The Analyses of High Infectivity Mechanism of SARS-CoV-2 and Its Variants

Yonghua Lu ^{1,2}, Tianfu Zhao ^{1,2}, Ming Lu ², Yaopeng Zhang ³, Xiang Yao ³, Guoyi Wu ⁴ , Fangyin Dai ¹ , Fengxiu Zhang ⁵ and Guangxian Zhang ^{1,2,*}

- ¹ State Key Laboratory of Silkworm Genome Biology, College of Sericulture Textile and Biomass Sciences, Southwest University, No.2 Tiansheng Street, Beibei, Chongqing 400715, China; lyh1249959090@163.com (Y.L.); zhaotf@swu.edu.cn (T.Z.); fydai@swu.edu.cn (F.D.)
- ² Chongqing Engineering Research Center of Biomaterial Fiber and Modern Textile, No. 2 Tiansheng Street, Beibei, Chongqing 400715, China; lumingswu@163.com
- ³ State Key Laboratory for Modification of Chemical Fibers and Polymer Materials, Shanghai Belt and Road Joint Laboratory of Advanced Fiber and Low-Dimension Materials, College of Materials Science and Engineering, Donghua University, Shanghai 201620, China; zyp@dhu.edu.cn (Y.Z.); yaoxiang@dhu.edu.cn (X.Y.)
- ⁴ Shanghai Public Health Clinical Center, Fudan University, 2901 Caolang Road, Shanghai 201508, China; wuguoyi@163.com
- ⁵ Institute of Bio-Organic and Medicinal Chemistry, College of Chemistry and Chemical Engineering, Southwest University, Chongqing 400715, China; zhangfx656472@sina.com
- * Correspondence: zgx656472@sina.com

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Abstract: SARS-CoV-2 has high infectivity and some of its variants have higher transmissibility. To explore the high infectivity mechanism, the charge distributions of SARS-CoV, SARS-CoV-2, and variants of concern were calculated through a series of net charge calculation formulas. The results showed that the SARS-CoV-2 spike protein had more positive charges than that of SARS-CoV. Further results showed that the variants had similar but higher positive charges than preexisting SARS-CoV-2. In particular, the Delta variant had the greatest increase in positive charges in S₁ resulting in the highest infectivity. In particular, the S₁ positive charge increased greatly in the Delta variant. The S₁ positive charge increased, and due to the large negative charge of angiotensin-converting enzyme-2 (ACE2), this resulted in a large increase in Coulomb's force between S₁ and ACE2. This finding agrees with the expectation that the positive charges in the spike protein result in more negative charges on SARS-CoV-2 antibodies than that of SARS-CoV. Thus, the infectivity of a novel SARS-CoV-2 variant may be evaluated preliminarily by calculating the charge distribution.

Keywords: SARS-CoV-2; SARS-CoV; ACE2; antibodies; infectivity; charge distributions

1. Introduction

Since the initial emergence of the novel coronavirus (SARS-CoV-2) infection, the coronavirus COVID-19 pandemic has been expanding nationwide and globally for over a year [1–3]. Although there is only a 22.5% difference in amino acid sequence between SARS-CoV-2 and SARS-CoV [4], SARS-CoV-2 has much higher infectivity than SARS-CoV, and a series of SARS-CoV-2 variants, such as the Alpha, B.1.1.7 + E484K, Beta, Gamma, and Delta variants, have much higher infectivity than the preexisting SARS-CoV-2 [5–9]. In particular, the Delta variant is present in countries and territories worldwide. Wrapp et al. reported that SARS-CoV-2 has a higher affinity for angiotensin-converting enzyme-2 (ACE2) than that of SARS-CoV. However, they did not discuss the reason for the high infectivity. Some reports have suggested that there is a mutation “PRRA” in SARS-CoV-2, making the SARS-CoV-2 spike protein can be cleaved and allowing SARS-CoV-2 to enter the cell faster [10–14]. Many studies have focused on SARS-CoV-2 and its high infectivity rate, but investigations into the mechanism of the highly infectious SARS-CoV-2 and its variants

are limited, particularly the Delta variant [15–23]. Obviously, revealing the high infectivity spike protein structure mechanism is very important for designing the medicine structures.

The interactions that occur between organic molecules are mainly Coulomb forces, hydrogen bonding forces, polar groups, and van der Waals forces. Among them, the Coulomb force is a major long-distance interaction that should be analyzed between SARS-CoV-2 (GenBank: QHU36824.1) [10,15] and ACE2 (GenBank: ACT66268.1) [10,24]. Therefore, in this study, we analyzed the charge distributions of SARS-CoV (GenBank: AAP13441.1) [10,15], SARS-CoV-2, some highly infectious SARS-CoV-2 variants, and numerous SARS-CoV and SARS-CoV-2 antibodies. The results suggest that SARS-CoV-2 and its variants have high Coulomb attraction to ACE2.

2. Methods

The charges of the various proteins were calculated using Equations (1) and (2) [25]:

$$X = \sum_{i=1}^2 \frac{K_{ai}m_i}{[H^+] + K_{ai}} \quad (1)$$

where X is the negative charge number of the protein and K_{ai} expresses the ionization constant of an acidic amino acid residue. In a protein, glutamic acid residues and aspartic acid residues ionize H^+ resulting in negative charges. Finally, m_i is the number of acidic amino acid residues in the protein:

$$Y = \sum_{i=1}^3 \frac{[H^+]n_i}{[H^+] + K_{bi}} \quad (2)$$

where Y is the positive charge number of a protein and K_{bi} is the ionization constant of a basic amino acid residue. In a protein, only arginine, lysine, and histidine residues combine with H^+ to produce positive charges. n_i represents the number of basic amino acid residues in the protein.

The net charge number (H) of a protein is calculated by Equation (3) as follows:

$$H = Y - X. \quad (3)$$

The calculation deviation is shown as Equations (4) and (5):

$$\Delta X = \sum_{i=1}^2 \frac{[H^+]m_i}{([H^+] + K_{ai})^2} \Delta K_{ai} \quad (4)$$

where ΔX expresses the deviation in the negative charge of a protein and ΔK_{ai} is the deviation in K_{ai} .

$$\Delta Y = \sum_{i=1}^3 \frac{[H^+]n_i}{([H^+] + K_{bi})^2} \Delta K_{bi} \quad (5)$$

where ΔY is the deviation in the positive charge of a protein and ΔK_{bi} is the deviation in K_{bi} .

The K_{ai} , K_{bi} , and ΔK_{bi} values are listed in Table 1.

Table 1. The ionization constant parameters.

Acidic Amino Acid	K_{ai}	ΔK_{ai}	pK_{ai}	Basic Amino Acid	K_{bi}	ΔK_{bi}	pK_{bi}
Glu	3.98×10^{-5}	0	4.4	Arg	1.38×10^{-12}	1.13×10^{-12}	11.6–12.6
Asp	5.1×10^{-4}	4.9×10^{-4}	3.0–4.7	Lys	2.12×10^{-10}	1.86×10^{-10}	9.4–10.6
-	-	-	-	His	1.31×10^{-6}	1.2×10^{-6}	5.6–7.0

The values of the ionization constant K_{ai} and K_{bi} were calculated from pK_{ai} and pK_{bi} [26] because the pK values are not constant in a protein, and K_{ai} and K_{bi} are the average values. The ΔK value is the difference between the maximum K_{ai} or K_{bi} and the average value.

3. Results and Discussion

3.1. The Charge Distributions of SARS-CoV-2, SARS-CoV, and ACE2

The spike proteins of the SARS-CoV-2 (S_p) and SARS-CoV (S_s) viruses consist of two subunits (S_1 and S_2). The S_1 domain is 13–685 amino acids in the sequence of the spike protein from the N-terminal domain, and S_2 is the 686 amino acids to the end [7,15,27]. The numbers of acidic and basic amino acid residues in every section of the SARS-CoV-2 and SARS-CoV spike proteins, as well as in ACE2, are listed in Table 2.

Table 2. The numbers of acidic and basic amino acid residues in the sections of the spike proteins of SARS-CoV-2, SARS-CoV, as well as in ACE2.

Amino Acid	S1	S2	Sp	Ss1	Ss2	Ss	ACE2
Glu	23	25	48	17	25	42	56
Asp	31	31	62	45	28	73	43
Arg	29	13	42	23	16	39	31
Lys	30	31	61	31	29	60	47
His	9	8	17	9	6	15	16

The charge numbers and calculated deviations of the spike proteins in SARS-CoV-2, SARS-CoV, and ACE2 at different pH values are presented in Table 3. As the pH of human blood is 7.25–7.35, the charge numbers of the proteins at the median pH of 7.3 are of particular interest. Table 3 shows that all of the above protein macromolecules have negative charges at pH 7.3. Intriguingly, the S_p charge number decreased significantly compared with that of S_s . Table 3 also shows that the deviations in the charges at pH 7.3 are sufficiently low to determine the accuracy of the calculation.

Table 3. The charge numbers of S_p , S_s , and the ACE2 protein at different pH values.

pH	5.0	5.5	6.0	6.5	7.0	7.3	8.0	8.5
H_{S_p}	18.9	8.9	1.6	−3.3	−5.8	−6.6	−8.1	−10.8
ΔH_{S_p}	±2.7	±3.6	±4.0	±2.5	±1.1	±0.8	±1.2	±3.2
H_{S_s}	7.1	−1.9	−8.3	−12.7	−14.9	−15.6	−17.1	−19.7
ΔH_{S_s}	±2.7	±3.3	±3.5	±2.2	±1.0	±0.7	±1.2	±7.6
H_{ACE2}	5.2	−5.3	−12.6	−17.5	−19.8	−20.5	−21.8	−23.9
ΔH_{ACE2}	±2.3	±3.3	±3.7	±2.3	±1.1	±0.7	±0.95	±2.5

Although S_p and S_s had negative charges at pH 7.3, the charges may not be distributed uniformly throughout the proteins as the amino acid sequences varied. S_1 had six more Arg and one fewer Lys compared with S_{s1} , which have positive charges, and had six more Glu and fourteen fewer Asp, which have negative charges, and S_2 had two more His, two more Lys, three more Asp, and three fewer Arg than S_{s2} . Although the S_s and S_p amino acid sequences are only slightly different, some of the amino acids that differ are the key acidic and basic amino acids. Therefore, the calculations are based on more accurate modules. Besides the two subunits, the receptor-binding domain (RBD) of each subunit was also calculated. The S_p RBD was 319–541 amino acids [7] and that of S_s was 306–527 amino acids [27]. All charge numbers are listed in Table 4.

Table 4. Charge distributions in the S_p and S_s sections.

pH	5.0	5.5	6.0	6.5	7.0	7.3	8.0	8.5
S_p (RBD)	8.5	7.3	6.6	6.3	6.1	6.0	5.8	5.2
S_1	18.2	13.2	9.5	6.9	5.6	5.2	4.4	3.1
S_2	0.7	−4.3	−7.9	−10.2	−11.4	−11.8	−12.6	−13.9
S_s (RBD)	4.9	4.1	3.5	3.2	3.1	4.0	2.8	2.2
S_{s1}	4.2	−0.1	−3.6	−6.1	−7.4	−7.8	−8.6	−9.9
S_{s2}	2.9	−1.7	−4.7	−6.6	−7.6	−7.9	−8.5	−9.8

Table 4 shows that the charge distributions were highly uneven in S_p and S_s , which is consistent with the predicted results. S_{s1} and S_{s2} almost had the same number of negative charges at −7.8 and −7.9, respectively. Additionally, S_1 unexpectedly had a positive charge of 5.2, while S_2 had a much higher negative charge of −11.8 than that of S_{s1} and S_{s2} .

The net charge distributions of the spike protein in SARS-CoV-2, SARS-CoV, and the interactions between the spike protein and ACE2 are shown in Figure 1. The binding part of SARS-CoV-2 during the infection process is S_1 , as shown in Figure 1b. S_1 was positively charged, while ACE2 had many negative charges that will generate two effects. The S_1 positive charges are attracted by ACE2 over a relatively long distance because the Coulomb interactions do not need a specific structured area. This means that the ACE2 receptor attracts SARS-CoV-2 easily causing enhanced transmissibility. However, the affinity between S_p and ACE2 was relatively strong due to the Coulomb interactions between the positive and negative charges, so as long as SARS CoV-2 is bound to ACE2, they are difficult to separate. Certainly, after the SARS CoV-2 combined the ACE2, there were hydrogen bonding forces, polar groups, and van der Waals forces between SARS CoV-2 and ACE2.

Figure 1. Distributions of the net charges of the SARS-CoV (a) and SARS-CoV-2 (b) spike proteins and the interactions between the spike proteins and ACE2. Blue represents the part of protein with a negative net charge and red expresses the part of the protein with a positive net charge.

Based on these results, we speculate that because the first section S_1 had positive charges and ACE2 had negative charges, S_p will tightly combine with ACE2. This speculation follows the result of Wrapp et al. that S_p and ACE2 have high affinity [10].

3.2. Analysis of the SARS-CoV-2 Variants

Many SARS-CoV-2 variants have been detected worldwide, as well as some in which the dominating sites of the mutants are in the spike protein sequence. The Centers for Disease Control and Prevention and the World Health Organization have primarily classified a system for distinguishing the SARS-CoV-2 variants into two categories, such as variants of concern (VOCs) and variants of interest (VOIs) [20]. The VOCs include four clusters (Alpha, Beta, Gamma, and Delta) with relatively high transmissibility and virulence. The VOIs are the variants exhibiting potentially enhanced transmissibility and virulence, with likely reduced effectiveness of available therapeutics or vaccination, such as Epsilon, Zeta, Eta, Theta, Iota, Kappa, and Lambda.

The requisite components of the SARS-CoV-2 variants (mutations with substitutions or deletions in the spike protein) and calculated charge numbers of each virus variant at pH 7.3 are listed in Table 5. Knowing the high infectivity structure characteristics of SARS-CoV-2 variants is useful to design new medicines for combating the SARS-CoV-2 variants.

Table 5. The calculated charge numbers of each SARS-CoV-2 variants [7,28–39] at PH 7.3.

SARS-CoV-2 Variant	S _{RBD} Mutations	S ₁ Mutations Except RBD	S ₂ Mutations	Charges of S _{p(RBD)} at PH 7.3	Charges of S ₁ at PH 7.3	WHO Label	Other
SARS-CoV-2	-	-	-	6.0	5.2	-	-
Alpha (B.1.1.7)	N501Y	ΔH69, ΔV70, ΔY144, A570D, D614G, P681H	T716I, S982A, D1118H	6.0	5.2 + 1 *	VOC	D1118H mutation decreased the Coulomb repulsion between S ₁ and ACE2
B.1.1.7 + E484K	E484K, N501Y	ΔH69, ΔV70, ΔY144, A570D, D614G, P681H	T716I, S982A, D1118H	8.0	7.2 + 1 *	VOC	D1118H mutation decreased the Coulomb repulsion between S ₁ and ACE2
Beta (B.1.351)	K417N, E484K, N501Y	L18F, D80A, D215G, R246I, ΔL242, ΔA243, ΔL244, D614G	A701V	7.0	8.2	VOC	
Gamma (P.1)	K417T, E484K, N501Y	L18F, T20N, P26S, D138Y, R190S, H655Y, D614G	T1027I	7.0	7.2	VOC	
Delta (B.1.617.2)	L452R, T478K	T19R, ΔF157, ΔR158, D614G, P681R	D950N	8.0	9.2 + 1 *	VOC	D950N mutation decreased the Coulomb repulsion between S ₁ and ACE2
Delta Plus	K417N, L452R, T478K	T19R, ΔF157, ΔR158, D614G, P681R	D950N	7.0	8.2 + 1 *		
Mu	R346K, E484K, N501Y	D614G, P681H	-	8.0	8.3	VOI	
Lambda	L452Q, F490S	D614G	-	6.0	6.2	VOI	

* Positive charge on S₂.

Table 5 shows that the Alpha variant had one more positive charge on Spike compared with SARS-CoV-2, and the N501Y mutation added a tyrosine amino acid residue to interact strongly with Y41 in ACE2 through an aromatic stacking interaction [10]. The S_{RBD} of the B.1.1.7 + E484K variant increased 2.0 positive charges compared with Alpha. This increased transmissibility caused an outbreak in the European Union. The S_{p(RBD)} of the Beta variant increased 1.0 positive charge, and S₁ increased 3.0 positive charges. The infectivity of the Beta variant also increased significantly. The S_{p(RBD)} of the Gamma variant increased 1.0 positive charge, and S₁ increased 2.0 positive charges. Therefore, the transmissibility of the Gamma variant should be lower than that of the Beta variant. The S_{p(RBD)} of the Delta variant was enhanced 2.0 positive charges, and S₁ increased 5.0 positive charges, as well as the D950N mutation decreased one negative charge, which is equal to an increase in the positive charge. In addition, the positive charges of two VOIs (Mu and Lambda) and the so-called Delta Plus all increased in some degrees to increase infectivity. Overall, the Delta variant had the greatest increase in positive charge, so the Coulomb attractive force was reinforced. The Delta variant has had the highest transmissibility, being detected in infected patients in different territories and regions [9,30,40]. Therefore, the results suggested that the SARS-CoV-2 variants increased their infectivity mainly through adding positive-charge mutations. Thus, through calculating the charge distribution, the infectivity of a novel

SARS-CoV-2 variant can be preliminarily evaluated. It is very interesting that tumor cells have more negative charges while ordinary cells only have few negative charges or even are neutral [41]. Therefore, because spike proteins have positive charges, the SARS-CoV-2 will attack the tumor cells preferentially, and the tumor cell will be destroyed. Indeed, a 61-year-old man infected with SARS-CoV-2 induced remission from Hodgkin lymphoma without execution of immunochemotherapy or corticosteroid [42] and a Spanish cancer patient infected with SARS-CoV-2 also induced remission afterward.

3.3. Analysis of SARS-CoV-2 and SARS-CoV Antibodies

The SARS-CoV-2 spike protein had more positive charges than that of SARS-CoV. We expected that SARS-CoV-2 antibodies would have more negative charges than those of SARS-CoV. Based on the host antibody detection data, we analyzed the electric charges of the amino acid sequences in the three binding regions of the heavy chains and light chains of 61 SARS-CoV and SARS-CoV-2 antibodies, respectively: HVR1 (CDR1), HVR2 (CDR2), and HVR3 (CDR3), in which the molecular structure of the antibodies was collected from B cells of virus-infected humans (<http://opig.stats.ox.ac.uk/webapps/covabdab/>, accessed on 4 June 2021). As shown in Table 6, among the 61 antibodies, none of the SARS-CoV antibodies with a net charge in the binding region (ABR) is -5 to -7 , but there are twelve SARS-CoV-2 antibodies with charges in that range. The most probable ABR charges are -2 and 0 for the SARS-CoV-2 and SARS-CoV antibodies, respectively, following the above expectation. The more net negative charges on the antibodies contribute to heightening the attraction, combination, and neutralizing reaction.

Table 6. The calculation of antibodies for SARS-CoV-2 and SARS-CoV.

Net Charge	−7	−6	−5	−4	−3	−2	−1	0	1	2	3	4
ABR of SARS-CoV-2	4	3	5	3	6	15	8	9	5	1	0	2
ABR of SARS-CoV	0	0	0	2	7	8	14	17	9	3	0	1

4. Conclusions

The charge distributions on the spike proteins of SARS-CoV, SARS-CoV-2, variants of concern, and ACE2, as well as some SARS-CoV and SARS-CoV-2 antibodies, were calculated with net charge calculation formulas. The results revealed that S_{s1} in the SARS-CoV spike protein had net negative charges, S_1 in the SARS-CoV-2 spike protein had net positive charges, and ACE2 had many net negative charges. In particular, the Delta variant had the greatest increase in positive charges in S_1 resulting in the highest infectivity. Thus, the high infectivity mechanism of SARS-CoV-2 is mainly on account of the interaction between positive charges on S_1 and negative charges on ACE2. Therefore, the results suggested that the SARS-CoV-2 variants increased their infectivity mainly through adding positive-charge mutations. As expected, the binding regions of the SARS-CoV-2 antibodies had more negative charges than those of SARS-CoV. Obviously, through calculating the charge distribution, the infectivity of a novel SARS-CoV-2 variant can be preliminarily evaluated.

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