Computational modelling predicts that Dengue virus antibodies can bind to SARS-CoV-2 receptor binding sites: Is pre-exposure to dengue virus protective against COVID-19 severity?

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Abstract

The world is going through the scourge of COVID-19 pandemic since last several months. The pandemic appears to be less severe in highly Dengue endemic countries. Furthermore, COVID-19 in two elderly patients (with no evidence of Dengue virus (DV) infection) elicited antibodies that gave false-positive results in DV serological tests. We anticipated that SARS-CoV-2 and DV share antigenic similarity and performed molecular docking studies. Our computational modelling studies predicted that human anti-DV antibodies can indeed, bind to RBD of SARS-CoV-2 Spike protein. Some of these interactions can also potentially intercept human ACE2 receptor binding to RBM.

Our computational analysis showed that m396 Ab (against SARS-CoV-1) did not dock with RBM of SARS-CoV-2, a fact already proven experimentally. This confirmed reliability and robustness of our approach. So, immunological memory to DV in endemic countries is thwarting COVID-19. Available Dengue vaccines can be repurposed against SARS-CoV-2 in DV non-endemic countries until approved vaccines/ antivirals become available against COVID-19.

Based on the observations that COVID-19 and Dengue severity maps do not tend to overlap and the fact that serological cross-reactivity has been reported for COVID-19 antibodies with Dengue antigen (s), together with results from our computational studies, it is imperative that serology-based diagnosis should be complemented with NAT/virus antigen detection-based tests for definitive diagnosis of either disease in regions where both of these viruses are now co-existent.

Furthermore, we still do not know whether antibodies to SARS-CoV-2 will hinder/ameliorate DV infections by binding to DV particles and reduce dengue incidences in the future or, augment DV infection and severity by means of antibody-dependent enhancement (ADE).

1. Introduction

For last several months people around the world are confronting the pandemic COVID-19, caused by SARS-CoV-2, a beta coronavirus. As of 1st June, 2020, 6,057,853 confirmed cases with 3,71,166 deaths have been reported worldwide (1). This infection is believed to originate from Wuhan city, Hubei province, China in December, 2019. The virus is highly contagious and easily transmissible from human to human. The virus caused numerous outbreaks across the globe and WHO declared a public health emergency of international concern (PHEIC) on January 30, 2020.

Studying the global map of the COVID-19 pandemic (1), it occurred to us that SARS-CoV-2 is showing less transmission, severity and overall mortality per million population in highly Dengue endemic countries (2), i.e. the COVID-19 and Dengue global severity maps do not overlap (3). Despite having large population size, high population density, less public health awareness, relatively poor health and hygiene conditions and inadequate healthcare facilities, the highly Dengue endemic countries in Southeast Asia, the Indian subcontinent, Latin America and Africa have experienced comparatively lower number of COVID-19 infections and deaths so far. On the other hand, developed countries in Europe, North America and Asia (China, Iran) with insignificant or sporadic Dengue virus infection history, have been worst affected by SARS-CoV-2. One reason behind this striking difference is that the number of COVID-19 testing/diagnosis is less in Dengue endemic countries due to limited resources and logistics compared to the developed world and there may be many more asymptomatic carriers in populations than detected. Having said that, the COVID-19 mortality in highly DENV endemic countries was estimated at 0.1-0.4 per million population compared to 11-25 in the DENV non-endemic regions, over a week's time (28th March to 4th April, 2020) (3).

As an exception to our proposition, Brazil, a DENV-endemic country recorded 4, 98,440 infections and 28,834 deaths as on 1st June, 2020 (1). It is universally accepted and

recommended that preventive measures are crucial to contain the spread of COVID-19 like social distancing, quarantine and lockdown in the early phases of the pandemic. Super-spreaders (high virus titre in nasopharynx, throat and sputum) have been already recorded for SARS-CoV-2 (4). Increased rate of transmission due to delay or lack of precautionary measures and exposure to high virus loads are important factors that can overwhelm the cross-protective effects induced by DENV pre-exposure.

Even in the face of COVID-19 pandemic, Dengue remains the most important arboviral disease of global concern. In last few years incidence of Dengue cases has increased rapidly although a vast majority of the cases (~80%) are mild, asymptomatic and self-limiting. One report estimated 390 million (95% CI: 284-528) infections per year globally, of which 96 million (CI: 67-136) manifested clinically. About 4 billion people across 129 countries are currently at the risk of Dengue virus infection, with 70% of global burden from Asia, namely the Indian subcontinent and Southeast Asia (5). Consequently, COVID-19 pandemic overlapped with high Dengue endemicity in many tropical and sub-tropical regions of the world as mentioned above.

Initially, it was hypothesized that COVID-19 spread would be thwarted by warmer climate and this was thought to be another reason why the highly Dengue epidemic countries, falling in hot and humid regions of the world, were less affected by COVID-19. But last few warmer months of disease progression and several published reports on impact of weather conditions on virus spread suggest COVID-19 to be equally infectious under hot and humid conditions (6).

From the above observations, it appeared that pre-exposure to Dengue virus (DV) may render partial protection against COVID-19 as may be the case in highly Dengue endemic regions of the world. One study from Singapore stated that an elderly man and a woman were actually

SARS-CoV-2 positive but mis-diagnosed for Dengue due to similarities in disease presentation and more importantly, false-positive results in serological test for DV IgM and IgG. Both the patients were confirmed qRT-PCR negative for DV-, ZIKA- and Chikungunya-RNA (7). A similar report has also been published from India in recent times (7a).

There could be two possible explanations of the aforesaid observations-first SARS-CoV-2 infection had stimulated the immunological memory to DV in these patients from previous DV- exposure(s) which could be asymptomatic. This resulted in production of anti-DV antibodies (Abs) resulting in positive results in DV serological tests. Alternatively, Abs against SARS-CoV-2 may have cross-reacted with DV antigens used in DV serological tests for detecting DV-specific IgM and/or IgG. Either one or both these explanations could hold true but both cases unequivocally indicate towards some degree of antigenic similarities between SARS-CoV-2 and DV. This led us to investigate the effects of human anti-DV Abs on SARS-CoV-2 Spike protein using molecular docking studies.

2. Results

2.1. Anti-Dengue virus antibodies are predicted to bind with RBD of SARS-CoV2 spike protein

Four monoclonal antibodies namely EDE2 A11, EDE2 B7, EDE1 C8 and EDE1 C10 that are elicited in response to natural DV infection in humans (8,9), have been used in this study. Each Ab has been docked with crystal structure of SARS-CoV-2 Spike protein (PDB 6VSB) (10), using two docking servers ZDOCK and ClusPro. From the output of each algorithm, top 10 predictions were considered. All the selected interactions were within a distance cut-off of 3.5Å (11). Available PDB files of aforesaid Abs and SARS-CoV-2 Spike proteins were

114 processed for docking as stated in supplementary methods section. In ZDOCK (12,13),
115 protein-protein interaction and in ClusPro (14,15), protein-protein interaction with Antibody
116 mode were used. Only those interactions that are predicted by both the algorithms, were
117 considered for interpretation. During analysis of docking results, interactions that were
118 predicted involving amino acid position 287 to 909 of SARS-CoV-2 Spike protein, were
119 considered as the immunogenic epitopes of the virus fall in this region (16).

120 For EDE1 C8 Ab docking with SARS-CoV-2 Spike protein, there were 48 occasions in 20
121 predictions when EDE1 C8 Ab was found to bind to different amino acid residues in the
122 SARS-CoV-2 Receptor Binding Domain (RBD, 333-527 amino acid positions on Spike (S)
123 protein). These 48 events include repetitions of different amino acids as stated in Table1 and
124 specific amino acid comes once in a particular prediction. Among these 48 interactions, 13
125 involve Ab binding to different residues of the Receptor Binding Motif (RBM, 438-506
126 amino acid positions on Spike protein).

127 Of twenty predictions for EDE1 C10 Ab binding, 38 events of interactions were observed in
128 RBD including 19 in RBM. Similarly, EDE2 B7 Ab was found to bind to different amino
129 acids in RBD for 28 times in 20 predictions. There were 18 incidences when EDE2 B7 Ab
130 interacted with RBM of S protein. In case of EDE2 A11 Ab, only five interactions were
131 detected, all occurring involving the RBM (Table 1). Overall, there were 119 events in 80
132 predictions where DV MAbs interacted with SARS-CoV-2 RBD, including 55 events
133 involving RBM (Fig 2A). Representative images of docking have been presented (Fig 1).

Docking of EDE1 C8 Ab with SARS-CoV-2 spike protein	
Total 20 predictions were considered (10 ZDOCK +10 ClusPro)	
Common interactions	Frequency
Y449	3
Y453	2
Q498	2
Y505	2
L335	3
E340	3
N343	5
V367	5
K529	4
N532	3
Q580	4
T345	4
S371	4
N440	4
N370	3
S373	3
F374	3
E654	2
N657	4
Q690	2
N437	2
Total interactions in RBD (333-527) : 48	
Total interactions in RBM (438-506) : 13	

A

Docking of EDE1 C10 Ab with SARS-CoV-2 spike protein	
Total 20 predictions were considered (10 ZDOCK+ 10 ClusPro)	
Common interactions	Frequency
K417	4
T415	2
Y421	4
P491	3
L492	2
Q493	4
P337	2
P499	2
T500	2
K424	2
R454	3
R346	2
Y449	3
L335	3
Total interactions in RBD (333-527): 38	
Total interactions in RBM (438-506): 19	

B

Table 1

Docking of EDE2 B7 Ab with SARS-CoV2 spike protein	
Total 20 predictions were considered (10 ZDOCK+ 10 ClusPro)	
Common interactions	Frequency
L335	5
P337	3
K417	2
L492	5
Q493	5
S494	3
Q498	5
Total interactions in RBD(333-527) : 28	
138	
Total interactions in RBM(438-506) : 18	
139	

C

Docking of EDE2 A11 Ab with SARS-CoV2 spike protein	
Total 20 predictions were considered (10 ZDOCK+ 10 ClusPro)	
Common interactions	Frequency
Q493	5
Total interactions in RBD(333-527) : 5	
Total interactions in RBM(438-506) : 5	

D

Docking of m396 Ab with SARS-CoV2 spike protein	
Total 20 predictions are considered (10 ZDOCK+ 10 ClusPro)	
Common interactions	Frequency
L335	4
G339	2
V367	3
N370	5
S371	2
S373	4
D364	4
S366	4
A372	3
Total interactions in RBD (333-527) : 31	
Total interactions in RBM (438-506) : 0	

E

Table 1

Table1. Amino acid residues in the RBD of Spike protein predicted to bind to anti-DV antibodies. (A) List of amino acid residues of Spike protein, which interact with EDE1 C8 Ab. The repetitive frequencies of particular interaction in total 20 predictions are listed against each residue. (B) Spike protein amino acid residues predicted to interact with EDE1 C10 Ab. The frequencies of each interaction in total 20 predictions are cited in the right column. (C) SARS-CoV-2 Spike protein residues interacting with EDE2 B7 Ab. (D) SARS-CoV-2 RBD amino acid residues which bind to EDE2 A11 in docking study. (E) Interacting amino acid residues on Spike protein of SARS-CoV-2 that bind to m396 antibody.

Interactions predicted in common by both ZDOCK and ClusPro, were considered only. Bold residues are in RBD. Bold and dark shaded residues are in RBM. Aforesaid interactions between EDE Abs and SARS-CoV-2 Spike protein that fall within the distance cut-off of 3.5Å were considered.

Figure 1. Representative images of anti-DV antibodies “docking” with SARS-CoV-2 Spike protein

(A) EDE1 C8 Ab (Red) is docked with Spike protein (green) of SARS-CoV-2 through ClusPro, Model 0. (B) EDE2 B7 Ab (Red) is docked with Spike protein (green) of SARS-CoV-2 through ZDOCK, Complex 5. (C) EDE1 C10 Ab (Red) is docked with Spike protein (green) of SARS-CoV-2 through ClusPro, Model 3.

Hydrogen bonds within distance cut-off of 3.5 Å are marked as yellow dotted lines.

A

B

Figure 2. Predicted interaction sites of Anti-DV antibodies with SARS-CoV-2 Spike protein

Yellow-marked region denotes RBD, spanning 333-527 amino acids. In RBD, sky blue-marked regions represent RBM, spanning 438-506 amino acids of the Spike protein. (A) All the residues, identified in overall 80 predictions to interact with anti-DV antibodies have been marked green, including those in RBD and RBM. (B) Amino acids marked red are crucial for interactions between RBD and ACE2 receptor. Among these receptor binding residues of SARS-CoV-2 Spike, the green highlighted positions denote the residues of the RBD that were predicted to interact also with anti-DV antibodies.

2.2. Anti-DV antibodies are predicted to bind with Spike-RBD amino acid residues which are crucial for interaction with ACE2 receptor

It is notable that anti-DV antibodies were also found to bind to RBD amino acid residues that are crucial for interaction with the human ACE2 receptors, important for virus entry. SARS-CoV-2 Spike RBD interaction with ACE2 receptor has already been elucidated through crystal structure analysis with resolution of 2.45Å (17). A total 17 residues (with a distance cut-off of 4Å) of SARS-CoV-2 RBD interact with 20 residues of ACE2 receptor (17). In our docking study, we discovered that anti DV-EDE antibodies bind with several of the above-mentioned S protein residues with a distance cut-off of 3.5Å. EDE1 C10 Ab contacts with four amino acid residues with a total frequency of 13 among 20 predictions. Similarly, EDE1 C8 Ab interacts with four amino acid residues in RBM (with a total frequency of nine) that have been predicted to interact with ACE2 receptors. Likewise, EDE2 B7 Ab and EDE2 A11 Ab bind with different receptor-engaging amino acid residues in RBD on 12 and 5 occasions respectively (Table 2). Overall, the DV Abs used in this study, docked with seven S protein amino acids that are crucial for binding to ACE2 receptor. These seven amino acid residues appeared on 39 occasions with repetitions in total 80 predictions (Fig.2B).

RBD residues that interact with ACE2 receptor	RBD residues interacting with EDE1 C8 Ab	RBD residues interacting with EDE1 C10 Ab	RBD residues interacting with EDE2 B7 Ab	RBD residues interacting with EDE2 A11 Ab
K417		4	2	
G446				
Y449	3	3		
Y453	2			
L455				
F456				
A475				
F486				
N487				
Y489				
Q493		4	5	5
G496				
Q498	2		5	
T500		2		
N501				
G502				
Y505	2			
Total frequency	9	13	12	5
Total interaction events in 80 predictions: 39.				

Table 2. Amino acid residues of SARS-CoV-2 RBD that interact with ACE2 receptor including the ones that were predicted to interact also with anti-DV antibodies. List of amino acid residues on SARS-CoV-2 RBD which are crucial for ACE2 receptor binding. Columns to the right show frequencies of anti-DV antibody interactions at some of those ACE2-occupying sites.

2.3. Reproducibility of this docking study with experimental data

Several neutralizing Abs against SARS-CoV-1 (like m396, 80R) are known to interact with RBD of Spike protein and compete with ACE2 receptor for binding (18). But these antibodies do not bind with SARS-CoV-2 RBD as determined experimentally (10). We “docked” m396 crystal structure with SARS-CoV-2 Spike in the same procedure as done before. Analysis of 10 ZDOCK and 10 ClusPro predictions revealed 31 interactions within amino acid positions L335 to A372 of SARS-CoV-2 Spike RBD (Table 1). However, not a single common interaction was found to occur involving the RBM, from both algorithms. Furthermore the above 31 interaction points were far away from the ACE2 receptor interacting residues, which fall between K417-Y505 (17). These observations confirmed the reliability and robustness of our approach.

Figure 3: Schematic diagram depicting why COVID-19 may be less severe in highly DV-endemic countries (Scenario 1); Possible outcome of hypothetical situation that DV-vaccines have been used for immunization against COVID-19 in non-endemic countries (Scenario 2).

3. Discussion

Our computational modelling studies predicted that anti-DV Abs can interact with SARS-CoV-2 RBD (Fig.2A) and are also capable of intercepting seven key RBD interactions that are crucial for binding to ACE2 receptors (Fig.2B, Table 2). From these findings we propose that anti-DV Abs have the potential to compete with ACE2 receptors for access to RBD of SARS-CoV-2. So, theoretically, they can “mask” SARS-CoV-2 RBD and block its interaction with host cell receptors and thereby prevent virus entry.

The aforesaid four DV Abs are known to neutralize DV and were identified from sera of Dengue fever convalescent patients (8). This ensures that both asymptomatic and symptomatic patients recovering from DV infection will possess immunological memory to these Abs. In highly Dengue endemic countries, where infections occur regularly, majority of the population have pre-exposure to DV and have turned DV sero-positive. We have already mentioned that one possible explanation of the report of Dengue false sero-positivity in COVID-19 patients from Singapore, was that immunological memory to previous DV exposure might have got triggered (*original antigenic sin*) due to SARS-CoV-2 infection, because of antigenic similarity between the two viruses. Consequently, anti-DV Abs were produced and detected in the serum samples (7). In our study, only four Abs have been considered but immunological response against any pathogen comprises of a repertoire of Abs; so, it is likely there will a larger repertoire of anti-DV antibodies which can bind to and block RBD in humans. All these evidences help explain our observation that SARS-CoV-2 infections are less severe in highly Dengue endemic countries of the globe, where more than 80% of the population can be sero-positive for Dengue (3).

One future challenge in case of COVID-19 is the yet undetermined impact of possible “Antibody Dependent Enhancement (ADE)” in already exposed populations (19,20). This happens when antibodies to one SARS-CoV-2 strain fail to effectively neutralize another

strain(s) (as often observed in case of Dengue serotypes) and at the same time, enable the virus of the other strain (s) to infect more cells by binding to the virus and bringing them closer to susceptible cells to which the antibodies are often attached by their Fc region.

From the results of our study, one can argue that anti-DV Abs may also bind to SARS-CoV-2 and cause ADE for SARS-CoV-2 infections. But this does not appear to be the case, otherwise all highly Dengue endemic countries would have been more hit by the COVID-19 pandemic than the Dengue non-endemic countries due to pre-existing DV antibodies in the population. On the contrary, we are observing just the opposite scenario globally and therefore, anti-DV antibodies are not involved in ADE of SARS-CoV-2 as per circumstantial evidence. Perhaps they are thwarting SARS-CoV-2 severity as explained above.

Further research to confirm the potential of EDE DV Abs to cross-react with SARS-CoV-2 is warranted. It would be also interesting to investigate whether, conversely, SARS-CoV-2 Abs can neutralize DV.

4. Methods and Models

4.1. Preparation of antibody for docking

The PDB files of all the antibodies were retrieved from RCSB PDB; PDB ID: 4UTA, 4UTB, 4UT6, 4UT9. Most of the dengue virus antibody structures in PDB were in neutralizing condition with their antigenic ligand molecule. From an original antibody PDB file, a separate PDB file consisting only the antigen binding fragment, Fab which is devoid of its natural antigenic counterpart was created using PyMOL Molecular Graphics System, Version 2.3.3, Schrödinger, LLC software. These newly created PDB files were then processed in Chimera software using the Dock Prep plugin(21). Subsequently solvent deletion, deletion of

alternate positions (retaining only the highest-occupancy positions), hydrogen addition, partial charge assignment, and output in Mol2 format were modulated through graphical interface. Standard residues (receptor amino acids) were assigned AMBER ff14sb partial charges (22,23). AM1-BCC charges were computed for the receptor cofactors with ANTECHAMBER, which is included in Chimera (24,25). The modified molecular structures were then used as receptor inputs in docking servers i.e. Z Dock 3.0.2 (12,13) and ClusPro (14,26,27).

4.2. Refined protein data input in ZDOCK 3.0.2 and ClusPro web server for protein-protein docking predictions

For each antibody-antigen interaction, two FFT algorithm based docking servers were used and the predictive results for each antibody were analyzed side by side to forage any similarity or pattern in the predictive interaction in accordance with our hypothesis. The ClusPro Server included FFT based protein-protein docking program PIPER. The simple user interface of the web server allowed inputting PDB ID or PDB files for respective docking predictions. We used special antibody mode plugin in the server for the docking (28), where each modified dengue virus antibody was uploaded as receptor input and novel corona virus (SARS-CoV-2) trimeric Spike protein (PDB ID: 6VSB) was uploaded as ligand input. Additional specification, such as automatic non-complement determining region masking of the antibody, was also enabled for the docking. The top 1000 results from the docking are then clustered using the optimal clustering algorithm in the server. The top 10 docking predictions were then visualized and can be downloaded as a PDB files from the server for analysis.

ZDOCK 3.0.2 is also a FFT algorithm-based server for initial-stage protein docking predictions. The user interface of the webpage enables to upload PDB files or specify PDB

ID. We put the modified antibody as input protein 1. Due to PDB file size restrain for uploading, we were unable to upload the entire trimeric Spike protein, 6VSB in the server as Input protein 2. So instead of the whole complex, it was decided to upload only one monomer of the Spike protein complex, i.e. chain A as Input protein 2.

In the residue selection module we blocked monomeric chain A, SARS-CoV-2 Spike protein amino acid 910-1146, as this region is unlikely to have any interaction with antibody (16) and mostly buried inside the trimeric Spike protein and envelope portion of the virus. After docking is done, the top 10 predictive structures were downloaded and analyzed.

4.3. Analysis of predictions and image refinement using PyMOL

We used the PyMOL Molecular Graphics System, Version 2.3.3, Schrödinger, LLC for analyzing the predicted PDB structures obtained from both the servers. For each predicted structure from molecular docking, the interaction surface between antigen and antibody was determined through the “find any interaction within 3.5Å cut-off” plugin. All the amino acid residues of the antigen which were involved in interaction with the target antibody were identified and marked. All pictures were also refined and modified using the software.

4.4. Data availability

The structures of docking models both in raw and analysed format is available at Mendeley, please click this link to access

(<https://data.mendeley.com/datasets/gc9p9gwjpr/draft?a=98b0f2e2-d4c1-45f6-bfef-087ad05f812b>). Further information and requests for resources should be directed to and will be fulfilled by corresponding author, Dr. Subhajit Biswas (subhajit.biswas@iicb.res.in)

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