MINI-REVIEW

A short review on antibody therapy for COVID-19

G. Venkat Kumar[1], **V. Jeyanthi**[2] **and S. Ramakrishnan**[3]

1) *Department of Biotechnology, Ponnaiyah Ramajayam Institute of Science and Technology, Thanjavur, 613403,* 2) *Department of Biotechnology, SRM Arts and Science College, Kattankulathur, Chengalpattu District, 603203, Tamil Nadu, India and* 3) *Structural Biophysics Laboratory, Center for Cancer Research, National Cancer Institute, Frederick, MD 21702, USA*

Abstract

The beginning of the novel SARS-CoV-2 human coronavirus in Wuhan, China, has triggered a worldwide respiratory disease outbreak (COVID-19). By April 07, 2020, SARS-CoV-2 has affected more than 1.36 million people worldwide and caused more than 75,900 deaths. To date, the anti-malaria drug hydroxychloroquine found to be a treatment option for SARS-CoV-2. In addition to supportive treatment, such as oxygen supply in moderate cases and extracorporeal membrane oxygenation in critically ill patients, unique medications for this condition are also under investigation. Here we reviewed the antibody therapy might be an immediate strategy for emergency prophylaxis and SARS-CoV-2 therapy.

Keywords: Convalescent plasma therapy, monoclonal antibody therapy, receptor binding domain, SARS-CoV-2, spike protein
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Corresponding author. G. Venkat Kumar, Department of Biotechnology, PRIST deemed to be University, Thanjavur, 613403, India. Mobile No. +91 9790111875.
E-mail: venki89.kumar@gmail.com

Introduction

The coronavirus is a family of viruses that can cause a range of illnesses in humans with the common cold and more severe forms like Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) which are dangerous. The first identified severe infection caused by a coronavirus arose with the 2003 SARS epidemic in China [1,2]. A second outbreak of severe infection began in 2012 in Saudi Arabia with the MERS [3,4]. The third outbreak of severe illness caused by the novel SARS-CoV-2 coronavirus (COVID-19) that emerged in the Wuhan city, China, is pandemic and spread to more than 200 countries [5–7]. More than half a million people worldwide have been infected by the novel SARS-CoV-2 coronavirus. As of 07 April 2020, there have been at least 75,900 confirmed deaths and more than 1.36 million affected people worldwide [7]. Every hour the numbers have been increasing, with the United States recording the maximum positive cases in the world. Italy, Spain, Germany, France in Europe continue to be the most affected, with more than 16,000, 13,000, 1000 and 8000 deaths respectively till April 7, 2020 [7]. Currently, the anti-malaria drug hydroxychloroquine found to be a treatment option for COVID-19. A non-randomized study in a small sample size from France shows that the hydroxychloroquine plus azithromycin treatment reduced the viral load in COVID-19 patients [8]. Following this study, another group from France reported that the hydroxychloroquine plus azithromycin have no strong antiviral activity in severely affected COVID-19 patients [9]. Clinical studies from China show that the hydroxychloroquine reduced the risk of progression to severe illness in COVID-19 patients [10,11]. Chloroquine and hydroxychloroquine are highly toxic in overdose, leading to the rapid onset of central nervous system toxicity (seizures and coma) and cardiovascular failure [12]. Hydroxychloroquine received an emergency use authorization from the FDA as of 3 April 2020, but there are still a lot of questions about optimal doses and treatments for COVID-19.

Coronavirus virions are spherical with a diameter of approximately 125 nm as revealed by cryo-electron

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tomography and cryo-electron microscopy [13]. The corona viral genome encodes four main structural proteins namely the surface spike (S) glycoprotein, the membrane (M) protein, the small envelope (E) glycoprotein, and the nucleocapsid (N) protein. All these proteins are required to provide the structure of complete viral particles called virion [14,15]. The spike protein is ~180KD glycoprotein which is present on the surface of the virus. It is crucial for the entry of coronavirus into the host cell. It contains two subunits namely S1and S2. The S1 subunit binds to the receptor on the surface of the host cell whereas S2 subunit mediates the cell membrane fusion [15,16].

Major research has focused on identifying antibody molecules targeting spike proteins as they mediate viral entry, and their potential to induce host immune responses and cause protective antibody responses in infected individuals. The drug manufacturer Takeda Pharmaceutical Co. from Japan is preparing an antibody mixture called TAK-888 from the blood plasma of recovered SARS-CoV-2 patients to develop a new drug. Similarly, Vir Pharmaceuticals from California testing antibodies obtained in 2003 from the serum of former SARS patients can neutralize SARS-CoV-2. Vir is also collaborating with China-based company WuXi Biologics, to develop serum therapy that could be useful as first aid for high-risk patients. In this mini-review, we highlight the therapeutic intervention that may have the potential for prophylaxis and SARS-CoV-2 therapy.

Convalescent plasma therapy

Convalescent plasma therapy can be considered as one of the way to control the SARS-CoV-2 pandemic. Researchers suggest that this technique is decades old approach which was used early 1930s and the theory is simple. The person who has recovered from viral infection blood is collected and serum is separated. The serum which contains antigen raised antibodies was injected into a newly infected person to combat the virus antigen. Antibodies are proteins that are produced by B cells of the immune system. They are able to bind to "Antigen" a specific molecule present on the pathogen that invades the Human system and directly neutralizes or activates an immune response [17,18]. Based on the previous studies and reports in treating other coronaviruses such as SARS and MERS, the early administration of convalescent plasma from patients that contains raised antibodies can possibly reduce the spreading of infection and mortality [19–22]. Shen et al. reported that the convalescent plasma transfusion may be beneficial in the treatment of critically ill patients with SARS-CoV-2 infections. After getting approval from the ethical committee, Shenzhen, Third People's Hospital, they administrated convalescent plasma containing neutralizing antibodies to 5 critically ill patients with SARS-CoV-2. Among those 3 patients discharged from the hospital and 2 patients under an incubation period of 37 days [23]. Casadevall and Pirofski highlighted the risks of passive administration of convalescent sera, which falls into two categories, serum disease and antibody-dependent enhancement of infection. Serum disease is those associated with the transmission of other blood infections, whereas the antibody-dependent enhancement is the theoretical concern that antibodies to one form of coronavirus could enhance infection to another viral strain [24]. Hence, it is important to identify the human monoclonal antibody that neutralizes SARS-CoV-2. Those cross-neutralizing antibodies can target a common epitope on these viruses and offers potential for the prevention and treatment of COVID-19.

Monoclonal antibody therapy

Targeting the trimeric spike (S) glycoproteins on the SARS-CoV-2 surface that mediate entry into host cells can be neutralized by monoclonal antibodies. The SARS-CoV-2 (SARS2-S; 1273 residues, Wuhan-Hu-1 strain) and SARS-CoV (SARS-S, 1255 residues, Urbani strain) spike proteins are 77.5 % identical to the primary amino acid sequence, are structurally very similar and usually bind to the human angiotensin-converting enzyme 2 (ACE2) protein as the host receptor [25]. Tai et al. identified that the receptor-binding domain (RBD) in SARS-CoV-2 S protein bound strongly to human and bat angiotensin-converting enzyme 2 (ACE2) receptors. Research reports stating that the SARS-CoV-2 RBD exhibited a significantly higher binding affinity to the ACE2 receptor than SARS-CoV RBD. This could block the binding of SARS-CoV-2 RBD to ACE2-expressing cells, thus constraining their infection to host cells [26]. Yushun Wan and his colleagues also reported that the sequence of SARS-CoV-2 which is similar to SARS-CoV, including its receptor-binding motif (RBM) that directly contacts ACE2, strongly signifying that SARS-CoV-2 uses ACE2 as its receptor [27]. Andersen and collaborators have used the sequencing data published by Chinese scientists who sequenced the genome of SARS-CoV-2. They explained two notable features of the SARS-CoV-2 genome. The first one is on the basis of the structural and biochemical experiments; SARS-CoV-2 performs to be enhanced for binding to the human receptor ACE2. The second thing is that the SARS-CoV-2 spike protein has a functional polybasic furin cleavage site on the S1–S2 boundary with O-linked glycan around it. Their functional activities are

unknown. Studies show that the most variable part in the SARS-CoV-2 is the RBD in the spike protein. Nearly 6 RBD amino acids L455, F486, Q493, S494, N501, and Y505 are shown to be critical for binding to ACE2 receptors [5]. Similarly, Hoffmann et al. demonstrated that SARS-CoV-2 uses the ACE2 receptor for entry and the TMPRSS2 serine protease for S protein priming [28]. Ou et al. demonstrated that SARS-CoV-2 S protein entry on 293/hACE2 cells is mainly mediated through endocytosis and that PIKfyve, TPC2, and cathepsin L are critical for virus entry [29]. Sui J et al. reported that an anti-S1 human monoclonal antibody 80R with a nanomolar affinity that potently neutralizes SARS-CoV infection by binding to the conformational epitope (amino acid residues 426-492) on S1 fragment of SARS-CoV and efficiently inhibits the interaction of S1 subunit protein with cellular receptor ACE2. Zhongyu Zhu reported that the m396 and S230.15 human monoclonal antibodies effectively neutralized GD03 strain isolates from the SARS first outbreak. Their antibodies also protected mice tested with the Urbani or recombinant viruses bearing the GD03 and SZ16 spike (S) glycoproteins. Sequence analysis and mutagenesis data showed that m396 might neutralize all zoonotic SARS-CoV isolates [30]. Brink et al. demonstrated that CR3014 reduced replication of SARS-CoV in the lungs of infected ferrets abolished shedding of SARS-CoV in pharyngeal secretions, and completely prevented the development of virus-induced macroscopic lung pathology. CR3014 binds to the amino acid residues 318-510 and amino acid residue 565 with high affinity on S1 fragment of SARS-CoV and blocks the interaction of S1 subunit protein with ACE2 [31]. Tian et al. reported that the RBD of SARS-Cov-2 differs largely from the SARS-CoV at the C-terminus residues. Their results implied that SARS-CoV specific neutralizing antibodies such as m396, CR3014 that target the receptor-binding domain of SARS-CoV ineffective to bind SARS-Cov-2 spike protein. Their research report stating that the antibody CR3022 completely neutralized both the wild-type SARS-CoV and SARS-Cov-2 at a concentration of 23.5 μg/ml. Tian et al. suggested that CR3022 can be used as a potential therapeutics, alone or in combination with other neutralizing antibodies, for the prevention and treatment of SARS-Cov-2 infections [32]. Chunyan Wang et al. were first to report that 47D11 (human) monoclonal antibody that neutralizes SARS-CoV-2. Research reports declaring that the 47D11 binds a conserved epitope on the spike receptor-binding domain and cross-neutralize SARS-CoV-2. The cross-reactive nature of 47D11 shows that the antibody is more possible to target the conserved core structure of the S1B receptor binding domain. Hence these neutralizing antibodies can reduce the course of virus action in the host or defend an uninfected host that is exposed to the virus [33]. Therefore, targeting the RBD amino acid in SARS-CoV-2 treatment will help scientists to develop effective therapeutic agents to treat and prevent this infection.

RBD mutations enhance the structure stability and infectivity

Amino acid mutations and recombination in RBD of different host coronaviruses are considered to be associated with host adaptation and infection across species. Recent research indicates that recombination and insertion of a cleavage site in the RBD may increase the infectivity and replication capacity of the virus [34]. Ou et al. analyzed RBD mutation worldwide and reported 10 mutants identified under high positive selection pressure during spread. They investigated the SARS-Cov-2 isolates collected from different parts of the world and compared the RBD mutations with the prototype Wuhan-Hu-1 strain. They identified that the two groups of amino acid mutations in the SARS-CoV-2 RBD domain: the "similar affinity" group (F342L, R408I) and the "higher affinity" group (N354D D364Y, V367F, W436R). The "higher affinity" group RBD mutations under the positive selective pressure enhanced the infection efficiency of the SARS-CoV-2 [35]. Hence, epidemiology data and mutation surveillance are very important to reveal more exact spreading routes of the pandemic SARS-CoV-2. Further, the RBD mutated strains in other countries need great consideration to find the therapeutic.

Conclusion

In conclusion, it is very essential to isolate the raised antibodies by SARS-CoV-2 disease recovered patient's regional wise. Raised antibodies should be produced on a large scale for the treatment of SARS-CoV-2 patients. These antibodies could provide an immediate strategy for emergency prophylaxis and SARS-CoV-2 therapy, while alternative and more time-consuming development of vaccines and new drugs are underway. As a result, SARS-CoV-2 neutralizing antibodies may be used to prevent infection in people exposed to SARS-CoV-2, such as hospital staff caring for suspected SARS-CoV-2 patients, and may also be used for early treatment of infected individuals to prevent the onset of serious SARS-CoV-2 disease and to reduce the chance of spreading the virus to exposed individuals.

Conflict of Interest

None.

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