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RESEARCH HIGHLIGHT

Tracking B-cell memory over time

Severe acute respiratory syndrome coronavirus-2 vaccine-induced B cells aspire to long-lived connections

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The development and global distribution of the coronavirus disease 2019 (COVID-19) vaccines has occurred at a truly unprecedented rate. Pfizer-BioNTech's BNT162b2 vaccine was the first severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccine to receive approval for public use by the FDA and quickly became the jab of choice for the majority of people living in the United States and Australia. Early studies revealed a high efficacy (~95%)[1] at protecting against symptomatic SARS-CoV-2 infection; however, with time gone by, new SARS-CoV-2 variants have arisen, and the long-term efficacy of these vaccines is once again being put to question. Booster doses are being administered to extend the longevity of the immune response and combat novel variants. As countries around the world debate the necessity of future booster shots, it is critical that we gain insight into the immune response that is generated by messenger RNA (mRNA) vaccines as well as their potential for long-term protection. In the latest issue of Nature, Kim *et al.*[2] provide insight into the humoral immune cells generated by the BNT162b2 vaccine that are responsible for upholding long-term immunity to SARS-CoV-2.

Vaccines take advantage of long-term immune memory populations. In the humoral system, long-lived bone marrow-resident plasma cells (BMPCs) are responsible for dispensing a steady supply of circulating protective antibodies. The second population, memory B cells, mount a vigorous immune response upon re-exposure to their cognate antigen.[3] Both BMPCs and memory B cells possess a heightened quality compared with newly activated B cells, mainly because of affinity maturation that occurs during the germinal center (GC) reaction (Figure 1a). The critical role of the GC in providing protective humoral immune cells to safeguard against poor outcomes was reinforced by Kaneko *et al.*,[4] who reported on an absence of GCs or participating T follicular helper cells in the lymphoid tissue of deceased COVID-19 patients. While limiting viral spread through the rapid work of immune memory in vaccinated individuals has been a primary objective during the current pandemic, ensuring long-term maintenance of immunity is also crucial to protect against future infection waves. However, predicting the longevity of immune memory generated to mRNA vaccines has been difficult given that the production and roll-out of these vaccines has occurred during the current pandemic. Studying GCs and the cells that are derived from them is notoriously difficult in humans, particularly at different time points within the same individual, because of the ethical challenges involved in studying an ongoing biological response occurring within the major organs of healthy individuals. The researchers in this study were able to do just that by employing specialized sampling methods that allowed them to investigate the immune potential behind novel mRNA vaccine technology in healthy participants. The authors took blood, lymph node fine-needle aspirates and bone marrow aspirates at intermittent time points from the same participants following two doses of the Pfizer-BioNTech BNT162b2 mRNA vaccine (Figure 1b). This research group previously reported on persistent lymph node GCs following vaccination with BNT162b2[5]; this study elaborates on the fate and functional quality of the BMPCs and memory B cells generated by the GC reaction within these same individuals.

SARS-CoV-2 gains entry to cells by binding to the human ACE2 receptor via the Spike (S) protein. Researchers at the start of the COVID-19 pandemic quickly

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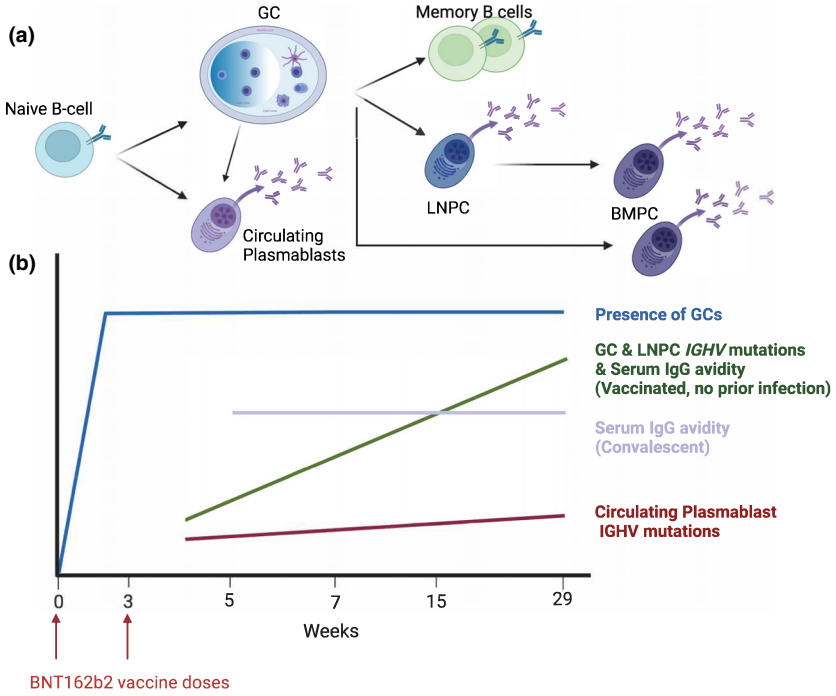

Figure 1. Schematic representation of the B-cell response to BNT162b2 vaccine. **(a)** During an initial T-dependent humoral immune response to immunization or infection, the germinal center (GC) is critical for production of affinity-matured memory B cells and plasma cell (PC) populations. **(b)** Schematic representation of the B-cell response to BNT162b2. The B-cell response to BNT162b2 can result in GCs that persist within the LNs for at least 6 months after vaccination. S-specific GC B cells and lymph node PCs (LNPCs) cumulatively gain *IGHV* mutations over time. Circulating plasmablasts, conversely, do not gain mutations at the same rate. Bone marrow-resident PCs (BMPCs) were detected more than 6 months after vaccination and were phylogenetically linked to the GC-derived LNPCs via B-cell receptor (BCR) mutation analysis. Serum anti-S immunoglobulin G (IgG)-binding avidity increased in uninfected vaccinated individuals, reflecting observed increases in *IGHV* mutation frequency; however, individuals with a prior history of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection did not experience a change in their antibody avidity between 5 and 29 weeks.

realized that S-specific antibodies were the most effective at neutralizing the activity of the virus.[6] For this reason, the spike protein became the antigen of choice for COVID-19 vaccine developers looking to induce high-quality neutralizing antibodies. All of the current vaccines for SARS-CoV-2 are capable of inducing high titers of anti-S antibodies. Yet findings of waning titers of circulating S-specific antibodies, generated by either vaccination or infection, have caused consternation in the public over the last year or so. Individuals who recover from symptomatic COVID-19 tend to possess more stable antibody levels; however, titers in asymptomatic individuals and BNT162b2 vaccine recipients reduce drastically over a period of 6 months.[7–9] It is important to consider, however, that antibodies waning to baseline is a typical feature of every humoral immune response and a loss of detectable antibody levels does not rule out the presence of long-term immune protection by memory B and T cells. The findings generated by Kim *et al.*[2] revealed that two-thirds of the cohort had antigen-specific GCs that persisted for more than 6 months. Moreover, as reported by other studies,[10] S-specific memory B cells were seen to remain at stable levels over time, providing assurance that these individuals will be able to respond to reinfection with superior efficacy than primary responses. Kim *et al.*[2] also demonstrated the vaccine was capable of generating memory B cells at comparable levels to convalescent participants.

The BNT162b2 vaccine was the first mRNA vaccine to be approved for human administration. It was therefore critically important to qualify its efficaciousness and potential for inducing long-term immunity. Kim *et al.*[2] provide clear evidence of the long-term potential of mRNA vaccine technology as an effective platform for delivering T-dependent antigens and inducing long-lived humoral immune cells. Similar to other more established vaccines targeting influenza or tetanus–diphtheria, the BNT162b2 vaccine was successfully able to induce BMPCs. Furthermore, the BMPCs detected 6 months after

vaccination possessed the highest somatic hypermutation frequencies and neutralizing potential than earlier time points, indicating that affinity maturation was ongoing even after antibodies were thought to have diminished. The long-term persistence of these cells provides strong evidence that S-specific serum antibody can be produced past 6 months. Future longitudinal comparisons of affinity-matured BMPCs and memory B-cell populations generated by different COVID-19 vaccine platforms may shed mechanistic light on the current vulnerability of countries to the Omicron wave that have not dominantly used mRNA vaccines for their constituents. It will also provide critical efficacy data that can shape global policy on vaccine platform preference.

Plasmablasts are rapidly generated early in a response to infection in order to generate antibodies quickly.[11] Early plasmablasts are generally thought to be short-lived and have low affinity. GC-derived BMPCs possess a higher affinity for antigen and a longer lifespan than their faster responding cousins. Several key differences were noted between the antigen-specific plasmablasts detected in the peripheral blood and affinity-matured PCs sampled from the tissues. In particular, *IGHV* mutation frequency remained consistent in circulating plasmablasts over time; however, it increased gradually and consistently by about 3.5-fold in the GCs and lymph node PCs over the course of 6 months in vaccinated participants. Moreover, BMPC-derived monoclonal antibodies (mAbs) possessed higher neutralizing potency than clonally related PB-derived mAbs. It is worth noting that while plasmablasts are typically described as a transient population, S-specific plasmablasts were detected for at least 6 months after vaccination. Phylogenetic analysis of B-cell clones confirmed that plasmablast clones were evolutionally closer to the germline, while lymph node PCs and BMPCs were more distant and clonally related to each other than to plasmablasts. It remains to be determined if BMPCs are directly derived from an intermediary lymph node PC population, or whether they both equally arise from the same GC and receive different signals that induce one subset to migrate to the bone marrow and the other to lodge itself within the lymph node. Understanding tissue-specific attractants that induce PCs to set up residency may assist in developing next-generation vaccines that are targeted to promote tissue-resident populations.

Kim *et al.*[2] also shed light on the impact of prior SARS-CoV-2 infection on the immune response by including convalescent individuals in parts of their study. Vaccinated individuals with a prior history of SARS-CoV-2 infection did possess higher antibody titers than those without prior infection. However, while the avidity of these antibodies increased in vaccinated individuals without prior infection over time, it did not change between weeks 5 and 29 in vaccinated convalescent donors. Given that the number of individuals exposed to SARS-CoV-2 is rapidly rising because of the highly transmissible Omicron variant, these findings raise questions about the adaptability of the immune memory compartment to future SARS-CoV-2 variants and their recalled descendants. Insight may be extrapolated into studies on a similar problem posed by influenza. Auladell *et al.*[12] demonstrated that prior exposure to certain strains of influenza virus shapes responses to influenza vaccines against similar strains. Indeed, a newly published study by Rodda *et al.*[13] discovered that prior infection can indeed increase memory B-cell numbers and antibodies capable of neutralizing different SARS-CoV-2 variants.

Together with other studies of vaccine effectiveness over the last year, this body of work reinforces the effectiveness of the Pfizer-BioNTech BNT162b2 vaccine in generating humoral immunity. However, while this elegant study used sophisticated methods to assess the GC reaction, fine-needle aspiration is not a technique that will be routinely used to assess the immune response in a large number of people across the globe. While we know that the longevity of immune protection can vary according to pathogen type or vaccine platform, we currently do not have an easy way of predicting whether a vaccine will in fact generate immune memory capable of lasting years, if not decades. Therefore, more understanding of B-cell memory itself may illuminate whether there are certain phenotypic or genotypic characteristics that can act as predictive markers of enhanced protective capabilities.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Liam Kealy: Conceptualization; Writing—original draft; Writing—review & editing. **Kim L Good-Jacobson:** Conceptualization; Writing—original draft; Writing—review & editing.

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