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MINIREVIEW

Natural immune response and protection from SARS-CoV-2 reinfection

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Summary. – The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the associated disease Coronavirus disease 2019 (COVID-19) continues to spread throughout the world, causing millions of infections and dead. One major question in predicting the course of the COVID-19 pandemic is how well and how long the immune response protects the host from reinfection. Although more studies are needed, evidence suggests that virus-specific B cell response in people with SARS-CoV-2 infection is rapidly generated and seems to be more reliable marker of long-lasting humoral responses than serum antibodies. Here we reviewed all related major studies of immune response to SARS-CoV-2 virus to better understand the natural protection against the virus, and the risk of reinfection. The ability of our community to eradicate this virus will mostly depend on our knowledge of the immune response, critical not only for vaccine development and distribution but also for therapeutic options.

Keywords: SARS-CoV-2 virus reinfection; humoral immune response; SARS-CoV-2 virus variants; vaccination

Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the associated disease Coronavirus disease 2019 (COVID-19) continues to spread throughout the world, causing by April 8th, 2021 more than 130 million infections (https://coronavirus.jhu.edu/map.html). There are important questions about this global outbreak emergency that must be urgently answered: Are individuals who have recovered from COVID-19 protected from a second SARS-CoV-2 infection? How long the SARS-CoV-2 immunity lasts after a previous infection? Do previously infected individuals need to be vaccinated? In the present work we revised all literature about immunity and SARS-CoV-2 infection in order to answer these questions.

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Abbreviations: COVID-19 = Coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

SARS-CoV-2 virus reinfection

One major question in predicting the course of the COVID-19 pandemic, caused by SARS-CoV-2, is how well and how long the immune responses protect the host from reinfection. For some viruses, the infection provokes a strong immune response and so immunity tends to last a long time, either from infection or vaccines. As an example, it has been shown that antibodies against measles, polio and smallpox last a lifetime (Smart, 2008; Slifka and Ahmed, 1996). Few cases of COVID-19 reinfection have been reported so far, and they were detected especially in healthcare workers that are intensely re-exposed to the virus (Gupta *et al.,* 2020; Bongiovanni, 2020; Abu Raddad *et al.,* 2020; Iwasaki, 2021). A pre-print papers reported that individuals who have recovered from COVID-19 are well protected from future SARS-CoV-2 infection (Hall *et al.,* 2021). The authors presented a five-month follow-up study of a large-scale multi-center prospective cohort including 20,787 healthcare asymptomatic workers that

underwent frequent SARS-CoV-2 PCR testing. Comparison between SARS-CoV-2 positive and negative cohorts resulted in 95% lower odds ratio of reinfection (Hall *et al.,* 2021). The authors concluded that in this cohort study the naturally acquired immunity protects against reinfection for at least five months after the first infection. It has been hypothesized that since a few cases of SARS-CoV-2 reinfection were reported so far, this does not mean that protection cannot be reached by the majority of the infected people but instead that few of them may have some immunological deficits not discovered yet (Overbaugh, 2020). *In vivo* experiments on rhesus macaques by Deng and colleagues (Deng *et al.,* 2020) had shown that after a trachea infection with SARS-CoV-2 the infected animals were protected against reinfection (Deng *et al.,* 2020). SARS-CoV-2 infected animals despite a mild-to-moderate disease showed abundant $CD4^+$ T cells, $CD8^+$ T cells, B cells, macrophages, plasma cells in the lungs, and serum anti-spike IgG antibody titers increased to 5000. The reinfection was performed 28 days after primary infection and no pathological changes of the lungs were seen, no viral RNA was detected, and no immune cell invasion of the lungs was observed. As the only reinfection markers detected were a transient increasing of body temperature, an increased IgG serum antibodies titer to 80,000 and a tenfold increased serum neutralizing activity of specific SARS-CoV-2 antibodies (Deng *et al.,* 2020). To further investigate SARS-CoV-2 reinfection, Chandrashekar and colleagues rechallenged rhesus macaques 35 days after the initial infection with SARS-CoV-2 virus and showed that primary infection was protective and prevented symptoms of COVID disease (Chandrashekar *et al.,* 2020). The authors did not observe full neutralizing immunity, as four of nine animals had detectable levels of viral RNA in the upper respiratory tract after the second infection, despite the viral load declined rapidly (Chandrashekar *et al.,* 2020). These studies show that SARS-CoV-2 infection induced protective immunity against re-exposure in non-human primates. Protection from SARS-CoV-2 reinfection in humans was firstly reported by Addetia and colleagues (Addetia *et al.*, 2020) (Addetia *et al.,* 2020), showing that all individuals who had neutralizing antibodies to SARS-CoV-2 virus were protected from reinfection during a SARS-CoV-2 outbreak, providing the first evidence for neutralizing antibodies as a correlation of protection in humans (Addetia *et al.,* 2020). A total of 1265 anti-spike-seropositive healthcare workers, including 88 in whom seroconversion occurred during follow-up, showed no symptomatic reinfections and only two PCR-positive results in asymptomatic healthcare workers were seen in previously infected subjects. This result suggests that previous SARS-CoV-2 infection, and the resulting immune response is associated with protection from reinfection for almost all participants and lasts for at least 6 months (Addetia *et al.,* 2020). Similarly, longitudinal assessment of SARS-CoV-2 infection in healthcare workers with a positive antibody titer was lower than among those who were seronegative (Lumley *et al.,* 2021).

Duration of humoral immune response

The immune system is a network of biological process that protect an organism from diseases by preventing infection and opposing pathogens proliferation. The basic classification of the immune system consists of the innate immune system and the adaptive immune system. During viral infection, the first line of defense against virus is the innate, or non-specific, immune response consisting of physical, chemical, and cellular defenses against pathogens. The main purpose of the innate immune response is to immediately prevent viral spreading throughout the body, while the adaptive immune system involves three major cell types: B cells, $CD4^+$ T cells, and $CD8^+$ T cells. B cells produce antibodies (Plotkin's Vaccines, 2018; Piot *et al.,* 2019; Orensteina and Ahmedb, 2017); $CD8^+$ T cells, also known as "killer T cells", can directly kill virus-infected cells and recruit other types of immune cells through the production of cytokines; $CD4^+$ T cells, act as "helper cells" by indirectly killing cells identified as foreign, using cytokine signaling to influence regulatory B cells directly, and other cell populations indirectly. Adaptive immune response is important for the control and clearance of almost all viral infections causing disease in humans. Evidence suggests that virus-specific B cell responses in people with SARS-CoV-2 infection occur in conjunction with $CD4^+$ T follicular helper cell responses after 1 week from symptoms of disease onset (Giménez *et al.,* 2021; Vabret *et al.* ,2020). The first antibody response targets nucleocapsid (N) protein, whereas antibodies directed against the receptor-binding domain (RBD) of the spike (S) protein, occur after 1 week from the viral infection (Seydoux *et al.,* 2020). As previously described in studies about common human coronaviruses and more recent in SARS-CoV-2 infected patients, neutralizing antibodies are elicited and can last for years providing protection from reinfection or, in the event of reinfection, attenuating the symptoms of the disease (Wilson *et al.,* 2020; Grzelak *et al.,* 2020; Burbelo *et al.,* 2020; Long *et al.,* 2020; Leung *et al.,* 2004; Huang *et al.* ,2020). As shown in a study by Wajnberg and colleagues (Wajnberg *et al.,* 2020) moderate to high anti-spike antibody titer was detected in 30,082 seropositive subjects and antibody levels were stable for at least all the observed period, of about 5 months (Wajnberg *et al.,* 2020). Moreover, the authors tested the neutralizing efficiency of SARS-CoV-2 anti-S antibodies to understand

the protective effects of the immune response. Neutralization assay shows that anti-S binding titer significantly correlates with neutralization of SARS-CoV-2 virus (Imai *et al.*,2020; Wajnberg *et al.*, 2020), as well as it was shown that transferring serum of convalescent animals or neutralizing monoclonal antibodies into naïve animals can be protective and it reduces SARS-CoV-2 virus replication significantly (Iyer *et al.*, 2020; Isho *et al.*, 2020). Several other studies indagate the question of durability of the antibody response to SARS-CoV-2 virus, demonstrating the long lasting antibody response (Ripperger *et al.*, 2020; Crawford *et al.*, 2021; Sette and Crotty, 2021). Like SARS-CoV infection, the main antibody targets in SARS-CoV-2 are S and N proteins (Suthar *et al.*, 2020). Several studies report very high rates of seroconversion to SARS-CoV-2, followed by a rapid decline in RBD specific antibody titer (Seow *et al.*, 2020; Gudbjartsson *et al.*, 2020; Ladhani *et al.*, 2020; Prévost *et al.*, 2020). Rapid decline of neutralizing antibody responses may not be a problem if robust memory B cell response is generated and can be reactivated upon reinfection. Does SARS-CoV-2 induce immune memory? Immunological memory is not straightforward to predict. Immune memory is the source of protective immunity from a subsequent infection (le Bert *et al.*, 2020). Studies of immune memory to SARS-CoV, the most related coronavirus to SARS-CoV-2, are limited, but there have been notable findings. Memory T cells have been detected 6 years after SARS-CoV infection (Tang *et al.*, 2011), whereas memory B cells were lost within 6 years (Tan *et al.*, 2020), although neutralizing antibodies were detectable for 17 years (Sariol and Perlman, 2020). Middle East respiratory syndrome (MERS) caused by another coronavirus has been less well studied, but MERS anti-spike IgG did not persist for 2 years in mild or subclinical cases, whereas T cell memory persisted (Sariol and Perlman, 2020). Data from two large studies, one cross-sectional and one longitudinal, have indicated that circulating anti-SARS-CoV-2 IgGs are well maintained for 3–4 months (Rodda *et al.*, 2021). Virus-specific memory B cells, antibodies, and memory T cells were detected in mild COVID-19 cases at about 90 days post-infection (Zuo *et al.*, 2021; Dan *et al.*, 2021). A few studies are now available that have assessed T cell and B cell memory at >6 months post-infection (Dan *et al.*, 2021). Specifically, assessing T cells at 6 months post-infection in 95 subjects, one study found in the 90% of patients the presence of memory $CD4^+$ T cells and 70% of patients were also positive for memory $CD8^+$ cells, despite $CD8^+$ T cells were less abundant than $CD4^+$ T cells (Dan *et al.*, 2021). Similarly, an independent study, using different experimental techniques, found 90% of cases positive for memory $CD4^+$ T cells and 70% positive for memory $CD8^+$ T cells at >6 months post-infection (Zuo *et al.* ,2021). It is possible, but not certain, that the decay of memory T cell titer will slow over time, which would be consistent with the observation of SARS-CoV memory T cells 17 years post-infection. In the study by Dan and colleagues (Dan *et al.*, 2021) including a cohort of 188 cases, memory B cells specific for S, RBD, and N proteins were detectable in 100% of subjects >6 months post-infection. A mixed cross-sectional and longitudinal design of a recent study estimated the durability of both $CD4^+$ and $CD8^+$ T cell memory to have half-lives of ~3–5 months (Dan *et al.*, 2021). There are very few studies comparing all four of those compartments of immune memory to a viral infection in the same individual; this was by far the largest such study. The majority of COVID-19 cases were positive for all five of those immune memory compartments at ~1 month. By >5 months, ~95% of individuals were still positive for at least three out of five SARS-CoV-2 immune memory compartments. Of note, heterogeneity is a defining feature of COVID-19 immune memory. Virus-specific antibodies, memory B cell, memory $CD4^+$ T cell, and memory $CD8^+$ T cells spanned large ranges between individuals and changed with differing patterns over time. Other two recent studies have examined the SARS-CoV-2-specific memory B cell response beyond 4 months (Vaisman-Mentesh *et al.*, 2020; Wheatley *et al.*, 2020). Encouragingly, both studies report that SARS-CoV-2-specific memory B cells are maintained, moreover antigen-specific memory T and B cells can be detected in convalescence (Vaisman-Mentesh *et al.*, 2020). Much more data on immune memory is expected in the coming months, but data so far indicate that antibodies, memory T and B cells are all likely to persist for years in most individuals infected by SARS-CoV-2 (Zuo *et al.*, 2021; Gaebler *et al.*, 2021; Grifoni *et al.*, 2020; Wajnberg *et al.*, 2020).

SARS-CoV-2 variants

Recent characterization from England regarding a SARS-CoV-2 variant of concern (VOC) lineage B.1.1.7, have further exacerbated the pandemic situation (Volz *et al.*, 2021). This variant firstly identified in south of England in September 2020 has since then spread over 30 countries around the world (https://www.gisaid.org/hcov19-variants/). Others two variants in late 2020 were identified both with increased transmission and potential clinical importance, the SARS-CoV-2 lineage P.1, discovered in Manaus City, Amazonas, Brazil (Faria *et al.* 2021, Naveca *et al.* 2021), and B.1.325 variant, first emerged in South Africa (Tegally *et al.* 2021). The P.1 variant has a unique genetic profile including three mutations in the receptor-binding domain (E484K, K417T, and N501Y) region that are also present in the B.1.325 variant. Whether SARS-CoV-2 variants will be able to exhibit sufficient

genetic flexibility to esc ape humoral immune responses in the near term is unclear. Many RNA viruses, such as measles and polioviruses, exhibit antigenic stability and unchanging serotypes over periods of many years. Measles and polio vaccines remain highly effective 70 years after they were first introduced. Although the situation for any coronavirus is unclear, it is highly unlikely that SARS-CoV-2 mutations could escape T cell immunity, because a very broad array of SARS-CoV-2 epitopes are recognized in infected subjects (Li *et al.,* 2020). $CD4^+$ and $CD8^+$ T cells response to more than 10 epitopes is distributed throughout the SARS-CoV-2 genome, and vary from person to person. Despite the above aspects, SARS-CoV-2 mutations could affect antibody response targeting binding domain epitopes. However, a key attribute of the neutralization epitopes on SARS-CoV-2 spike site is that the surface area on RBD that is targeted by neutralizing antibodies is large enough that no single viral mutation is expected to avoid neutralization by polyclonal human serum. This is consistent with the broad range of SARS-CoV-2 neutralizing antibodies isolated from humans, indicating that SARS-CoV-2 is a relatively easy to neutralize considering that it elicits a different array of antibodies in each infected individual. Despite that, there is evidence that SARS-CoV-2 variants may evade immune responses triggered by vaccines or previous infections (Wang *et al.,* 2021; Callaway, 2021). Recently, Shi and colleagues assessed the neutralization of BNT162b2 vaccine-elicited sera by using engineered mutant viruses. The three engineered variants, including N501Y from B.1.1.7 and B.1.325 lineage; 69/70-deletion + N501Y + D614G from B.1.1.7 lineage; and E484K + N501Y + D614G from B.1.325, showed minimal effect on neutralization of twenty BNT162b2 vaccine-elicited sera (Xie *et al.,* 2021). Another research demonstrated that E484K mutant strain significantly reduced the neutralizing activity of human convalescent and post-vaccination sera (Jangra *et al.,* 2021). However, the significant limitation of all current studies is that the engineered pseudovirus cannot fully present the biological properties of the wild-type viruses. So, to date, the available data suggest the importance to improve the vaccine's design by modifying existing vaccines in order to defeat SARS-CoV-2 emerging variants.

SARS-CoV-2 vaccination and reinfection

Poor data are available regarding the real need of vaccination for people who have already contracted the disease. In this regard it is important to understand the effect of serum antibodies on susceptibility to reinfection for identifying at-risk populations. At this date, we know that most patients who recover from COVID-19 have antibodies and that reinfection is a rare event. Harvey and colleagues (Harvey *et al.,* 2021) reported that patients with seropositive status, after previous SARS-CoV-2 infection, are well protected when comparted with seronegative individuals. They have observed an approximately 10-fold decreased risk to contract the disease among the seropositive individuals, suggesting a protective effect of antibodies (Harvey *et al.,* 2021). Their findings are consistent with a study of healthcare workers that found that the incidence of SARS-CoV-2 infection revealed after PCR-positive results in 1265 workers with anti-spike antibodies was 0.13 per 10,000 days at risk compared with 1.09 per 10,000 days at risk for 11,364 workers who were seronegative (Lumley *et al.,* 2021). For this reason, as today, vaccination against SARS-CoV-2 is recommended regardless of antibody status. A recent article describes the antibody responses in 109 individuals with and without previous SARS-CoV-2 infection (68 seronegative; 41 seropositive) who received the first dose of vaccine (BNT162b2/Pfizer; mRNA-1273/Moderna) (Krammer *et al.,* 2021a). Repeated sampling after the first dose indicates that most of seronegative individuals exhibit relatively low responses within 9–12 days of vaccination. On the contrary, the 41 seropositive patients with a previous infection rapidly develop high and uniform antibody titers within 5–8 days from vaccination. The antibody titers of vaccinates with pre-existing immunity were 10–20 times higher than that of subjects without pre-existing immunity (Krammer *et al.,* 2021b). Interestingly, vaccinates with pre-existing immunity had systemic side effects (fatigue, headache, chills, muscle pain, fever, and joint pain) at higher frequencies than those without pre-existing immunity (Krammer *et al.,* 2021b). Another study also reported antibody titers of vaccinates with pre-existing immunity 10 to 45 times higher than those without pre-existing immunity at the same time points after the first vaccine dose (Bradley *et al.,* 2021). These findings suggest that in individuals with seropositive status the vaccine elicits higher antibody response providing a rationale for considering a single dose vaccine regimen in this (Burbelo *et al.*, 2020)population, at this date. Unfortunately, at the date neither study can answer how long antibody protection after vaccine or SARS-CoV-2 infection will last, but seems to decline over time (Ibarrondo *et al.,* 2020). For this reason, at the present state of knowledge about SARS-CoV-2 and immunity, vaccination is strongly recommended regardless of antibody status.

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