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Conflict of Interest
The author declares no potential conflicts of
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Abbreviations
BCR, B cell receptor; CCCoV, common cold
coronaviruse; COVID-19, coronavirus disease
2019;FDC, follicular dendritic cell; GC,
germinal center; LLPC, long-lived plasma cell;
MBC, memory B cell; SARS-CoV-2, severe
acute respiratory syndrome coronavirus 2;
SHM, somatic hypermutation; VOC, variant of
concern.

Germinal Center Response to mRNA Vaccination and Impact of Immunological Imprinting on Subsequent Vaccination

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ABSTRACT

Vaccines are the most effective intervention currently available, offering protective immunity against targeted pathogens. The emergence of the coronavirus disease 2019 pandemic has prompted rapid development and deployment of lipid nanoparticle encapsulated, mRNA-based vaccines. While these vaccines have demonstrated remarkable immunogenicity, concerns persist regarding their ability to confer durable protective immunity to continuously evolving severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants. This review focuses on human B cell responses induced by SARS-CoV-2 mRNA vaccination, with particular emphasis on the crucial role of germinal center reactions in shaping enduring protective immunity. Additionally, we explored observations of immunological imprinting and dynamics of recalled pre-existing immunity following variants of concern-based booster vaccination. Insights from this review contribute to comprehensive understanding B cell responses to mRNA vaccination in humans, thereby refining vaccination strategies for optimal and sustained protection against evolving coronavirus variants.

Keywords: B-Lymphocytes; Vaccination; SARS-COV-2; Memory B cell; Germinal center

INTRODUCTION

Over the course of several decades, a multitude of infectious disease have persisted as significant threat to human well-being, constituting a considerable burden on public health. Vaccination is widely recognized as the most effective intervention to confer protective immunity against infectious diseases. Once protective immunity is achieved through vaccination, exposure to vaccine-matched virus will trigger a rapid and robust immune response. Vaccination proactively exposes our immune system to targeted pathogen Ags, thereby engendering the formation of immunological memory and significantly minimizing the occurrence of severe cases and fatalities.

The onset of the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a substantial number of infections and fatalities with considerable societal and economic losses. To address this crisis, mRNA-based vaccines were developed, initially by Pfizer-BioNTech and Moderna,

and administered at an unprecedented speed to millions of people worldwide. Compared to traditional vaccines composing of protein Ags, mRNA-based vaccines are composed of mRNA strands encapsulated in lipid nanoparticles. Initially authorized COVID-19 vaccines were designed to encode surface spike proteins of SARS-CoV-2, eliciting immune responses directed against them. Spike protein plays a pivotal role in facilitating entry of the virus into host cells by interacting with human angiotensin-converting enzyme 2 (1). In addition to mRNA-based vaccines, other distinct vaccine platforms were also developed, including adenovirus vector-based vaccines (AstraZeneca's ChAdOx1, Johnson & Johnson-Janssen's Ad26.COV2.S), adjuvanted protein vaccines (Novavax's NVX-CoV2373), and inactivated virus vaccines (Sinopharm's Covilo, Sinovac's CoronaVac). Several study comparing B cell and Ab response to diverse vaccines in humans suggested that mRNA-based vaccines induce exceptional short-term neutralizing Ab response and formation of memory B cells (MBCs) (2-4). Although mRNA vaccines have demonstrated notable immunogenicity with protection rates surpassing 90% (5,6), SARS-CoV-2 has undergone rapid evolution, leading to continuous emergence of divergent variants of concern (VOCs). In this context, uncertainties persist regarding the capacity of mRNA-based vaccine to induce durable protective immunity and the strategy for efficiently updating vaccine Ags to confront emerging variant strains.

This review focuses on B cell and Ab response observed in humans following administration of SARS-CoV-2 mRNA-based vaccines. Firstly, we specifically examined the B cell response model primarily developed from murine models. We then extended our discussion to incorporate recent findings in humans who received SARS-CoV-2 mRNA vaccines. Secondly, we discussed how B cell immune system would respond to booster vaccination. Contrast to in context of primary vaccination, where *de novo* response occurs against novel Ag, pre-existing immunity competes with naive B cells to contribute to immune responses in subsequent vaccination. To understand the impact of pre-existing immunity on immune response to additional vaccination, we discussed the phenomenon of immunological imprintings and findings from studies on human B cell response to variants-based vaccine.

MAIN 1: GERMINAL CENTER (GC) RESPONSE TO mRNA VACCINATION

Formation of immune memory through GC responses

Throughout history, the core objective of vaccination has been to induce durable protective immunity (7). The effectiveness of vaccination primarily relies on the generation and function of effector B-cell subsets including MBCs and long-lived plasma cells (LLPCs). These effector B-cell subsets mainly derive from GCs, which are as distinct microanatomical structures within follicles of secondary lymphoid organs (8,9). The forthcoming section will provide a comprehensive examination of fundamental mechanisms and dynamics of GC reactions in response to immunization. Myriad findings and mechanisms underlying GC reactions have been elucidated through murine models employing model Ag system. Our primary objective here is to initiate a discussion on these findings, drawing comparison with those observed in humans.

The initiation of B cell response to vaccination necessitates encounters between B cells and Ags (**Fig. 1A**). These encounters typically occur in secondary lymphoid tissues located near the injection site (10). In humans, vaccination is typically administered in the deltoid muscle of the upper arm, an area that primarily drains into the lateral axillary lymph node (11,12). Human GC reactions to vaccination were observed in draining axillary lymph nodes for at
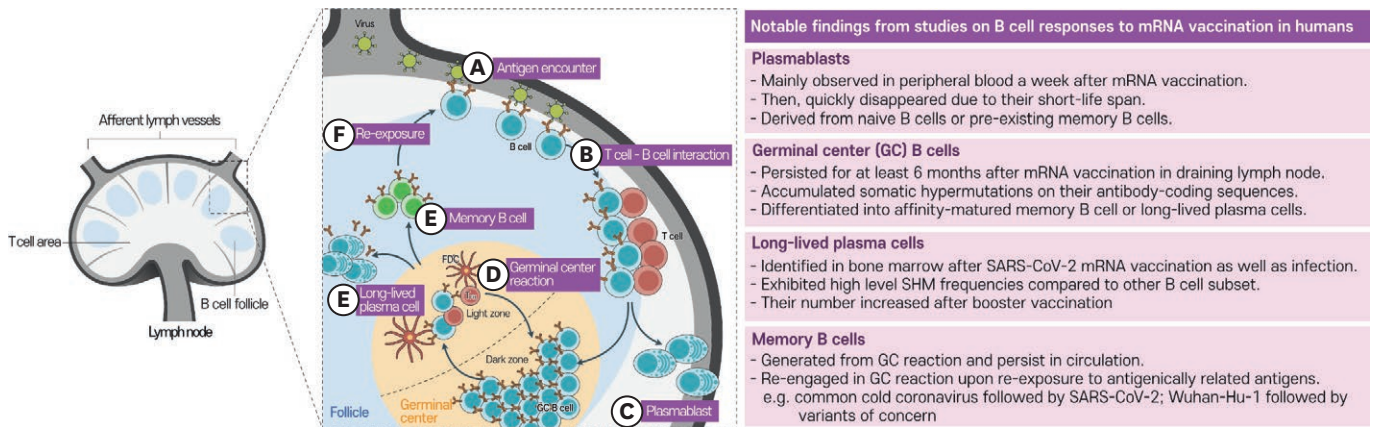
Figure 1. Dynamics of GC reaction.
The left figure illustrates the lymph node structure with afferent lymph vessels, T cell area, and B cell follicle. The right figure depicts dynamics and outcomes of B cell response in GC. (A) Pathogens entering the draining lymph node are recognized by naive B cells or, if pre-existing immunity is present, memory B cells. (B) Upon encounter with Ag, B cells undergo initial activation and proliferation, migrating to B cell-T cell boundary to interact with cognate T cells. (C) This interaction leads cognate B cells either to differentiate into plasmablasts or to relocalize back to the follicle and undergo GC reaction. (D) GC B cell undergo proliferation and somatic hyper mutation in the dark zone before exiting to the light zone. In the light zone, GC B cells with high-affinity BCR for Ags undergo positive selection processes mediated by both FDC and follicular helper T cells. (E) An interactive cycle of GC reaction generates LLPCs and circulating memory B cells. (F) Upon re-exposure to antigenically related pathogen, memory B cells reengage in GC reaction to undergo further affinity maturation. Right table presents the summary of dynamics and characteristics observed within indicated B cell subsets following SARS-CoV-2 mRNA vaccination or infection in humans.

least 6 months following mRNA vaccination ([13-17]). In secondary lymphoid tissues, B cells that have encountered Ags will move to the interface of the B cell follicle and T cell zone, where they can interact with cognate CD4^{+} T cells (**Fig. 1B**) ([18]). Upon receiving survival and co-stimulatory signals from cognate CD4^{+} T cells, B cells will then migrate to the center of the follicle to initiate GC reactions. Active GC reactions consist of two distinguished regions: a lymphocyte-rich dark zone and a light zone where lymphocytes are distributed among a network of follicular dendritic cells (FDCs; **Fig. 1D**). While GC B cells can intensively proliferate and diversify B cell receptor (BCR) repertoire through somatic hypermutations (SHMs) in the dark zone, GC B cells compete each other to get limited survival signals from FDCs and follicular helper T cells in the light zone ([19]). As results of competition, GC B cells with high affinity BCR will undergo positive selection and then return to the dark zone to undergo further rounds of SHMs and proliferation. GC B cells exhibit bidirectional migration between the dark zone and light zone, enabling them to undergo iterative maturation cycles including BCR diversification and affinity-based positive selection. This dynamic progression culminates in enhanced affinity of GC B cells towards Ags ([8]).

Another outcome of GC reactions is the generation of effector B cell such as MBCs and LLPCs (**Fig. 1E**). These two types of B cells play pivotal roles in sustaining long-term protective immunity. Their persistence directly influences the durability of vaccine efficacy. GC B cells with high-affinity BCR can undergo differentiation into LLPCs ([20,21]). These terminally differentiated effector B cells specialize in sustained production of Abs targeting previously encountered Ags. The majority of LLPCs reside in tissues such as the bone marrow and serve as a first line of defense against pathogen reinfection by consistently supplying high-affinity Abs ([22-24]). Simultaneously, MBCs are generated early during GC reaction. Accordingly, they exhibit low levels of SHMs ([20,21]). They persist in circulation for extended durations. They are capable of re-entering GC reaction for additional rounds of affinity maturation upon secondary exposure, leading to the production of even higher-affinity Abs ([25,26]). In the early phase of the pandemic, evidences indicating that SARS-CoV-2 infection and vaccination

can induce re-engagement of pre-existing MBCs into GC reactions, concomitant with polyclonal Ab responses, have been reported. These observations suggest that pre-existing immunity to common cold coronaviruses (CCCoVs) can be stimulated following SARS-CoV-2 infection and vaccination, indicative of the potential for antigenic cross-reactivity between pre-existing immunity against CCCoVs and SARS-CoV-2 (27,28). Notably, Turner et al. (17) have directly observed the presence of CCCoVs-reactive MBC clonal groups within GC reaction following SARS-CoV-2 mRNA vaccination. In this framework, MBCs and LLPCs collaborate in a division of labor to provide protection against reinfection by the original pathogen or related variants (29,30). Specifically, MBCs could be primed to mount a rapid and specific immune response against pathogen infection not completely neutralized by LLPC-derived Abs.

Meanwhile, the initial interaction with cognate CD4+ T cells prior to entering GC reaction can induce extrafollicular differentiation of B cells towards short-lived plasmablasts (**Fig. 1C**) (31). In context of repeat exposure to antigenically related Ags such as annual seasonal influenza vaccination or SARS-CoV-2 booster vaccination, the majority of short-lived plasmablasts derive from recall responses of pre-exsiting MBC populations (26,32). In humans, plasmablasts appear transiently in the blood approximately one wk after vaccination (33,34). These plasmablasts can rapidly generate large amount of Abs, which can reach the maximum titer around one month after vaccination. Subsequently, Ab levels gradually decline to a plateau that is maintained by durable populations of LLPCs. This decline is primarily attributed to the intrinsically short life span of plasmablasts detectable for approximately a week after vaccination (17,33). The frequency of short-lived plasmablast observed after vaccination correlates with both peak and plateau levels of vaccine-induced Ab titers, thereby providing a useful early indicator of vaccine responsiveness (35).

Induction of long-term protective B cell immunity by SARS-CoV-2 mRNA vaccination

This section discusses recent findings on human B cell responses following a primary SARS-CoV-2 mRNA vaccination. Clinical trials of Pfizer-BioNtech's BNT162b2 vaccine and Moderna's mRNA-1273 have demonstrated that a two-dose vaccination can elicit a robust Ab response in individuals without prior infection history (36). However, concerns regarding the durability of vaccine efficacy have been raised due to declining levels of Abs in the blood over time as well as the emergence of SARS-CoV-2 VOCs (37-40). It is important to note that a decrease in Ab level in the circulation is a typical characteristic of humoral immunity. It does not necessarily imply a loss of long-term protective immunity. Indeed, significant reduction in mortality rate among vaccinated individuals strongly suggests that vaccination can effectively establish protective immunity.

Duration and robustness of GC reaction following vaccination are primary determinants of a long-term protective immunity (38,41). As previously highlighted, GC responses within draining lymph nodes play a pivotal role in the establishment of long-term protective immunity by generating circulating MBCs and LLPCs. To evaluate the capacity of mRNA vaccines to elicit enduring protective immunity, it is imperative to investigate draining lymph nodes in humans. Despite challenges with respect to sample collection and analytical techniques, multiple studies analyzing immune responses within lymph nodes have been reported throughout the COVID-19 pandemic (13-17). Ultrasound-guided fine needle aspiration enables sequential sampling of draining lymph nodes from multiple cohorts. This approach allows for a longitudinal examination of the dynamics and characteristics

of human GC responses to mRNA vaccination. These studies have consistently reported a robust and persistent GC reaction in draining axillary lymph nodes. Substantial frequencies of spike-binding GC B cells have remained detectable for at least 29 wks after the primary two-dose mRNA vaccine series in 11 out of 15 individuals (16). Compared to seasonal quadrivalent inactivated influenza vaccine, where vaccine-binding GC B cells were detected for only 2 to 4 months post-vaccination in three of eight participants (26), mRNA vaccination appeared to elicit significantly more robust and durable GC responses. While extensive history of influenza virus exposure and the presence of pre-existing immune memory might complicate the comparison between GC responses to these vaccines in humans, this phenomenon can be attributed to immune-enhancing properties conferred by self-adjuvanting characteristics of lipid-nanoparticle encapsulated mRNA vaccine platform (42-44) and prolonged duration of Ag dissemination in draining lymph nodes (15,45). Röltgen et al. (15) have demonstrated that vaccine mRNA and spike proteins are still detectable in lymph nodes for up to 60 days post-vaccination. This suggests that GC persistence may indeed be contingent on Ag availability. Furthermore, it has been observed that FDCs exhibit a remarkable capacity of long-term retention of Ags, thereby contributing to sustained maintenance of GC response (46,47).

Persistent GC reactions in draining lymph nodes lead to continual accumulation of SHMs on BCR sequences of vaccine-responding B cells (16,48). Notably, a 3.5-fold increase in SHM frequency over six months was observed in GC B cells responding to the vaccine, indicating ongoing affinity maturation processes after vaccination. This sustained elevation in SHM frequencies ultimately culminated in the generation of affinity-matured MBCs in the blood and LLPCs in the bone marrow. Not only circulating MBCs and bone marrow-resident LLPCs are detectable after mRNA vaccination, but also their SHM frequency is progressively increased over time, concomitant with enhanced binding breadth and neutralization potency (16,48-52).

In addition to SHM-mediated affinity maturation, GC B cells undergo Ig class switching. Akin to a natural infection (53), mRNA vaccination can induce notable transition over time in the proportion of isotypes expressed by GC B cells, shifting from IgG to IgA (16,17). Consequently, class-switched MBCs are detectable after mRNA vaccination and the frequency of IgA-expressing MBCs is increased over time (50). Dimeric IgA, the main form of IgA, exhibits an improved ability to neutralize the virus compared to IgG. It may play a critical role in preventing reinfection within mucosal tissues (54,55). Although it is uncertain whether SARS-CoV-2 vaccination can result in an increase of IgA level in mucosal tissues in human (56), intramuscular vaccination is known to result in a minimal mucosal IgA response and demonstrate reduced efficacy in mediating viral clearance at mucosal (57,58). Furthermore, it is yet to be determined whether IgA+ GC B cell compartment induced by mRNA vaccination can lead to the formation of mucosal tissue-resident IgA+ MBCs and LLPCs. To address the limitation of intramuscular vaccination, the alternative routes such as intranasal or nebulization administration have been proposed (57,59,60). In animal models, airway administration offers advantages over intramuscular delivery by inducing robust mucosal immunity, thereby preventing infection and onward transmission. Both the coronavirus vaccine roadmap (61) and Project NextGen (62) also underscored the importance of developing next generation vaccines and vaccination strategies to augment mucosal immunity.

MAIN 2: IMMUNOLOGICAL IMPRINTING ON SUBSEQUENT VACCINATION

Immunological imprinting by previous exposures to antigenically related pathogens

Administration of a two-dose primary vaccination can induce robust immune responses, leading to a substantial decrease in mortality rate. Nevertheless, the emergence of highly infectious variant viruses underscores the necessity for supplementary vaccine doses or the development of vaccines targeting variants (40,63-67). It is necessary to approach additional vaccination as a distinct scenario from primary vaccination, particularly in terms of prior exposure history. In contrast to primary vaccination, which occurs in the absence of pre-existing immunity against SARS-CoV-2 viruses, administering additional doses against VOCs requires careful consideration of the impact of pre-existing immunity on subsequent immune response.

In 1960, Francis (68) conducted serological analyses of different age groups following influenza vaccination, revealing that Ab response to influenza strains encountered during childhood continued to dominate the overall anti-influenza virus Ab response throughout life. Even as an individual ages and elicits subsequent Ab responses against different strains, childhood-derived Abs can consistently maintain dominant levels over time. This phenomenon is known as "original antigenic sin" or, more recently, as "immunological imprinting." The term "immunological imprinting" generically describes the impact of prior exposure history, such as viral infection or vaccination, on future patterns of Ab response upon re-exposure to antigenically related viruses (69). It reflects the back-boosting of pre-existing immunity, where immune memory established through prior exposures to an Ag is recalled to rapidly respond to re-exposure (**Fig. 2**). This phenomenon represents a fundamental immunological mechanism known as immune memory recall that underlies vaccine efficacy (70). When exposed to vaccine-matched pathogens, pre-existing MBCs formed by vaccination promptly can produce Abs to protect from severe infections (**Fig. 2B**). By leveraging this immunological feature, vaccinations can greatly reduce mortality rates caused by vaccine-matched viruses.

However, in context of infections caused by antigenically evolving viruses, cross-reactive pre-existing immunity is mostly recalled (**Fig. 2C**). In other words, recall response tends to focus on conserved epitopes shared between primary and re-exposure Ags (71). Mechanistically, unlike a primary vaccination, wherein naive B cells primarily participate in immune response responses, both naive B cells and circulating MBCs compete to recognize re-exposure Ags. The circulating MBCs have competitive advantage over naïve B cells not only due to GC-driven affinity maturation, but also due to intrinsically lower activation threshold (72), thereby restricting participants of naïve B cells. Consequently, the majority of recall response is directed towards shared epitopes, leading to diminished Ab diversity and rare occurrence of variant-specific B cell response. In such scenarios, immunological imprinting could potentially increase an individual's susceptibility to infection when these shared epitopes acquire escaping mutations. To effectively prevent variant infections, additional vaccinations should be designed to stimulate the generation of *de novo* B cell responses that can specifically recognize the novel epitope unique to variants.
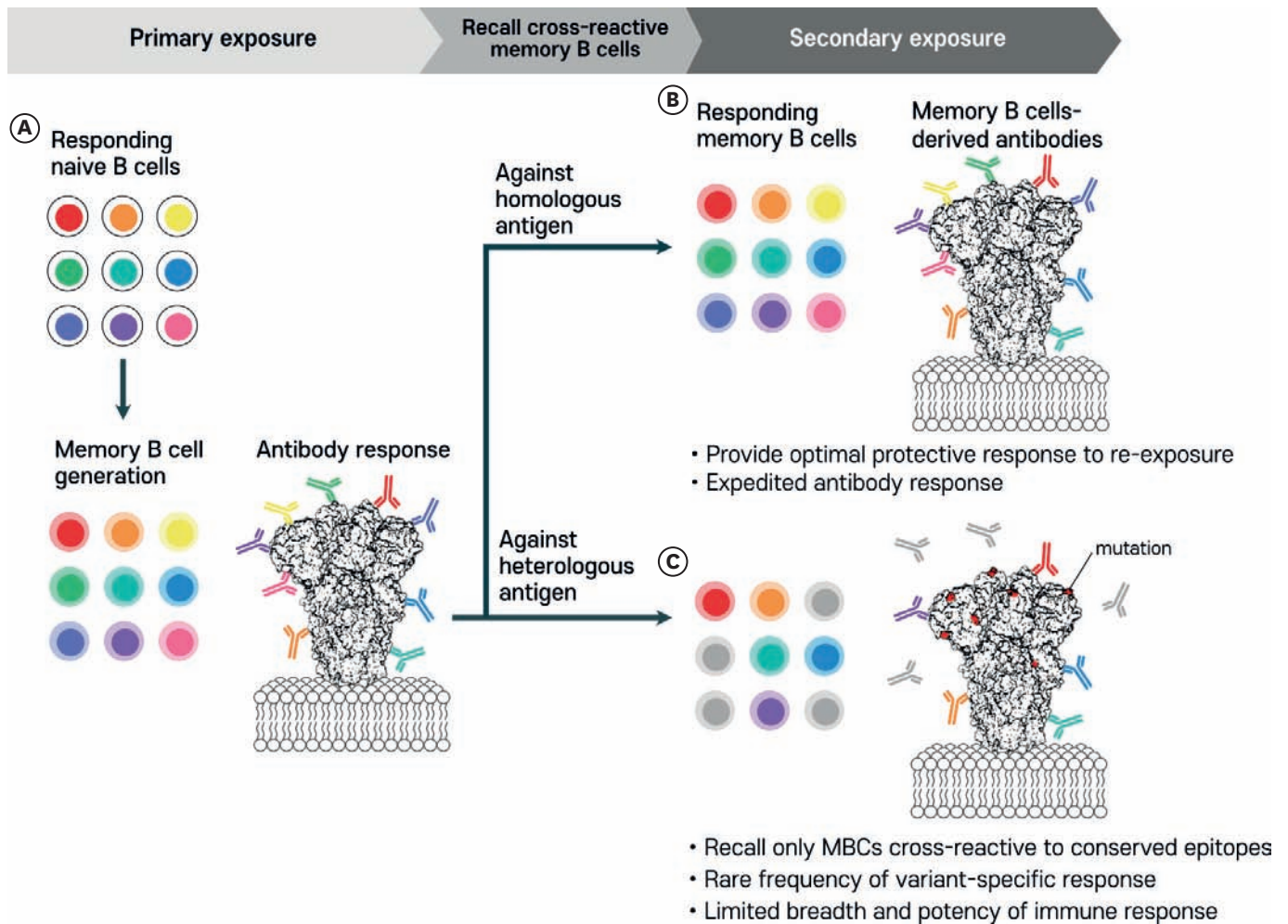
Figure 2. Recall of pre-existing immunity following exposure to homologous or heterologous Ags.
(A) Upon primary exposure to novel Ags, such as the two-dose SARS-CoV-2 primary vaccination, naive B cells actively participate in immune response, leading to establishment of memory B cell population. Memory B cells generally participate in subsequent immune response to antigenically related Ags. (B) Upon secondary exposure to homologous Ags, the majority of memory B cells induced by primary exposure predominantly are recalled, contributing to an enhanced Ab response against either homologous infection or vaccination. (C) However, on secondary exposure to heterologous Ags, breadth of following Ab response is confounded by pre-existing immunity, a mechanism known as immunological imprinting. A limited pool of memory B cells that are predominantly cross-reactive to heterologous Ags is recalled, resulting in comparatively restricted breadth of Ab response to either VOCs infection or vaccination. The extent of the detrimental effect from immunological imprinting correlates with the antigenic distance between primary and secondary Ags.

B cell response to VOCs-based booster vaccination

The ongoing evolution of SARS-CoV-2 viruses, characterized by mutations in the spike protein, has endangered the efficacy of the initial two-dose of primary vaccination, leading to recommendations for additional booster shots (64,73). Multiple studies have suggested that administrating repeated doses of homologous boosters containing the ancestral Wuhan-hu-1 spike can substantially improve Ab responses against both the Wuhan-Hu-1 and VOCs (74-76). Concurrently, vaccines based on VOCs' spike proteins have been developed to more effectively address these continuously evolving viruses (77-81). However, efforts to improve the effectiveness of vaccine by incorporating spike Ags from VOCs have encountered challenges due to the immunological imprinting induced by ancestral spike-based primary vaccination. A main concern is whether VOCs spike proteins-based vaccines can induce *de novo* Ab responses to VOC-specific, non-conserved epitopes.

Recent studies have compared immune responses in individuals who have received third doses of the monovalent Wuhan-Hu-1-based vaccine, a monovalent B.1.341 (Beta)-based vaccine (mRNA1273.351), a bivalent B.1.351/B.1.617.2 (Beta/Delta)-based vaccine (mRNA-1273.213), and an monovalent BA.1 (Omicron)-based vaccine (mRNA-1273.529) (32,82). Alsoussi et al. (32) focused on participants without prior COVID-19 infection history who had completed a two-dose primary vaccination. The primary objective was to assess the exclusive impact of booster vaccination on immune response against VOCs, considering both quantitative and qualitative aspects. Vaccine spike-specific plasmablasts were detected in blood samples of all participants. Their maturation was confirmed through increased SHM frequencies in their Ig heavy chain variable region gene (*IGHV*). Interestingly, plasmablasts identified after the booster vaccination exhibited significantly higher mutation frequencies than those after the primary two-dose vaccination series. This suggests that these plasmablasts might have originated from MBCs that have undergone affinity maturation after completion of the primary vaccination series (33,34). Meanwhile, administration of booster vaccination elicited a robust GC response specific to vaccine spike Ags in draining axillary lymph nodes, persisting for a minimum of eight wks post-vaccination. Consistent with B cell responses observed in conventional seasonal influenza vaccinations (26), it was observed that pre-existing MBCs participated and re-engaged in GC reactions after booster vaccination. The quantity of bone marrow-resident LLPCs was also notably increased following a booster vaccination. This phenomenon is a result of persistent GC reactions induced by the initial two vaccine doses combined with additional GC reactions induced by repeated Ag exposures from the booster vaccination.

Additionally, Alsoussi et al. (32) provides important insights regarding the extent and dynamics of immunological imprinting after VOCs-based vaccination. Even if any booster vaccines did not encode ancestral spike Ags, the majority of GC B cells and MBCs identified after bivalent beta/delta or monovalent omicron vaccination could recognize the ancestral spike protein. This implies that vaccine-responding B cells predominantly originate from pre-existing clonal lineage established by the primary vaccination. Given that the degree of immunological imprinting could be determined by the antigenic distance between prior and subsequent exposures (83-85), a high antigenic similarity between beta/delta spike and ancestral spike might have contributed to highly cross-reactive responses. As shown in the case of monovalent omicron vaccine, where spike Ags were antigenically distant from the ancestral spike, MBCs specific to omicron spike Ag were definitely observed. These B cells appeared to originate from *de novo* responses as they recognized omicron-specific epitopes with low SHM mutation frequencies. The immunological imprinting induced by ancestral spike-based vaccination was also reflected in serological responses, which are outcomes of B cell responses to subsequent exposures. Individuals who have received two doses of primary vaccination and encountered omicron infection still exhibit low levels of omicron-specific Ab responses (86-88). Moreover, a bivalent booster BA.1 (mRNA-1273.214) and a bivalent booster BA.4/BA.5 (mRNA-1273.222) demonstrated superior neutralizing activity to Wuhan-Hu-1 booster against Wuhan-Hu-1 as well as matched Omicron sublineages (89,90). Collectively, the abundant presence of serum Ab titer and MBCs that can recognize the ancestral spike protein following subsequent exposures serves as evidence of immunological imprinting. This phenomenon indicates that B cell responses to previously encountered Ags can maintain dominance even after exposure to antigenically related other Ags. Accordingly, the WHO Technical Advisory Group on COVID-19 Vaccine Composition recommended using monovalent Omicron XBB.1.5-based immunogen instead of Wuhan-Hu-1-based immunogen for future booster vaccine formulations due to antigenic divergence and the potential for immunological imprinting (91). This recommendation is supported by recent experimental

evidence indicating that repeated boosting with omicron spike Ags has been shown to alleviate immunological imprinting (92). Taken together, these findings offer support to the idea that vaccination strategies with appropriately designed Ags are necessary to counter immune imprinting and activate infrequent naive B cells targeting novel variant epitopes.

CLOSING

The return to normalcy from COVID-19 pandemics is facilitated by innovative mRNA-based platform vaccines. This global health crisis offers a unique opportunity to examine the dynamics and outcomes of GC-driven *de novo* B cell response in humans and to investigate the role of immunological imprinting in subsequent B cell responses. Our exploration of B cell responses to SARS-CoV-2 mRNA vaccination revealed several key findings. First, the induction of enduring protective immunity is intricately linked to the formation and persistence of GC reactions within draining lymph nodes. It was demonstrated that the mRNA vaccine platform, with its self-adjuvanting lipid-nanoparticle encapsulated structure, could foster robust and prolonged GC reactions, surpassing responses observed with traditional influenza vaccines. These reactions give rise to MBCs and LLPCs, crucial components for sustaining long-term immunity. Second, the inherent flexibility of mRNA-based vaccines enables rapid adaptation and development of vaccines specifically tailored to VOCs. Numerous studies investigating B cell responses after VOCs-based vaccination have highlighted the potential of mRNA vaccine to overcome the detrimental effect of immunological imprinting. To achieve long-term control of COVID-19 and improve immune response to VOCs, sustained research efforts are imperative, including continuous refinement and design of future vaccine boosters to effectively stimulate optimal, durable, and broadly protective B cell responses against continuously evolving coronavirus variants. Based on the insights discussed here, future approaches to developing next-generation vaccines could benefit from targeting specific epitopes from the spike Ags of future variants, rather than utilizing the full-length spike Ag, to mitigate immunological imprinting. Additionally, to effectively prevent infection and reduce virus transmission, mucosal vaccination that induces protective immune responses in the airway would be highly advantageous.

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