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Unpredicted Protective Function of Fc-Mediated Inhibitory Antibodies for HIV and SARS-CoV-2 Vaccines

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Developing effective vaccines is necessary in combating new virus pandemics. For human immunodeficiency virus (HIV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the induction of neutralizing antibodies (NAb) is important for vaccine protection; however, the exact mechanisms underlying protection require further study. Recent data emphasize that even Abs that do not exhibit neutralizing activity may contribute to immune defense by Ab Fc-mediated inhibition. Abs exhibiting this function may counter virus mutations, which are acquired to escape from NABs, and therefore broaden the protective Ab response induced by vaccination. The steps leading to inhibition are complex. How can these functions be measured *in vitro*? What inhibitory assay is physiologically relevant at mimicking effective *in vivo* protection? This review provides a comprehensive update on the current knowledge gaps on the Ab Fc-mediated functions involved in HIV and SARS-CoV-2 protection. Understanding the inhibitory effects of these Abs is vital for designing the next generation of protective HIV and SARS-CoV-2 vaccines.

Keywords. HIV; SARS-CoV-2; vaccine; neutralizing antibody; Fc-mediated immune response.

HISTORY OF VACCINE-INDUCED PROTECTIVE ANTIBODIES

For previously developed and approved vaccines, specific antibodies (Abs) capable of binding to the pathogen were used as surrogates for vaccine efficacy. This was primarily achieved by detecting Abs that bind to pathogen-specific epitopes using enzyme-linked immunosorbent assay (ELISA). The induction of these pathogen-specific antibodies was previously associated with vaccine protection. It rapidly became clear that these Abs were not associated with human immunodeficiency virus (HIV) vaccine efficacy.

Discovered in 1983, HIV remains a major global public health issue, having claimed 40.1 million lives thus far [1]. According to the World Health Organization, an estimated 38.4 million

people were living with HIV at the end of 2021 [1]. To fight the HIV pandemic, an efficient vaccine is needed; however, after 40 years of research, studies are ongoing to develop new vaccine strategies for protection. Following infection, HIV-specific Abs are extensively induced; however, they rarely display functional inhibitory activity (ie, neutralizing and Fc-mediated activities) for several reasons. First, HIV-specific Abs induced following infection are primarily directed against immunodominant epitopes and are devoid of functional activity. Second, the extremely high mutation rate of HIV results in the selection of escape variants. Third, the high glycosylation rate of the HIV envelope masks functionally conserved epitopes. These subtle escape mechanisms render traditional vaccine strategies completely inefficient for protection [2]. To contract these mechanisms, an HIV vaccine will need to induce highly specific Abs with functional inhibitory activities.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a coronavirus causing the coronavirus disease 2019 (COVID-19) respiratory illness, is responsible for an ongoing pandemic already leading to more than 6.4 million deaths globally [3]. Similar to HIV, the fight against SARS-CoV-2 relies on the development of an efficient vaccine. SARS-CoV-2 vaccines were developed quickly on the basis of the new mRNA vaccine platform [4]. These vaccines efficiently protect from the ancestral vaccine-driven strain; however, protection decreases markedly with the emergence of new variants of concern (VOC), which exhibit numerous mutations [5]. However, after

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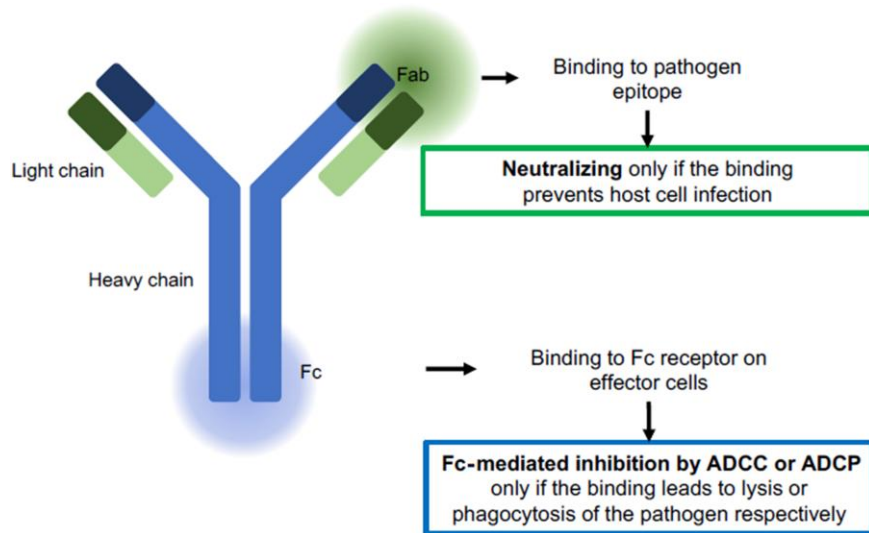


Figure 1. Fab and Fc domains of antibodies (Abs) involved in Ab functions. Neutralization and Fc-mediated inhibition by antibody-dependent cellular cytotoxicity (ADCC) or antibody-dependent cellular phagocytosis (ADCP).

infection, vaccinated people retain a residual protective effect against the most severe forms of the disease [6]. The mechanisms by which this residual effect occurs remain unclear, suggesting a possible role for other functional inhibitory antibodies.

Although HIV and SARS-CoV-2 are 2 very distinct viruses—HIV requires sterilizing immunity whereas the major goal for SARS-CoV-2 is preventing disease severity—the functional inhibitory determinants of vaccine-induced HIV and SARS-CoV-2 Ab responses remain unclear, and we highlight the knowledge gaps that need to be filled to enhance vaccination development efforts.

ROLE OF NEUTRALIZING ANTIBODIES IN VACCINE PROTECTION

Neutralizing antibodies (NAbs) bind to specific epitopes at the virion surface through their Fab domain, which prevents them from infecting host cells (Figure 1). Abs that do not prevent cell infection are considered nonneutralizing; One of the advantages of NAbs is that their inhibitory mechanism does not require other immune components. Thus, for the development of an effective HIV vaccine, NAbs are considered the best-in-class functional Abs with the capacity to inhibit HIV infectivity *in vitro* while blocking the initial infected cells *in vivo*, thus providing sterilizing immunity and avoiding latent infection of cells [7]. To obtain broad neutralizing activity against multiple HIV variants, Abs that can target highly conserved masked epitopes on the trimeric HIV envelope spike must be induced. A limited number of Abs directed to specific conserved epitopes can neutralize a broad range of HIV strains [8]. These broad NAbs (bNAbs), are detected after several years of infection in

a few HIV-infected individuals [8, 9], bNAbs are the best correlates of protection *in vivo*. Passive transfer of bNAbs followed by experimental challenge results in sterilizing protection in numerous assays in a nonhuman primate (NHP) model [10]. This protection completely reboosted HIV vaccine research programs. Novel prototype immunogens were subsequently conceived to target specifically conserved epitopes. Unfortunately, bNAbs could not be induced by these new vaccination strategies. To display a broadly neutralizing activity, rapid B-cell maturation is required for the long complementary-determining region of the heavy chain 3 and/or high levels of somatic hypermutations to obtain access to the neutralizing conserved epitopes that are often hidden [11]. The induction of extremely complex maturation by vaccination is challenging and cannot be achieved by classical vaccination strategies. Prime–boost approaches by the successive administration of newly developed vaccine platforms (eg, antigens, vectors, DNA, and mRNA) have been evaluated to improve Ab maturation.

With respect to SARS-CoV-2, vaccines using the mRNA platform have been developed rapidly. These vaccines induce high and efficient SARS-CoV-2–specific NAbs against the homologous vaccine strain [12]. These NAbs are associated with a decreased risk of SARS-CoV-2 acquisition [13]; however, vaccine protection is not unambiguously associated with their neutralizing activity [14, 15]. SARS-CoV-2–specific Abs decrease rapidly, and reboosting is necessary to reactivate the SARS-CoV-2–specific and -protective NAb response [15]. Moreover, these NAbs do not provide broad neutralization as their inhibitory activity decreases markedly against the new emerging SARS-CoV-2 variants. Indeed, the new VOCs progressively escape these neutralizing responses [16], although they are still sensitive to Fc-dependent Ab

effector function [17]. Vaccinated individuals lacking neutralizing activity against the new VOCs of SARS-CoV-2 can acquire the infection, but they are still protected from severe disease, which further suggests the participation of Fc-dependent Ab effector functions for disease protection [14].

USE OF NEUTRALIZING ANTIBODIES AS THERAPEUTICS

Because of their high potency, bNAbs have been developed as a new treatment to fight HIV or SARS-CoV-2. Recently, numerous HIV-specific monoclonal bNAbs have been isolated from HIV individuals selected for their neutralizing activity. They are currently being tested for treatment and prevention [18]. Although they have shown inhibition potential, additional studies are needed to increase their breadth by efficient combination or to complement antiretroviral therapy [18]. Interestingly, additional functions besides classical neutralization are being evaluated, such as lysis of the infected cells and targeting anatomically cryptic latently infected HIV reservoirs [19].

With respect to SARS-CoV-2 therapy, different monoclonal NAbs have been used as therapeutics to combat infection and disease. Treatment with these Abs can help immunodeficient individuals and patients with known comorbidities. The new VOCs progressively escape from the recognition and neutralizing response induced by vaccination. Therefore, to improve prognosis and prevent new infections, new classes of NAbs that exhibit broad activity against the latest VOCs are needed [20].

ROLE OF Fc-MEDIATED ANTIBODY INHIBITORY FUNCTIONS IN HIV AND SARS-COV-2 VACCINE PROTECTION

Because of the capacity of viruses to escape NAbs, other Ab inhibitory functions were evaluated. In the HIV field, by searching for other Ab functions, it became obvious that the Fc domain of the Ab has an additional inhibitory role in vitro [21]. Subsequently, the Fc-mediated inhibitory function was found to be associated with a decreased risk of HIV acquisition in the phase 3 RV144 vaccine trial [22, 23]. This trial, which involved more than 16 000 volunteers with a low risk of HIV infection, showed a 31.2% decreased risk in HIV acquisition without NAb induction [22]. The decreased risk was correlated with non-NAbs that were directed against the V1/V2 portion of the HIV envelope protein (gp120) and antibody-dependent cellular cytotoxicity (ADCC) [23–25]. ADCC involves an effector cell (eg, natural killer [NK] cells), wherein dual binding of the Fc domain of the Ab to an Fc receptor on the effector cells and that of the Fab domain of the surface antigen expressed by an infected cell will induce its lysis (Figure 1 and Figure 2). Interestingly, anti-V2 monoclonal non-NAbs elicited in HIV-1-infected individuals induce strong cross-reactive ADCC activity in vitro using different primary isolates (subtype

B and C) as well as transmitted/founder viruses (subtype B) [26]. Moreover, monoclonal non-NAbs against V1/V2, similar to those induced in the RV144 vaccine trial, exhibit strong ADCC activity in vitro against primary infected cells [23].

The results from the RV144 vaccine trial raised significant questions including: (1) accuracy of the limited reduction in HIV acquisition, (2) mechanisms associated with this protection, and (3) reproducibility of the results [27]. Other questions include whether the 31.2% decreased risk of HIV acquisition is real and whether this protection is associated with Fc-mediated functions. If Fc-mediated inhibitory Abs can prevent infection and/or influence disease prognosis, for which vaccine and against which pathogen should we induce such Abs? Can this be reproduced in other clinical settings and for other viruses with varied infection rates? [27]

Many studies were conducted to identify correlates of protection that are distinct from neutralization (Table 1). HVTN 702 was conducted in South Africa using an approach related to RV144, although with different settings (eg, different envelopes, adjuvant, and at-risk population). Despite the lack of efficacy and a distinct immunogenicity profile, the results showed a similar correlation of anti-V1/V2 Ab induction with a decreased risk of HIV-1 acquisition in a subset of noninfected volunteers, which suggests a possible protective role for these Abs [37]. Moreover, the HVTN 505 vaccine trial testing DNA, followed by recombinant adenovirus serotype 5 (rAd5), which also lacked overall efficacy, showed that antibody-dependent cellular phagocytosis (ADCP) and antibody binding to FcγR correlates with decreased HIV-1 risk in a prespecified immune correlate analysis [34]. Similar to ADCC, ADCP involves an effector cell (eg, macrophage), wherein dual binding of the Fc domain of the Ab to FcR on the effector cells and the Fab domain to the surface antigen expressed by an infected cell induces phagocytosis of the infected cell (Figure 1 and Figure 2). Another vaccine trial aimed at inducing nonneutralizing, but Fc-mediated inhibitory Abs, was conducted. This phase 2b Imbokodo study (HVTN 705) evaluated the efficacy of Ad26.Mos4.HIV and the subtype C gp140 combination in women from southern Africa [38]. This trial also failed to decrease HIV acquisition rate. The lack of overall efficacy has put into question future HIV vaccine development strategies [27].

Data obtained from HIV-infected individuals support the role of non-NAbs in HIV protection (Table 1). First, in mother-to-child HIV-1 transmission, preexisting Fc-mediated functional Abs in mothers correlated with lower morbidity, reduced HIV-1 acquisition, and improved survival rates of infected children [28, 39]. Second, ADCC correlated with a slower disease progression rate [30]. Third, in NHP, the infusion of Abs with ADCC activity reduced viremia [40–42]. These results suggest an impact of Fc-mediated Abs on HIV replication; however, whether the induction of such Abs is required to fight the HIV pandemic requires further study [27, 43, 44].

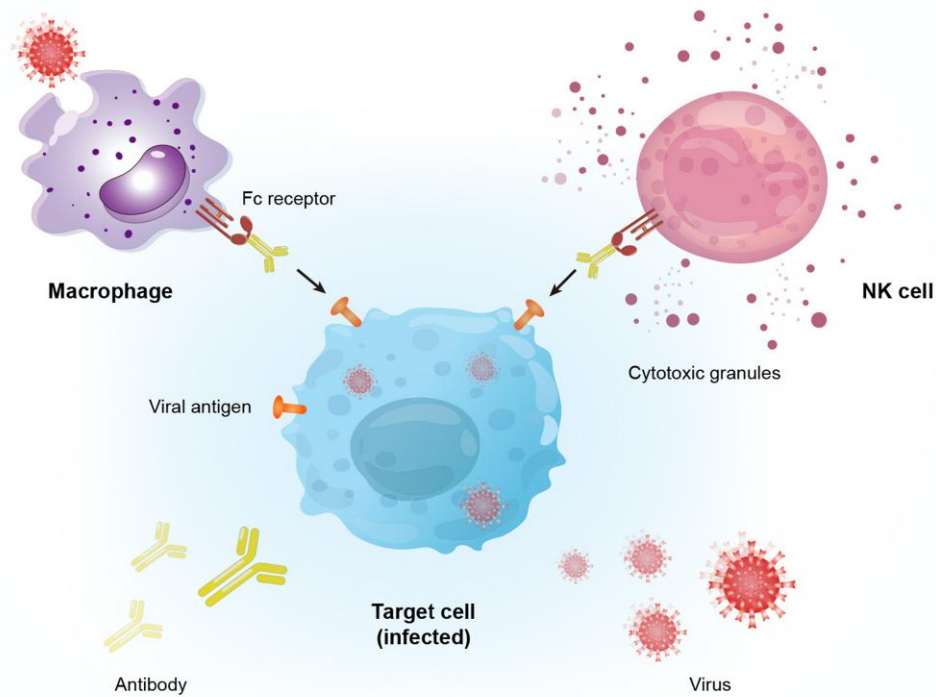


Figure 2. Fc-mediated functions, ADCC and ADPC. Dual binding of antibody to Fc receptor and virus epitope leads either to the lysis of the infected target cell (ADCC) or the engulfment and digestion of the infected cell by phagocytosis (ADPC). Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; ADPC, antibody-dependent cellular phagocytosis; NK, natural killer cell.

Table 1. Induction of Fc-Mediated Function and Clinical Correlates for HIV and SARS-CoV-2 Infections

Fc-Mediated Antibody-Induced	Association	HIV	SARS-CoV-2
Preexisting (mother-to-child)	Reduced mortality	Yes [28]	Yes [29]
Following infection	Slowed disease progression Reduced viremia	Yes [30, 31]	Yes [32]
	Lower systemic inflammation	Not evaluated	Yes [33]
By vaccination	Related to prevention (vaccine efficacy)	Yes [23, 25, 34]	Yes [14, 15]
Hybrid infection + vaccination	Increased binding, neutralizing, and ADCC potential	Therapeutic [19]	Yes [35, 36]

Abbreviation: ADCC, antibody-dependent cellular cytotoxicity.

For SARS-CoV-2 infection, the rapid decline of NAb following vaccination and the escape-neutralizing response by VOCs have revealed additional functional Ab activities [14]. Indeed, non-NAb have an important role in driving the Fc function [45]. Abs displaying ADCC are associated with protection

(Table 1) [15, 32, 33]. The detection of ADCC activities in SARS-CoV-2-infected individuals is associated with lower systemic inflammation [33]. Moreover, Abs with Fc effector functions are transferred from mother to child, which is enhanced by the combination of vaccination and infection [29]. Finally, hybrid immunity of vaccinated individuals who previously experienced COVID-19 offers a qualitatively improved Ab response able to better leverage Fc effector and ADCC potential [35, 36].

Regarding dual infection of SARS-CoV-2 in people with HIV (PWH), recent studies showed that, in addition to a delayed humoral response, the magnitude of ADCC induced in response to infection by the SARS-CoV-2 Beta strain was lower in PWH [46]. However, this difference leveled out after the third immunization [47]. Despite this delay, an improved coordination between binding, neutralization, and Fc function was observed in PWH [46]. A similar increase in Fc polyfunctionality was observed following influenza vaccination [46], which suggests that a more balanced or synergistic immune response may be induced after an already-existing infection. This hypothesis and the mechanisms underlying improved Fc polyfunctionality following multiple infections require further study.

Table 2. In Vitro ADCC Assays for HIV and SARS-CoV-2

Virus	Target Cell	Effector Cell	Antigen/Virus	Readout	Reference
HIV	CEM.NKR.CCR5	Coated FcR Cell line	Antigen-coated beads	Binding to FcR	[31, 48–50]
	HIV-infected	Primary cell	Pseudovirus	GzB uptake	
	Reporter virus- infected		Infectious virus	Expression of Luc in infected cells	
	Antigen-pulsed			Targeting cell death or virus production	
	Primary CD4 ⁺ T cell				
SARS-CoV-2	Reporter-only cell line (S-protein expressed)	Cell line Primary cell	Antigen-coated beads Pseudovirus	Binding to FcR Expression of Luc in infected cells	[17, 32, 33, 51, 52]

Abbreviation: FcR, Fc receptor; GzB, granzyme; Luc, luciferase.

These results indicate the potential participation of additional Fc-mediated Ab functions in protection; however, it is unclear to what extent and how they contribute to protection. Additional studies are necessary to identify the mechanisms associated with this protection. We also need to determine the precise role of Fc-mediated functions, how and to what extent they participate in protection, and how the immune response must be driven to efficiently induce such additional functional Ab responses.

Fc-MEDIATED FUNCTION IN VITRO

To further understand the role of Fc-mediated function, in vitro characterization of these Abs was conducted. These functions involve complex mechanisms with Abs interacting with virus and effector cells that render in vitro detection very challenging. In vitro assays reproducing in vivo settings are difficult to conceive [17, 31]. An optimal in vitro assay to detect physiologically relevant Fc-mediated inhibitory Abs needs to be established.

Two Fc-mediated inhibitory functions have been examined in vitro: ADCC and ADCP (Figure 2). For these, the Abs need to recognize an infected target cell through its Fab domain and bind via its Fc domain to a specific Fc receptor (FcR) expressed on the surface of an effector cell (eg, NK cells, dendritic cells, macrophages, or neutrophils) (Figure 1). This dual binding then leads either to the lysis of the infected target cell (ADCC) or to the engulfment and digestion of the infected cell by phagocytosis (ADCP).

Assays have been developed to facilitate the in vitro measurement of ADCC and ADCP function, particularly for HIV and SARS-CoV-2 (Table 2). These assays sometimes record different events, for example, FcR binding or capture of beads coated with antigens; however, binding or capture cannot fully recapitulate the intrinsic interaction leading to in vivo effector function. In the HIV field, only a few assays that analyze infected cell lysis with primary cells and replication-competent virus have been developed. Detecting the lysis of infected cells is important for this assay as it has been demonstrated that some Abs can bind to noninfected CD4 T cells, resulting in their unwanted destruction [48]. Consequently, assays analyzing cell lysis on primary cells do not necessarily yield comparable results

to those using cell lines or analyzing simpler outcomes, such as dual binding. The former is more physiologically relevant but much more time-consuming and difficult to standardize. Interestingly, the magnitude of ADCC lysis varies according to the HIV strain used, leading to the classification of viruses that are more or less sensitive to ADCC lysis [50], influencing ADCC results. The significance of these different in vitro results and their correlation with HIV in vivo protection have been questioned [31]. Such a complex array of assays is also currently under implementation for SARS-CoV-2 [17].

HOW CAN WE DETERMINE THE ROLE OF Fc-MEDIATED FUNCTION IN PROTECTION?

The challenge now is to prove that the various associations between Fc-mediated function and protection are relevant. Thus, it is important to demonstrate that Abs displaying Fc-mediated functions are worthwhile to induce by vaccination. What are the mechanisms leading to Fc-mediated Ab inhibition in vivo?

To answer this question the passive transfer of HIV-specific Abs displaying nonneutralizing Fc-mediated functions has been carried out in animal models. These experiments have shown decreased viral load or number of founder viruses and reduced viral burden following experimental infection challenge [40–42, 53]. However, sterilizing protection was not observed in these experiments. Nonetheless, using a viral dynamic approach, Wang et al found that Fc-mediated effector functions accounted for 25%–45% of the total antiviral activity [54]. Moreover, non-NAbs protected or altered the course of HIV infection in a mouse model, which indicated that such Abs accelerate virus and/or infected cell clearance by Fc-mediated mechanisms [55]. Another study showed improvement in Ab responses by coadministration of vaccine vector and protein to the same draining lymph node; this could provide an immunological advantage with the induction of non-NAbs, ADCC activity, and HIV Env Ab binding to FcγR [56].

To improve Fc-mediated function, Fc domains of the Abs were engineered to bypass the binding limitation and modulate effector function, half-life, and the biochemical properties of the Abs [57]. Modification of the fucosylation site in the Ab heavy chain to increase Fc–FcR binding did not improve protection in the challenge experiments with the NHP model

[52]. The main concern of these experiments is the relevance of the NHP model for investigating the Fc-mediated function of human Abs. Bias may be observed because of the biophysical and functional differences between immunoglobulin G (IgG) subclasses and FcRs and the potential triggering of Fc function between humans and NHP [58]. Numerous engineered Fc domains are currently being evaluated to improve Fc-mediated function in vivo [59].

Passive transfer of these Abs is another caveat for analyzing the Fc-mediated Ab function. Indeed, passive transfer of Ab results in high Ab concentration in the periphery, but is limited in tissues. Nonetheless, Fc-mediated function may be of major importance in tissues [60]. Antigen-presenting cells bearing the FcR are primarily located in tissues, which is where protective Fc-mediated inhibitory function may be detected. Of note, these functions will rely on the capacity of Ab to bind to effector cells in an in vivo microenvironment. This binding directly depends on the presence of FcR-bearing cells, FcR expression, and affinity of the Fc domain of the Ab to FcR. Numerous studies have already demonstrated that FcR interaction is complex and depends on a plethora of factors, including the type of FcR and its polymorphisms [43, 44].

Additional studies are urgently needed to characterize the inhibitory steps leading to infected cell destruction by Fc-mediated Abs in vivo. This information will help to ascertain the role of Fc-mediated Ab function for HIV and SARS-CoV-2.

VIRUS-ANTIBODY RELATIONSHIP

HIV has been classified according to its sensitivity to neutralization (tier classification) [61]. Interestingly, this classification does not correlate with ADCC. Therefore, some HIV strains may be sensitive to neutralization but resistant to ADCC or vice versa, meaning that virus characteristics are associated differently with neutralization or Fc-mediated function [50]. For neutralization, it has been proposed that HIV selects closed trimeric envelope conformations and highly glycosylated strains to escape from NAbs [8]. Therefore, only Abs that can bind to masked epitopes exhibit neutralizing activity. For ADCC, recent studies suggest that non-NAbs restrict viral replication and expansion. One study showed that ADCC-mediating antibody responses apply selective pressure by constraining the NAb escape pathway [62]. Moreover, proteolytic cleavage of the HIV-1 envelope protects infected cells from Ab lysis [63]. In addition, recent studies showed that the vpu HIV auxiliary protein restricts Fc-mediated effector function by closing the envelope to prevent Ab interaction [64]. This indicates that HIV has evolved differently to escape either from NAbs or for Fc-mediating Ab function.

For SARS-CoV-2, the new VOCs undoubtedly evade NAbs by successive mutations and cell-cell fusion; however, the driver of these mutations is not well understood [16]. Moreover, Abs

induced by mRNA vaccination exhibit decreased capacity to bind to FcRs while still binding to Omicron BA.2 [65, 66]. The relationship between SARS-CoV-2 immune escape and Fc-mediated function is unclear. Current studies suggest that Fc-dependent Ab effector function is preserved for the new VOCs. This information may provide hints for the development of the next generation of SARS-CoV-2 vaccines and therapeutics [17, 66].

These different virus-escape mechanisms indirectly highlight the potential protective activity of neutralizing and Fc-mediated inhibitory Abs in vivo. A combination of the 2 Ab functions may, therefore, be particularly favorable to limit virus escape. Compared with HIV, SARS-CoV-2 mutates at a slower rate; however, the large infection number and vulnerable immune cell population have promoted the generation of new variants with high immune escape abilities. Monitoring the emergence of escape mutations and decreasing the infection rate are important to control the pandemic.

CONCLUSION

Tremendous efforts have been made to develop protective vaccines against HIV and SARS-CoV-2. The comprehensive research undertaken for the development of effective vaccines against these viruses has generated substantial knowledge on the judicious virus-Ab relationship. Vaccine response induces neutralizing and Fc-mediated inhibitory Abs. For HIV and SARS-CoV-2, only a fraction of the specific Abs exhibit neutralizing or Fc-mediated inhibitory function, which indicates that specific Ab characteristics are associated with these two functions. With respect to HIV, NAbs have been characterized as highly mature and recognizing conserved (difficult to assess) epitopes. The judicious combination of these difficult-to-induce NAbs with Abs displaying Fc-mediated Ab function confers a therapeutic advantage [67].

At present, Ab features associated with Fc-mediated function have not been determined; however, the vital role of the Fc domain for Ab binding to FcR on cells has been shown. Expression, polymorphism, and FcR function have been largely investigated [27, 53, 54]. Understanding the features associated with protective Abs is fundamental for the development of new vaccine strategies. The next generation of vaccines against emerging pathogens should focus on multiple Ab attributes, combining the induction of both neutralizing and Fc-mediated inhibitory Abs to increase the scale and durability of the humoral protective response.

Notes

Author contributions. C. M. and L. Y. L. contributed to the writing. P. G., S. L., and B. S. edited and amended the article. All authors provided feedback on the report.

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