

**In silico Discovering STRA 6 Vitamin A Receptor, as a Novel Binding Receptor of COVID-19**

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**ABSTRACT**

A global pandemic of pneumonia caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in Wuhan, China, at the end of 2019. Although, the ACE2 receptor has been demonstrated to be the main entry receptor of COVID-19, but our docking analysis, predicted and discovered a novel receptor termed STRA 6 that may play a critical role in the pathogenicity of COVID-19. STRA6 receptor expressed in many organs and immune cells, upregulated by retinoic acid jm6 (STRA 6) was the first protein to be identified in a novel category of proteins, cytokine signaling transporters, due to its ability to function as both a cell surface receptor and a membrane protein that binds to retinol binding protein facilitating cellular uptake of retinol. The primary ligand of STRA6 (vitamin/retinol) was shown to be drastically reduced during COVID-19 infection, which agrees with our findings. We analyze the STRA6 and ACE2 receptor networks to predict the specific association among certain other proteins which might rely on similar functionality. Molecular docking showed a high affinity between the Spike protein with STRA6, the docking score of COVID-19 spike protein with STRA6 (-354.68) kcal/mol was higher than the docking score of spike protein with ACE2 (-341.21) kcal/mol. Results of MD simulations revealed significant stability of the spike protein with STRA6 up to 100 ns. SARS-CoV-2 spike protein binds strongly and directly to STRA6. Which are highly expressed in Lymphatic system revealed significant stability of the spike protein with STRA6 up to 100 ns. SARS-CoV-2 spike protein binds strongly and directly to ACE2 receptor. This study paves the way towards understanding the complex mechanism of COVID-19 infection complications such as immune suppression and ineffective RIG-I pathway. Restoring the balance between the STRA6 and ACE2 in the context of spike protein RBD may be promising target in SARS CoV-2 Pathogenesis and may reveal new drug targets for new variants of COVID-19.

**Keywords:** COVID-19, STRA6, ACE2, Molecular docking.

**INTRODUCTION**

Normal cellular function depends on Vitamin A homeostasis. Plasma Retinol-Binding Protein (RBP) is the only specialized transporter of retinol, the most common form of Vitamin A, in the plasma. By recognizing RBP-retinol and triggering retinol release and internalization, the integral membrane receptor STRA6 initiates and controls cellular uptake of Vitamin A.¹ Due to its capacity to function as both a membrane protein and a cell surface
receptor, which allows it to attach to retinol binding protein, STRA6 is a particularly significant receptor. It was discovered to be the first protein to be recognized as a cytokine signaling transporter. Because of the critical function of Vitamin A in the immune cell development, STRA6 was found to be expressed on all subsets of peripheral blood mononuclear cells at varying amounts. A recent study showed that all T cell, monocyte, natural killer cell and dendritic cell subsets expressed the retinol binding receptor (STRA6). STRA6 initiates cellular retinol uptake, in immune cells for improving the immune system homeostasis in various populations. The association of intracellular proteins with Vitamin A absorption mediated by STRA6 from holo-retinol/retinol binding protein complex (holo-RBP) has been demonstrated by several independent investigations and the mechanism by which it joins to specific intracellular proteins has been explained. It was recently showed that Single Nucleotide Polymorphisms or mutations (SNPs) in STRA6 are connected with the recurrence of type 2 diabetes in humans. Moreover, Pasutto et al. reported that STRA 6 mutations associated with lung malformations and many heart, eye, diaphragm as well as retardation in mentality as in syndrome of Matthew-Wood in humans, validating its reported functions in Vitamin A uptake by cells as Vitamin A/retinoic acid is very critical in the process of organogenesis. STRA 6 mutations results in a broad spectrum of complication related to malformations counting congenital heart defects, lung hypoplasia, anophthalmia, alveolar capillary dysplasia, diaphragmatic hernia, and mental retardation.

Recent findings showed that mutations in the gene of STRA 6 are connected to the congenital microphthalmia of eye malformations, coloboma and anophthalmia. STRA 6 genetic null mutation in mice model leads to significant reduction of retinoid in the neurosensory retina and retinal pigment epithelium, diminished eye morphology and visual responses, despite the fact the last-mentioned complication is not as serious as in individuals with mutant STRA6. According to a recent publication, STRA 6 is not only a receptor of Vitamin A transporter, but it can also act as a cytokine receptor. Upon attaching to holo-RBP, STRA 6 is directly phosphorylated at its region of tyrosine residue 643, which, in turn, triggers and recruits activation of STAT 5 and the Janus Kinase 2 gene (JAK2).

STRA 6 seems to be very important receptor and transporter of Vitamin A which critically participate in synthesis of retinoic acid which is the active and the main Vitamin A metabolite. All animals need a nutrient that contains Vitamin A. It is required for the proper process of vision in its form of retinaldehyde (retinal); as Retinoic Acids (RAs), it provides ligands for RAR (retinoic acid receptor) and RXR (retinoid X receptor) nuclear receptor transcription factors. Consequently, retinoid metabolism affects numerous biological processes with many disease implications from viral infection and cancer to blindness. In the world Vitamin A deficiency is the third most popular nutritional deficiency, affecting of millions of children and pregnant women life.

Retinoic Acid (RA) is a morphogen and important metabolite synthesized from Vitamin A (retinol). Two dehydrogenase-catalyzed enzymatic reactions are essential for the production of RA from retinol. Vitamin A (Retinol) is converted to retinal, which is then converted to RA. The RA interacts with Retinoic acid X Receptor (RXR) and Retinoic Acid Receptor (RAR) which then regulates the expression of targeted gene. Based on the investigations and previous researches it is clear that RA play a major modulatory function in the immune system. Actually, retinol is an important hormone and immune system regulator. It participates with zinc for improving the function of the immune system. Retinoids are molecules that possess qualitative activity relative to all-trans retinol (Vitamin A), that includes all-trans-Retinoic Acid (RA) retinyl-esters and all-trans retinal. RA is the biologically active retinoid metabolite that, works through its receptors RA receptors (RAR β, α and γ) regulates the generation of various genes involved many biological pathways including both innate and adaptive immune responses. Retinoids act as enhancers of the T-cell mediated innate immune responses and adaptive immunity via induction of antigen presenting Dendritic Cells (DCs), NK cells and Innate Lymphoid Cells (ILCs).

It has been established that retinoic acid induces gut-homing receptors on B cells, T cells and ILCs. A mounting body of evidence indicates that RA exerts far-reaching impact on fate and functional differentiation of these lymphocytes. Retinoids can directly stimulate the messenger RNA (mRNA) expression of Interferon-Stimulated Gene (ISG), including IFN Regulatory Factor 1 (IRF-1) and Retinoic acid-inducible Gene I (RIG-I).

Furthermore, retinoic acid plays critical physiological roles in synaptic plasticity, learning and memory, hormone production, and adult neurogenesis. Retinoic acid insufficiency in the olfactory epithelium, both in mouse and chick models, causes progenitor cell maintenance failure and, consequently, olfactory neurons differentiation is not maintained. An explant system showed that renewal of olfactory neurons is inhibited if retinoic acid synthesis was failed in the olfactory epithelium. In the immune system, Retinoic Acid (RA), metabolite of Vitamin A is known for its critical function in increasing gut-homing molecules in B and T lymphocyte cells, boosting tolerance and regulatory T cells (Tregs). Synthetic and natural retinoids also have potent inhibitory effects on replication of many viruses, such as MeV, cytomegalovirus, influenza, norovirus and Hepatitis B Virus (HBV). There is additional evidence that retinoid signaling activation can effectively suppress coronaviruses.

Our docking study reveals that COVID-19 spike protein binds directly to the integral membrane receptor (STRA 6). STRA 6 mediates cellular uptake of retinol (Vitamin A) by recognizing a molecule of RBP-retinol to trigger release and internalization.
of retino. Therefore COVID-19 may lead to down regulation of STRA 6 receptor leading to inhibition the regulatory function of retinoic acid and helps in existing of pre- and post-covid-19 infection symptoms and complications such as immune suppression, ineffective RIG-I pathway and interferon inhibition.

**MATERIALS AND METHODS**

**Sequence Retrieval**

The amino acid sequence of SARS CoV-2 spike protein with STRA6 and ACE2 PDB (7DMU, 5SY1) for the Spike-ACE2 and STRA6 receptor was retrieved from the protein data bank in FASTA format as per earlier researchers, to determine the 3-D structure of the target protein for further conformational investigations.

**Molecular docking**

HDOCK server (http://hdock.phys.hust.edu.cn/) was used to perform molecular docking to assess the binding mode of SARS CoV-2 spike protein with STRA6 and ACE2 (Angiotensin-converting enzyme 2). PDB accession numbers (7DMU, 5SY1) for the Spike-ACE2 and STRA6 receptor proteins illustrate their binding mechanism. To evaluate whether the spike protein of the virus binds with the STRA6 receptor or not and, if so, with what affinity the binding happens, we studied the Spike-ACE 2 and STRA6 receptor proteins. The HDOCK server was used to conduct docking studies on the Spike-ACE 2 and STRA6 receptor proteins.

The spike protein was put into the SAMSON software (https://www.samson-connect.net) and Discovery Studio Visualizer (https://discover.3ds.com/discovery-studio-visualizer-download) after downloading it from the PDB with accession number 6MOJ. Then, we separated the ACE 2 and Spike proteins to conduct docking between them. Finally, we used the result as a control result to test and know how complex the spike-STR A6 receptor is and how much its efficiency, after that, the HDOCK server performed global docking to sample putative binding modes using an FFT-based search method. Following that, the putative binding modes were evaluated.

**Protein-Protein Interaction Network Analysis**

The STRA6 receptor protein was submitted to STRING v10.0 (https://string-db.org/) to analyze functional STRA6-associated networks, where interactions were analyzed at a medium confidence level as per the investigation of earlier researchers.

\[ \text{RMSD}_x = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (r_i(t_x) - r_i(t_{0i}))^2} \]

**Molecular Dynamics Simulation**

The outcomes of simulations of molecular dynamics are immensely complex. The Cartesian values of each atom in the system are recorded together with each time interval of the trajectory, which can again fluctuate in length from hundreds to millions of steps. The RMSD (root-mean-square deviation) is a commonly used parameter for topological isolation across variables. It establishes the usual separation between a collection of atoms such as the backbone atoms of a protein. The number serves as a gauge of how much the protein shape has altered when the RMSD is calculated over two different sets of atomic coordinates, such as two points in the trajectory.

The RMSF (root-mean-square fluctuation) determines the quantum state mean distances throughout time (for instance, from a peptide sequence) from a point of comparison (typically the time-averaged position of the particle). Therefore, RMSF investigates the structural components that deviate most from their mean composition.

The trajectory files were analyzed using the g_rms and g_rmsf GROMACS utilities to obtain the RMSD and Root Mean Square Fluctuation (RMSF) values. The numbers of distinct intermolecular hydrogen bonds formed during the simulation were calculated using the g_hbond utility. The trajectory files of the Principal Component Analysis (PCA) were analyzed using the g_covar and g_anaeig utilities in GROMACS, in this order. The analysis of the secondary structure elements of the protein was performed using the do_dssp command, which utilizes the DSSP program.

**RESULTS AND DISCUSSION**

We use computational approaches to investigate the mechanistic process for investigating the role of the retinal receptor-STR A6 as a novel binding receptor in SARS CoV-2. We plan to anticipate the receptor usage infectivity of potential SARS-CoV to identify their anticipated genetic or historical origins based on the patterns of their spike proteins and the known particle structural features of the initial SARS-CoV RBD/ACE2 complexes. Here, we regularly employ this forecasting approach based on the recently released data of the 2019-nCoV RBD to offer hitherto unheard-of insights into the receptor utilisation and expected invading potential of 2019-nCoV.

Furthermore, we study the receptor binding and protease activations of SARS-CoV-2 spike using SARS-CoV spike as a baseline. Our results, which are based on computational analysis, highlight significant SARS-CoV-2 cell entry routes, where the virus’s spike protein selectively attaches to with an integral receptor complex, likely facilitating signal transduction, cell transmissibility, and widespread transmission (STRA 6). The intention was to learn more about the molecular mechanism.
as per earlier researchers, through which the SARS-CoV-2 virus causes patients to have difficult symptoms by examining the binding affinity and mode of interaction between the two proteins. This might pave the way for therapeutic strategies that do not only rely on ACE2 to make first contact with the spike protein of the virus. By creating and docking the spike protein, ACE2 protein, and STRA6 receptor using the HDOCK server, the mode and process of the interaction were examined in this study, and our analysis was compared to past studies.

We reinvestigate whether STRA6, particularly recognises RBP-retinol and encourages its escape and enculturation, improves Retinol (Vitamin A) absorption into cells. The findings contradict prior claims about SARS-CoV-2 that retinol and retinoids are efficient therapies for COVID-19 sickness and associated etiologically ambiguous symptoms. Because of our deterministic explorations, which are very remarkable methods where Novel Binding Receptor in SARS CoV-2 provides ground-breaking feedback to regulate RBD/ACE2 complexes in the context of Spike proteins to boost attempt to escape immunologic regulatory, the current study offers a novel insight of potential therapeutic strategies by targeting SARS-CoV-2 specific sites.

Protein-protein docking (STRA6 and SARS CoV-2 spike protein)

By using molecular docking, the molecules in a libraries are compared based on their potential for the selected receptors as per the role of Dias, de Azevedo. The folding of the biomolecules into the cavities of the receptor is necessary for the binding energy, which depends on a number of interactions, including charge transfer, hydrogen bonds, Van der Waals interactions, and others. We observed that Hydrogen bonding can be ordinary or non-conventional, therefore the production of regular hydrogen bonds (H-bonds) between molecules with adequate functional groups that may serve as H-bond acceptors is dependable as per earlier research. The static phase of the receptor serves as the foundation for molecular docking screening, thus it’s critical to understand the MD trajectories across this interaction between receptor and ligands as well as the change in energy throughout dynamics.

The interactive residues of the target protein STRA6 and the ligand spike protein can aid the design and development of more efficient and specific drugs for their target protein. The docking of STRA6 target protein with the viral spike protein revealed the involvement of the spike protein in the extracellular and membrane part of the STRA6 receptor. It showed the amino acid residues of STRA6 interacting with those of the spike protein, which are responsible for the protein-protein complex formation. The STRA6-spike protein complex (PDB ID 5SY1 and 6LZG, respectively) reveals that chains A and B have Align_lengths of 582 and 194, and then the quarry coverage of 0.793 and 1.000 and sequence identity of 96.2% and 100.0%, respectively. The surface view of the complex indicates that the binding pocket of the STRA6-spike and spike-ACE2 protein complexes have RMSD values of 189.44 Å and 1.00 Å, respectively.

The docking scores are -341.21, and -354.68 kcal/mol, and the quality of the ACE receptor and the ligand represented by the LGscore and MaxSub scores are 2.416, 0.147, respectively, confirming the correctness of the structures. On the other hand, the STRA6 receptor protein’s LGscore and MaxSub scores are 5.056, and 0.217, showing that the structures are very good and correct for the spike ligand and the receptor protein, as seen in Table 1. The RDB binding motif outside the cell, the STRA6 receptor’s membrane component outside the cell, and the

| Complex Template Information between (STRA6 – SARS CoV-2 Spike protein) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Molecule       | PDB ID | Chain ID | Align length | Coverage | Seq ID (%) | Docking Score | Ligand rmsd (Å) | LGscore | MaxSub: |
| Receptor (STRA6) | 5SY1 | A | 582 | 0.793 | 96.2 | -354.68 | 229.41 | 2.416 | 0.147 |
| Ligand (spike) | 6LZG | B | 194 | 1.000 | 100.0 | | 5.056 | 0.217 |

| Complex Template Information between (ACE2 – SARS CoV-2 Spike protein) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Molecule       | PDB ID | Chain ID | Align length | Coverage | Seq ID (%) | Docking Score | Ligand rmsd (Å) | LGscore | MaxSub: |
| Receptor (spike) | 6MOJ | B | 196 | 1.000 | 100.0 | -341.21 | 1.00 | 4.504 | 0.201 |
| Ligand (ACE2) | 7DMU | A | 597 | 1.000 | 100.0 | | 6.618 | 0.396 |
Receptor’s cytosolic third component are all shown in Figure 1. Figures 2-4 show the different views of STRA6 receptor, which bind to spike protein both extracellularly and at the membrane.

A virus’s Receptor-Binding Domain (RBD), which is part of its “spike” region and allows docking to host receptors for entrance into cells and invasion, is an integral part, as shown in Figure 1. Here, we defined the Receptor-Binding Domain (RBD) of the SARS-CoV-2 S protein as observed that the RBD protein was tightly coupled to human STRA6 receptors. SARS-CoV-2 RBD attracted the STRA6 receptor considerably better than SARS-CoV RBD and was able to prevent activation. The RBD is a core part of viral spike glycoprotein or a crucial factor that allows virus infections to bind to various bodily receptors like the STRA6 receptors and readily penetrate to transmit illness is the attachment of the RBD to the spike domains.

Substantial research has focused on SARS-CoV-2 spike protein changes in the RBD throughout this aspect. A minimal investigation has been carried out on deletions and mutations in the N-Terminal Domain (NTD), which lies close to the RBD. Many of these are found inside certain sheet-linking loops that are particularly long in SARS-CoV-2 compared to SARS-CoV or other related retroviruses. We show that both short- and long-contacts are required for the maintenance of the spike protein’s NTD loops in Figure 1, which are both essential for being detected by various autoantibodies. Isolates demonstrating great infectiousness may have an impact on the data of NTD loops, similar to alterations in amino acids. In Figure 1, we can see the cytosol area and extracellular membrane, where SARS spike protein is mostly concentrated in the lysosome and localised in the ER or ERGIC area, as per earlier research on intracellular trafficking and localisation. The several new motifs found in the cytoplasm of the SARS spike protein may aid in the localization of the ER or ERGIC.

### Protein-Protein Interaction Network

The protein-protein interaction associative network for the STRA6 receptor through STRING server shows that the active interaction sources were set based on seven parameters: experiments, co-expression, gene fusion, co-occurrence, databases, text mining, and neighbourhood with a maximum of five interacting partners from both shells of interactions. The red colour node describes query proteins, and the other coloured nodes represent the first shell of interactors. The network interaction showed Interactions between STAR6 and other proteins have been observed. These proteins include RBP4 (Retinol-binding protein 4), which mediates retinol transport in blood plasma; TTR (Transthyretin), which transports thyroxine from the bloodstream to the brain; RBPI (Retinol-binding protein 1), which accepts retinol from the transport protein as shown in Figure 4.

### Binding energy analysis of STRA-6 and SARS CoV-2 spike protein complex

The interactive residues of the target protein STRA6 and the ligand spike protein may help design and develop potential anti-SARS CoV-2 drugs that are more efficacious and specific.
for their biological targets. The docking of STRA6 target protein with SARS CoV-2 spike protein reveals the involvement and interaction of the spike protein into the extracellular and membrane part of the STRA6 receptor and amino acids residues of STRA6. The corresponding distances for the residue contacts between proteins STRA6 and the spike protein are listed in Table 2.

**Molecular Dynamics (MD) Simulation**

In order to confirm the stability of the predicted docked ligand-ACE 2 and STRA6 complexes, a study of all-atom Molecular Dynamics (MD) simulations was carried out. Such a study would be helpful to get further understanding of the dynamic interactions between the ligand and the protein receptors 7DMU and 5SY1, as well as to assess the ligand’s major binding contacts with important enzymatic domain regions. Therefore, a 100 ns all-atom MD simulation took into consideration the expected ligand-protein interactions for both the ACE 2 and STRA 6 proteins. We looked at the dynamic behavior of the ACE 2 (7DMU) and STRA 6 (5SY1) receptor proteins in complex with SARS CoV-2 spike protein as a complex as a consequence of the docking study results mentioned above. Calculations were
made for the Root Mean Square Deviation (RMSD) and Root Mean Square Fluctuation (RMSF). The primary goal of the MD simulation studies was to investigate the protein’s positional and structural changes. Root Mean Square Fluctuation is a useful method for detecting regional changes throughout the chain of interactions involving a protein.

MD studies revealed the RMSF plot in Figure 5(A) and 5(B) for ACE 2–SARS CoV-2 spike protein complex and STRA6-SARS CoV-2 spike protein complex, respectively. An MD modeling investigation showed that simply changing the conformation of the N-terminal site in the range of 580:800, ACE 2 may successfully activate the biological pathway. The RMSF of the ACE 2 receptor protein in association with SARS CoV-2 spike protein was assessed, and the results showed that the protein has a high RMSF in the bound state that ranges from 0.6 to 5.6. The variations in RMSF suggest that the protein’s structure has changed as a result of the binding of its residues to the ligand. The involvement of these residues in the interaction with the ligand is shown by a large variation in RMSF at the N-terminal locations.

The residue position 690 had the most variation. The outcomes, therefore, demonstrate an active interaction between the ligand and the target leading to protein conformational changes. STRA6 activates at the C-terminal in the range of 250–500 and then in the middle in the range of 500–1000 with significant RMSF ranging from 1.3–10.5. The residue position 270 had the most variation.

During the MD simulations, RMSD was utilized to assess the stabilities of the ACE 2 and STRA6 complex with the SARS CoV-2 spike protein for 100 ns for each trajectory frame. The protein complexes’ time (ns) for frame x was calculated with respect to the original structures along the 100 ns trajectory using the provided trajectories. RMSD for ACE 2 was found to be 3.4 and 10.6 for STRA6 (Figure 6).

SSE structures such as α-helices β-strands were monitored throughout the simulation. Figure 7A and 7B report the SSE distribution by residue index throughout the protein structure. Figures 7C and 7D summarize the SSE composition for each trajectory frame over the course of the simulation. Figure 7E and 7F show each residue and its SSE assignment over time.
Our aim is very diverse to explore the mechanistic process for the investigation of Retinol Receptor-STRA6 as a Novel Binding Receptor in SARS-CoV-2 using some computational approaches where we strategize to anticipate the receptor usage infectivity of potential SARS-CoV to recognize their expected historical roots or genetic elements based on the patterns of their spike proteins and the known particle structural features of the initial SARS-CoV RBD/ACE2 complexes. Here, based on the newly published data of the 2019-nCoV RBD, we consistently use this forecasting methodology to provide unprecedented insights into the receptor use and anticipated capacity to invade 2019-nCoV. Here, using the SARS-CoV spike as a baseline, we investigate the receptor binding and protease activations of the SARS-CoV-2 spike. Our findings, which are based on computational analysis, reveal important SARS-CoV-2 cell ingress pathways, where spike protein from the virus specifically binds to an integral receptor complex, probably assisting in signal transduction, cell transmissibility, and broad transmission (STRA6). We extensively examine the method by which STRA6, which recognizes RBP-retinol and triggers its release and internalization, facilitates Retinol (Vitamin A) absorption into cells. The findings settle prior claims on SARS-CoV-2, where Retinol and retinoic acid are promising options for COVID-19 infection and its unknown etiological symptoms. Our Mechanistic Investigations are very surprising strategies where Novel Binding Receptor in SARS-CoV-2 provides breakthrough feedback to regulate RBD/ACE2 complexes in the context of Spike proteins to boost escaping immune regulation, that’s why the current investigation provides a novel insight into prospective treatment means via targeting SARS-CoV-2 specific sites.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS’ CONTRIBUTIONS

Mahmoud Elkazzaz, Israa M. Shamkh and Amr Ahmed: Conceptualization Mahmoud Elkazzaz, Israa M. Shamkh, Amr Ahmed, Abdullah Haikal, data curation, formal analysis, investigation, methodology, software, validation, visualization, writing – original draft, writing – review, editing, validation, visualization, writing – original draft, writing – review and editing.

ABBREVIATIONS

STRA6: Signaling Receptor and Transporter of Retinol; ACE2: Angiotensin-converting enzyme 2.

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