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Review Article

Multifaceted roles of Fcγ receptors in COVID-19 and vaccine responses

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Abstract: Recent data have revealed various effector functions of FcγRs in immune responses against challenges with SARS-CoV-2 virus. FcγRs act as a bridge between antibody specificity and effector cells. In many cases, IgG/FcγR interactions generate cell-mediated immune protection from infection via ADCP or ADCC. These responses are beneficial, as they may participate in virus elimination and persist longer than neutralizing anti-Spike antibodies. In contrast, these interactions may sometimes prove beneficial to the virus by enhancing viral uptake into phagocytic cells via ADE and causing excessive inflammation. Here, we summarize key features of FcγRs, discuss effector functions, clinical relevance, and factors influencing FcγR-mediated immune responses in COVID-19 and vaccine responses, and consider IVIg and kinase inhibitors for targeting FcγRs signaling in COVID-19.

Keywords: SARS-CoV-2, vaccination, FcγR, Fc glycosylation, ADCP, ADCC, ADE

Introduction

Coronavirus disease 2019 (COVID-19) is a febrile respiratory disease triggered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its different variants of concern (VOCs) or interest (VOIs) that lead to a spectrum of symptoms ranging from mild and moderate to severe or even critical. At this time, the primary prophylaxis measure against severe COVID-19 or death is the vaccination [1], which is designed to induce T helper (Th) lymphocytes, cytotoxic T lymphocytes (CTLs), and potent neutralizing antibody (Nab) responses [2-4]. Nabs act through fragment antigen-binding domain (Fab), by preventing the interaction between the spike (S) glycoprotein and human angiotensin-converting enzyme 2 (ACE2) on the host cell membrane. Although neutralization of newly emerging VOCs was significantly decreased in vaccine and convalescent sera [5-7], several vaccines maintain effectiveness against severe COVID-19 illness caused by these variants [1, 8]. These data suggest an important role for antibody-mediated effector activities in SARS-CoV-2 control and disease outcome [8, 9]. Most of these functions are initiated by the fragment crystallizable domain (Fc) of IgG Abs that bind Fc gamma Receptors (FcγRs) on immune cells [8]. SARS-CoV-2 Fc antibody signatures associated with the enhanced engagement of the high-affinity FcγRs can also influence the occurrence of the infection [10]. Along with enhancing FcγR-mediated effector activities, Fc arm can augment neutralizing human monoclonal Abs-mediated protection from SARS-CoV2 infection and lung disease *in vivo*, indicating a synergy between the Fab and Fc domains to optimize antibody effector function and therapeutic efficacy [11, 12]. Disrupt FcγRs binding of nAbs by introducing leucine-to-alanine substitutions (L234A/L235A or LALA) in their Fc regions significantly decreased the protection from lethal challenge with SARS-CoV-2 virus [13]. Traditionally, humans respond similarly to IgG-FcγR interactions, but that binding strength can differ between individuals due to e.g., different glycosylation and subsequently influence the Fc-mediated functions. Here, we summarize key features of FcγRs, discuss effector functions, clinical relevance, and factors influencing FcγR-mediated immune responses in COVID-19 and vaccine responses, and con-

sider IVIg and kinase inhibitors for targeting FcγRs signaling in COVID-19.

Fcγ receptors and IgG subclasses

Fcγ receptors

FcγRs are a group of cell surface receptors belonging to the immunoglobulin superfamily that interact with the Fc arm of IgG and serve as a link between humoral and innate immunity. There are three broad subfamilies of FcγRs in humans: the high-affinity FcγRI and low-affinity receptors FcγRII and FcγRIII. These cell surface glycoproteins are encoded by different genes on the 1q21.1-24 region of chromosome 1. They can also be defined based on their function as either activating receptors such as FcγRI, FcγRIIa, FcγRIIc, and FcγRIIIa or as inhibitory receptors (FcγRIIb). The FcγRIIIb is the only receptor that does not trigger intracellular signaling cascades.

Activating FcγRs

An early and essential event in the signaling cascade initiated upon FcγRs cross-linking by monomeric IgG or immune complexe (IC) is phosphorylation of the tyrosine residues within immunoreceptor tyrosine-based activation motif (ITAM) by Src-family kinases, leading to the recruitment and activation of Spleen tyrosine kinase (Syk) and Bruton tyrosine kinase (Btk) [14-16] that induce downstream signaling and cellular responses of which cytokine production is an example (**Figure 1**) [17]. ITAM signaling is either on the same ligand-binding α-chain as for FcγRIIa and FcγRIIc or on the associated γ-chain for FcγRI and FcγRIIIa. The FcγRI subfamily is composed of three extracellular domains and a very short intracytoplasmic region. The extracellular region of FcγRI can bind significant fractions of monomeric IgG at physiological concentrations. It is expressed mainly on macrophages, neutrophils, eosinophils and dendritic cells (DCs) [18]. The presence of the common γ-chain subunit is indispensable for its stable expression. Within the three isoforms of FcγRII, FcγRIIa and FcγRIIc are both single α-chain activating receptors that are very similar in structure. Both FcγRIIa and FcγRIIc contain an ITAM within their larger cytoplasmic tails. However, they differ in expression and function. FcγRIIa is a widely expressed receptor detected on monocytes, macrophages, DCs, neutrophils, basophils, and eosinophils [17]. FcγRIIa is encoded by the FCGR2A gene as two alleles that generate two variants differing at aa131: (H131 and R131) [19]. As a result, the FCGR2A-H131 allele increase FcγRIIa binding affinity for IgG2 than the R131 variant [20]. FcγRIIc is closely linked to, but distributed more restrictedly than, FcγRIIa. The FcγRIIIa comprises two extracellular domains and a very short intracytoplasmic region. NK cells, neutrophils, monocytes and macrophages express cell surface FcγRIIIa [21, 22]. The presence of the common γ-chain homodimer and CD3 ζ-chain containing ITAM sequences are crucial for maintaining stable FcγRIIIa expression and targeting this receptor at the cell membrane [23]. As with FCGR2A, FCGR3A exist as two alleles that generate two variants differing at aa 158: Phenylalanine (F) 158 and valine (V) 158 [24]. It is worth noting that the F158 variant decrease FcγRIIIa binding for IgG1 and IgG3 than the V158 allele [25].

Inhibitory FcγRIIb

FcγRIIb (a member of the CD32 cluster) is single-chain inhibitory receptor that is constitutively expressed on the B lymphocytes and interacts only with complexes aggregated IgG [26]. It is the only FcγR containing an immunoreceptor tyrosine inhibitory motif (ITIM) in its cytoplasmic domain that is responsible for the inhibitory activity toward ITAM-containing receptors in almost all immune cells, including B cells and platelets. It binds less efficiently to IgG1, IgG3, and IgG2 than all other FcγRs [25]. In the context of SARS-CoV-2 infection, it has been shown that Abs in the sera of lethal COVID-19 individuals antagonized interferons (IFN)-alpha (α) and -beta (β) signaling receptor by impacting FcγRIIb signaling (**Figure 1**) [27].

IgG subclasses

Four isoforms of IgG have been identified in human: IgG1 (66%), IgG2 (23%), IgG3 (7%) and IgG4 (4%). These isoforms differ in their upper CH2 domains and hinge region. CH2 domain is implicated in binding to FcγRs. Consequently, the different IgG subclasses bind with varying affinity to different FcγRs on innate immune cells, resulting in different Fc effector functions. Bruhns P and colleagues [25], found that IgG1 and IgG3 bind to all FcγRs, that IgG2 binds

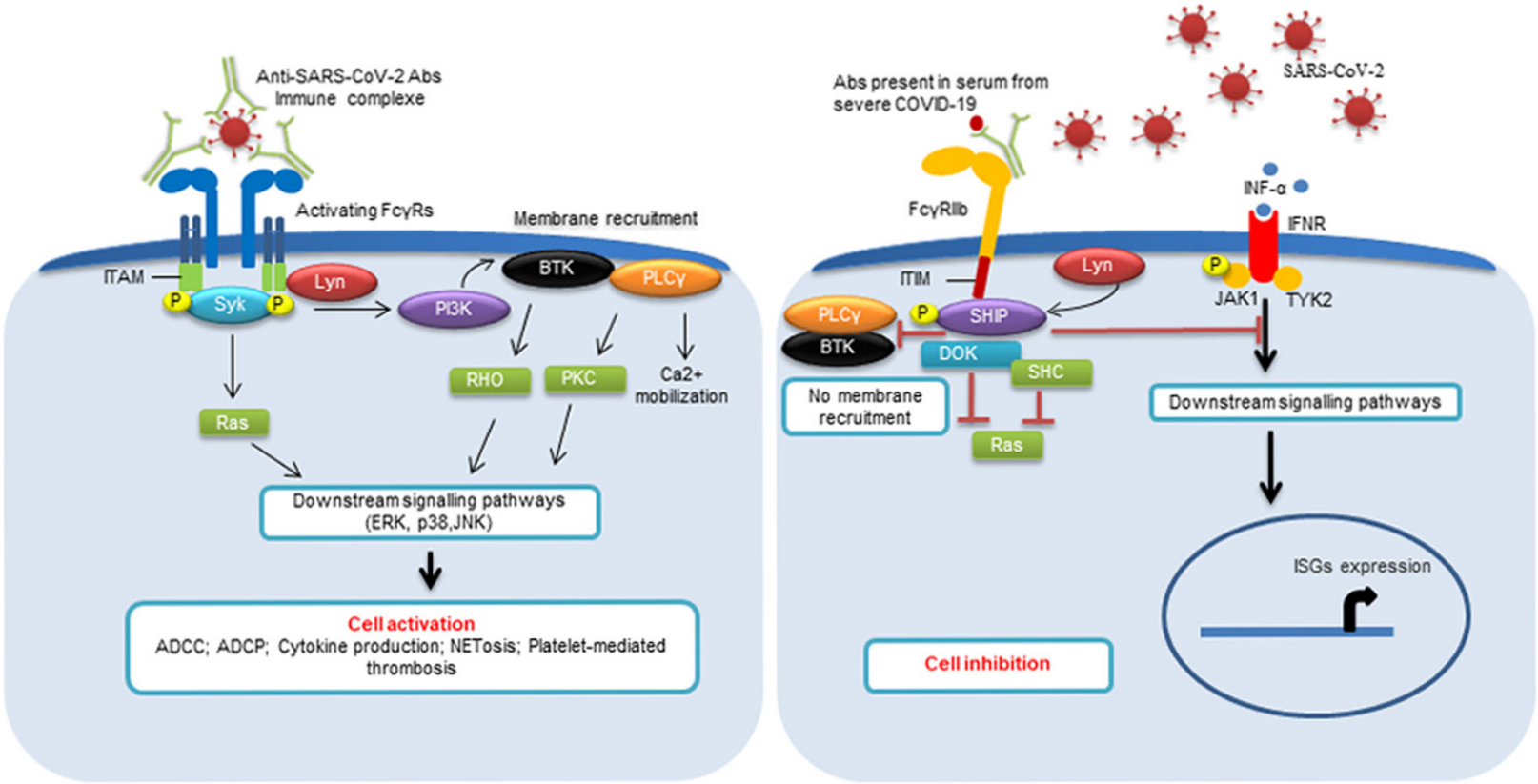

Figure 1. FcγRs signaling (LEFT), the cross-linking by anti-SARS-CoV-2 IC of activating FcγRs induces phosphorylation of the tyrosine residues within ITAM motif by Src-family kinases, leading to the activation of Syk and recruitment of Btk and PLCγ that induce downstream signaling and cellular activation (RIGHT), Abs present in serum from severe COVID-19 patients induce inhibitory FcγRIIb signaling through phosphorylation of the tyrosine present within the ITIM motif by Lyn responsible for the recruitment of inositol phosphatases (SHP), which inhibits ISGs expression following IFNAR engagement. Syk: Spleen tyrosine kinase; PLCγ: Phospholipase C gamma 1; Btk: Bruton's tyrosine kinase; PI3K: phosphoinositide 3-kinase; PKC: protein kinase C; IFNAR: Interferon-α/β receptor; ISGs: IFN-stimulated genes.

to FcγRIIaH131, FcγRIIaR131 and FcγRIIIaV-158, and that IgG4 binds to FcγRI, FcγRII, and FcγRIIIaV158. In general, IgG1 and IgG3 are the predominant subclasses produced in response to viral infections [28]. In addition, IgG3 is primarily characterized by increased hinge region, extensive polymorphisms and improved Fc effector functions [29].

Fcγ receptor effector activities during SARS-CoV-2

Binding of FcγRs by monomeric IgG and IC regulate diverse protective Fc effector functions involved in host defense, such as antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) and the release of inflammatory cytokines [30, 31]. However, these FcγRs intended to protect the host may sometimes prove beneficial to the virus by facilitating antibody-dependent enhancement of infection (ADE) [32] (**Figure 2**).

ADCC

ADCC activity is triggered when FcγR (e.g., FcγRIIIa, FcγRIIa) on immune cells is engaged by the Fc tail of specific IgG Abs bound to virus-infected cells (**Figure 1**). This process has been shown to form a determining component of effective humoral immunity against diverse clinically relevant viral infections such as HIV-1 [33], Ebola [34] and influenza [35]. Most ADCC assays have relied on NK cells isolated from peripheral blood mononuclear cells (PBMC) of normal donors or semi-purified NK cells. Specifically, it has been demonstrated that ADCC may contribute to SARS-CoV-2 control and clearance in vitro [36]. Additionally, Tso FY and colleagues showed that both serum specific-SARS-CoV-2 non-neutralizing and Nabs from recovered COVID-19 individuals are capable of eliciting ADCC via NK cells *in vitro* [30]. The preformed cytoplasmic granules containing toxins such as perforins and granzymes liberated by NK cells are essential for this process. A recent study characterized ADCC against SARS-CoV-2 by analyzing degranulation marker CD107a in activated NK cells [37]. The authors showed that natural infection and vaccination induce a robust ADCC activity via NK cells [37]. Like neutralization, the sequence of the infecting S sequence affects the breadth of the ADCC activity. A recent study by Hagemann et al. showed that previous exposure to one or more endemic human coronaviruses can elicit ADCC Abs that can cross-react with SARS-CoV-2 S glycoproteins in some rare individuals [37]. An extensive analysis of antibody-mediated functions in convalescent sera and after vaccination revealed that B.1.351 can trigger significant cross-reactive ADCC-activity against a panel of global VOCs [38].

The level of ADCC measured *in vitro* was also associated with clinical course, suggesting that this activity is a key factor in the varying clinical outcomes of COVID-19 [39]. Recovery from severe COVID-19 is associated with more robust ADCC responses [39]. Further, Abs directed against viral variants can efficiently induce ADCC activity in vaccinated mice and patients, highlighting the relevance of ADCC in lethal COVID-19, and particularly in the context of emerging neutralization-resistant VOCs [39]. In contrast, patients with severe COVID-19 requiring intensive care unit (ICU) treatment had reduced levels of ADCC activity [40]. Since low levels and functional exhaustion of CD16-expressing cells, such as NK cells, CD8γδ+ T cells and eosinophils have been associated with severe COVID-19 [41-43], it can be assumed that reduced levels of these cells may be linked to decreased ADCC activity observed in the PBMCs of individuals with poor COVID-19 progression.

Taken together, ADCC levels could effectively assess disease severity and predict outcome in COVID-19 individuals.

ADCP

Phagocytosis is the mechanism whereby Abs bind to extracellular pathogens to promote their Fc receptor-mediated ingestion and subsequent intracellular killing by phagocytes (e.g., monocytes, macrophages, neutrophils, and DCs). Already in 2014 Yasui et al. investigated the key role of ADCP activity during the first days of SARS-CoV-1 infection by using phagocytes-depleted mice [44]. They showed that mice were highly vulnerable to pulmonary SARS-CoV-1 infection, even in the presence of neutralizing anti-S protein Abs. Complement and NK lymphocytes were not required for Ab mediated protection, but infiltrating and tissue-resident macrophages, but not neutrophils,

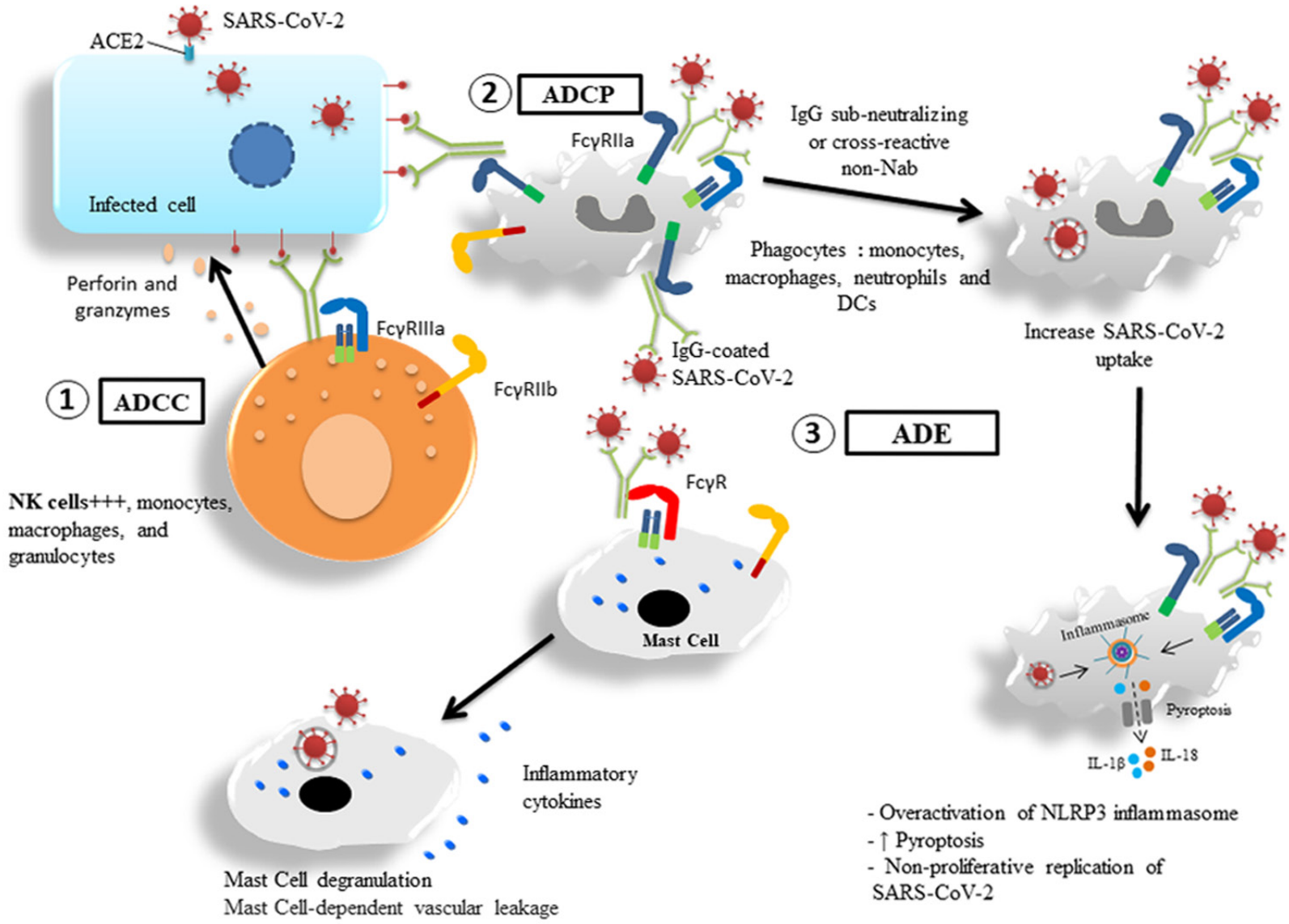

Figure 2. Fcγ receptors effector activities during SARS-CoV-2. Abs against SARS-CoV-2 are able to deploy a plethora of FcγRs effector activities over the course of Covid-19. These include but are not limited to the following: 1) The stimulation of NK cell degranulation to kill infected cells by ADCC. 2) The stimulation of macrophage opsonophagocytosis by ADCP. 3) The ADE by enhanced viral uptake via FcγRIII-mediated endocytosis into CD16+ monocytes causing overstimulation of inflammasome without net viral replication. FcγRs: Fc gamma Receptors; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2 virus; Nab: neutralizing-antibody; ACE2: angiotensin-converting enzyme 2; ADCP: antibody-dependent cellular phagocytosis; ADCC: antibody-dependent cellular cytotoxicity; DCs: dendritic cells; ADE: antibody-dependent enhancement.

could actively take up opsonized virus particles indicating that ADCP can be of major importance in clearing off SARS-CoV-infected lung cells in mice models. Further indications for a role of ADCP activity in SARS-CoV-2 came from studies in which purified plasma IgG Abs were analyzed for their ability to mediate phagocytosis of S1 and RBD antigen-coated beads [31]. Adeniji OS et al. found that these Abs were demonstrated to block infection by pseudoviruses and mediate robust ADCP of both S1-protein-coated beads and fluorescently-labeled RBD. A similar mechanism has been described in other infections such as HIV-1 [45, 46] and human papillomavirus [47]. The substantial differences in the FcγR binding in the different phagocytes may affect their functions. The RBD-specific antibody-dependent monocyte phagocytosis was lower in non-survivor individuals of severe illness but was comparable in non-survivor and survivor individuals suffering from moderate disease [48]. By contrast, higher levels of S-specific neutrophil-mediated ADCP activity were reported in critically ill patients compared to those with moderate disease [48]. By comparing clinical phenotypes of circulating phagocytic cells from COVID-19 patients and healthy controls, Peyneau and collaborators showed that phagocytosis activity was significantly lower in non-survivor patients as compared to survivors [49]. They also found that $CD13^{low}$ and $CD10^{low}$ immature neutrophil populations were significantly increased in critically ill individuals as compared to both non-ICU individuals and healthy controls. It is likely that in non-survivors with COVID-19, SARS-CoV-2 may trigger overstimulation of the phagocytic cells, and delayed evolution of high-affinity FcγR binding Abs, resulting in the apparition of abnormal subpopulations and exhaustion of ADCP.

ADE

ADE is the mechanism whereby sub-neutralizing or cross-reactive Abs enhance the infectivity and the pathophysiology of some viral diseases [50-53], and the SARS-CoV-2 virus is no exception. It can be categorized into at least two distinct pathways: by enhanced viral uptake via FcγRIIa-mediated endocytosis into phagocytic cells causing viral replication and further dissemination, or by excessive FcγR effector functions and IC formation causing leading to enhanced inflammation and immunopathology [54]. The current dogma and results gathered so far seem to clearly indicate that SARS-CoV-2 uptake in macropahges/monocytes goes through mainly FcγRIII in the CD16+ monocytes only [55]. This leads to enhanced viral uptake, but actually is detrimental to functional replication of SARS-CoV-2, as the monocytes undergo pyroptosis mediated by overstimulation of the inflammasome, resulting in net non-proliferative replication of the virus in those cells [55, 56]. Shimizu et al. [57] further show that sera from severe COVID-19 patients had the potential to cause ADE and to induce the secretion of inflammatory cytokines *in vitro*. In addition to cytokines from infected macrophages, mast cell stimulation and degranulation with Fc receptor-bound SARS-CoV-2 Abs are likely to participate in the escalated production of inflammatory mediators which can promote vascular leakage in predisposed children [58, 59]. Anti-SARS-CoV2 monoclonal Abs with high neutralization potency also enhanced viral uptake in Raji and Daudi B cells [60]. Enhancement is typically mediated by bivalent interaction of Nabs-virus complexes that could induce formation of IC and more stronger cross-linking of FcγRIIb on B cells [60]. The same mechanism has also been found in SARS-CoV [61].

There is no preclinical or clinical evidence that COVID-19 vaccination increases the risk of ADE [62, 63]. One reason is that vaccines focused on eliciting nAbs to the S-glycoprotein reliably protect animals from SARS-CoV-1 challenge without proof of ADE [64, 65]. Another is that neither mRNA nor inactivated COVID-19 vaccines generate Abs responses with FcγR-dependent ADE activity *in vitro* [62, 63]. Thus, COVID-19 vaccination strategies that elicit highly nAbs are believed to have a high chance of success without the risk of ADE [66].

Factors influencing FcγR-mediated effector functions in COVID-19 and vaccine response

Several factors govern the host immunological response to SARS-CoV-2 infection and to vaccination, including the antibody isotype and subclass selection, the antibody Fc glycosylation, polymorphism of FcγRs, vaccine regimen, and host-related factors (**Figure 3**).

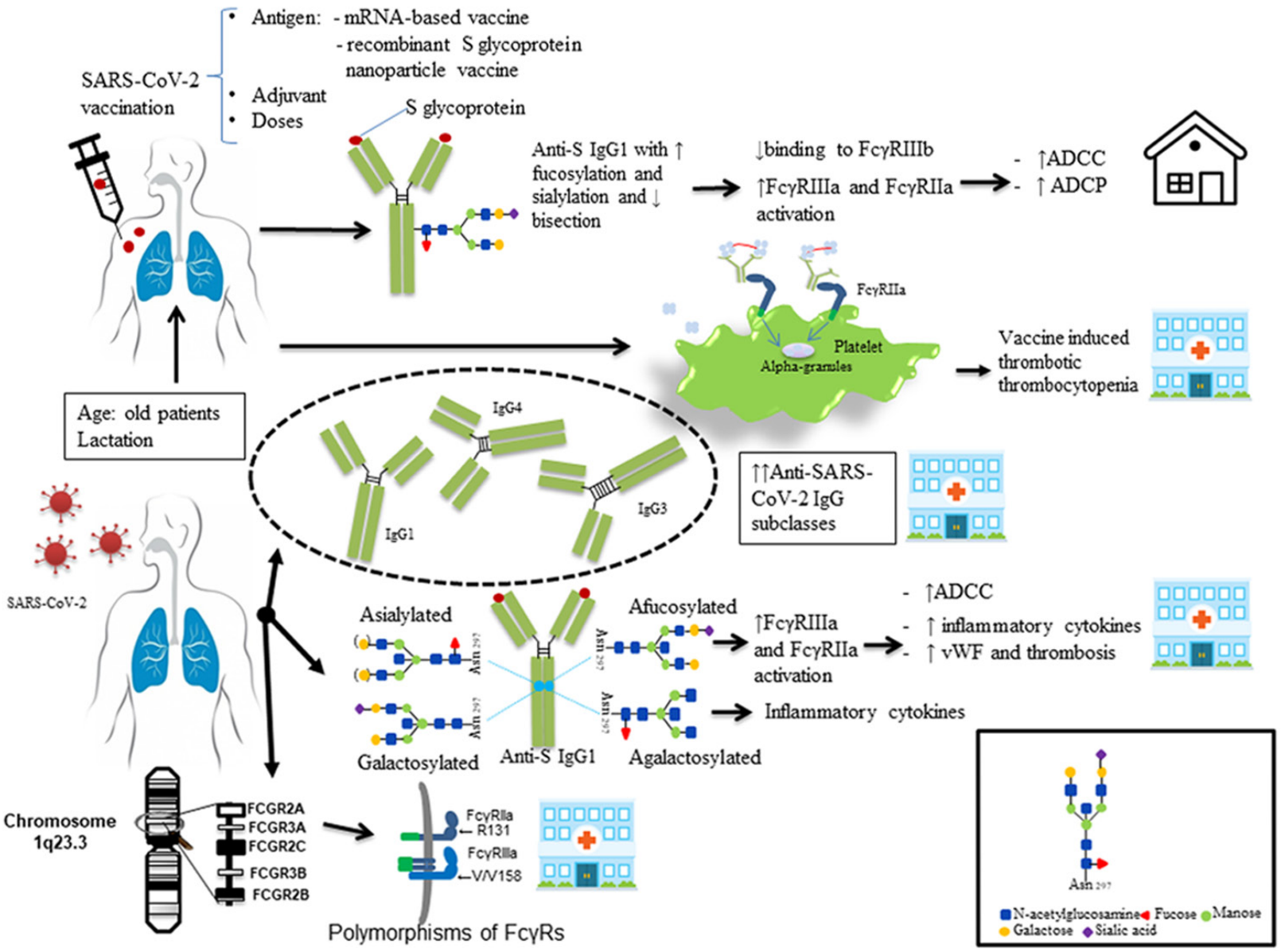

Figure 3. Factors that may affect FcγR-mediated effector functions in COVID-19 and vaccine responses. The ability of binding between IgG Abs and FcγRs to result in FcγR-mediated effector functions is affected by several factors, including the antibody isotype and subclass selection, the antibody Fc glycosylation, genetic variation of FcγRs, vaccine regimen (antigen, adjuvant and doses) and age. These factors dictate the likelihood of producing either a protective response to vaccination and infection or an undesirable excessive inflammatory reaction.

Table 1. Clinical relevance of IgG subclasses in SARS-CoV-2 infection

IgG subclasses	Clinical relevance
Total IgG	High titer:
	• Recovery after critical illness
IgG1	Afucosylated anti-SARS-CoV-2 IgG1:
	• Increased susceptibility to severe forms of SARS-CoV-2 infection
	• Increased binding capacity to FcγRIII
IgG2	Least functional potency
IgG3	High titer IgG3:
	• Increased susceptibility to severe forms of SARS-CoV-2 infection
	• Increased binding capacity to FcγRIIIa (158V allele)
	• Increased ADCC (FCGR3A-158V/V)
	• Overstimulation: proinflammatory cytokines
IgG4	High titer IgG4:
	• Increased mortality to SARS-CoV-2
	• Low affinity for the SARS-CoV-2

Specific characteristics of the antibody Fc region during COVID-19

Antibody isotype and subclass selection

The complexity in the FcγR engagement is mirrored by the presence of four IgG subclasses, which bind with varying affinity to different FcγRs (**Table 1**). IgG1 and IgG3 Abs are far more commonly found after exposure to SARS-CoV-2 than IgG2 and IgG4, however, these could elicit both pro- and anti-inflammatory functions [67-70]. The distribution and levels of IgG isoforms are primarily controlled by the nature of the antigen and Th cells. It is worth noting that IgG1 Abs are the dominant IgG subclasses formed in response to receptor-binding domain (RBD), S1 subunit and nucleocapsid (N) antigens [71], whereas IgG3 is predominantly reactive with the S2 subunit [71]. The importance of IgG levels as factors influencing COVID-19 outcomes is highlighted by the association of higher level of Ab titers, particularly for N-specific IgG1 and RBD-specific IgG1 and IgG3 with severe COVID-19 [72]. Additionally, increased levels of almost all the S-specific Ab classes and subclasses, and increased levels across all SARS-CoV-2 antigens, were also reported after the second week of infection in survivors of severe disease compared to those with moderate disease and those who died [48]. Yan et al. [73] also found that persistence and relatively higher titer of virus-specific IgG were correlated with recovery from severe COVID-19 [73]. This severity-associated IgG increase has been postulated to be caused by a disproportionate IgG subclass response dominated by IgG3 and elevated FcγRIIIa binding [71]. Although increased IgG3 level was mirrored by elevated binding for FcγRIIIa, other factors such as increased hinge length of IgG3 and IgG3 variants also may potentially contribute to this effect. Curiously, elevated serum IgG4 concentration and tissue infiltration by IgG4-secreting plasma cells have also been found to be correlated with mortality and severe COVID-19 [74, 75]. The molecular mechanisms that drive class switching are not fully understood. Because IgG4 induction is controlled mainly by Th2 cells [76], it is possible that the increased Th2 response, induced by severe SARS-CoV-2 infections [77], triggers in some patients a clonal expansion of relatively non-neutralizing IgG4-switched B cells, leading to further and further proliferation without clearing the bug, which may end up in increased serum concentration of IgG4. It is likely that the mortality-associated IgG4 increase may be associated with a low affinity of IgG4 for the SARS-CoV-2.

Antibody Fc glycosylation

Beyond antibody isotype, the glycosylation diversity of the N-linked sugars in the constant CH2 domain within the IgG Abs can impact their ability to interact with FcγRs on effector cells and, consequently, alter antibody functionality (**Figure 3**). The N297-linked Glycan of IgG is a complex-type oligosaccharide composed of a

constant part with a core consisting of two consecutive N-acetylglucosamine (GlcNAc) molecules, followed by a mannose, followed by two additional mannose antennae, each with a single GlcNAc attached [78] and can be found in plasma with variable numbers of fucose, galactose, terminal sialic acid, and sometimes bisecting GlcNAc [79]. Of the FcγRs, FcγRIIIa binding is mainly controlled by fucosylation of IgG1, and when afucosylated, hyper-galactosylation also influences binding, resulting in enhanced NK cell-mediated ADCC [80-86].

Afucosylation of IgG: It has been known that any deviation from 100% fucosylation in the Fc domain of all IgG subclasses affects their binding affinity toward human activating FcγRIIIa and FcγRIIIb as well as their Fc effector activities, such as ADCC [84, 85], phagocytosis [87] and inflammation [88]. Specifically, the lack of core fucosylation of anti-S/-RBD-specific IgG1 from severe COVID-19 patients increases IgG Fc affinity to FcγRIII and leads to enhanced ADCC activity of NK cells as well as secretion of pro-inflammatory cytokines by engagement of INF dependent pathway on lung myeloid cells *in vitro* (**Table 1**) [80, 82]. The positive binding effects were primarily caused by the lack of fucose, which was further strengthened by additional galactose [81]. The reasons for this additional effect are unknown but may be linked primarily to conformational changes in the CH2 domain of IgG1 Abs that stabilize and increase FcγRIIIa binding [89-91]. However, low IgG1 fucosylation is not necessarily associated with high secretion of inflammatory cytokines in all critically ill patients with COVID-19, suggesting a different regulation and/or the temporal resolution of fucosylation on anti-S IgG1 and cytokine secretion dynamics *in vivo* [92, 93]. The increased level of inflammatory cytokines is also found to be mediated by a cross-talk of different toll-like receptors (TLRs), like TLR3, recognizing replicates double-stranded RNA SARS-CoV-2, with activating FcγRIIa and FcγRIII [80]. Additionally, whilst low IgG1 fucosylation is associated with FcγRIIIa-mediated protection in HIV-1 elite controllers [94], it clearly marks high disease severity in COVID-19 [81] and dengue [95]. Thus, the capacity of Fc fucosylation to engage FcγRs with distinct Fc effector responses is a dynamic process that is modulated by multiple layers of regulation.

Galactosylation and sialylation: Unlike Fc fucosylation, the respective effects of galactosylation or sialylation on FcγR binding and antibody function in COVID-19 are still rather ambiguous. Tamas Pongracz et al. [93] demonstrated a large, single center cohort result that increased galactosylation and sialylation levels on S-specific IgG1 were associated with a less severe disease course upon hospitalization, and no ICU admission. Similarly, individuals with severe COVID-19 change the balance of these glycan species largely toward a loss of galactosylated and sialylated IgG compared with age- and sex-matched healthy controls [96]. In parallel, loss of galactosylation and sialylation in IgG from patients with a poor prognosis of COVID-19 increases IgG Fc affinity to FcγRIII and leads to enhanced NK cell activation, with the production of pro-inflammatory cytokines (IFN-γ and TNF-α) [97]. Bye et al. [83] reported an opposite result that increased galactosylation and decreased fucosylation of anti-S IgG immune complexes were associated with thrombosis disorders in severe SARS-CoV-2-infected individuals, a state which favors IgG binding to activating platelet FcγRIIa and secreted von Willebrand factor (VWF) *in vitro*. Furthermore, Althaus et al. support the role of antibody-mediated platelet FcγRIIa stimulation as one of the drivers in thromboembolic complications in severe COVID-19 [98]. Contrary to these, Petrović T et al. [99] have failed to reproduce these findings and refuted any association between galactose on total IgG and disease progression or severity, but anti-S and anti-RBD IgG galactosylation patterns were not measured. These discrepancies are probably related to the methodologies and confounding host-related factors (age and sex), polymorphisms of FcγRs, methods for the assessment of antibody glycosylation or to differences between populations.

Genetic variations of FcγRs

Single nucleotide polymorphisms (SNPs) in human FcγRs have been involved in variable immune responses and outcome of viral infections [100, 101]. Recently, two functional variants in FCGR locus have been identified that may affect the progression to critical illness in some COVID-19 patients. Vietzen et al. [102] reported that FCGR3A-158V/V genotype was associated with severe COVID-19. *In vitro* ex-

periments also found that CD56+CD16+ NK cells bearing the FCGR3A-158V/V or FCGR3A-158V/F variants mediate ADCC response more effectively [102]. Given that neutrophils, monocytes and macrophages also expressed FcγRIIIa, studies investigating ADCC response in FcγRIIIa-expressing cells beyond NK cell response are required. Mechanistically, the disease severity may be best explained by the heightened affinity for IgG3 of the high-binding 158V allele compared to the low-binding 158F, which may result in increased activity of ADCC by FCGR3A-158V/V (**Table 1**). Another functionally important SNP is located in the extracellular coding sequence of FcγRIIa (rs1801274). It has been reported that patients with the FCGR2A-131R/R genotype have a greater risk of more severe SARS-CoV-1 infection than individuals with the H/H genotype [103]. Of interest, in a small single population study performed on DNA obtained from PBMC, FCGR2A-131R allele might be also implicated in worse outcome and death of COVID-19 [104]. No such association was observed for SNP FCGR3A. The mechanisms that might link the polymorphic allelic forms of FcγRIIa, the binding selectivity of specific IgG subclasses for this receptor, and the antibody-dependent responses (ADCP, the release of inflammatory cytokines, and clearance of IC) to disease severity are not yet known.

COVID-19 vaccination

The antibody glycosylation and FcγR binding can be further influenced through vaccination and host-related factors (**Figure 3**). In fact, elevated RBD-specific IgG1 fucosylation was positively correlated with older populations after a third dose of the COVID-19 vaccine [105], most likely reflecting the strong correlation between COVID-19 mRNA-induced IgG Fc structures and age. Vaccine booster shots can increase FcγR-binding titers in lactating women compared with both pregnant and non-pregnant women, substantially increasing *in vivo* NK cells ADCC and neutrophil ADCP [106]. Like HIV [107], it is thus likely that young infants can be protected from COVID-19 via a high level of breastmilk ADCC activity. Additional regulation of IgG-FcγRs interactions required for vaccine response occurs via vaccine types. Interestingly, a study that investigated correlates of protection following NVX-CoV2373 immunization in animal models reported that high antibody titers bound more efficiently to both FcγRIIa and FcγRIIIa plays a significant role in controlling several VOCs [108, 109], but the exact contribution of IgG-FcγRIIa/RIIIa interactions in protection against these variants was not measured. These results indicate that select adjuvanted, recombinant S glycoprotein nanoparticle vaccine is able to modulate both FcγRIIa and FcγRIIIa binding. Overall, these factors may directly impact antibody production or modify expression of some glycogenes that encode IgG Fc glycosylation associated enzymes.

Many studies have revealed that the risk of excessive inflammation and thrombotic disorders following COVID-19 vaccination is relatively higher in some individuals, and this has been proposed to be linked to host factors such as some human leukocyte antigen genes [110, 111] and selective FcγRs expression in effector immune cells [112, 113]. Huynh A et al. [113] indicate that vaccine induced thrombotic thrombocytopenia (VITT) Abs may exert similar effects of heparin through recognition of the same epitope on platelet factor 4 (PF4)-polyanion complexes; this enables PF4 tetramers to form ICs, which in turn stimulates platelets through FcγRIIa. However, the anti-PF4/polyanion glycosylation patterns were not measured. A similar mechanism for thrombosis induced by heparin has been found in heparin-induced thrombocytopenia, whereby IgG Abs against heparin/PF4 complexes activate monocytes [114] and neutrophils [115] via FcγRIIa.

Targeting FcγRs for immunomodulation

Intravenous immunoglobulin (IVIg)

IVIg contains polyclonal IgG Abs from donors. Known for its immunomodulatory effects at high-dose, it has been used to treat patients with acute inflammatory and thrombosis diseases [116-118]. Xiang et al. [119] reported a meta-analysis study that IVIg were correlated with a lower risk of death in critically ill individuals with COVID-19 compared with healthy control subjects. The use of IVIg therapy within two days of admission to the ICU led to a decrease in mortality and shorter length of hospital duration in severe COVID-19 patients [120, 121]. Early administration of high-dose IVIg has also the potential to become an important treatment adjunct for VITT, particularly in patients with severe thromboembolic complica-

tions [122, 123] and Guillain-Barré syndrome (GBS) related to COVID-19 [124]. According to these results, IVIg can be an effective therapeutic intervention when administered early for covid-19 patients especially for severe or critically ill patients.

The mechanism of IVIg is not completely unraveled yet, but it may modulate inflammatory responses observed in severe COVID-19 via multiple mechanisms. For example, Bohländer et al. [125] demonstrated that Ig preparations such as IVIg and trimodulin suppress COVID-19 associated hyperinflammation by induction of inhibitory ITAM (ITAMi) signaling via IgG-FcγRIIa-axis *in vitro*, potentially increasing ADCP of viral-like particles. Other mechanisms mediated by the Fc fragment have platelet as their target. IVIG allow the inhibition of serum-induced platelet stimulation and aggregation in VITT by saturation as a result of high IgG concentrations; high-dose IVIg probably competitively inhibits the binding of PF4/polyanion ICs with the platelet FcγRIIa, thus decreasing platelet activation [126, 127].

Kinase inhibitors for COVID-19 therapy

As detailed above, signaling from multiple FcγRs converges on a few kinases such as Syk and Btk, which has made protein kinases potential targets to modulate hyperinflammatory response in a targeted fashion in COVID-19 (**Figure 1**) [128, 129]. Fostamatinib is a small prodrug inhibitor of Syk that is approved for the second-line therapy of immunological diseases such as chronic immune thrombocytopenia [130]. Hoepel et al. [80] reported that fostamatinib potently inhibits excessive inflammation caused by anti-S IgG on alveolar macrophages from severely ill individuals. Within severe cases of COVID-19, NETosis and, in turn, excessive neutrophil extracellular traps (NETs) production may contribute to microvascular thrombosis, tissue damage, and organ failure [131-133]. Also, fostamatinib can inhibit NETs formation among healthy donor neutrophils stimulated with COVID-19 patient plasma [134]. This finding supports the hypothesis that ICs can stimulate FcγRIIa on neutrophils to induce NETs formation in COVID-19 via Syk activation and downstream signaling [135].

Another study that investigated platelet stimulation mediated by serum samples from subjects suffering from severe COVID-19 disorders also reported that kinase inhibitors such as fostamatinib or acalabrutinib targeting Btk may be effective not only in limiting the excessive host inflammation, but also in reducing platelet-mediated thrombosis caused by IgG with low fucosylation and high galactosylation [83, 112, 136].

Taken together, targeting SYK and Btk kinases has implications in various Fc effector functions that these pathways modulate, such as cytokine secretion, NETosis and platelet activation.

Concluding remarks

The FcγR-IgG interactions and signaling outcomes in COVID-19 and vaccination are modulated in complex ways according to multiple mechanisms. While anti-S/-RBD IgG with low fucosylation, low sialylation and high galactosylation have an active role in COVID-19 associated inflammation, Fc fucosylation is regulated to drive appropriate anti-inflammatory effector cell functions following SARS-CoV-2 vaccination. The particular circumstances of patients and vaccinees such as age, lactation and specific FcγR variants may affect whether the overall influence of the glycosylation in FcγR-IgG interactions is more beneficial or not. Altogether, experimental models are needed to answer question about the linkage between FcγR-IgG interactions and variability of clinical outcomes following infection with SARS-CoV-2.

While Fc effector mechanisms will result in an increased efficacy against infection, this could also mean that the overall immune reaction is increased, which is not necessarily beneficial in COVID-19. Understanding this will be necessary to tune the interaction between Fc arm of IgG Abs and their FcγRs for therapeutic benefit, which could potentially be done to treat excessive host inflammation and thrombosis in severe COVID-19 to IVIg therapy and kinase inhibitors, to enhance the quality of Abs generated during vaccination or to reduce the mortality associated with disease.

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Disclosure of conflict of interest

None.

Abbreviations

FcγRs, Fc gamma Receptor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2 virus; COVID-19, coronavirus disease 2019; VOC, variants of concern; Nab, Neutralizing antibody; S, Spike protein; N, Nucleocapsid protein; Fab, fragment antigen-binding domain; Fc, fragment crystallizable domain; ACE2, angiotensin-converting enzyme 2; RBD, receptor-binding domain; HIV-1, human immunodeficiency virus type 1; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; PTKs, protein tyrosine kinases; ITAM, immunoreceptor tyrosine-based activation motif; ITIM, immunoreceptor tyrosine-based inhibitory motif; NK, natural killer cells; DCs, dendritic cells; IFN, interferon; IL, interleukin; IVIg, intravenous immunoglobulin; IC, immune complexe; ADE, antibody-dependent enhancement; CTLs, cytotoxic T lymphocyte; MC, mast cells; TLR, toll-like receptor; VITT, vaccine induced thrombotic thrombocytopenia; PF4, platelet factor 4.

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