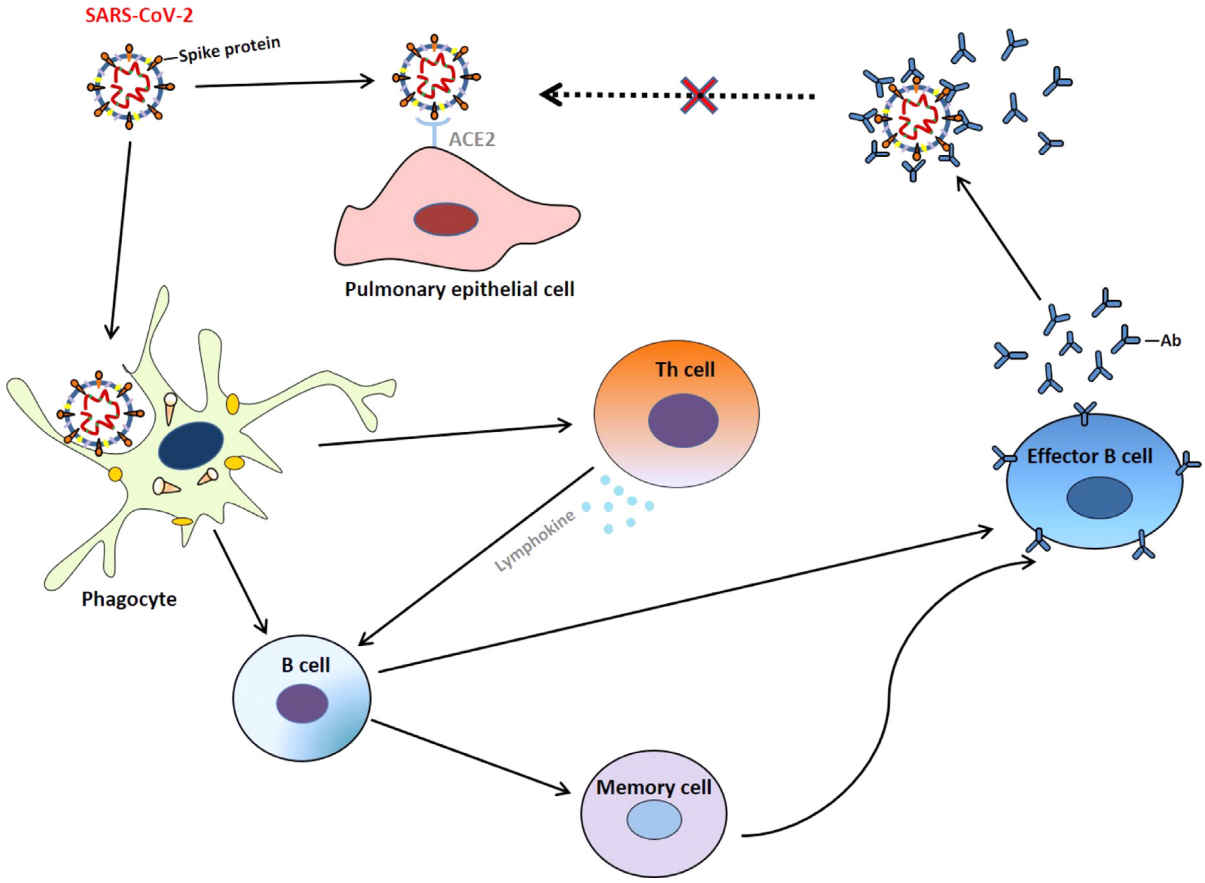

Fig. 1. SARS-CoV-2 infection and viral-specific humoral immunity. Schematic diagram showing the elicitation of humoral immune responses following SARS-CoV-2 infection of host cells. After SARS-CoV-2 virions invade the human body, the virions can be engulfed by phagocytes and processed to expose hidden antigenic determinants. Subsequently, the phagocytes present the viral antigens to Th cells and stimulate T cells to produce lymphokines that can activate B cells; only certain viral antigens can directly stimulate B cells. After stimulation by viral antigens, B cells undergo a series of proliferation and differentiation processes to form effector B cells termed plasma cells. Among these processes, a small proportion of B cells develop into specific memory B cells, which can convert into plasma cells to produce specific Abs against SARS-CoV-2 reinfection. Finally, a large proportion of SARS-CoV-2-specific Abs secreted by plasma cells play a neutralization role in binding to the viral spike protein and blocking its interaction with the virus-specific receptor ACE2. This leads to the occurrence of an inhibitory conformational change in the spike protein and development of resistance to viral host cell invasion. Ab, antibody; ACE2, angiotensin converting enzyme 2; Th cells, T helper cells.

Table 1
Characteristics of SARS-CoV-2-specific antibody production in patients with COVID-19.

				Positive rate (%)		Initial seroconversion time (days)		Peak time (days)	
	Case No.	Antibody type	Diagnostic test	IgM	IgG	IgM	IgG	IgM	IgG
Long et al.	285	Specific Ab	MCLIA	94.1	100.0	≤6	≤6	20-22	17-19
Wang et al.	23	Specific Ab	ELISA	–	–	≤6	6-9	12-18	>18
Zhao et al.	173	Specific Ab	ELISA	94.3	79.8	12	14	14–21	21–28
Xiang et al.	85	Specific Ab	ELISA	93.8	90.9	4	4	4-	12
Wang et al.	23	NAb	Pseudotype neutralization test	–	–	–	9	14-22	15-24
Wang et al.	30	NAb	Pseudotype neutralization test	–	–	–	10	4-	33

ELISA, enzyme-linked immunosorbent assay; MCLIA, magnetic chemiluminescence enzyme immunoassay; NAb, neutralizing antibody.

2. Humoral immunity against SARS-COV-2 infection and reinfection

It is well established that effective humoral immunity is critical for the clearance of cytopathic viruses, as well as the prevention of virus reinfection. Similarly, viral-specific NAbs are also of considerable importance for the recovery of SARS-CoV-2-infected patients and the prevention of this virus reinfection. In addition to neutralizing SARS-CoV-2 by viral-specific NAbs, there was a significant positive correlation of the NAb titers with the count of nucleocapsid protein specific T cells in recovered patients with COVID-19 [5], suggesting a possible synergism between specific B and T cells in immune-mediated protection against the SARS-CoV-2 infection. Additionally, the humoral immune response induced by SARS-CoV-2 infection can prevent viral reinfection in rhesus macaques [2]. Unfortunately, there were some reinfection cases reported in different individual reports. Therefore, we should investigate

whether the recovered patients who have developed specific humoral immunity against SARS-CoV-2 are protected against reinfection; further research is warranted.

Notably, the following three aspects cannot be ignored in SARS-CoV-2-specific antibody responses. Firstly, higher levels of specific antibodies in patients with COVID-19 could be an indication of the presence of a more serious condition existing independently of age and sex. Secondly, as SARS-CoV-2 exhibits many similarities with SARS-CoV and MERS-CoV, a potential cross-reaction of antibodies between these similar viruses cannot be excluded, nor can the potential impact on the immune response and clinical outcome. Additionally, we cannot also exclude the possibility that the convalescent patients could be re-infected in subsequent waves of SARS-CoV-2 infection.

3. Vaccine development and antibody-dependent enhancement

Specific antibody responses caused by SARS-CoV-2 infection may help restrain the infection and spread of the virus in the human body via NAb production, and this response can be considered for developing strategies pertaining to prophylaxis, post-exposure prophylaxis, or treatment of SARS-CoV-2 infection. The major target of NAbs against SARS-CoV-2 is the spike (S) protein, which is composed of S1 and S2 domains. Importantly, the S1 domain has a receptor-binding domain (RBD) that interacts with the host viral receptor ACE2, eventually mediating host attachment and endocytosis. The S proteins of SARS-CoV and SARS-CoV-2 share 77% identity with each other and both bind to ACE2 with high affinity. Certain monoclonal antibodies generated against the spike protein of SARS-CoV can cross-neutralize SARS-CoV-2. Thus, specific monoclonal antibodies possessing potent antiviral activity could be used and adopted for treating SARS-CoV-2 infections.

Since the COVID-19 pandemic emerged and spread on a large scale, scientists around the world continue to engage relentless efforts to develop SARS-CoV-2 vaccines, including spike-based DNA/RNA vaccines, inactivated virus vaccines, live attenuated virus vaccines, recombinant viral-vectored vaccines, and protein subunit vaccines. Vaccine design considerations include the selection of antigens, vaccine platforms, and vaccination routes and regimens. The main purpose of developing a SARS-CoV-2 vaccine is to generate a sustained memory humoral immune response and to produce specific NAbs to prevent the entry of SARS-CoV-2 into host cells. We propose that vaccines designed to elicit specific NAbs will be effective in preventing SARS-CoV-2 infections.

The potential risk of vaccine-induced ADE cannot be ignored in the course of vaccine development and use. Regarding SARS-CoV, MERS-CoV, and dengue virus infection, it has been found that the presence of sub-neutralizing or cross-reactive non-NAbs has a theoretical potential to enhance infection and to trigger harmful immunopathology. Considering these cases, anti-SARS-CoV-2-specific antibodies may fail to protect the body and, instead, exacerbate the disease severity. Although there is no proof available on the occurrence of ADE in SARS-CoV-2 infection, it should be considered a general concern for formulating antibody therapy strategies for SARS-CoV-2 vaccine development.

4. Conclusion

Under the current COVID-19 pandemic, there is an urgent need for the development of safe and effective COVID-19 vaccine strategies to combat SARS-CoV-2 infection. To date, there exists a rudimentary understanding of the characteristics of the SARS-CoV-2-specific antibody response; strategies using specific NAbs possessing potent antiviral activity may be adopted for controlling SARS-CoV-2 infection. The development of specific vaccines against SARS-CoV-2 is a time-consuming process; thus, these vaccines may not control the initial wave of the pandemic in an appropriate timeframe. However, a vaccine is essential to preventing occurrence of additional waves and reinfection as SARS-CoV-2 continues to spread and possibly return as a seasonal virus, such as the influenza virus. While it is important to pursue various vaccine strategies in parallel, it is imperative to consider safety issues, including the ADE phenomenon observed in the process of vaccine development and testing.

Author contributions

YL and AH conceived this article; YL, ZZ, and JZ wrote the original draft and prepared figures or tables; YL, JL, and AH edited and reviewed the manuscript.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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