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Antibody Fragment VH ab6: Universal Neutralizer for SARS-CoV-2 Variants

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Abstract

The recent COVID-19 outbreak demonstrated how ineffectively may face newly emerging viruses. Antiviral drugs are the most effective way to combat the COVID-19 pandemic. However, their rapidly declining immunity and a large population of unvaccinated people will provide a recombinant ground for the virus's spread and the era of novel variants, posing a continuous threat of infection for vulnerable groups with inadequate immune responses. In order to treat infected people, effective treatments must be developed. In this short note, discuss a breakthrough in engineered antibody fragment that could be neutralized the shield against the battle of the continuous waves of SARS-CoV-2 variants as well as future other viral infections.

Keywords: SARS-CoV-2 • Omicron variants • COVID-19 Variants of Concern (VOCs) • VH ab6

Introduction

The recent COVID-19 outbreak demonstrated how ineffectively we are for newly emerging viruses [1,2]. Antiviral drugs are the most effective way to combat the COVID-19 pandemic. However, their rapidly declining immunity and a large population of unvaccinated people will provide a recombinant ground for the virus's spread and the era of novel variants, posing a continuous threat of infection for vulnerable groups with inadequate immune responses. In order to treat those who become infected, effective treatments must be developed [3].

The SARS-CoV-2 spike protein's precise structure is well characterized, and because this protein is essential for viral infection, its Receptor Binding Domain (RBD) has been a primary target for therapeutic antibody discovery. SARS-CoV-2 is an RNA virus with a high genetic drift, especially when subjected to the selective pressures of actively administered preventive vaccinations and neutralizing antibody; the use of antibodies is considered to be a critical strategy for efficient COVID-19 management [4]. Furthermore, SARS-CoV-2 can trigger an overzealous immune response, leading in a cytokine storm that accelerates disease severity. Antibodies to counteract cytokine storms are also being researched as COVID-19 therapies [5].

It's well known that antibodies are "Y"-shaped proteins that the immune system produces to detect antigens, which can be proteins from invading pathogens, or any abnormal cells [6]. Each antibody identifies and binds to its specific antigen, provoking an immune response that neutralizes the antigen-displaying cells.

Description

The antibodies may suppress viral replication through neutralization but might also participate in COVID-19 pathogenesis through a process termed antibody-dependent enhancement [7]. In viral infections, Antibody dependent enhancement has been shown to occur *via* two different pathways: Elevated antibody mediated virus uptake into Fc gamma receptor IIa (FcRIIa)-expressing phagocytic cells, resulting in higher viral infection and replication, or excessive antibody Fc-mediated effector functions, resulting in increased inflammation and immunopathology [8]. But the bright side, Clinical studies indicate that antibody therapies can reduce the number death and hospitalizations in people with moderate or mild COVID-19 [8,9].

Neutralizing antibodies (Nabs) frequently identi ies unique, occasionally non-overlapping epitopes in the Receptor Binding Domain (RBD) of the Spike (S) protein of SARS-CoV-2 [10]. Only a fragment of these antibodies can inhibit viral entry, typically by impairing with the viral S protein's binding to the cellular receptor Angiotensin Converting Enzyme 2 (ACE-2) [11]. The discovery of new SARS-CoV-2 Omicron variants with mutations in the viral S protein raised concerns about the efficacy of current vaccinations and therapeutic antibodies [12,13]. Furthermore, multiple independent investigations have found that mutant versions are

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largely or totally resistant to therapeutic antibodies that have been approved for use in an emergency [14].

Antibodies attach to a virus in a very speci ic manner, like a key going into a lock, but when the virus mutates, the key no longer its. Therefore, researchers have been looking for “master key”; these are antibodies that continue to neutralize the virus even after extensive mutations. The “master key” identi ied in this study is the antibody fragment VH ab6. Which was shown to be effective against the alpha, beta, gamma, delta, kappa, epsilon and Omicron variants?The fragment VH ab6 neutralizes SARS-CoV-2 by attaching to the S protein and blocking the virus from entering human cells [15].

Recently, researchers discovered a novel antibody “master key” that could neutralize all COVID-19 variants (Figure 1); these include the recently emerged BA.1 and BA.2 Omicron. Researchers used cryo-Electron Microscopy (cryo-EM); this technique allows them to reveal the atomic-level structure of the vulnerable spot on the virus’ spike protein. The study concluded that an antibody fragment called VH ab6 is able to attach to this site (grey in Figure 1) the SARS-CoV-2 spike protein and neutralized each major variant.

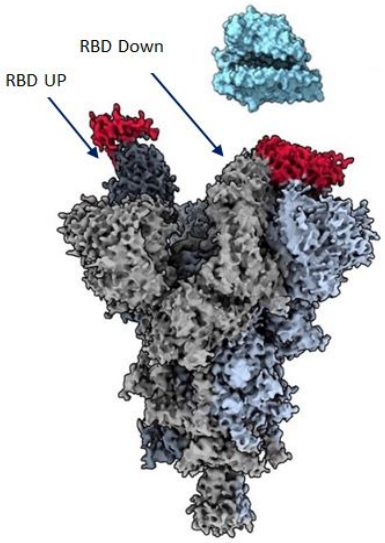

Figure 1. VH ab6 antibody fragment (red) binds to the weak site on the SARS-CoV-2 spike protein (grey) to prevent the virus from attaching with the human ACE2 cell receptor (Cyan).

VH ab6 is a phage display derived antibody with the unique molecular property of having higher RBD affinity as a monomeric fragment versus a bivalent fusion [16]. And it has recently been demonstrated to be robust to various circulating RBD variants [17]. The ab6 pro ile contains many RBD residues and corresponds with that of ACE2, indicating that ab6 competition is used to neutralize ACE2. Ab6 can binds to the inner RBD face and contacts the receptor binding motif, allowing ACE2 competitive pressure, close to the receptor-binding domain-4 antibody community, which, remarkably, did not include any widely neutralizing antibodies; or are non-ACE2 competing antibodies that bind the outer RBD face [18].

The Complementarity Determining Region 1 (CDR1) and CDR3 loops of ab6 occupy positions that result in confrontations with ACE2 when superposed with an ACE2 bound RBD, with the CDR3 region actively interacting with the amino terminal helix of ACE2 for RBD binding contacts, although the CDR1 loop poses a steric conflict with the second helix of ACE2 without creating RBD contacts.

Conclusion

COVID-19 is a highly adaptable virus that has evolved to evade most existing antibody treatments; as well as much of the immunity conferred by vaccines and natural infection. This study reveals a weak site that is largely conserved across variants and can be neutralized by an antibody fragment. Antibody fragments are interesting therapy approaches because they penetrate deeper into tissues than traditional mAbs. It set the stage for the design of pan-variant treatments that could potentially help a lot of vulnerable people.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical Approval Statement

N/A.

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