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Adaptive immune responses to SARS-CoV-2 [☆]

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ABSTRACT

This review focuses on adaptive immune responses against SARS-CoV-2, the coronavirus that causes COVID-19. A great deal of work has been accomplished in a very short period of time to describe adaptive immune responses and to ascertain their roles in determining the course of infection. As with other viral infections, SARS-CoV-2 elicits both antibody and T-cell responses. Whereas antibody responses are likely effective in preventing infection and may participate in controlling infection once established, it is less clear whether or not they play a role in pathogenesis. T cells are likely involved in controlling established infection, but a pathogenic role is also possible. Longer term evaluation is necessary to determine the durability of protective immune responses.

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1. Introduction

This review will primarily focus on adaptive immunity to SARS-CoV-2 and will cover the potential role of T cells and antibody in pathogenesis and in recovery from infection.

1.1. T-cell responses against SARS-CoV-2.

1.1.1. Lymphopenia during COVID-19

COVID-19 is often characterized by lymphopenia, particularly in more severe cases, with reduction in both CD8+ and CD4+ T cells [1–5]. Greater depletion of CD8+ T cells may result in an increase in the CD4:CD8 ratio [5–7]. In addition, functional impairment and increased expression of activation and/or exhaustion markers have been noted [8–12]. Lymphopenia eventually resolves with recovery from infection [13].

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1.1.2. T cells and COVID-19 pathogenesis

Whether the T-cell response is associated with disease pathogenesis, recovery from infection, or both remains unclear. Moreover, studies have concentrated on different aspects of the T-cell response or on patients at different times during the course of infection, rendering a lack of big-picture clarity. The T-cell response in critical patients was found to often be robust and comparable or superior to that of non-critical patients [14]. In addition, virus clearance and survival were not associated with T-cell kinetics or magnitude of response [14]. Suggestive of a pathogenic role for T cells, higher CD4+ and CD8+ T-cell responses, both in terms of breadth and magnitude, were observed in severe cases when compared to mild cases [15]. However, a higher proportion of the T-cell responses to SARS-CoV-2 structural proteins were contributed by CD8+ T cells in mild cases compared to severe cases, indicating that the CD8+ T-cell response might be beneficial, whereas the CD4+ T-cell response might play a role in pathogenesis [15]. On the other hand, Oja, et al., found that critically ill ICU patients had a diminished CD4+ T-cell response in terms of numbers and quality as measured by the cytokine profile [2]. Another group addressing the role of T cells found that in convalescent patients >21 days after onset, there were higher interferon γ (IFN- γ) responses to nucleocapsid (N) or spike (S) proteins in mild compared with severe cases [16]. Others found more robust T-cell activation, particularly in CD8+ T cells, in female patients compared to male patients and found that T-cell activation negatively correlated with age and, in males only, was associated with worse disease outcomes [17]. However, Moderbacher, et al. reported that SARS-CoV-2-specific CD4+ and CD8+ T cell responses were associated with milder disease, but that a disruption of coordinated T-cell responses in individuals >65 years of age could contribute to worse outcomes [18].

Using transcriptome analysis of blood lymphocytes, it was reported that SARS-CoV-2-reactive CD8+ T cells with an “exhausted” profile were increased in frequency and displayed lower cytotoxicity and inflammatory features in mild compared with severe cases [19]. The cells in the non-exhausted subset from patients with severe disease were enriched for transcripts linked to costimulation, pro-survival NF κ B signaling and anti-apoptotic pathways, suggesting robust CD8+ T memory responses in the more severe patients. This further suggests that the magnitude and quality of the CD8+ T-cell response may be important in limiting excess tissue damage. The study also reported substantial differences in CD8+ T cells reactive to coronaviruses compared with those reactive to influenza or RSV [19].

At the tissue level in the absence of infection, resident CD8+ T-cell numbers correlated inversely with ACE2 mRNA in lung [20]. During infection, CD8+ T cells were more abundant in BAL in mildly or moderately affected compared to severe cases [20]. Similarly, moderate cases were shown to have higher levels of CD8+ T cells than severe cases, and the CD8+ T cells were more clonally expanded in the moderate cases [21]. These observations suggest that local CD8+ T cells could be playing a beneficial role in COVID-19 infection. In addition, these findings suggest that individuals with higher ACE2 expression and its associated low CD8+ T-cell numbers in the lungs pre-infection may be particularly susceptible to severe infection. An analysis in rhesus macaques experimentally infected with SARS-CoV-2 found that both Th1 and Th2 cells in lung tissue increased during the late stage of infection, and the authors attributed lung pathogenesis to this local T-cell response. However, even animals with severe pneumonia demonstrated rapid improvement [22].

With particular regard to CD4+ T cells and pathogenesis, Laing, et al. found severely depleted $\gamma\delta$ T cells as well as CD4+ Th17 cells and Th1 cells, particularly in severe patients [23]. In addition, CD4+ T cells, like CD8+ T cells, had reduced antiviral cytokine production [11]. Higher CD4+ T-cell activation might be associated with worse

outcomes [6], whereas higher IFN- γ -producing cells have been associated with better outcomes [1,24]. Patients who died were more likely to show no response. Patient age and comorbidity correlated with the frequency of interleukin-2-secreting CD4+ T cells but lower IFN- γ -secreting cells [25]. In patients with mild infection, CD4+ SARS-CoV-2-specific cells were Th1 and predominantly central memory (Tcm) with robust helper function and persisted for >2 months [26]. Finally, severe COVID-19 disease was characterized in one study by an unexpectedly robust Th2-mediated immune response [27].

Several studies have associated T cells, particularly circulating T follicular helper cells (Tfh) with SARS-CoV-2-specific antibody levels [15,28–30]. Gong, et al. found that more severely affected individuals had a higher frequency of T-effector memory cells (Tem) and Tfh-em cells, but lower frequency of Tcm, circulating Tfh-cm and Tnaive cells [28]. Circulating Tfh-em cells correlated with lower blood O2 levels, which might explain the higher ratio of class-switched antibodies in more severe COVID-19 cases [28]. However, SARS-CoV-2-reactive cytotoxic Tfh cells, which can kill B cells, correlated negatively with antibody levels [29]. In another study, a low proportion of circulating CCR6+ CXCR3- Tfh cells were associated with plasma neutralizing antibody activity [30].

It is important to note that longitudinal data, where they are reported, are often based on small sample sizes [11,31]. Moreover, time from infection is unknown and date of symptoms onset is quite variable between subjects. Thus, caution should be exercised in interpreting results correlating features of T cells and pathogenesis, and overall, whether T cells are helpful, harmful, or both (depending on the individual) remains unclear. In any case, there appears to be diverse patterns of CD8+ T-cell responses in COVID-19 patients, and outcomes may depend on T-cell or overall immune coordination [6,18].

1.2. T cell protective immunity and antigen specificity

SARS-CoV-2-specific CD8+ T cells are induced within 1 week of infection, and are present in 70–100% of infected individuals [7,14,15,18,32–34]. One study found that CD4+ T cell responses were directed against matrix (M), N and S proteins, with comparable magnitude, proliferation and proportion of responding patients, although anti-N cells were less likely to produce IFN- γ , IFN- β and TNF- α [25]. Other investigators found that SARS-CoV-2-specific CD4+ T cells were mostly Tcm cells and expressed CXCR5, a marker of circulating Tfh cells [26]. CD8+ T cells were reported to be predominantly RA45+ effector memory [Temra] cells [26]. Additionally, CD8+ T cell responses were driven by a few immunodominant, HLA-restricted epitopes. T cells peaked at 1–2 weeks after infection and remained detectable for several months [35]. Importantly, T-cell memory likely occurs, as CD4+ and CD8+ T cells were found in 100 and 70%, respectively, of patients who recovered [32]. M, S and N each accounted for 11–27% of total CD4+ responses, with nsp3, nsp4, orf3a and orf8 contributing as well. S and M and several other orf proteins were recognized by CD8+ T cells. Similarly high detection rates of SARS-CoV-2-specific T cells were found by Kared, et al. [34], again mainly to internal and non-structural viral proteins. CD4+ T-cell responses to S correlated with the magnitude of IgG and IgA antibody titers [32].

This same study found that 40–60% of unexposed subjects had reactive CD4+ T cells, primarily against nsp14, nsp4, nsp6 and S. Interestingly, marginal or no reactivity against N or M were detected [32]. Similarly, Braun et al. found 35% of unexposed individuals had CD4+ T cells reactive against SARS-CoV-2 S protein [36]. S-reactive T cells in unexposed subjects reacted primarily to C-terminal S epitopes, which show a greater degree of homology to the human CoVs that cause the common cold. Consistent with

the idea that common cold CoVs induce T-cells cross-reactive with SARS-CoV-2, T-cell lines generated from S-reactive T cells respond to the C terminal of the common cold CoVs 229E and OC42 S [36]. In addition, long-lasting memory T cells reactive against N of SARS-CoV-1 display robust cross-reactivity to N of SARS-CoV-2 [33]. In that study, individuals who had neither SARS nor COVID-19 had T cells reactive with SARS-CoV-2 nsp7 and nsp13, possibly due to animal CoVs [33].

Similar findings of a range of pre-existing memory CD4+ T cells, especially against S were observed by Mateus, et al. [37]. In another study, an even higher proportion of unexposed individuals (81%) were found to have SARS-CoV-2-reactive T-cell responses reactive to epitopes presented by MHC class I and II [38] after a 12-day stimulation. Reactivity against SARS-CoV-2 epitopes in orf1 and orf8 were particularly noted. On alignment, these epitopes had similarities to common cold CoVs. This study also reported that 56% of antibody-negative patients diagnosed with COVID-19 nevertheless had T responses (again, after 12 days of stimulation with antigen), and similar to above, a correlation between HLA DR-restricted T-cell responses and antibody was noted. Diversity of T-cell responses, in terms of recognition rate of epitopes, was decreased in patients with more severe symptoms.

SARS-CoV-2-specific T cells have been documented in recovered patients in the absence of antibody responses. Of 13 infected patients who had no detectable IgG by ELISA against S1 after a median time of 60 days, 78% had SARS-CoV-2-specific T cell responses [39]. Schulien, et al. demonstrated SARS-CoV-2-specific CD8+ T cells in eight convalescent individuals who were negative for S and N IgG [40]. Similar findings of T-cell responses in the absence of circulating antibodies were reported by Sekine, et al. [12]. SARS-CoV-2-specific peripheral Tfh cells (especially against S) were shown to correlate with antibody neutralization [41].

Of particular interest to vaccine development and to understanding pathogenesis will be determining if the presence of cross-reacting T cells, presumably generated by other coronaviruses, play a role in the outcome of SARS-CoV-2 infection.

2. Antibody responses against SARS-CoV-2

Antibody responses to pathogens can be measured using assays that determine the ability of an antibody to bind to its cognate antigen or by functional assays, such as those that measure neutralizing activity. IgG, IgM and IgA binding assays against S (or various segments of S) or N can be measured using ELISA, chemiluminescence immunoassays, and various other platforms [42–47]. Neutralizing assays have made use of infectious SARS-CoV-2, which requires biosafety level 3 (BSL3) or of SARS-CoV-2 S protein pseudotyped with either retroviruses or vesicular stomatitis virus (VSV) [48,49]. Infectious virus neutralizing assays, pseudotyped-virus neutralizing assays and binding assays have generally correlated with each other [43,50–53]. Other types of functional assays, such as those that rely on interactions between the Fc segment of antibody and Fc receptors on natural killer cells or macrophages, have also been used to study SARS-CoV-2 antibody responses [54,55].

2.1. Antibody kinetics

Anti-S and anti-N binding IgM, IgA, and IgG antibodies become detectable between 7 and 12 days after symptom onset in approximately 50% of COVID-19 patients [47,56–58]. Whereas most viral infections elicit measurable IgM prior to IgG, in some patients with COVID-19, IgG precedes IgM [47,57]. Interestingly, this reversal of the usual order of IgM preceding IgG has also been observed with infections caused by SARS-CoV-1 [59,60].

IgM and IgA antibody levels peak at about 2–3 weeks after symptom onset, and they are present in most infected individuals by that time [32,57,61]. IgM declines to low or undetectable levels by about 4–5 weeks in most patients [62]. IgG antibody is measurable in 50% of patients by about 10 days and peaks at about 21 days after symptom onset [58]. Nearly all infected patients develop an IgG response [32,57,61]. After this peak, levels slowly decline, but remain present in most individuals over a period extending to 5–7 months [63]. Interestingly, anti-N IgG titers decline more rapidly than antibodies directed against the receptor-binding domain (RBD) or S2 [63].

Neutralizing antibodies develop along a similar timeline, peaking at about 14–21 days [58] and are measurable in nearly all infected individuals [64]. Neutralizing antibodies also decline by 8–12 weeks but are still measurable in the majority of patients by 5–7 months (see below for further discussion) [63,65]. Although the long-lasting neutralizing antibodies are no doubt IgG, plasma or serum IgM and, less potently, IgA1 anti-S antibodies can also neutralize virus [66]. It should be noted that individuals with low titers or even undetectable levels of neutralizing antibody may still be protected from subsequent infection, as memory B cells are present in recovered patients [67,68]. The memory B cells continue to undergo somatic hypermutation over six months, possibly due to persistence of antigen in the gut [68].

Notably, several studies have demonstrated that more severely ill patients generate higher levels of antibody, especially IgG, to either S or N than do patients with milder infections [56,69–72]. IgG avidity to the RBD, S and N, which increases over time, was also found to be higher in more severely affected individuals [73,74]. A similar relationship between antibody levels and severity has been noted for infections with other viruses as well, including SARS-CoV-1 and MERS-CoV [75,76]. The likely explanation for this is that greater antigen exposure, associated with higher or more persistent viral loads, elicits a greater antibody response. However, it is also possible that antibody responses are involved in the pathogenesis of COVID-19 (see below).

Antibody responses in children seem to differ from those in adults. In a study comparing adults with mild infection, adults with severe infection, children hospitalized with multisystem inflammatory syndrome (MIS-C) and children with COVID-19 but not MIS-C (about half of whom were asymptomatic), higher anti-S IgG, IgM and IgA responses were noted in the adults with severe infection than all other groups [77]. Anti-S antibody titers did not differ between the two pediatric cohorts and the adults with mild infection. In contrast, the anti-N IgG responses were significantly lower in both pediatric cohorts compared to the two adult cohorts. These results suggest that the anti-N response is dependent on age but not on disease severity. The authors also observed a modest negative correlation between age and anti-S IgG in the non-MIS-C pediatric patients and a positive correlation between age and anti-N IgG titers in the adults with mild infection [77]. Neutralizing antibody responses were lower among both pediatric groups compared to the two adult groups. Whereas there was a significant decline in neutralizing activity with patient age in the pediatric non-MIS-C group, there was no correlation between neutralizing activity and patient age in either adult group [77]. Overall, these results indicate distinct immune responses, as well as infection courses, in children and adults.

2.2. Protective antibody responses

It is of interest for vaccine development, as well as for immunoprophylaxis and immunotherapy, to understand both the epitope specificity and the functional activity of protective antibody responses. Based on animal models, particularly mice, hamsters and non-human primates, it is clear that neutralizing monoclonal

antibodies (mAbs) directed against S or against the RBD of S can modulate SARS-CoV-2 infection. For example, Hassan et al. demonstrated in mice transduced with adenovirus encoding human ACE2 (hACE2) that the infusion of a chimeric neutralizing mAb one day before intranasal challenge with SARS-CoV-2 could reduce viral burden in lung and lessen inflammation and weight loss [78]. Another study demonstrated similar protective activity of human mAbs in hACE2-transgenic mice challenged with SARS-CoV-2 and in wild-type BALB/C mice challenged with a mouse-adapted strain of SARS-CoV-2 [79]. The same mAbs given three days prior to challenge in rhesus macaques resulted in no detectable virus in nasal swabs or in bronchioalveolar lavage fluid [79]. Prophylactic use of a neutralizing human mAb has also been effective in reducing lung tissue viral load and weight loss in hamsters [80]. Less effect was observed when mAb was given two hours after virus challenge. Another study in hamsters with a different mAb also demonstrated *in vivo* protection with reduced lung virus load and less weight loss [81].

Some neutralizing mAbs also have *in vitro* Fc-receptor-mediated activity [55,82]. However, to our knowledge, there is no direct evidence that non-neutralizing antibodies that might result in antibody-dependent cellular cytotoxicity (ADCC) or other Fc-receptor-mediated antibody activities can prevent or modulate infection.

In humans, convalescent plasma obtained from individuals who have recovered from COVID-19 are being evaluated for both prevention and treatment of established infection. With respect to treatment, there are signals from data obtained outside of randomized trials that when given early, convalescent plasma has some effect on the course of infection. Such plasma may work better when given earlier, and there may be a correlation between efficacy and the neutralizing activity of the plasma [83]. However, a large, open-label randomized clinical trial conducted in India did not support the efficacy of convalescent plasma among hospitalized patients with moderate COVID-19 [84]. There are other large ongoing randomized trials evaluating the use of convalescent plasma in prevention and treatment. mAbs with neutralizing activity are also being evaluated for treatment of mild and severe COVID-19 in randomized clinical studies. Results from one of the ongoing trials have been published and showed a decrease in viral load and in hospitalizations in subjects receiving the mAb [85].

While awaiting more definitive information on the role of neutralizing antibodies in protecting humans from COVID-19, it is reassuring that persons with prior neutralizing antibodies who were exposed on a fishing vessel to SARS-CoV-2 were not re-infected [86]. Moreover, one patient with re-infection was shown not to have a neutralizing response to the primary infection, suggesting the possibility that such non-responsiveness allowed re-infection to occur [87]. Finally, in a family of two parents with PCR-confirmed symptomatic SARS-CoV-2 infection, all three of their asymptomatic, repeatedly PCR-negative children had salivary anti-CoV-2 antibodies (predominantly IgA) [88]. This suggests that children may mount an immune response that prevents the establishment of SARS-CoV-2 [88].

In view of the promising animal data, it is likely that vaccines that can elicit sufficient levels of neutralizing antibodies will at least improve outcomes following SARS-CoV-2 infection.

2.3. Neutralizing antibody epitopes

Given the benefit of passive infusion of neutralizing mAbs in animal models, it is important to characterize the epitopes that bind to such mAbs. Several epitopes within S have been documented to bind to neutralizing antibodies. Inhibition of binding by the RBD to hACE2 is the mechanism by which most neutralizing antibodies inhibit SARS-CoV-2 [55,89]. However, neutralizing epi-

topes that do not block ACE2 or that bind outside the RBD have been identified [90–94]. Presumably, some of these antibodies sterically inhibit RBD-hACE2 interactions or mediate conformational changes that limit binding. mAbs could also neutralize virus by inhibiting fusion, a process that is mediated by the S2 region of the spike protein. Although neutralizing activity occurs with antibodies of several germline genes, there is a strong preference for three Ig heavy chain variable genes [89].

2.4. Antibody-dependent enhancement of infection (ADE)

ADE refers to the phenomenon where antibodies increase viral replication, often through Fc or complement receptors, and has been described *in vitro* for many viruses [95]. *In vivo*, ADE may be responsible for most cases of severe dengue virus infections [96,97]. In addition, ADE has been shown to be involved with the pathogenesis of the coronavirus feline infectious peritonitis virus [98,99]. *In vitro* and some *in vivo* data point to a possible role of ADE in MERS and SARS [100–102].

With respect to COVID-19, ADE has been brought up as a concern for vaccines and for proposed convalescent plasma or mAb treatment and as a possible contributor to pathogenesis. However, to date, there have been no reports of worse outcomes among vaccine recipients, and neither clinical trials nor the expanded use of convalescent plasma or mAbs have revealed adverse events related to ADE. In fact, apart from one study in hamsters where antibody treatment appears to have resulted in a non-statistically significant greater weight loss than in untreated animals, there is currently no *in vivo* evidence of ADE occurring in the setting of SARS-CoV-2 infection [81].

In addition to concerns raised about vaccines or the therapeutic use of antibodies, the *de novo* antibody response has the potential for mediating ADE or to contribute to pathogenesis in some other manner. This would be consistent with the fact that severe manifestations of COVID-19 often appear after the first week of illness, at a time when antibody becomes discernible and when viral loads are decreasing [4,103,104].

As noted above, the positive correlation between antibody levels and disease severity is also consistent with a role for pathogenesis in the *de novo* antibody response against SARS-CoV-2. In this regard, one recent paper, not yet peer reviewed, found an association between antibodies to an epitope in N and disease severity [45]. Finally, although data are lacking, pre-existing antibodies to other CoVs could also affect the outcome of COVID-19 in a deleterious (or beneficial) manner.

3. Conclusions

Over the brief span of less than one year, much has been learned about SARS-CoV-2-specific adaptive immunity. In many ways, immunity appears to be similar to that elicited by other viral infections. In that regard, it is likely that vaccine-mediated protection will rely on neutralizing antibodies and that an adequate and durable response will require T-cell help. In addition, it is likely that T cells will contribute to controlling established infection. However, critical questions remain unanswered. Although, neutralizing antibodies are very likely sufficient for preventing infection or, when given early after infection, able to modify the disease course, their potential role in pathogenesis remains unclear. Similarly, whether or not SARS-CoV-2-specific T cells can prevent infection or play a role in pathogenesis is unknown. Since viruses evolve under immune pressure, it is important to be vigilant for SARS-CoV-2 strains that evade infection-induced or vaccine-induced humoral or cellular immunity. Fascinating uncertainties remain regarding whether immunity to other coronaviruses contribute to COVID-

19 outcomes and whether exposure to SARS-CoV-2 can result in an immune response in the absence of demonstrable virus replication. Finally, the durability of both humoral and T-cell immunity acquired after infection is necessarily uncertain, given the short period of experience with the pathogen.

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