Not just antibodies: B cells and T cells mediate immunity to COVID-19

Rebecca J. Cox[1] ✉ *and Karl A. Brokstad*[2]

Recent reports that antibodies to SARS-CoV-2 are not maintained in the serum following recovery from the virus have caused alarm. However, the absence of specific antibodies in the serum does not necessarily mean an absence of immune memory. Here, we discuss our current understanding of the relative contribution of B cells and T cells to immunity to SARS-CoV-2 and the implications for the development of effective treatments and vaccines for COVID-19.

COVID-19 is caused by infection with SARS-CoV-2, which is a member of the coronavirus family. There are currently four human coronaviruses (HCoVs) that cause respiratory infections or the 'common cold' (namely, 229E, NL63, OC43 and HKU1), as well as three coronaviruses that have arisen through zoonosis and cause severe diseases in humans, namely, SARS-CoV, MERS-CoV and SARS-CoV-2, which emerged in 2003, 2012 and 2019, respectively. Immunity after infection with the coronaviruses may last from months to several years[1]. Interestingly, cross-reactive immune responses to HCoVs may be boosted after severe infection; 12 of 20 patients infected with SARS-CoV had at least fourfold increases in IgG that cross-reacted with OC43 and/or 229E HCoVs[2]. It is still unclear how long immunity to SARS-CoV-2 lasts after recovery from infection. A recent report suggesting that antibodies to the virus may only be maintained for 2 months has caused speculation that 'immunity' to the virus may not be long lived[3]. Similarly, a rapid decline in antibodies was reported in mild cases[4], although with a half-life of approximately 21 days for IgG we would expect this decrease. It is important to remember that memory B cells and T cells may be maintained even if there are not measurable levels of serum antibodies. Below, we outline our current understanding of B cell and T cell immunity to SARS-CoV-2 and potential immune correlates of protection that could inform vaccine efficacy studies (FIG. 1).

Infection with SARS-CoV-2 induces diverse outcomes, ranging from a large proportion of asymptomatic infections to fulminant pneumonia, acute respiratory distress syndrome (ARDS), multiple organ failure and death. Although SARS-CoV-2 infection induces antibody responses, antibody levels may be dependent upon the severity of disease and the virus inoculum. Upon viral clearance, there will no longer be stimulation and proliferation of new B cells. IgG and IgM antibodies have been found in asymptomatic individuals who tested positive for SARS-CoV-2, but these antibodies were present at markedly lower levels than in patients with COVID-19 (REF.[5]); these findings need to be confirmed in larger studies. Antibodies to the spike protein and its receptor-binding domain (RBD) are the main target for neutralizing antibodies as they prevent the virus binding to epithelial cells in the airway through its entry receptor ACE2. Potent neutralizing antibody responses have been found in hospitalized patients with COVID-19, and human monoclonal antibodies (mAbs) generated from these patients target multiple epitopes of the spike protein[6] and could be a promising therapy. These neutralizing antibodies did not show extensive somatic hypermutation, which is encouraging for development of spike-protein-based vaccines. Furthermore, treatment with convalescent plasma therapy in severely ill patents is reported to reduce mortality. However, we do not yet know the durability of the antibodies induced by SARS-CoV-2 or the antibody titres that will protect against reinfection; variations in laboratory methodology may make this even more complex to determine.

The induction of SARS-CoV-2-specific memory T cells and B cells (as opposed to circulating antibodies) is important for long-term protection. In particular, T follicular helper (T_{FH}) cells indicate maturation of the humoral immune response and the establishment of a pool of specific memory B cells ready to rapidly respond to possible reinfection. SARS-CoV-2-specific T cells are recruited from a randomly formed and pre-constituted T cell pool capable of recognizing specific viral epitopes. Specific $CD4^+$ T cells are important for eliciting potent B cell responses that result in antibody affinity maturation, and the levels of spike-specific T cells correlate with serum IgG and IgA titres[7]. Robust immune responses with spike-specific neutralizing antibodies, memory B cells and circulating T_{FH} cells have been found in patients who have recovered from COVID-19 infection[8]. Although spike-specific $CD4^+$ T cells are found in patients with COVID-19, 30–50% of healthy people with no detectable COVID-19 infection also had SARS-CoV-2-specific $CD4^+$ T cells and 20% had $CD8^+$ cytotoxic T cells[7]. These T cells are probably cross-reactive with

[1]*Influenza Centre, Department of Clinical Science and Department of Microbiology, University of Bergen and Haukeland University Hospital, Bergen, Norway.*

[2]*Broeglemann Research Laboratory, Department of Clinical Science, University of Bergen, Bergen, Norway.*

✉*e-mail: rebecca.cox@uib.no*

https://doi.org/10.1038/s41577-020-00436-4

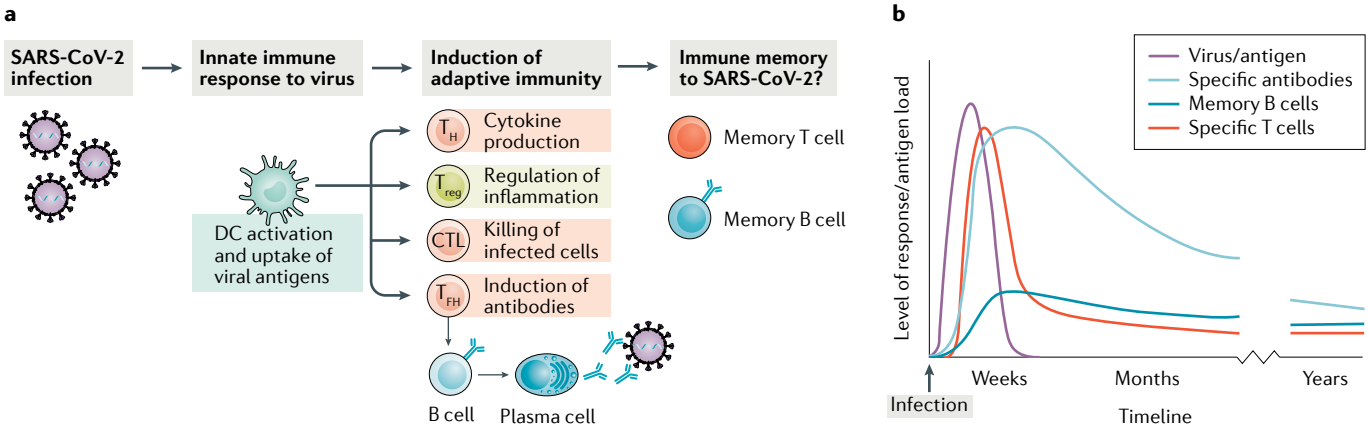

Fig. 1 | **T cells and B cells in immunity to SARS-CoV-2. a** | Infection with SARS-CoV-2 leads to activation of innate immunity and dendritic cells (DCs), which will drive the induction of virus-specific T cell and B cell responses. Little is currently known concerning the memory response to SARS-CoV-2, but this will be important for developing an effective vaccine. **b** | A predicted time-course of adaptive immunity to SARS-CoV-2. CTL, cytotoxic T lymphocyte; T_{FH}, T follicular helper cell; T_H, T helper cell; T_{reg}, regulatory T cell.

other HCoVs, but whether they can provide protection from COVID-19 disease remains to be determined. Furthermore, $CD4^+$ T cells and $CD8^+$ T cells specific for SARS-CoV-2 were found in the convalescent phase after mild COVID-19 and these T cells were shown to recognise peptides derived from the viral spike, nucleoprotein and matrix as well as other viral proteins[7]. As we learn more about the multifaceted immune response to SARS-CoV-2 virus, we will begin to understand the correlates of protection and how pre-existing immunity to HCoVs may impact upon the outcome of infection.

Lymphopenia with reduced numbers of $CD4^+$ and $CD8^+$ T cells is a hallmark of severe COVID-19 disease, often associated with exhausted T cells with less proliferative ability and increased levels of pro-inflammatory cytokines. Studies of patients who became infected with SARS-CoV in 2003 suggested that the infection induced durable T cell responses lasting for 6 years but no long-term memory B cells[9]. Importantly, these T cells were shown to cross-react with the SARS-CoV-2 virus 17 years later[10], but the extent to which they can provide protection is not known. Most importantly, the early global sharing of scientific data is vitally important to understand the complexities of the B cell and T cell responses in COVID-19 and to elucidate which immune responses provide protection from both the initial infection and reinfection.

Many vaccines are currently being developed and the lessons learnt from development of SARS-CoV and especially MERS vaccines have provided an advantage for rapid development of candidate vaccines for SARS-CoV-2. Encouraging results, often measuring antibody responses, have been reported from several versatile vaccine platforms (for example, nucleic acid and virus vector vaccines), and these vaccines have now entered later stage human clinical trials. During the swine influenza pandemic of 2009, the first vaccines were available within 6 months in the Western world based on seasonal influenza vaccine production. As there are no licensed CoV vaccines and with the urgency of the ongoing pandemic, controlled human challenge experiments of young healthy volunteers to identify correlates of protection may be necessary to speed up the evaluation of vaccines and to provide definitive data on which immune responses provide durable protection. Ultimately, we will need to harness immune memory responses to develop effective vaccines, which must be made available to people in all regions of the word in order to bring the pandemic under control.

1. Huang, A. T. et al. A systematic review of antibody mediated immunity to coronaviruses: antibody kinetics, correlates of protection, and association of antibody responses with severity of disease. Preprint at *medRxiv* https://doi.org/10.1101/2020.04.14.20065771 (2020).
2. Chan, K. H. et al. Serological responses in patients with severe acute respiratory syndrome coronavirus infection and cross-reactivity with human coronaviruses 229E, OC43, and NL63. *Clin. Diagn. Lab. Immunol.* **12**, 1317–1321 (2005).
3. Seow, J. et al. Longitudinal evaluation and decline of antibody responses in SARS-CoV-2 infection. Preprint at *medRxiv* https://doi.org/10.1101/2020.07.09.20148429 (2020).
4. Ibarrondo, F. J. et al. Rapid decay of anti–SARS-CoV-2 antibodies in persons with mild Covid-19. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMc2025179 (2020).
5. Long, Q. et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat. Med.* **26**, 1200–1204 (2020).
6. Liu, L. et al. Potent neutralizing antibodies against multiple epitopes on SARS-CoV-2 spike. *Nature* **584**, 450–456 (2020).
7. Grifoni, A. et al. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. *Cell* **181**, 1489–1501 (2020).
8. Juno, J. A. et al. Humoral and circulating follicular helper T cell responses in recovered patients with COVID-19. *Nat. Med.* https://doi.org/10.1038/s41591-020-0995-0 (2020).
9. Tang, F. et al. Lack of peripheral memory B cell responses in recovered patients with severe acute respiratory syndrome: a six-year follow-up study. *J. Immunol.* **186**, 7264–7268 (2011).
10. Le Bert, N. et al. SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. *Nature* **584**, 457–462 (2020).

Acknowledgements
R.J.C. leads the Influenza Centre at the Department of Microbiology, Haukeland University Hospital, and the University of Bergen, Norway. K.A.B. also works at the Department of Safety, Chemistry and Biomedical laboratory sciences, Western Norway University of Applied Sciences, Norway. The Influenza Centre is funded by the Ministry of Health and Care Services, Norway; Helse Vest (F-11628), the Trond Mohn Stifftelse, the Norwegian Research Council Globvac (284930); the European Union (EU IMI115672, FLUCOP, H2020 874866 INCENTIVE); and Nanomedicines Flunanoair (ERA-NETet EuroNanoMed2 i JTC2016).

Competing interests
The authors declare no competing interests.