The inhibitory effect of a coronavirus spike protein fragment with ACE2

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ABSTRACT In this article, we investigate the binding processes of a fragment of the coronavirus spike protein receptor binding domain (RBD), the hexapeptide YKYRYL on the angiotensin-converting enzyme 2 (ACE2) receptor, and its inhibitory effect on the binding and activation of the coronavirus-2 spike protein CoV-2 RBD at ACE2. In agreement with an experimental study, we find a high affinity of the hexapeptide to the binding interface between CoV-2 RBD and ACE2, which we investigate using 20 independent equilibrium molecular dynamics (MD) simulations over a total of 1 µs and a 200-ns enhanced correlation guided MD simulation. We then evaluate the effect of the hexapeptide on the assembly process of the CoV-2 RBD to ACE2 in long-time enhanced correlation guided MD simulations. In that set of simulations, we find that CoV-2 RBD does not bind to ACE2 with the binding motif shown in experiments, but it rotates because of an electrostatic repulsion and forms a hydrophobic interface with ACE2. Surprisingly, we observe that the hexapeptide binds to CoV-2 RBD, which has the effect that this protein only weakly attaches to ACE2 so that the activation of CoV-2 RBD might be inhibited in this case. Our results indicate that the hexapeptide might be a possible treatment option that prevents the viral activation through the inhibition of the interaction between ACE2 and CoV-2 RBD.

INTRODUCTION

In December 2019, a novel respiratory disease appeared in Wuhan, Hubei, China. Although it is still under debate, there are strong indications that a first cluster of infections occurred at the Huanan seafood market (1–3). A novel coronavirus, CoV-19, and a later phenotype, CoV-2, were identified as the primary cause for a severe acute respiratory syndrome (SARS CoV-2). The spike (S) protein of CoV-2 is one target for the development of a vaccine to prevent the viral entry into human cells. The inhibition of the direct interaction between angiotensin-converting enzyme 2 and the S-protein could provide a suitable strategy to prevent the membrane fusion of CoV-2 and the viral entry into target cells. Using molecular dynamics simulations, we investigate the assembly process of a coronavirus spike protein fragment, the hexapeptide YKYRYL on the angiotensin-converting enzyme 2 receptor, and its inhibitory effect on the aggregation and activation of the CoV-2 spike receptor protein at the same receptor protein.
an entry receptor for membrane fusion (12–17). One of the key factors for its infectious potential for humans is the high conservation of ACE2 in different mammalian organisms (18), which allows its transmission from animals to humans. The receptor binding domain (RBD) of the S1 subunit contains five antiparallel β-strands, whereas α-helical and loop motifs form the connecting entities between the β-sheets. Between two β-sheets, an extended insertion forms the receptor binding motif, which binds to ACE2 at its N-terminal helix (19–21). Among a large number of potential targets, the inhibition of the direct interaction between ACE2 and the S-protein (SARS CoV-S) provides a suitable strategy to prevent the membrane fusion of CoV-2 and the viral entry into human cells (22,23). In a combined experimental and theoretical study, a hexapeptide ((438)YKYRYL (443)) of the receptor domain of SARS CoV S has been identified as an efficient inhibitor of the interaction between the S-protein and ACE2 (24). In vitro infection of Vero E6 cells by SARS coronavirus (SARS CoV) was blocked by the hexapeptide. It also has been shown that the peptide inhibits SARS coronavirus (SARS CoV) entry into human cells (22,23). In vitro infection of Vero E6 cells by SARS coronavirus (SARS CoV) was blocked by the hexapeptide. In a combined experimental and theoretical study, a hexapeptide ((438)YKYRYL (443)) of the receptor domain of SARS CoV S has been identified as an efficient inhibitor of the interaction between the S-protein and ACE2 (24). In vitro infection of Vero E6 cells by SARS coronavirus (SARS CoV) was blocked by the hexapeptide. It also has been shown that the peptide inhibits SARS coronavirus (SARS CoV) entry into human cells. Because of a damping effect by the cleavage of the peptide by proteases, a chemical modification that hinders that cellular process might increase the therapeutic potential of this peptide (25–27).

METHODS

CORE-MD

CORE-MD uses the path along the reduced action \( L_i \) as function of the momenta \( p_i \) and coordinates \( q_i \) for an atom with the index \( i \) (28–32):

\[
L_i = \dot{p}_i dq_i,
\]

where a finite time summation is applied over the path over momenta and displacements along the trajectory. For the calculation of the momentum \( p_i = m v_i \), we use a uniform atomic mass. A path-dependent correlation function \( C_i(t) \) is calculated as follows:

\[
C_i(t) = \sum_{T \geq t} \frac{(L'_i - \langle L_i \rangle)(L_i - \langle L_i \rangle)}{|L'_i - \langle L_i \rangle||L_i - \langle L_i \rangle|},
\]

where \( \langle \ldots \rangle \) denotes the time average, and \( L'_i \) is determined at a time \( t' \) with a probability \( \mathcal{P}_i(t') \):

\[
\mathcal{P}_i(t') = \frac{1}{1 + e^{-C_i(t')}}.
\]

At each time step. To define a correlation-dependent probability density, the space of the correlation function is discretized into a histogram ranging from \(-1\) to \(+1\), and a probability density \( \rho_i(t) \) is defined at the time \( t \) for the history-dependent number of states \( N_{C_i(t)} \) and the total number of states in this state of the correlation function \( C_i(t) \):

\[
\rho_i(t) = \frac{N_{C_i(t)}}{\sum_i N_{C_i(t)}}.
\]

That definition allows for the discretization of the path-dependent correlation and the definition of a log likelihood function (see below). The correlation-dependent density \( \rho_i(t) \) as a function of the correlation function \( C_i(t) \) for an atom with index \( i \) is then defined by:

\[
\rho_i(t) = \frac{\sum_i \sum_{C_{a}=-1}^{1} e^{\frac{(C_i(t) - C_{a})^2}{2\sigma}}}{\sum_i \sum_{C_{a}=-1}^{1} e^{\frac{(C_i(t) - C_{a})^2}{2\sigma}}},
\]

where \( \sigma \) defines the width of the Gaussian function (because of the fact that we apply a histogram over \( 10^5 \) bins, we apply \( \sigma = 2 \times 10^{-5} \)). Subsequently, a log pseudolikelihood function \( l \) of the correlation-dependent density is defined, which describes a form of a correlation-dependent potential:

\[
l_i(t) = - \log(\rho_i(t)),
\]

which leads to the corresponding bias \( A_i \) with an additional parameter \( \alpha \) with the units of an energy:

\[
A_i = \alpha \nabla l_i(t),
\]
as the derivative along a unit vector with a unit length because of the dimensionality of the correlation function. As a consequence, the bias gradient evolves as the gradient of the potential of the history-dependent probability density \( \rho_i(t) \), which is described by the log functional in Eq. 6. That way, the correlation-dependent likelihood is maximized in analogy to the principle of maximal entropy (33).

As a second element of the CORE-MD algorithm, a factorization of the total gradient by a factor \( r_i \) is introduced. The application of the bias gradient using only the bias derived from the path-dependent correlation requires the sufficient sampling of the correlation space. The correlation space of the path correlation is sampled along a first-order rate equation:

\[
\dot{C}_i(t) = -k_i t, \tag{8}
\]

where \( k_i \) stands for the first-order rate constant. To reach a sufficient sampling efficiency of the correlation space, the resulting gradient is scaled by a correlation-dependent factor \( r \) to enhance the decay of the autocorrelation and to achieve a faster access of the conformation space. As a consequence of the factorization, the time-dependent behavior of the correlation function is then described by a second-order rate equation:

\[
\dot{C}_i(t) = -(k_i + k^*_i) t, \tag{9}
\]

We define the factor \( r_i \) as:

\[
r_i(t) = e^{-\beta C_i(t)}(1 + \beta \dot{C}_i(t)), \tag{10}
\]

where \( \beta \) stands for a second dimensionless constant. In the global picture, the log likelihood function converges to the global log likelihood of the total correlation-dependent density \( \Xi \):

\[
\lim_{t \to \infty} l_i(t) = -\log(\Xi_i), \tag{11}
\]

where \( \Xi_i \) is approximated as the probability function \( P_i \) of the path-dependent correlation:

\[
P_i \approx \Xi_i. \tag{12}
\]

The last expression shows that the CORE-MD algorithm samples the global free energy in the infinite time limit because of the definition of \( \Delta F_i = -k_B T \log(P_i) \).

### Simulation parameters and system setup

For all simulations, we used the structures of the CoV-2 RBD-ACE2 complex from the Protein Data Bank (PDB) structure PDB: 6M0J (chain A: ACE2, chain B: CoV-2 RBD) (19). For the first set of 20 independent NPT-MD simulations over 50 ns in explicit solvent, we centered the PDB structure of ACE2 (PDB: 6M0J, chain A) in a triclinic box with dimensions 7.419 \( \times \) 8.361 \( \times \) 8.614 nm\(^3\) and filled the box with 17,026 SPC/E waters. For the preparation of 20 starting structures, we placed the hexapeptide YKYRYL at 20 different initial positions in the vicinity to the potential binding site of ACE2 (see Fig. 1b). In parts, we reduced the accessible conformation space by the placement of the 20 peptide conformations in the vicinity of the CoV-2 RBD-ACE2 interface in the PDB structure. For the selection of random orientations, larger simulation times and a larger number of starting structures would have to be applied. For the enhanced sampling simulation of the hexapeptide-ACE2 system in implicit solvent using CORE-MD enhanced sampling, we modeled one hexapeptide-ACE2 conformation and simulated the system over 200 ns using the parameters \( \alpha = 5.0 \) and \( \beta = 0.5 \) (Table 1). For a third and a fourth CORE-MD enhanced sampling simulation with and without the presence of the hexapeptide, we modeled a separated CoV-2 RBD-ACE2 system with an increased contact distance of \( \sim 2.2 \) nm by which the two domains are separated from each other. For the separated ACE2-CoV2 RBD complex with the hexapeptide, we inserted the hexapeptide 1 nm away from ACE2.

Both systems were centered in a triclinic box with dimensions 7.419 \( \times \) 8.361 \( \times \) 8.614 nm\(^3\) and filled the box with 17,026 SPC/E waters. For the preparation of 20 starting structures, we placed the hexapeptide YKYRYL at 20 different initial positions in the vicinity to the potential binding site of ACE2 (see Fig. 1b).

### Inhibition spike protein binding to ACE2

![Figure 1](image)

(a) Crystal structure of the SARS CoV-2 spike protein CoV-2 RBD bound with ACE2 (PDB: 6M0J (19)). ACE2 is shown in blue, cyan, yellow, and green, and CoV-2 RBD is shown in orange. (b) 20 different hexapeptide (YKYRYL) conformations are used as initial starting models of independent 50-ns equilibrium MD simulations in explicit solvent. (c) Shown is the starting structure of the enhanced CORE-MD simulation of CoV-2 RBD to ACE2. (d) Shown is the starting structure of the enhanced CORE-MD simulation of the same system in the presence of the hexapeptide. The distances \( d_1 \) and \( d_2 \) used in the free energy projections (see Fig. 4) are indicated in (c) and (d). To see this figure in color, go online.

### Table 1: MD and CORE-MD enhanced sampling simulations that were performed in this study to investigate the effect of the hexapeptide on the binding process of CoV2-RBD with ACE2

| Simulation                  | Length | System                                      |
|-----------------------------|--------|---------------------------------------------|
| 20 independent simulations, NPT-MD | 50 ns   | Hexapeptide-ACE2, explicit solvent (different starting positions) |
| 1 CORE-MD enhanced sampling | 200 ns  | Hexapeptide-ACE2, implicit solvent          |
| 1 CORE-MD enhanced sampling | 200 ns  | CoV-2 RBD-ACE2, implicit solvent            |
| 1 CORE-MD enhanced sampling | 200 ns  | CoV-2 RBD-ACE2, hexapeptide, implicit solvent |
the total number of frames in the trajectory $N_t$. We define the relative affinity by the fraction of the affinity $\eta$ divided by the maximal affinity $\eta_{\text{max}}$ measured for the specific system. The total affinity $\epsilon$ is given by the logarithm of the relative affinity:

$$
\epsilon = \log\left(\frac{\eta}{\eta_{\text{max}}}\right),
$$

(13)

We define the free energy $\Delta F$ by the probability $P$ along two order parameters (i.e., the distances $d_1$ and $d_2$ between pairs of atoms):

$$
\Delta F = k_B T \log\left(\frac{P}{P_{\text{min}}}\right),
$$

(14)

where $P_{\text{min}}$ stands for the minimal probability by which the histogram is populated. We assessed the convergence of the 20 NPT-MD simulations and CORE-MD simulation of the hexapeptide-ACE2 system using the average root mean-square deviation of the individual distances $d_j$ and the final value:

$$
\langle d_j - d_{j_{\text{final}}} \rangle = \frac{1}{N} \sum_{i<j} \sqrt{(d_{ij} - d_{j_{\text{final}}})^2},
$$

(15)

over N distances. We used the GROMACS version 4.6 package for the equilibrium MD simulations and a modified GROMACS version 4.5.5 for the CORE-MD simulations (36). We identified the preferential binding site of the hexapeptide at ACE2 through a distance-based clustering. We then used the conformation of the hexapeptide at ACE2 for the calculation of protein interaction energies using the PRODIGY program (37). We modeled the individual hexapeptide conformers using the PyMOL modeling program (38).

RESULTS AND DISCUSSION

Simulations of hexapeptide binding to ACE2

We tested the affinity of the hexapeptide to the ACE2 protein in 20 independent equilibrium MD simulations over a total simulation time of 50 ns. For this first set of simulations, we modeled 20 different starting conformations of the hexapeptide at an approximate distance of 1 nm away from the potential binding site between ACE2 and CoV-2 RBD. To examine the specific affinity of the hexapeptide for binding sites at ACE2, we determined the complete Ca-Ca distance matrix and averaged over all 20 trajectories. We find that the hexapeptide binds with 55% of the total affinity to the interface between the N-terminal helix and a $\beta$-sheet located at Glu329 and a lowered contact propensity of 43–50% to the residues Asn330 and Trp328 (see region (4) in Fig. 2, a and c). We observe another contact cluster at Asp382 and Met383, in which the affinity reaches values of 13 and 15%. A third contact cluster is located at Thr55, in which the affinity of the hexapeptide to ACE2 reaches a value of 21% (see Fig. 2, a and c).

In an enhanced MD simulation, we simulated the binding of the hexapeptide to ACE2 in implicit solvent. We used this simulation to cross-validate our equilibrium MD simulations. In the enhanced MD simulation over 200 ns, we observe approximately identical binding patterns of the hexapeptide to the surface of ACE2. We observe a first cluster of contacts at Gly354 with an affinity of 27%. We find that a second contact cluster with a propensity ranging from 80 to 100% is located at Trp328 and Glu329 (see region (4) in Fig. 2, b and d). We observe another contact pattern at Gln325 with a propensity of 96%. A fourth contact cluster is located at Leu132 with a relative propensity equal to 56%. Finally, we observe a last cluster of contacts at the N-terminus of ACE2 between the residues Ser124 and Gly130 with affinities ranging from 1 to 71% (see regions (2) and (3) in Fig. 2, b and d). An additional minor contact formation with a propensity of 2% resides at Glu57 (see region (1) in Fig. 2, b and d). To assess the convergence of the simulations, we measured the average root mean-square deviation of the distances from their final value (see Fig. 2, e and f). In the set of 20 NPT-MD simulations, we observe that the average root mean-square deviation decreases to a value below 0.5 nm at $\sim$30 ns, which shows that the simulation length of 50 ns is sufficient for a convergent sampling (see Fig. 2 e). The CORE-MD simulation over 200 ns in implicit solvent shows that the hexapeptide accesses five different states (see Fig. 2 f).

Our set of 20 equilibrium MD simulations agrees with the enhanced MD simulation on the general contact patterns of the hexapeptide at ACE2. In both sets of simulations, we find a major binding pattern in the vicinity of the N-terminal region of ACE2, where specifically Arg4 binds to Asn322, which is in agreement with the experimental study (24). The residues Tyr3 and Tyr5 are interacting with Ala387 in a hydrophobic binding mode (see Fig. 3, a and b). We conclude that the hexapeptide binds preferentially to the N-terminal helix and the helical interface close to the N-terminus, which indeed blocks the binding interface between CoV-2 RBD and ACE2 (19,20). Based on our findings, the hexapeptide shows a high affinity for the ACE2 binding region, which has the potential to inhibit CoV-2 RBD activation, membrane fusion, and the viral entry into the human cell (24). Subsequently, we used the conformation of the hexapeptide at ACE2 to model five further peptide variants and used a protein binding energy predictor (37) to determine the interaction strength of the models with ACE2 (see Fig. 3, c and d). We find that the hexapeptide YKYRYL binds with $-7.4$ kcal/mol and $K_d = 3.4 \times 10^{-7}$ M. A modification of the C-terminal residue to arginine and a hydrophobic modification at the position 4 to Leu leads to a lower interaction energy as we find for the models YNYLYL and YNYLYR ($\Delta G = -6.8$ and $-7.1$ kcal/mol). A mutation at the position two to Leu has only a moderate effect and leads to an interaction energy equal to $-7.3$ kcal/mol. In contrast to the other variants, we found that Lys at position two should remain conserved, whereas a replacement of Arg at the position 4 with Asn increases the affinity of the hexapeptide to energies equal to $-7.6$ kcal/mol. The conformation with the lowest dissociation constant $K_d$ is the variant...
YKYNYI, in which the C-terminal Ile stabilizes the interaction, leading to a value of $K_d = 2.8 \times 10^{-6}$ M. Finally, we state that the hexapeptide variants YKYNYI and YKYNYL contain potential alternative sequences for the binding to ACE2 and the inhibition of CoV-2 RBD activation.

**Simulations of CoV-2 RBD ACE2 assembly formation**

We tested the effect of the hexapeptide on the binding process of CoV-2 RBD on ACE2 (see Figs. 4 and 5). Therefore, we used a starting structure in which CoV-2 RBD is separated by a distance of 2.2 nm away from the surface of ACE2 (see Fig. 1, c and d). We simulated the system in and without the presence of the hexapeptide using CORE-MD enhanced sampling. In the simulation of binding of CoV-2 RBD to ACE2, the hydrophilic interface formed by the loop region between the $\beta$-sheets of CoV-2 RBD rotates away from the surface of ACE2, mainly because of an electrostatic repulsion. In a comparatively fast translatory process, CoV-2 RBD binds to the N-terminal helix (blue) of ACE2 (see Fig. 4, a and c). The interface between CoV-2 RBD and ACE2 is mainly stabilized by hydrophobic interactions between residues in the range between Leu535 and Thr351 (CoV-2 RBD) and Gln60 to Glu75. A hydrophobic interaction between Leu63 and His537 plays a major role in the stabilization of CoV-2 RBD at ACE2 (see Fig. 4 e). The relaxed final conformation of CoV-2 RBD at ACE2 is rotated by $\sim 90^\circ$ in its attached orientation when we compare the structure in an overlay with the experimental x-ray structure (PDB: 6M0J (19)) (see Fig. 5 a). Additionally, the global contact pattern changed from a hydrophilic interface to a hydrophobic interaction at a different region of CoV-2 RBD, which is initialized by a rotatory motion in the beginning of the simulation that is induced by an electrostatic driving force.
In the simulation of CoV-2 RBD binding to ACE2 in the presence of the hexapeptide, we observe a fast binding process of the hexapeptide to CoV-2 RBD at Glu465 (CoV-2 RBD) and Lys2 (hexapeptide). We find a secondary contact between the hexapeptide and CoV-2 RBD between Ser349 (CoV-2 RBD) and Arg4 (hexapeptide) in the initial stage of the simulation. The hexapeptide then diffuses along the surface of CoV-2 RBD until it binds strongly to Glu465 (see Fig. 4, d and f). An initial rotatory process of CoV-2 RBD is highly analogous to the simulation without the hexapeptide, in which the binding motif of CoV-2 RBD rotates away from the surface of ACE2 because of an electrostatic driving force. In the implicit solvent environment, the formation of the contact interface is driven by the surface charge of CoV-2 RBD and ACE2. Therefore, the formation of a contact interface between polar residues as shown in the PDB structure is less probable. This behavior can potentially change at high salt concentrations. In contrast to the simulation without the hexapeptide, we find that CoV-2 RBD attaches only weakly at the peripheral region of the N-terminal helix 4 nm away from the conformation without the hexapeptide (see Figs. 4, b and d and 5 b). In this case, we again emphasize that the hexapeptide changes the electrostatic patterns, leading to a change in the structure of the assembly. The hexapeptide binds to CoV-2 RBD, leading to the weak attachment of CoV-2 RBD to ACE2. We anticipate that this conformation corresponds to an inhibited state, in which CoV-2 RBD does not become activated, and the process of membrane fusion might get inhibited because of the low affinity of CoV-2 RBD for ACE2. Because of thermal fluctuations and longer timescales, CoV-2 RBD might dissociate away from ACE2, which would inhibit CoV-2 activation.

We were surprised by the high specificity with which the hexapeptide bound to ACE2 and CoV-2 RBD. Because we observed that the hexapeptide inhibits the binding process of CoV-2 RBD, we performed a BLAST search over all organisms that contain the specific fragment in their protein sequences (39,40). Surprisingly, we found that 47 out of 50 hits in the sequence search returned SARS CoV organisms, whereas only three hits were contained in bacteria, which shows that the hexapeptide pattern preferentially occurs for SARS CoV but not in human proteins (see Fig. 5 c). That result shows that an a priori affinity for another function in the human organism can be excluded, which makes the hexapeptide a suitable candidate as a potential drug. When we analyzed the sequence of CoV-2 RBD, we find a hexapeptide sequence YNYLYR, which contains the same Tyr repeat at the positions 1, 3, and 5 but different residues at the positions 2, 4, and 6, which might be an indicator that Tyr at the positions 1, 3, and 5 is imminent for the specificity of CoV-2 RBD (see Fig. 5 d). However, we found that this hexapeptide sequence leads to the lowest interaction energy $\Delta G = -6.8 \text{ kcal/mol}$ as we found in a modeling approach using the preferential hexapeptide ACE2 binding site as a structural model (see Fig. 3, c and d). We only can speculate that the amino acids at the positions 2, 4, and 6 are affecting the relative affinity of the fragment for
the ACE2 receptor, whereas we find that Tyr at the positions 1, 3, and 5 is essential for the binding. We assume that Tyr at the positions 1, 3, and 5 has to be conserved for the design of a peptide mimetic used as a potential drug against SARS CoV-2, whereas the hexapeptide sequence YKYRYL inhibits the viral interaction with ACE2, as we have shown in this work. Finally, we conclude that binding of CoV-2 RBD to ACE2 is unexpectedly highly heterogeneous, which is also the case for the interaction of the hexapeptide with ACE2. We anticipate that the CoV-2 RBD-ACE2 interaction (as well as the hexapeptide-ACE2 complex) depends on the ionic strength. At high ionic strengths, a polar CoV-2 RBD-ACE2 binding interface as given in the experimental structure might be stabilized in a strong field of surrounding ions and water (19,41).

CONCLUSIONS

In this article, we investigated the binding process of a fragment of the SARS CoV spike protein receptor domain (CoV RBD), the hexapeptide YKYRYL on the ACE2 receptor, and its effect on the assembly formation and activation of CoV-2 RBD at ACE2. In agreement with an experimental study, we find a high affinity of the hexapeptide to the binding interface between CoV-2 RBD and ACE2, which we investigated using 20 independent equilibrium MD simulations over a total of 1 μs and a 200-ns enhanced MD simulation. We then evaluated the effect of the hexapeptide on the binding process of CoV-2 RBD to ACE2 in long-time enhanced MD simulations. In that set of simulations, we found that CoV-2 RBD does not bind
FIGURE 5 Structural overlays of the PDB structure (PDB: 6M0J) of CoV-2 RBD in complex with ACE2 (green) and the two final structures from the enhanced MD simulations without (a) and in the presence of the hexapeptide (b) (cyan). (c) Shown is a list of SARS CoV viruses as a result from a Basic Local Alignment Search Tool search over the protein sequence space of all organisms. Surprisingly, the hexapeptide fragment preferentially occurs in SARS CoV viruses, which makes it suitable as a potential drug because of its dissimilarity with human proteins. (d) Shown is a hexapeptide fragment YNYLYR in SARS CoV-2 RBD (PDB: 6M0J, chain E), indicating that the tyrosine repeat at the positions 1, 3, and 5 might be important for the design strategy of a potential peptide mimetic for the treatment of SARS CoV-2 infections. To see this figure in color, go online.
to ACE2 with the binding motif shown in experiments, but it rotates because of an electrostatic repulsion and forms a hydrophobic interface with ACE2. Surprisingly, we observed that the hexapeptide binds to CoV-2 RBD, which has the effect that this protein only weakly attaches to ACE2 so that the activation of CoV-2 RBD might be inhibited in this case. Our results indicate that the hexapeptide might be a possible treatment option that prevents the viral activation through the inhibition of the interaction between ACE2 and CoV-2 RBD.

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