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Review Article

Neutralizing Antibodies to COVID-19 Virus: Merits and Limitations

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS COV 2), a newly emerged coronavirus swept over globally causing coronavirus disease 2019 (COVID -19) pandemic. Immunological response to SARS COV 2 is a major focus of discussion at present, from the perspectives of clinical presentation in patients, and prophylactic and therapeutic measures against the disease. A good understanding of the immunopathogenesis of the condition, and host response to the pathogen is pertinent for guiding effective treatment. In the current review, we discuss the essential concepts of neutralizing antibodies against SARS COV 2, elaborating on their mechanism of action, and their association, if any, in limiting the progression of the disease vis-à-vis in causing disease severity.

Keywords: *COVID 19, SARS COV 2, ACE2, CDC*

Introduction

COVID-19 caused by severe acute respiratory syndrome Coronavirus-2 (SARS-COV-2) is a global challenge to public health (Callaway *et al*, 2020). This newly emerged virus is closely related to the SARS-COV that was responsible for the severe acute respiratory syndrome epidemic which popped up in 2002-2003.

The clinical spectrum due to COVID-19 virus infection is often varied; starting from asymptomatic or mild infection to severe pulmonary and extra pulmonary manifestations (Cohen, 2020). In severe cases, pathogenic mechanisms like inflammation associated with thrombo-embolic phenomena, extensive dysregulation of the immune system and renin-angiotensin system are associated with multi-organ failure (Cohen, 2020; Wrapp *et al*, 2020). In all these different spectra, the immune response of the host gives a variable picture. It is not yet fully clear, whether the immune response plays an important role in defining the severity. Thus it is important to understand the underlying relationship between the degree of host immune response to COVID-19 virus and the inconsistent clinical picture in terms of severity.

Immune Response against SARS-COV-2

The outer surface of SARS-COV-2 contains the spike (S), matrix(M), and envelop (E) proteins. The S protein plays an important role in the pathogenicity and is a critical target against which antibodies specific to SARS-COVID-2 are produced. Like all other coronaviruses, the S protein is a large trans membrane molecule on the virus surface, that has vital role in binding of the virus to host cell receptor and entry of the virus inside the host cell. S protein has two domains, namely S1 and S2. The receptor binding portion is located within the S1 domain which allows the virus to dock to the cellular receptor, which is known as, angiotensin converting enzyme 2 (ACE2) receptor (Wajnberg *et al*, 2020; Wu *et al*, 2020), Following this attachment, there is fusion of viral and host membranes mediated by the S2 subunit. These events facilitate entry of genomic RNA into the host cell cytoplasm (Arvin *et al*, 2020).

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Apart from ACE-2, other receptors taking part could be TLRs (toll like receptors), otherwise called pathogen recognition receptors (PRRs), which specifically recognize surface molecules on the microorganisms named as pathogen associated molecular patterns (PAMP). TLR-4, for example, recognizes the S protein on SARS-COV-2 and induces the production of proinflammatory cytokines. It could be possible that early T cell response may be protective. Such innate immune response may contribute to viral clearance. On the other hand, adaptive immune response may eliminate virally infected cells, or may cause virus neutralization. Removal of virally infected cells could be mediated by way of antibody dependent cell mediated cytotoxicity (ADCC) or complement mediated cytotoxicity (CDC) (Van *et al*, 2019; Lu *et al*, 2017).

Another very important mechanism of virus clearance is the host neutralizing antibody response. Neutralizing antibodies, once produced, bind to the free virus, and prevent it from infecting the cells (Overbaugh & Morris, 2011), by way of preventing conformational changes needed for the fusion of the virus with the host cell membrane.

To understand the interaction between neutralizing antibodies and SARS COV-2, we have to again recall virus attachment with the host cell. As has been mentioned above, it is undoubtedly true that SARS COV-2 adheres to the host cell with the aid of spike (S) glycoprotein, which has got S1, and S2 subunits that need to be cleaved in order to allow viral fusion with the cell membrane, followed by virus entry and replication inside the cell. And it is also known that ACE-2 receptor located on a wide variety of host cells is the primary target of the receptor binding domain (RBD) of S1 subunit of SARS COV-2. This would imply that disruption of the RBD-ACE2 interaction would block SARS COV2 cell entry. Therefore, RBD has been suggested as the main target of neutralizing antibodies against SARS COV2 (Ju *et al*, 2020).

Hence , SARS COV2 neutralization encompasses the following aspects ; (a) blocking the interaction of S glycoprotein with ACE2, (b) blocking the binding of coreceptors which is a subsequent step essential for the avid interaction of the virus with host cell, following the binding with ACE2, and (c) inhibition of conformational changes in the transmembrane S2 , thereby not allowing the virus internalization

Neutralizing Antibody Response in COVID-19

In natural infection, most patients infected with SARS COV 2 develop increasing titers of neutralizing antibody between day 14-20 post infection, that may last upto 6-8 months, after which the titers start declining (Altawalah, 2021) . Patients who recovered from severe disease had higher neutralizing antibody levels than those who had mild or asymptomatic infection. This may be due to the prolonged stimulation of B cell receptors or due to higher production of interferon Y (IFN Y) in the course of severe disease (Schreiber, 2020). As is well known, IFN Y induces the activation of dendritic cells, thus allowing these cells to present antigen to virgin CD4 and CD8 T cells. CD4+ T cells upon activation stimulate production of specific antibodies by B cells, while CD8+ T cells behave as cytotoxic cells (Schreiber, 2020).

Neutralizing Antibodies after Vaccination

Although neutralizing antibody production and their effects were worked out for all approved vaccines, the specific assays gave changing picture; and thus were not comparable. Most of the studies, though reported good humoral response following few days post vaccination, the antibody response showed a trend to decrease over time. However, memory B cells can rapidly deploy more antibodies on a re-exposure to virus and this is also true for T cells, which can recognize already infected cells (Altawalah, 2021).

However, one concern that threatens the vaccine induced neutralizing antibody response is the emergence of SARS-CoV variants with antibody escape mutants. Even then, based on some observational studies, it was concluded that the current vaccines still provide clinical benefits against most strains by effectively reducing COVID-19 disease severity (Schreiber, 2020).

Mechanism of action of Neutralizing Antibodies

Before discussing about the mechanism of action of neutralizing antibodies, it is important to know the pathogenesis of COVID-19 for a clear understanding of their mechanism in neutralizing the virus.

As is known, SARS-CoV-2 attaches to the host cell with the aid of S glycoprotein present on its envelop. S glycoprotein is composed of two subunits; S1 and S2 that have to be cleaved to allow viral fusion with the host cell membrane, entry into the cell and initiation of replication process. Protease

cleavage at the S2 site frees the fusion peptide from the new S1 N terminal region. This fusion peptide is inserted into the host membrane and facilitates the pulling of the viral and host cell membrane to close proximity , leading to membrane fusion (Duan, 2020).

ACE2, the enzyme present on the outer surface of a wide variety of cells, is the primary host cell target of the receptor binding domain of S1 subunit. This suggests that the disruption of the RBD ACE2 interaction would block SARS CoV2 cell entry, and therefore, RBD has been suggested as the main target of neutralizing antibodies against SARS-CoV2.

Neutralization mechanisms refer to the early steps in the viral replication cycle being blocked. The enveloped virus enters the host cell by bridging the receptor on the cell surface. In contrast, nonenveloped viruses enter through cell membrane lysis or by creating pores in the membrane. The process of viral fusion (nonenveloped/enveloped) with the host cell membrane requires particular conformational changes in the viral protein that a low pH can cause in endosomes.

Considering the above, it could be presumed that neutralization could be achieved via the following mechanisms

1. Binding of neutralizing antibody to virus protein epitopes that interact with host cell co-receptor which are the key elements to viral infection.
2. Binding of neutralizing antibody to viral epitopes that are not essential for host cell receptor binding, but are necessary for conformational changes needed for membrane fusion.

All the above mechanisms are in relation to inhibition of entry of virus into the host cell. The other mechanism of neutralization could occur, when the virus is inside the endosome, where the antibodies to viral surface proteins inhibit the necessary changes for the fusion of the viral membrane causing neutralization (post-internalization neutralization).

In certain instances, the virus can escape antibody neutralization per se. However, the Fc fragments of the antibodies exert mechanisms that help the elimination of the virus such as ADCC, CDC, which are effector mechanisms rather than neutralization mechanisms. These mechanisms also require Fc interaction with Fc receptors present on the surface of some immune cells.

Notwithstanding the afore mentioned encouraging reports on the effects of neutralizing antibodies, there are yet some controversies on the precise role of these antibodies in so far as the clinical outcomes in patients are concerned. For example, it is not clearly known whether the balance tilts in favor of immune protection or progression of immunopathogenesis. In a recent study from India (Srivastava *et al*, 2021), the authors, after estimating the antibody titers in patients with different clinical presentations, suggested that irrespective of fatal outcome, progression to disease severity and fatality were predominantly associated with induction of early and high levels of neutralizing antibodies.

In summary, therefore, it seems quite probable that there is a strong association of neutralizing antibody titers with disease severity as documented by studies conducted on certain sectors of population in India and other parts of the world (Srivastava *et al*, 2021; Okba *et al*, 2020). These observations could bring up an important issue on the critical role of these antibodies , whether these are involved in immunopathology or simply reflect a different cause or marker which is currently unknown. Although correlates of protection against COVID-19 are not yet available, recent updates on success in plasma therapy in humans and animal models (Duan *et al*, 2020; Rogers *et al*, 2020) suggested a definite role of antibodies in protection. Data related to disease specific cellular immunity in general and severity of clinical manifestations in particular, are lacking. Hence, in depth studies relating to both areas of immunity in different disease formats are urgently required, keeping in view the global immunization strategies and programs.

Conclusion

Current literature review, indicate that there can be higher neutralizing antibody levels in the majority of severe COVID-19 disease. However, it is not clearly known whether these antibodies are effective in virus clearance, or in disease progression. Information on the onset, peak and persistence of these antibodies is useful in evaluating host immunity against COVID-19 virus. Thus, before the introduction of plasma therapy which is being advocated by many institutional groups, it is strongly recommended that convalescent sera from donors recovered from severe COVID-19, should be titrated, using a

sensitive neutralization assay. This is all the more important, considering the constantly evolving virus with the emergence of multiple new mutations.

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