Monoclonal Antibodies as Potential Treatment Drugs for Nsp15 and 3CL^pro Proteins

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Selected monoclonal antibody molecules were conducted using the antibody-antigen docking mode, as well as the antibody-antigen docking approach. The objective of the study was to check the effects of Cetuximab COVID-19 proteins (Nsp15 and 3CLpro) by using antibody-antigen docking mode, as well as the antibody-antigen docking approach. The results of molecular docking revealed that Cetuximab, a cancer-fighting antibody, ranks first among antibodies to both COVID-19 proteins (Nsp15 and 3CLpro). In cetuximab-3CLpro and cetuximab-Nsp15 complexes, the antigen interacts with both antibody chains, H and L. According to the findings, Cetuximab can be added to the COVID-19 treatment protocol, which may have the desired effect of inhibiting viral replication and decreasing mortality by targeting COVID-19 proteins (Nsp15 and 3CLpro). Validation of these computational findings will require additional in vitro and in vivo research, which can be considered as a contribution in the field of biotechnology.

INTRODUCTION

Monoclonal antibodies originate from a single parent clone of a single B cell; therefore, they recognize only one epitope per antigen and are less likely to cross-react with other proteins as compared to polyclonal antibodies [1]. The B cells, which produce specific monoclonal antibodies, are immortalized by fusion with the hybridoma cells, allowing identical monoclonal antibodies to be produced over a long period of time [2]. Generally, the monoclonal antibodies are produced ex-vivo by mixing myeloma cells with mouse

spleen cells immunized with the target antigen to form a hybridoma [3]. Polyclonal antibodies are produced by various B cells and recognize multiple epitopes on the same antigen [4].

Monoclonal antibodies are increasingly employed in the treatment of various cancers and immunological disorders [5, 6]. Their immunotherapeutic efficacy is based on three main mechanisms: (1) Antibody activation inhibits factors and receptors that unlock signal pathways by dividing cancer cells and angiogenesis. (2) Antibody-dependent cell cytotoxicity consisting of target monoclonal antibodies binding to specific tumor-related antigens, and (3) Complement-dependent cytotoxicity by complement

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activation [6-8]. Even though monoclonal antibodies have different modes of action, they have all become part of the standard treatment protocol in combination with chemotherapy and/or radiotherapy [9]. Monoclonal antibodies are laboratory-made proteins that imitate the ability of the immune system to destroy dangerous antigens like viruses [10].

The coronavirus disease 2019 (COVID-19) pandemic caused by SARS-CoV-2 virus has massively affected the whole world over the last few years [11]. SARS-CoV-2 is an enveloped β-coronavirus whose viral envelope is coated by spike (S) glycoprotein, which mediates host cell binding and entry [12,13]. Most patients with SARS-CoV-2 infection (without advanced age or comorbidity) recover without treatment at variable rates, indicating the need to research treatments in vulnerable patients who are most likely to benefit from early therapy [14,15]. Several SARS-CoV-2 monoclonal antibodies have reached clinical trials [16]. Bamlanivimab is one such neutralizing IgG1 monoclonal antibody that has been given emergency use approval (EUA) for use against SARS-CoV-2 infection [17]. It directly targets SARS-CoV-2 glycoprotein by binding to the glycoprotein's receptor-binding domain and is designed to neutralize the virus by inhibiting viral attachment and entry into human cells [18]. This study aims to display and assess the potential inhibitory activity of specific monoclonal antibody molecules against SARS-CoV-2 (3CLpro and Nsp15), with the hope of identifying new drugs to combat the new pandemic coronavirus disease (COVID-19).

METHODOLOGY

The structures of coronaviral targeted proteins included pp1ab from SARS-CoV-2 (chain A of PDB ID: 6LU7 [19]; 3CL^{pro} protein) and (chain B of PDB ID: 6VWW [20]; Nsp15 protein). Selective monoclonal antibody compounds obtained from the DrugBank database (https://go.drugbank.com/) are listed in Table 1.

UCSF Chimera 1.15 [21] was used for modeling and analysis processes. All mismatched residues were corrected to the right amino acids. Ligands and solvent molecules were removed from the receptor (or antigen) structures. Missing hydrogen atoms were added, Dunbrack 2010 rotamer library [22] was used for building incomplete side chains, Gasteiger method [23] was used for assigning charges using Antechamber [24], and the AMBER14SB force field [25] was used for standard residue parameterization. The default AMBER force field parametrization is to fulfill the physiological pH condition (*i.e.*, pH = 7.4) in each receptor. That is, Asp and Glu residues were deprotonated, Arg and Lys residues were protonated, and His residues kept neutral. Molecular docking was conducted on the ClusPro server [26-30]using the antibody-antigen docking mode, and ROSIE server [31-36] using the antibody-antigen docking approach.

RESULTS AND DISCUSSION

The objective of the study was to check the effects of Cetuximab COVID-19 proteins (Nsp15 and 3CLpro) by using the antibody-antigen docking mode, as well as the antibody-antigen docking approach. We explored Cetuximab can be added to the COVID-19 treatment protocol, which may have the desired effect of inhibiting viral replication and decreasing mortality by targeting COVID-19 proteins (Nsp15 and 3CLpro).

Table 1. Selected Monoclonal Antibodies Used in the Docking Study

	DB00054	6V4P	H	Anticoagulant	[37]
Adalimumab	DB00051	4NYL	H, L	Anti-inflammatory	To be published
Alemtuzumab	DB00087	1CE1	H, L	Anticancer	[38]
Atezolizumab	DB11595	5XXY	H, L	Anticancer	[39]
Bevacizumab	DB00112	6BFT	H, L	Anticancer	To be published
Cetuximab	DB00002	6AXP	H, L	Anticancer	[40]
Eculizumab	DB01257	5I5K	H, L	Anticoagulant	[41]

Recent studies displayed that sundry monoclonal antibodies (mAbs) are forthright against the S protein receptor binding domain of SARS-CoV-2 and could ban the transmission of Covid-19 infection and defend subjects from advanced severe conditions [16,42].

Among the widely used tools for protein–protein docking is the ClusPro server [26-30] and the ROSIE server [31-36]. The ClusPro server uses the global search method for protein-protein docking, which is useful when the binding site is unknown, whereas the ROSIE server uses the local search method for protein-protein docking; thus, the binding site must be known. In our study, the original PDB structures of the antibodies and antigens have been entered into the ClusPro server, and the outputs of the ClusPro server, after determining the binding site, have been entered into the ROSIE serve. The antibody-antigen docking results are shown in Table 2.

For the coronaviral3CL^{pro} protein, the antibodies are ranked according to the ClusPro cluster size as follows:

Abciximab > Eculizumab > Adalimumab > Alemtuzumab > Bevacizumab > Cetuximab > Atezolizumab. On the ROSIE server, the order of the antibodies according to rosetta energy unit (REU) at the interface is as follows: Cetuximab < Eculizumab < Atezolizumab < Alemtuzumab < Adalimumab < Bevacizumab. The antibody Abciximab has been excluded from the list because its structure does not have the L chain.

On the other hand, and for the coronaviralNsp15 protein, the antibodies have the following order according to the ClusPro cluster size: Cetuximab > Alemtuzumab > Abciximab > Eculizumab > Adalimumab > Bevacizumab > Atezolizumab. On the ROSIE server, the order of the antibodies according to rosetta energy unit (REU) at the interface is as follows: Cetuximab < Bevacizumab < Atezolizumab < Adalimumab < Eculizumab < Alemtuzumab. Again, the antibody Abciximab has been excluded from the list because of the same previous reason.

Because all these antibodies except Abciximab have typical rosetta energy unit values, that means they are good

Table 2. Antibody-antigen Docking Results Using Global and Local Methods

Antibody	Antigen	ClusPro results (Global docking)			ROSIE results (Local docking)	
		Cluster size	Weighted score		Score (REU)	
			Center	Lowest energy	Interface	Total
Abciximab	3CL^{pro}	176	-326.1	-359.3	No L chain	No L chain
Adalimumab	3CL^{pro}	110	-258.3	-337.8	-9.026	-521.297
Alemtuzumab	3CL^{pro}	106	-287.1	-287.1	-10.678	-582.486
Atezolizumab	3CL^{pro}	63	-314.6	-326.2	-11.561	-539.875
Bevacizumab	3CL^{pro}	70	-345.8	-349.6	-8.700	-586.144
Cetuximab	3CL^{pro}	70	-286.0	-347.0	-13.764	-584.213
Eculizumab	3CL^{pro}	119	-249.3	-304.9	-12.125	-487.993
Abciximab	Nsp15	59	-332.8	-334.4	No L chain	No L chain
Adalimumab	Nsp15	50	-273.6	-327.2	-8.443	-546.845
Alemtuzumab	Nsp15	74	-275.0	-319.7	-7.535	-606.917
Atezolizumab	Nsp15	45	-279.6	-343.5	-8.587	-584.094
Bevacizumab	Nsp15	46	-308.6	-331.6	-9.319	-615.112
Cetuximab	Nsp15	144	-371.6	-382.8	-10.287	-615.312
Eculizumab	Nsp15	53	-257.0	-283.5	-8.149	-524.609

(a)   **(b)**

Cetuximab–3CL^{pro} Cetuximab–Nsp15
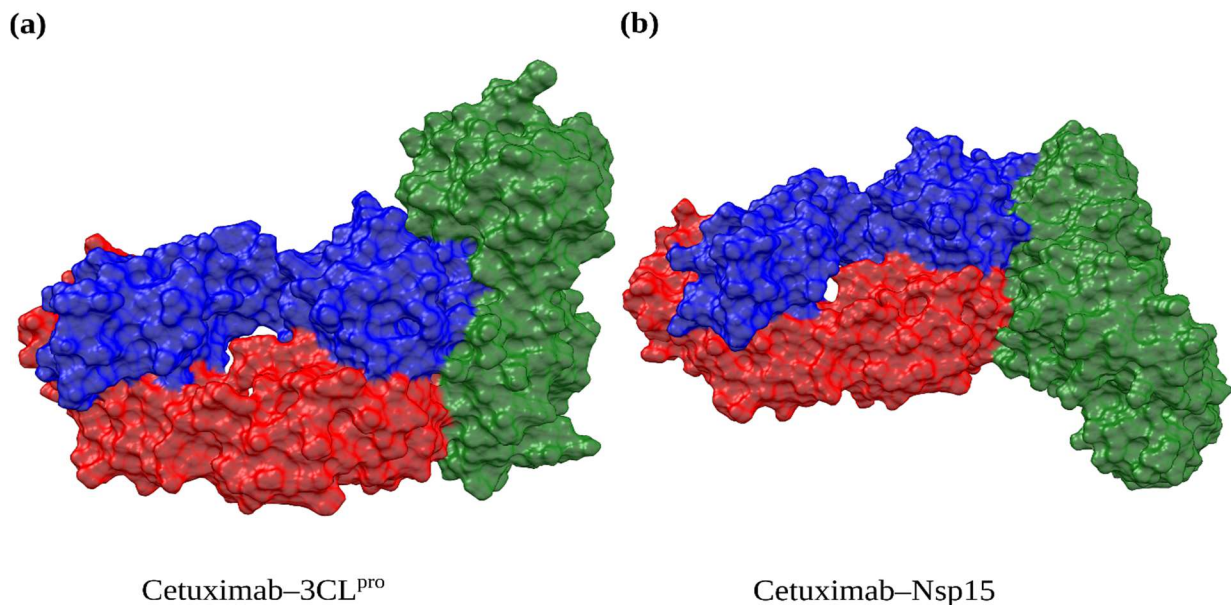
Fig. 1. Antibody-antigen complex. (a) Cetuximab-3CL^{pro} complex and (b) Cetuximab-Nsp15 complex. Colors show the chains of the antibody and antigen molecules: Chain H; blue, Chain L; red, and antigen; green.

decoys. However, it seems that Cetuximab, which is classified as an anticancer, has an outstanding rank among the antibodies for both coronaviral proteins. The structures of the Cetuximab-3CL^{pro} and Cetuximab-Nsp15 complexes are shown in Fig. 1. In both complexes, the antigen interacts with both antibody chains, H and L.

CONCLUSIONS

ClusPro server's antibody-antigen docking mode and ROSIE server's antibody-antigen mode were used to examine specific monoclonal antibody molecules on two active coronavirus proteins (Nsp15 and 3CLpro). All of the examined antibodies, with the exception of Abciximab (because its structure lacks the L chain), have typical rosetta energy unit values, indicating that they are good decoys, according to the results of molecular docking. However, it appears that Cetuximab, an anticancer antibody, ranks first among antibodies for both coronaviral proteins. The antigen interacts with both H and L antibody chains in both complexes. As a result, Cetuximab has the potential to be a novel coronavirus inhibitor. Further *in vitro* and *in vivo* research is required to validate these computational findings.

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