Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

a simpler and more cost-effective strategy to rapidly induce high levels of these antibodies *in situ*—as has been recently undertaken against Chikungunya virus (August et al., 2021). Using an mRNA format would also allow for rapid modifications of the antibody constant region to tailor the respective downstream effector functions as needed. Continued investment is necessary to address the current lack of treatments effective against SUDV and BUDV, and these studies by Milligan et al. and Gilchuk et al. have introduced two additional critical building blocks for the future of pan-ebolavirus mAb-mediated treatments.

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DECLARATION OF INTERESTS

The authors declare no competing interests. The views and conclusions contained in this document are those of the authors and should not be interpreted as representing the official policies, either expressed or implied, of the U.S. Department of Health and Human Services or of the institutions and companies affiliated with the authors.

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Getting to the (germinal) center of humoral immune responses to SARS-CoV-2

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Long-term protection against SARS-CoV-2 requires effective and durable immunity. In this issue of *Cell*, two papers closely examine germinal centers, the physiological birthplace of adaptive immunity, to quantify the specificity, breadth, magnitude, and persistence of systemic and local humoral immune responses following natural infection with, or vaccination against, SARS-CoV-2.

The SARS-CoV-2 pandemic has highlighted the necessity of robust immunity to reduce infection, minimize disease severity, and prevent death following exposure to pathogens. As repeatedly demonstrated throughout history, a key strategy is the development of effective vaccines that induce long-lasting protective immunity (Slifka and Amanna, 2014). Vaccine efficacy is largely mediated by sustained humoral immunity comprising high-affinity memory B cells, which

re-circulate and rapidly respond following encounter with the initiating antigen, and plasmablasts (PBs), which secrete neutralizing antibodies (Abs). The generation of memory cells and PBs requires interactions between naive B cells and T follicular helper (Tfh) cells in germinal centers (GCs) that enable somatic hypermutation (SHM) and selection of high-affinity antigen-specific B cells (Laidlaw and Ellebedy, 2022; Slifka and Amanna, 2014).

A remarkable achievement during the current pandemic has been the rapid development of numerous SARS-CoV-2 vaccines, resulting in significant and dramatic decline in disease severity and fatalities due to SARS-CoV-2 infection (Bok et al., 2021). However, unlike other pathogens or vaccines that can prevent infectious diseases for decades (Slifka and Amanna, 2014), immunity against SARS-CoV-2 wanes rapidly, with SARS-CoV-2-specific serum immunoglobulin G (IgG) declining dramatically 6–8 months after vaccination or infection (Laidlaw and Ellebedy, 2022; Sette and Crotty, 2021). Despite this, SARS-CoV-2-specific immune responses continue to evolve following infection, with rapid recovery from SARS-CoV-2 infection and disease correlating with memory B cell SHM and prolonged IgG responses (Chen et al., 2020). This suggests that protective humoral immune responses against SARS-CoV-2 require efficient and sustained GC reactions. Most SARS-CoV-2-specific neutralizing Abs target the receptor binding domain (RBD) on the spike protein, which mediates viral entry. Consequently, immunity is jeopardized by viral variants with spike mutations that enable immune evasion (Bok et al., 2021). To enhance our understanding of the requirements for protective immunity against SARS-CoV-2, it is paramount to identify correlates of durable and broadly reactive humoral immunity induced following infection or vaccination that provide sustained protection against viral variants and how this can be affected by immunomodulation.

By examining lymph node (LN) aspirates, Lederer et al. assessed the immune cell microenvironment elicited in healthy individuals following delivery of a SARS-CoV-2 mRNA vaccine (BNT162b2) (Lederer et al., 2022). This revealed a strong adaptive response comprising SARS-CoV-2-specific GC B cells, memory B cells, Th1-type Tfh cells, and PBs in draining, but not contralateral, LNs following initial vaccination, increasing further after the second dose. High levels of SARS-CoV-2 neutralizing IgG were detected in blood, as were Tfh cells, SARS-CoV-2-binding memory B cells, and PBs, with greater proportions evident after two vaccinations. Consistent with the interdependent and non-redundant functions of these cell types (Laidlaw and Ellebedy, 2022; Sette and Crotty, 2021), correlations were found between proportions of SARS-CoV-2-specific GC B cells and PBs, LN Tfh cells, and levels of total or neutralizing IgG. Notably, proportions of circulating Tfh cells did not correlate with LN Tfh cells nor any of the blood or LN B cell subsets analyzed, highlighting the importance and benefits of measuring immune responses in secondary lymphoid tissues, at least during the early post-vaccine time frame (Figure 1). To further define correlates of successful SARS-CoV-2 immunity, Lederer et al. also tracked humoral immune responses of vaccinated immunosuppressed kidney transplant recipients. Analysis of these individuals revealed a marked paucity of total—and an absence of SARS-CoV-2-binding—GC B cells in LNs, striking reductions in LN T cell subsets, PC and memory B cells, as well as reduced serum IgG neutralizing capacity, compared to healthy donors (Figure 1).

Röltgen et al. explored the fundamental kinetics of responses to COVID-19 vaccines. This revealed an initial peak in anti-RBD IgG responses following two doses of BNT162b2, which waned dramatically within 9 months but was eclipsed after the third dose (Röltgen et al., 2022). This study also found that SARS-CoV-2-specific IgG induced in uninfected individuals by adenoviral vector-based and inactivated viral vaccines was inferior to BNT162b2 mRNA vaccine. In contrast to natural infection (Sterlin et al., 2021), vaccination induced an IgG-dominated response, with reduced levels of other Ab isotypes (IgM, IgA) (Figure 1). Due to the differing function of these isotypes in humoral immunity induced at mucosal (IgA) versus systemic (IgG) sites, these findings raise the possibility that despite higher IgG responses, the quality of protection against reinfection conferred by vaccines may differ to natural infection.

Röltgen et al. also highlighted how the initial viral variant leaves an "imprint" on the SARS-CoV-2-specific Ab response (Figure 1; Greaney et al., 2021; Röltgen et al, 2022). Imprinting occurs when there is significant cross-reactivity between antigens, resulting in a secondary response that preferentially boosts responses generated against the primary antigen. This may have advantageous effects, such as ancestral imprinting associated with protection against H1N1 in the 2009 influenza pandemic in older individuals. However, by directing responses to more conserved but non-neutralizing sites and impeding the magnitude of the response to current variants, imprinting can be detrimental to host defense (Wheatley et al., 2021). Imprinting occurred irrespective of the SARS-CoV-2 variant causing primary infection. Interestingly, imprinting toward Wuhan-Hu-1 RBD was more pronounced in naturally infected versus vaccinated individuals, although immunity occurring following natural infection did broaden overtime. Ongoing studies should investigate whether this breadth of binding correlates with breadth of neutralization against different variants.

Considering the potential clinical implications of imprinting and waning Ab titers, the specificity of memory B cells and subsequent GCs may have greater influence on the response against novel variants in breakthrough or re-infection than serum Abs. However, the finding of predominant nucleocapsid-specific GCs and a paucity of spike-specific GCs in severe infection suggests the ability of memory B cells to diversify upon reinfection, especially in severe COVID-19, could be affected. Determining if this bias exists in mild, breakthrough, or re-infection will be important. Both Röltgen et al. and Lederer et al. hypothesize that vaccination, as opposed to infection, generates a superior response due to greater spike-specific GC formation that may enable broader recruitment of germline BCRs and could explain why vaccines generate responses across more RBD epitopes (Greaney et al., 2021). Imprinting highlights the importance of generating sufficiently broad responses during initial exposure (Wheatley et al., 2021). Influenza research has extensively

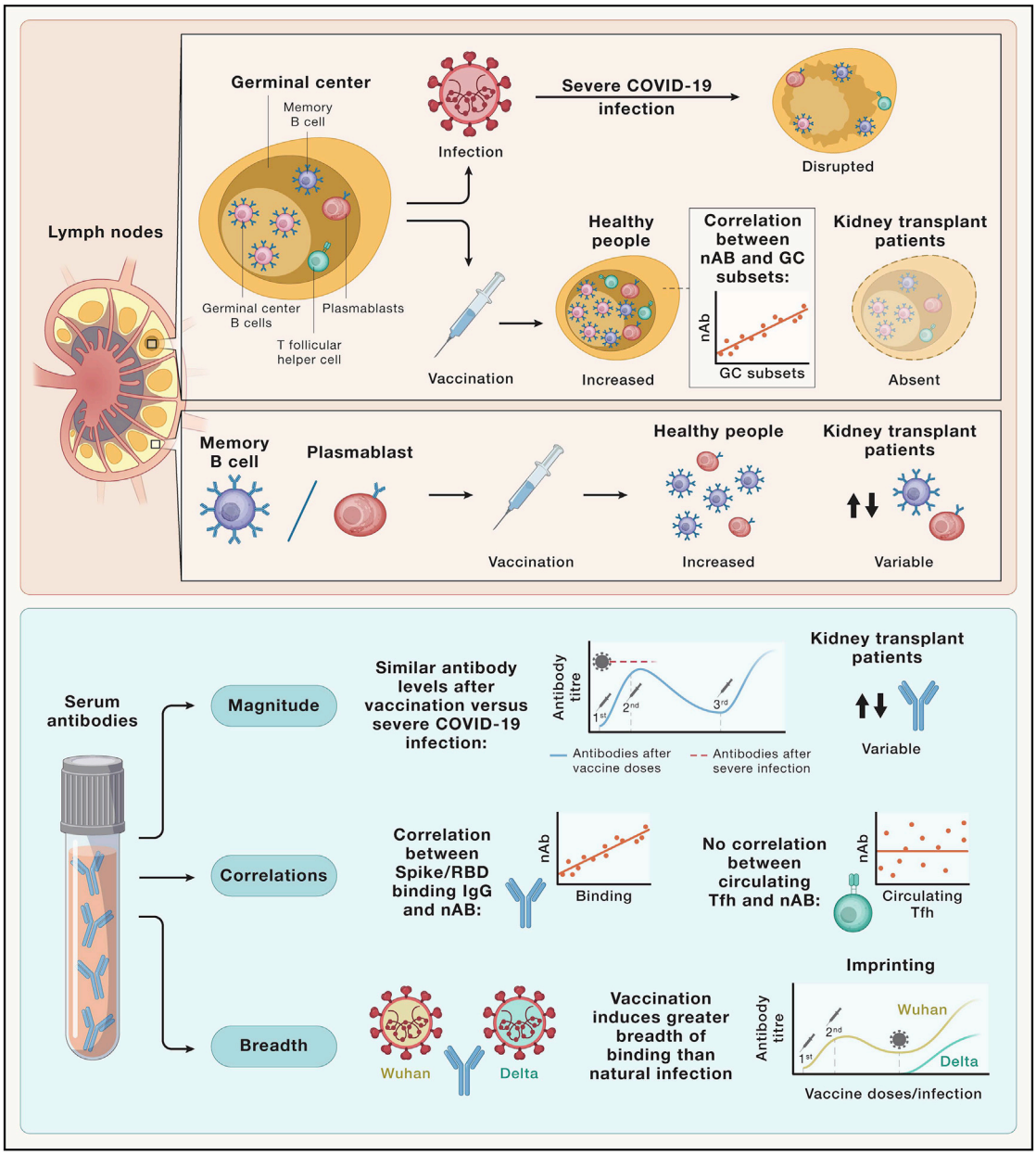

Figure 1. Comparison of peripheral and systemic humoral immune responses to SARS-CoV-2

Schematic diagram summarizing the key findings of the articles in this issue of *Cell*. Investigation of LNs through either biopsy or fine needle aspiration revealed an increase in total and antigen-specific GC B cells following vaccination, which correlated with T follicular helper (Tfh), memory B and PBs, as well as neutralizing Abs. GCs were sparse in kidney transplant patients secondary to treatment with immunosuppressive agents. Severe COVID-19 disrupts GC architecture. LN memory B cells and PBs were also increased following vaccination. Analysis of serum Abs in healthy vaccinees showed peak magnitude one week after the third dose, equivalent to the peak response observed in SARS-CoV-2 infected individuals who developed severe COVID-19. In contrast to healthy donors, the GC B, memory B, Tfh cell, and PB response, as well as Ab levels, were variable in immunosuppressed patients. Unlike in the GCs, neutralizing Abs poorly correlated with circulating Tfh. Vaccination induced a greater breadth of binding than natural infection and resulted in an imprint signature.

explored different strategies to target conserved neutralizing epitopes such as antigen design, epitope masking, and truncating proteins. Similar strategies have recently been assessed as alternative approaches to induce a broader initial response to SARS-CoV-2 (Burnett et al., 2021).

Overall, these studies add to the growing body of evidence (Chen et al., 2020; Laidlaw and Ellebedy, 2022; Turner et al., 2021) that robust and sustained GC responses yielding memory B cells and PBs are critical to generate effective humoral immunity following SARS-CoV-2 vaccination. Not surprisingly though, numerous questions remain. It is unknown whether vaccine boosters will

induce improved and sustained responses in therapeutically immunosuppressed individuals. Evidence from Lederer et al. suggests that patients who responded to initial vaccination showed higher titers following booster; however, a proportion of patients remained unresponsive. Analysis of individuals with monogenic immune dysregulatory conditions may define molecular and cellular requirements for inducing sustained humoral immunity against SARS-CoV-2 and shed light on strategies to improve vaccination efficacy in settings of immunocompromised vulnerable populations. Natural infection by SARS-CoV-2 at mucosal surfaces, but not intramuscular vaccination, induces early but transient IgA (Sterlin et al., 2021). It will be interesting to understand how the presence or absence of specific IgA protects against infection following re-infection or vaccination. Lastly, although these studies shed important light on the quality of immunity induced following vaccination versus natural infection, they must be considered concurrently with longitudinal studies assessing risk of breakthrough infection in a population setting (https://www.ons.gov.uk/releases/coronaviruscovid19infectionsurveytechnicalarticleimpactofvaccinationontestingpositiveintheukoctober2021). Regardless of these unknowns, these studies provide a framework to assess real-time GC responses in humans and determine the fundamental non-redundant requirements for generating broad protective immunity against known and novel pathogen and interrogate the efficacy of vaccines.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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