Review Article

IgG-2 antibody as a Potential Target for COVID-19 Vaccine

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Abbreviations

ADE: Antibody Dependent Enhancement; COVID-19: Coronavirus Disease 2019; FcγR-IIA: FC Gamma Receptor II A; HIV: Human Immunodeficiency Virus; IFN-γ: Interferon- Gamma; IgG: Immunoglobulin G; SARS-COV-2: Sever Acute Respiratory Syndrome 2.

Abstract

The global threat of COVID-19 is still continued with no commercially available vaccine or drug yet. While the application of convalescent therapy is mostly beneficial, for critically ill patients, the detrimental effect associated with some antibodies is also reported. The immunoglobulin G (IgG) antibody in response to severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) infection is described, albeit the lack of defining whether the difference in subclasses has a beneficial or detrimental role. IgG2 has limited ability to activate innate immune cells and complement-mediated inflammation, which has been described inversely in SARS-COV-2 pathogenesis. The expansion of IgG2 is promoted by interferon γ (IFN-γ), whereas there is a low level of IFN-γ in COVID-19 patients. Therefore, this review describes the importance of targeting IgG2, with IFN-γ in minimizing the SARS-COV-2 associated inflammation, and may provide insight in the design of vaccine to COVID-19.

Key words: IgG2, IFN-γ, SARS-COV-2, COVID-19 vaccine

Introduction

From mid-1890's passive immunization has been used for the treatment of various bacterial and viral infections, when there were no anti-microbial treatments available (1). In particular, the use of convalescent sera (CS) collected from recovered individuals was recommended by world health organization (WHO) as an empirical treatment for Ebola virus by 2014 (2). This approach has also been applied, and was effective for other viral infections such as influenza A H1N1, avian influenza H5N1 and SARS-COV (3-5). Given the clinical and viral sequence homologue between SARS-COV, MERS-COV and SARS-COVID-2, it has recently been used for the treatment of severely infected patients with SARS-COV-2, the etiologic agent of COVID-19 (6). The transfusion of CS is associated with diminished viral load, serum cytokine response, length of hospital stay and death (7). One of the presumable explanations for the success is the presence of neutralizing antibodies (Nab), because an increment of virus specific Nab titer and vanishing of viremia was observed (6).

Beside this, the antibody response to some viruses including SARS-COV-2 also have detrimental role, the state of antibody dependent enhancement (ADE). Not only during infection, it has also been the most frequently mentioned challenge in the area of antibody therapy or antibody-based vaccines (8). Among the antibody types, the presence of IgG antibodies to S and N protein has been used as a diagnostic and indicative of long-term COVID-19 infection (9). In addition, the high level of these antibodies is correlated with worsen clinical outcome (10). In contrast, the majority of patients who recovered from mild SARS-COV-2 infection exhibited the high level of neutralizing antibodies (11). However, it is not clearly described whether high level IgG is correlated with protection from SARS-COV-2 infection (12). As reported from clinical trial, there are antibodies with or without ADE effect, although the classes or subclasses are not characterized (13). Remarkably, the IgG response that comprises IgG2 mostly appeared lower activation of innate immune cells, such as neutrophil, and complement pathway (14). However, the activation of these cells, and the corresponding hyper-production of cytokines, including tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6), was correlated to acute respiratory distress syndrome (ARD) and death in SARS-COV-2 infection (15). This indicates the induction of IgG2 may reduce the ADE.

Furthermore, the class-switching of IgG2 is enhanced by IFN-γ. The spike glycoprotein (S) of SARS-COV-2 is the frequent target for COVID-19 vaccines under different lines of clinical trials (16). Therefore, S based vaccines with IFN-γ encoding gene, along with ensuring the high level of IgG2 antibodies could have paramount importance for immune related disease including COVID-19. However, there is lack of data on defining the role of IgG2 to SARS-COVID-2 infection or vaccination. In this perspective, we aimed to discussed the role of IgG2 in reducing the effect of ADE, and its function towards modulating immune-pathologies associated with COVID-19.

Antibodies-based pathogenesis

Antibodies are serum proteins, capable of bind and neutralize heterogenous strains of a given pathogen with highly unstable immunogenicity (17). In addition to the clearance of free virus and block new infection, they are also involved in the expedite of infected cell clearance, as observed in vivo trial for HIV infection (18). This is also demonstrated in mouse model SARS-CoV, where antibody induces antibody-dependent cytotoxicity (ADCC) mediated lysis of infected cells mediated via interaction phagocytes (19).

The antibody therapies including convalescent sera and immunoglobulin therapy are not without drawback, and the most frequent scenario is antibody dependent enhancement (ADE). It is obvious that antibodies are supposed to control the spread and prevention of infection. Instead, the pre-existing antibodies augment internalization of the virus into the host cells, which is alternative way of immune mediated viral infection, called ADE. Many viruses including dengue, HIV, Ebola and influenza A take advantage of ADE as a means of infecting host cells. The precise mechanism of ADE is yet undefined. The most frequently mentioned mechanism is linked to the binding of virus bound antibody to FC receptors (FcRs) on the surface of immune cell, and activate complement (20).

ADE has also been observed in SARS-COV infection particularly by antibodies against S protein. The Fc portion of anti-spike antibodies have shown to activate and infect immune cells including monocytes, macrophage and B cells via FcRs, which promote inflammation and tissue injury (21). This mechanism of infection was independent of utilizing the angiotensin I converting enzyme 2 (ACE2), known receptor for SARS-CoV and SARS-COV-2 (22). These evidences indicate several factors would come into consideration to wipe out the effect of ADE while keeping antibodies

ability to neutralize the virus and protects the host. These may include the concentration, avidity, affinity and isotypes of the antibodies.

Roles of IgG2 in infectious diseases

It is well known that each isotypes of antibody have distinct effector functions. Generally, the IgG response that involves IgG2 subclasses is associated with non-inflammatory response (14). Despite that IgG2 usually participates in protection against carbohydrate antigens like bacterial capsular polysaccharide, it is also responsible for protein antigens (23). Its effector function is mediated by activating FcγRIIa (CD32) receptor, and the IgG deficiency has been linked to the susceptibility of some diseases such as Haemophilus influenzae type b (Hib) infections (24), and the fail to develop immunity when vaccination for Hib (25). Apart from the effect of antibody, the genetic variation in FcRs can affect the interaction of FcRs with IgG subclasses, and thereby alter the effector function to whether pathologic or immune protection. For instance, allelic polymorphisms in the FcγRIIa are associated with the sever course of SARS-COV (26).

In addition to bacterial infections, the role of IgG2 has been also described in viral infections such as HIV, where HIV infected children displayed selective deficiency of IgG2 with normal total IgG level (27). The high level of IgG2 is very uncommon, as its class-switching is highly inhibited by HIV (28). On the contrary, the high level of IgG2 antibodies to Gp41 was inversely correlated with HIV disease progression (29). In SARS-COV infection, a study showed that individuals with FcγRIIa that can bind only IgG2 have shown less severe as compared to individuals with FcγRIIa that bind to both IgG1 and IgG2 (26). Furthermore, although the antibodies response to SARS-COV-2 infection is not fully elucidated, various literatures reported the seroconversion of IgM and IgG, which reaches the peak level within 14 days of infection (30). It remains to be determined that the presence of these antibodies have protective role. Considering the above evidences, the IgG response that includes IgG2 might be important to consider in SARS-COV-2 infection.

IgG2 and IFN-γ in SARS-COV-2 infection

The infection with SARS-COV-2 is characterized by hyper-expression of cytokines, such as IL-6, TNF-α, IL-1β and IP-10, along with chemokines, such as IP-10, with higher levels in those who are severely ill (31-33). Viral infection usually mediated by Th1 response; however elevated Th2 cytokines, including IL-4 and IL-10 are also reported in COVID-19 patients (34). Consequently, the appearance of "cytokine storm", is a phenomenon where cytokines are produced in higher amount. The cytokine storm is linked to super-inflammatory responses, acute respiratory distress syndrome (ARD), and even death (15).

Similar to SARS-COV and MERS-COV, SARS-COV-2 provokes the seroconversion for IgG and IgM in majority of infected patients after 2 weeks of symptoms onset (30). The antibodies are produced against the spike (S) followed by nucleocapsid (N) proteins. The high level of anti-N IgG is found from non-intensive care unit (ICU) patients, while the anti-S in patients who require ICU (35). It needs to be determined whether which IgG subclasses have determinantal, of beneficial effect for SARS-COV-2 infection. In both SARS and MERS, the pre-existing anti-S IgG antibodies, particularly IgG1 and IgG3 facilitate the uptake of virus, and infection of macrophages, monocytes and B cells. These antibodies also activate complement via complement receptor and cause ADE, which has been linked to the occurrence of cytokine storm (36).

The sequencing of S protein, followed by the vaccination with immunodominant peptides has induced combination of IgG antibodies with neutralization and result ADE. Notably, from these antibodies, IgG2 exclusively belongs to only neutralization, whereas IgG1 and other subclasses with both neutralization and ADE effects (13). This indicates, unlike IgG1, IgG4 and IgG3, IgG2 response is related to the minimal effect of ADE. Therefore, although IgG2 based therapy has not been applied for coronaviruses, it might be a preferable target to get away the effect of ADE, and facilitate vaccine development or antibody-based drug therapy for COVID-19.

The production of IgG2 is enhanced by interferon-γ (IFN-γ). IFNs are the crucial innate immune defense response against viral infections, particularly in the early stages (37). However, in cases of SARS and MERS, studies have demonstrated the delayed expression and production of type I IFN, and thereby delay the overall host antiviral response (38). In SARS-COV-2, contradictory results are reported. The earlier study showed the low innate anti-viral defense including the level of type I IFN (39), while recently the hyperexpression of interferon stimulating genes is also

reported (31). Further, the very low level of IFN-I is found in critically ill patients (40), and with high viral load. More specially, the variable pattern of IFN-α, low level of IFN-γ and undetectable IFN-β and λ were observed in SARS-COV-2 infected patients (33).

Besides, early administration of IFN-I prevented lung inflammation in murine model of SARS-COV-1 infection (41). In vitro, the greater sensitivity of SARS-COV-2 to type I IFN was indicated, compared to SARS-COV (42). At cellular level, the diminished frequency of IFN-γ^+ natural killer and CD8 T-cells is reported (32). Despite the controversy, it seems clear the lack of IFN has negative impact. Therefore, the early administration of IFN may be valuable for infected patients. Additionally, targeting it in vaccine design induces IgG2, and may lead to the development of immune protection against COVID-19.

Targeting IgG2: implication for COVID-19 vaccine/immunotherapy

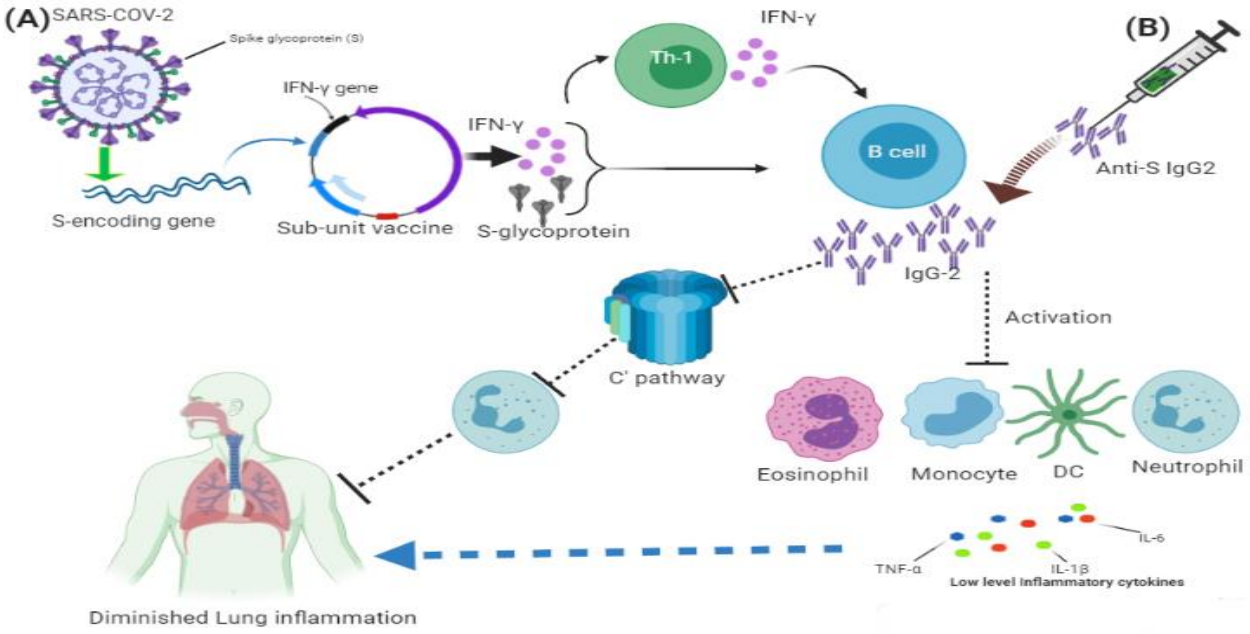
Given the above evidences, one can assume that therapies intended to IFN-γ and IgG2 might be helpful in harnessing the aggressive inflammatory reactions, as of COVID-19 disease. Among the different approaches of vaccine design are, subunit vaccine has a long history of success for viral infections including the recombinant hepatitis B vaccine (43). In addition, it has been noteworthy; the design of vaccine or immunotherapy anticipated in targeting the surface molecule, to prevent the anchoring to cellular receptor (44).

Nowadays, vaccines for COVID-19 are under fast development, which is mainly based on the experiences from the SARS and MERS vaccine. The majority of these target the S glycoprotein, and coffered better immunogenicity (16). These include the vectored recombinant adenovirus type-5 (Ad5), virus-like nanoparticles, trimerized SARS-CoV-2 S-protein. and only the receptor binding domain (RBD) of S vaccine (44-46). The full-length recombinant nanoparticle vaccine adjuvanted with Matrix M surpasses phase 1 clinical trial. Notably, it induces the high level of IgG antibodies after 35 days of vaccination. Whereas, vaccination with Ad5 also showed high level of neutralizing antibodies at 28 days (44). Despite the debate in the optimization of S-glycoprotein whether to use full length or RBD region, and the progress is still on phase I clinical, considerable efficacy has been recorded, which is primarily mediated by antibodies.

The S glycoprotein, chemically composed of protein and carbohydrate, and B cells response to carbohydrate antigens usually render the class-switching of IgG2 (23). As indicated above, the high level of IgG2 antibodies is associated with low activation of complement pathway. Inhibition of the complement activation is correlated with the reduced pathogenesis of SARS-COV, such as reduced viral load, neutrophilia in lungs and reduced systemic inflammation (47). The protection from a disease has also been recorded, from the production of IgG2 against the glycoprotein of Maedi- visna virus in sheep (48).

Moreover, compare to other subclass, the IgG2 antibody has lower affinity to FcγR-IIA, which is expressed by neutrophil, basophil, eosinophil, monocytes and dendritic cells (49). Thus, the low level of activation of these cells by IgG2 could be attributable to low inflammatory response than high activation. On the other side, the immune complex of IgG4 that binds to FcγR-IIA has shown to cause cytokine storm, with anti-CD28 IgG4 therapy (50). The notion of targeting IgG2 for treating viral infection is supported by a clinical trial, where the transfer of recombinant CD4-IgG2 antibody successfully reduced HIV viral load (51). Similarly, in pig and human model of inflammation, IgG1 therapy with a hybrid Fc portion, which consists of sequences from human IgG2 and IgG4 considerably reduced the inflammatory response (52). So, it may reasonable to consider IgG2 in designing therapies or vaccines for SARS-COV-2.

In addition to focusing on S region and targeting IgG, incorporating molecules with immune-potentiation outcome might have an extra value for the success of COVID-19 vaccines. For instance, the insertion of IFN-γ gene. It is well known the class-switching of antibodies is highly depends on the cytokine milieu. IFN-γ induces the class-switching of IgG2, at the same level of inhibition of IL-4 induced production of IgG1 (53). In randomized clinical trial, the vaccination with rFPV that encoding HIV Gag-Pol and IFN-γ results in the production of IgG2 antibodies to P24 antigen, and these antibodies exhibited control of HIV replication in HIV patients (54).



An overview of targeting IgG2 for COVID-19 vaccine: (A), the structure of SARS-COV-2 with its proteins is shown on the upper left corner, As S-glycoprotein is a frequent target, the S encoding gene, and the IFN-γ gene inserted in plasmid, is depicted, as sub-unit vaccine. The expression of these genes leads to the activation of Th1 and B cells, thus IgG2. **(B)**, The adoptive transfer of anti-S IgG2 is shown on the upper right corner, as needle containing antibodies. The expansion of IgG2 reduces activation of immune cells like monocytes, neutrophil, eosinophil and DC, and their cytokine expression. IgG2 also block the activation of complement mediated recruitment of the neutrophils in to the lung. All these are attributable to low inflammatory responses and the protection of the lung inflammation. The picture is created at https://biorender.com/

Concluding marks

Overall, the effectiveness of clinical trials with vaccine or immunotherapy for COVID-19 may be enhanced by means of incorporating genes encoding IFN-γ, while keeping the high level of IgG2 antibody. More specifically, vaccine induced IgG2 antibody needs to be assessed in the process of clinical trials for S glycoprotein-based SARS-COV-2 vaccines. The limited effector functions of IgG2 could improve the safety of the vaccine, by reducing ADE. Moreover, the adoptive transfer of anti-S IgG2 may contribute to the prophylaxis and/or recovery of COVID-19 patients. Although targeting the S glycoprotein has already been established, experimental study on the enrichment of IgG2 class-switching by IFN-γ and/or other molecules is warranted when designing vaccine for SARS-COV-2.

Author contributions

HA conceive the idea. HA, MK, SG, and WH analyze and made the figure. All authors participated in all steps of the manuscript preparation.

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Conflict of interests

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