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NEWS AND COMMENTARY

A lifelong COVID-19 vaccine response?

Walking down the memory lane with SARS-CoV-2 B cells

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The end of the coronavirus disease 2019 (COVID-19) pandemic is in sight. We have scientists to thank for that. However, while years of meticulous research by vaccinologists, molecular biologists and immunologists provided the framework for rapid deployment of vaccines, we are still learning what constitutes an effective lifelong immune response to pathogens. A more detailed understanding of human B-cell development and the nature of the antibody response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or immunization may aid vaccine development for known pathogens and further reduce vaccine development times in the event of future pandemics.

Neutralizing antibodies are produced upon infection with SARS-CoV-2,[1,2] but the transition to lifelong immunity awaits ongoing studies, and is of central importance to ending COVID-19. Immunological memory is the pillar by which vaccines offer education to our immune system to protect us from future exposure to pathogens, yet the nature and length of this memory vary. Some natural infections and vaccines provide a lifelong lesson to the immune system, thereby enabling it to "remember" pathogens and antigens for decades, while in other cases the immune system "forgets" the exposure, leading to a waning immune response over months to years. With the advent of vaccines against SARS-CoV-2, along with the emergence of variants of concern, understanding the nature and duration of protective immunity is key to SARS-CoV-2 eradication or, at least, minimalization of severe infections leading to hospitalization and death.

To study long-term immunity to SARS-CoV-2 infection and vaccination, Wang *et al.*[3] have investigated memory B-cell responses to SARS-CoV-2 for a 12-month period in convalescent individuals, some of whom received a COVID-19 messenger RNA (mRNA) vaccine. SARS-CoV-2 convalescent individuals are advised to receive one dose, and in some countries two doses, of a COVID-19 vaccine to increase titers of SARS-CoV-2 antibodies to a level considered effective at virus neutralization. This recent study enables a longitudinal comparison of the natural B-cell response with infection, with and without a supplemental COVID-19 vaccine.

The study investigates a cohort of 63 convalescent individuals,[2] 26 of whom received either Moderna (mRNA-1273) or Pfizer-BioNTech (BNT162b2) COVID-19 mRNA vaccine. Serum was collected from participants at 1.3, 6 and 12 months after infection. The authors have previously shown for the same cohort that titers of serum anti-SARS-CoV-2 antibodies decline between 1.3 and 6 months after infection.[4] In the present study, they report that these levels remain stable between 6 and 12 months. The reduction in anti-SARS-CoV-2 antibodies in the first months after infection has also been reported by others,[5–7] although other studies show that some isotypes may persist.[8,9] In comparison, Wang *et al.* observed a dramatic increase in both SARS-CoV-2 serum antibody titers and serum neutralizing activity following mRNA vaccine administration in convalescent individuals: the 26 vaccinated individuals demonstrated a >10-time increase in their serum neutralizing antibodies compared with peak levels identified 1.3 months after infection. Although previous studies showed that serum IgG levels positively correlate with COVID-19 severity,[2] how disease severity influences the longevity and magnitude of serum responses over time was not investigated here. An increase in antibody neutralization efficiency of the different SARS-CoV-2 variants (B.1.351, B.1.1.7, B.1.526 and P.1) was observed at later timepoints for all individuals in

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the cohort, indicating an evolving antibody repertoire and affinity. This acquisition of both neutralization and breadth suggests a functional selection as a result of residual viral reservoirs that are still detected after the acute SARS-CoV-2 infection has resolved,[4,10] as well as a change in production from short-lived extrafollicular plasmablasts to long-lived affinity-matured germinal center-derived plasma cells.[11]

With the knowledge that the SARS-CoV-2 antibody response to variants evolves with time, Wang *et al.*[2] further characterized the memory B-cell compartment. To profile the memory B-cell response, they used a "baiting strategy," where the highest affinity memory B cells are stained with the SARS-CoV-2 spike receptor-binding domain (RBD). RBD is the protein component of the viral spike that binds the ACE2 receptor and is also the target of many neutralizing SARS-CoV-2 antibodies.[12] The researchers examined these high-affinity B cells at the same three timepoints (1.3, 6 and 12 months after infection) in both convalescent nonvaccinated and convalescent vaccinated individuals. RBD-specific high-affinity memory B cells were stable over 12 months in convalescent nonvaccinated individuals, but were increased tenfold following vaccination. This provides further mechanistic data to support public health strategies to vaccinate individuals previously infected with SARS-CoV-2, rather than relying on natural immunity acquired only from infection. However, this study only monitored antibody status 2–82 days after vaccination (with an average of 40 days after the second dose), so whether this peak in immune response relative to nonvaccinated convalescent individuals persists 12 months after vaccination remains unknown. In addition, longer studies are needed to determine how a vaccine alters reinfection susceptibility for asymptomatic carriers and nonvaccinated convalescent COVID-19 patients that experienced mild, moderate and severe disease.

Evolution of the SARS-CoV-2 antibody response could result from the emergence of new B-cell clonal lineages, or an expansion of existing lineages. Wang *et al.*[2] therefore analyzed the sequences of antibodies expressed on RBD-specific high-affinity memory B cells, finding evidence for both these scenarios. New B-cell clones were identified indicating an evolution of the memory compartment between 1.3 and 12 months following infection. Simultaneously, some antibody clones persisted over time in both vaccinated and nonvaccinated individuals. Cloning and analysis of almost 500 monoclonal antibodies from emergent and persistent clones of six different individuals (three vaccinated and three nonvaccinated) revealed that antibodies from memory B cells increased their neutralization potency and breadth in the 12-month period following infection. The most dramatic effect was observed in antibodies belonging to persistent clones—those that were conserved between timepoints—and not from emergent clones. When assessing antibody function from persistent clones, there was a remarkable shift in the memory repertoire, resulting in loss of non-neutralizing antibodies with time and a simultaneous expansion in neutralizing antibodies. Consistently, this improvement is not just in the potency of antibodies but also in their ability to neutralize different SARS-CoV-2 variants. For persistent clones, two randomly selected antibodies were analyzed from samples collected at 1.3 or 12 months after infection, and studied for RBD binding affinity and for neutralization of SARS-CoV-2 variants. For each pair of antibodies studied, antibodies isolated 12 months after infection were more effective at neutralizing a set of nine mutated pseudoviruses representing SARS-CoV-2 variants. This increase in both neutralization and breadth was correlated with an increase in affinity to RBD of the antibodies from the 12-month timepoint.

Next, Wang *et al.*[2] studied the effect of vaccination on the relative representation of persistent clones within the memory B compartment and on the levels of somatic hypermutations over the course of a year. Here, the absolute numbers of cells in the neutralizing persistent clones increased only in the vaccinated individuals. Surprisingly, the clones extracted from vaccinated individuals did not acquire more somatic hypermutations compared with the clones derived from nonvaccinated individuals, and the overall rates of somatic hypermutations increased in all individuals equally over time. These data suggest that vaccination may increase both antibody titers and frequency of SARS-CoV-2 memory B cells, but it most likely does not drive additional cycles of somatic hypermutation in the germinal center. The precise identity of the mechanism as well as the viral epitopes driving this evolution requires additional investigation. These data suggest that high-affinity memory B cells generated in the germinal center during natural infection improve over time regardless of vaccine status.

Therefore, if not for the events in the germinal center, what drives the increase in antibody titers and absolute numbers of memory B cells in convalescent vaccinated individuals? Wang *et al.*[2] explain this by noting that vaccine provides more antigen to existing memory B cells, which then capture and present it to T cells. These capturing events, most likely occurring outside the germinal center, cause B

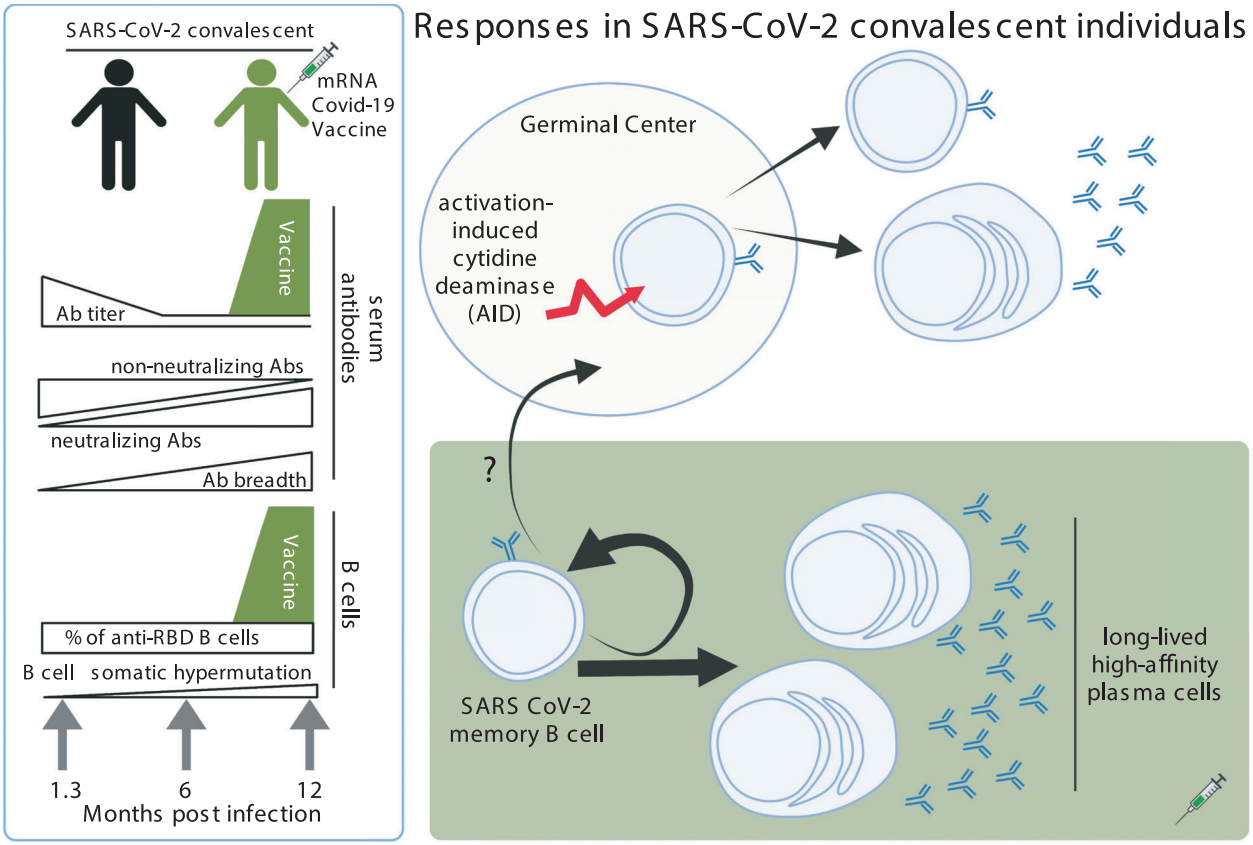

Figure 1. SARS-CoV-2 mRNA vaccines boost antibody titers and numbers of high-affinity RBD-specific B cells in convalescent COVID-19 individuals. Left panel: Wang and colleagues examined the SARS-CoV-2 antibody and B-cell responses in convalescent individuals with and without the mRNA vaccine (indicated in black and green, respectively) 1.3, 6 and 12 months after infection (indicated at the bottom by gray arrows). Natural immunity to SARS-CoV-2 involves a gradual reduction in serum antibody titers, along with an increase in neutralizing antibodies and a corresponding decrease in non-neutralizing antibodies. A vaccine boost elevates this response, as well as the frequencies of anti-RBD B cells. Right panel: anti-SARS-CoV-2 memory B cells in convalescent individuals evolve over time in GCs and acquire somatic hypermutations introduced by AID, resulting in post-GC memory and plasma B cells. A vaccine boost (indicated in a green insert) drives expansion of existing memory B cells and differentiation to long-lived plasma cells in the absence of a significant GC response or further somatic hypermutation. Ab, antibody; AID, activation-induced cytidine deaminase; COVID-19, coronavirus disease 2019; GC, germinal center; mRNA, messenger RNA; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

cells to divide and expand, and also to differentiate into antibody-producing plasma cells, while avoiding the germinal center (see Figure 1). Therefore, upon vaccine boost, high-affinity memory B cells "favor" the plasma cell compartment, leading to high titers of neutralizing antibodies and clonal expansion without additional cycles within the germinal center. The main effect of the mRNA vaccine in convalescent individuals is therefore increasing the magnitude of the antibody response by providing more antigen.

These important results reported by Wang *et al.* explain how mRNA vaccines work in convalescent COVID-19 individuals. It remains unknown whether a single or double vaccine dose in these individuals will provide long-term protection, but the current data imply that immunity acquired from natural infection may be protective to some degree because of the presence of high-affinity memory B cells that continue evolving long after acute infection. However, rare cases of reinfection in convalescent individuals have been reported,[13] and similar molecular B-cell studies are required to define the immunological basis for SARS-CoV-2 reinfection. Furthermore, it is still unknown how current vaccination protocols modulate B-cell responses to SARS-CoV-2 variants in uninfected fully vaccinated individuals and whether additional booster doses are needed.

The antibody landscape described by Wang *et al.* reveals that non-neutralizing antibodies are lost with time, distinguishing this SARS-CoV-2 B-cell response from the B-cell responses to other pathogens such as

influenza and HIV-1. Here it is possible that the SARS-CoV-2 spike protein exposes sites of vulnerability in a manner that can be readily bound and neutralized by antibodies. By contrast, chronic antigenic stimulation in HIV-1 infection does not result in selection for broadly cross-neutralizing antibodies. Rather, HIV-1 deceives the immune system by revealing sites that do not result in virus neutralization, while hiding the epitopes that are targets for neutralizing antibodies. Cross-neutralizing antibodies can arise, but only after years of coevolution, and these are highly mutated and contain various features indicative of a long developmental path required to efficiently neutralize the virus.[14]

Consistent with low rates of SARS-CoV-2 reinfections, this study demonstrates long-lasting immunity against SARS-CoV-2 with maintenance of a memory B-cell population. Will this translate to lifelong protective immunity? Several questions will need to be addressed to understand the long-term immune response to SARS-CoV-2 vaccines. Does vaccination alone (in nonconvalescent individuals) promote the retention of long-lasting memory B cells? And, if not, is a third boost needed? Is a vaccination boost needed for convalescent individuals following the first vaccine dose? Finally, are there B-cell profiles that correlate with rare pathological outcomes, and what screening strategies can provide appropriate levels of protection to SARS-CoV-2 while minimizing these rare outcomes?

In summary, this landmark study portrays the inner workings of a highly effective B-cell response to SARS-CoV-2 and the mechanism by which mRNA vaccines boost this natural immunity. The selection against non-neutralizing antibodies is remarkable and fortuitous in the context of a pandemic—it may be a central feature of what makes the problem of SARS-CoV-2 variants solvable by our immune system and, most importantly, by vaccination.

CONFLICT OF INTERESTS

We declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Natalia T Freund: Conceptualization; Writing-original draft; Writing-review & editing. **Motti Gerlic:** Conceptualization; Writing-original draft; Writing-review & editing. **Ben A Croker:** Conceptualization; Writing-original draft; Writing-review & editing.

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