STRA6, as A Novel Binding Receptor of COVID-19, A Breakthrough That could Explain COVID-19 Symptoms with Unknown Aetiology.

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Research Article

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Abstract

Background

The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected over 100 million people causing over 2.4 million deaths over the world, and it is still expanding. Although, ACE2 has been identified as the principal host cell receptor of 2019-nCoV, and it is thought to play a critical role in the virus's entrance into the cell and subsequent infection, many cells can be infected by COVID-19 while also expressing little or no ACE2. Furthermore, COVID-19 may case a variety of pre and post symptoms with unknown etiology . It was documented that COVID-19 infection leads to a loss of smell (anosmia) but The COVID-19 entry receptor, angiotensin-converting enzyme 2 (ACE2), is not expressed in the receptor of olfactory neurons, or its generation is limited to a minor fraction of these neurons. Moreover It was demonstrated that COVID-19 infects and kills lymphocyte thorough its ACE2 receptor. But numerous studies found that lymphocytes did not express ACE2 receptors or express it with a little, insufficient amount. It is clear from the information and findings presented and addressed below that COVID-19 not only binds to ACE2, but also to additional receptors, leading to existence of pre- and post-covid-19 symptoms which remain unexplained. As a result, discovering and identifying these receptors could lead to the development of new treatments that could suppress COVID-19 and reduce its severity and pathogenicity

Methods

The STRA6 receptor protein were submitted to the server for functional interaction associated network between partners for the STRING (Research Online of Interacting Genes/Proteins Data Basis version 10.0)13 .Docking study of each Spike -ACE 2 and STRA6 receptor protein were carried out using HDOCK server (http://hdock.phys.hust.edu.cn/). The binding mode of Spike -ACE 2 and STRA6 receptor protein is retrieved form the PDB https://www.rcsb.org/ with accession number (7DMU , 5sy1)

Results

Our results showed that COVID-19 Spike protein exhibited a high binding affinity for human STRA6 and a low binding energy with it. 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. Spike protein Receptor Binding Domain(RDB) of COVID-19 strongly and efficiently binds to STRA6 receptor, definitely to the RDB vital residues of RBP-binding motif located in STRA6 receptor. The docking of STRA6 target protein with spike viral protein revealed the involvement of the spike protein into the extracellular and membrane part of the STRA6 receptor and amino acids residues of STRA6 along with spike protein which make interactions and play an important role in formation of complexes. The corresponding distances about the residue contacts between proteins STRA6- Spike protein complex are documented here where the STRA6- Spike protein complexes binding site are the RDB of the CHOLESTEROL in STRA6 receptor which bind with interface residue(ARG 511A , VAL 512A THR 515A ALA 516A ASN 519A with interface residue degree (2.965 , 3.595 , 3.286 , 4.592 , and 4.235) representatively, also the ability of the spike to bind to RDB of the STRA 6 protein in the ILE 131C , MET 145C , HIS 86A with interface residue(4.961 , 4.953 and 3.271) representatively. STRA6- Spike protein complex with PDB ID (5SY1 , 6LZG) representatively ,the chain A ,B with Align – length (582 ,194) then the quarry coverage of proteins 0.793 and 1.000 with sequence identity 96.2 % and 100,0 % representatively. The surface view of complex reveals that the binding pocket of STRA6- Spike protein and Spike ACE 2 complexes with RMSD (189.44 Å , 1.00 Å) representatively and docking score (-341.21 ,-354.68) kcal/mol, the quality of the receptor and

the ligand are LGscore and MaxSub (2.416 , 0.147) where the structure are correct representatively for the STRA6 receptor protein, and LGscore and MaxSub ,(5.056 ,0.217) .

Conclusion

STRA6 is a critical regulator of many biological processes thorough initiating cellular retinol uptake, in different organs and tissues as in immune cells for improving the immune system homeostasis in various populations. Our docking study reveals that COVID-19 spike protein binds directly to The integral membrane receptor (STRA6) in addition to its binding sites of the cholesterol. STRA6 mediates cellular uptake of retinol (vitamin A) by recognizing a molecule of RBP-retinol to trigger release and internalization of retinol . Therefore COVID-19 may leads to downregulation of STRA6 receptor leading to inhibition the regulatory function of retinoic acid and cholesterol helps in existing of pre and post-covid-91 symptoms and complications including lymhopenia, Nuerogical disorders, Ineffective RIG-I pathway, Interferon inhibition, Cytokine storm, Diabetes, Hormonal imbalance, Thrombosis, and Smell loss. Therefore, we believe that this novel discovery that STRA6 receptor acts as a novel binding receptor for COVID-19 could explain many previously unexplained pre and post-covid-91 infection symptoms . Moreover, retinoic acid metabolism was found to be defective in COVID-19 (cytokine storm), sepsis, ARDS and SIRS .As a result reconstitution of the retinoid signaling may prove to be a valid strategy for COVID-19 management. We suggest that Vitamin A metabolites ,especially, retinoic acid will be promising and effective treatments for COVID-91 infection and its unknown aetiology symptoms. It worth mentioning that aerosolized all- trans retinoic acid and 13 cis retinoic acid is currently under clinical investigation (ClinicalTrials.gov Identifier: NCT05002530, NCT04353180)

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). STRA6 is a particularly important receptor. because it was found to be the first protein to be recognized as a cytokine signaling transporter, owing to its ability to work as both a membrane protein and a cell surface receptor that facilitates cellular uptake of retinol by attaching to retinol binding protein (2,3). 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)(3). STRA6 initiates cellular retinol uptake , in immune cells for improving the immune system homeostasis in various populations(3).Many independent studies confirmed that vitamin A uptake mediated by STRA6 from holo-retinol/retinol binding protein complex (holo-RBP) is joined to intracellular proteins (4,5) and the mechanism by which it joins to specific intracellular proteins has been explained (6).It was recently showed that single nucleotide polymorphisms or mutations (SNPs) in STRA6 are connected with the recurrence of type 2 diabetes in humans (7). Moreover, Pasutto et al. (7)reported that STRA6 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. STRA6 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(8).

Recent findings showed that mutations in the gene of STRA6 are connected to the congenital microphthalmia of eye malformations, coloboma and anophthalmia(7), (9) (10). STRA6 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 (11) .According to a recent publication, STRA6 is not only a receptor of vitamin A transporter, but it can also act as a cytokine receptor. Upon attaching to holo-RBP, STRA6 is directly phosphorylated at its region of tyrosine residue 643, which, in turn, triggers and recruits activation of STAT5 and the Janus Kinase 2 gene,(JAK2) (12).

STRA6 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 . Nutrients that contains Vitamin A is needed by all mammals. It is required for the proper process of vision in its form of retinaldehyde (retinal). (13) ; as retinoic acids (RAs), it provides ligands for RAR (retinoic acid receptor) and RXR (retinoid X receptor) nuclear receptor transcription factors (14). Consequently, retinoid metabolism affects numerous biological processes (15) , with many disease implications from viral infection and cancer to blindness(16,17) . In the world Vitamin A deficiency is the third most popular nutritional deficiency, affecting of millions of children and pregnant women life (18) .

Retinoic acid(RA) is a morphogen and important metabolite synthesized from vitamin A (retinol) (19). 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 regulate the expression of targeted gene (19).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(20) . Retinoids are a 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 (20) . 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 (21). 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)(21,22).

It has been established that retinoic acid induce gut-homing receptors on B cells , T cells and ILCs. A mounting body of evidence indicates that RA exert far-reaching impact on fate and functional differentiation of these lymphocytes(23). 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) (24,25,26) .Furthermore, retinoic acid plays critical physiological roles in synaptic plasticity, learning and memory(27), hormone production(27,28) and adult neurogenesis(27). 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(29) . 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) (30,31). 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) (32,33) (27-30). There is additional evidence that retinoid signaling activation can effectively suppress coronaviruses. (34).

Our docking study reveals that COVID-19 spike protein binds directly to The integral membrane receptor (STRA6). STRA6 mediates cellular uptake of retinol (vitamin A) by recognizing a molecule of RBP-retinol to trigger release and internalization of retinol(1). Therefore COVID-19 may leads to downregulation of STRA6 receptor leading to inhibition the regulatory function of retinoic acid and helps in existing of pre and post-covid-91 infection symptoms

and complications such as immune suppression (lymhopenia), Nuerogical disorders, ineffective RIG-I pathway, interferon inhibition, Cytokine storm, Diabetes, Hormonal imbalance, Thrombosis, and Smell loss.

Material And Methods

Preparation of COVID-19 S-protein and vitamin A STRA6 receptor structure

The 3D of the human coronaviruses spike -ACE2 protein of the Covid-19 with accession no. 7DMU was downloaded from PDB https://www.rcsb.org/ The protein structure was retrieved in the PDB format as an amino-acid length sequence and used to separate the structure of the spike protein from the SPIKE -ACE2 protein complex then redock th RDB of the spike protein with the RDB of the ACE2 again to get result to know the score of them as a reference result and dock RDB of spike protein against the 3d structure of STRA6 receptor (vitamin A) which is transported. The integral membrane receptor STRA6 mediates cellular uptake of vitamin A by recognizing RBP-retinol and RDB of cholesterol also to trigger release and internalization of retinol and the opening stat of the receptor(1), with accession no. 5sy1 was downloaded from PDB databases The protein structure was retrieved in the PDB format

Selection and preparation of the receptor proteins and ligand proteins

The 3D structure of Spike -ACE 2 and STRA6 receptor protein, which presented to determine the conservative residues of binding of Spike protein with the ACE to be a control results also Spike with STRA6 receptor .the structures were selected and defend to separate them to select the ligand protein and the receptor protein, Docking study of each Spike -ACE 2 and STRA6 receptor protein were carried out using HDOCK server For pre-docking, all water molecules and ligands were removed after determe the binding site of them to get the effective site to dock with the spike while hydrogen atoms were added to the target protein and RDB are defined in the STRA6 protein to determine the pocket for preparation for docking. In addition, the affinity minimization was performed using MOE software (https://www.chemcomp.com/Products.htm) and also 3DREFINE server (http://sysbio.rnet.missouri.edu/3Drefine/index.html) and. The docking system of the 3D structure binding models was built by using HDOCK server (http://hdock.phys.hust.edu.cn/).

Binding site determination of the Receptor proteins for docking

The published receptor protein Spike - ACE2 (Fig. 1) (Lan et al., 2020) was downloaded from RSCP protein data bank. Pre docking was carried out as described using SAMSON 2020 software and Discovery studio. The 17 interacting amino acid residues (GLN24, THR27, PHE28, ASP30, LYS31, HIS34, GLU35, GLU37, ASP38, TYR41, GLN42, LEU79, MET82, TYR83, ASN330, LYS353, GLY354) (Fig. 1) that represent bounded region of the ACE2 to the COVID 19 spike protein were previously reported (Lan, 2020) also the STRA6 receptor (Fig. 2) published protein RDB of the protein are docked into two sites the first RDB in the protein are really in the extracellular side and membrane which is for cholesterol which bind to the extracellular side, in The 10 interacting amino acid residues (ILE520 ASN519 THR515 LEU419 ILE416 ILE520 ASN519 THR515 LEU419 ILE416) that represent bounded region of the cholesterol to the STRA6 receptor protein the bounded ligands were analyzed with Discovery Studio Software (https://www.discngine.com/discovery-studio). but on the periphery of STRA6, a deep outer pocket is formed within the NTD (Fig. 2). and lined by two histidine residues (H41 and H160) along TM1 and TM4 and two tyrosine residues (Y130 and Y131) along TM3, all of which are conserved. A smaller pocket on the intracellular side of the NTD is lined by histidine (H145 and H86) and tyrosine (Y150 and Y200) residues, were the residues are selected to study the

interaction with the protein using HDOCK server as described before. The specific docking process and the grid were made for this specific region to find the binding ability of with the viral S-protein and STRA6 receptor protein.

(Fig. 1)

HDOCK server and docking parameter

HDOCK server (http://hdock.phys.hust.edu.cn/) is a highly integrated suite of homology search, template-based modeling, structure prediction, macromolecular docking, biological information incorporation and job management for robust and fast protein–protein docking the server automatically predicts their interaction through a hybrid algorithm of template-based and template-free docking. The HDOCK server distinguishes itself from similar docking servers in its ability to support amino acid sequences as input and a hybrid docking strategy in which experimental information about the protein–protein binding site and small-angle X-ray scattering can be incorporated during the docking and post-docking processes also it has detailed important information about the Complex Template Information in protein protein docking like the ID of the protein which is receptor and ligand protein ID of the chain in each protein which its used in docking complex then the alien length and this important information can allowed us to know where exactly the receptor protein are bind to ligand protein then the quarry coverage and sequence identity to know if the protein are realable and good or its un realable. Correspondingly, new challenges have been presented during the development process of molecular docking approaches, as seen by the community-wide experiment, Critical Assessment of Prediction of Interactions(CAPRI:https://www.ebi.ac.uk/pdbe/complexpred/capri/)14,15. First, with the rapid development of structural genomics16, more and more protein–protein complex structures are being experimentally determined. As such, more information about the binding interfaces of involved proteins is becoming available in the PDB1.In addition, information about The docking energy scores, The ligand RMSDs from the input structures or modeled structures by homology modeling and The interface residues within 5.0 Å from their interacting partner or each other, and the corresponding distances about the residue contacts between proteins may also be derived through an evolutionary analysis in sequences17 or deep learning18. However, how to efficiently incorporate such binding interface information into docking

Redocking of spike – ACE2 protein complex molecules

For the spike – ACE2 protein we separate the complex into two structure by using SAMSON 2020 software (https://www.samson-connect.net/elements.html) which chain A are the ACE2 receptor and chain B is spike protein receptor then we redock them against each other again the RDB resedues of the protiens are previously reported the docking made by using HDOCK server to get detailed information about the docking score also RMSD to compare the result with the main target of the result of the study which its docking spike protein with STRA6 receptor .

Docking of spike and STRA6 proteins molecules

For of spike and STRA6 proteins molecule docking are made between the chain B of the spike receptor separated structure and STRA6 chain C and A protein where the spike are the ligand proteins and the STRA6 are the receptor proteins to know and discover if the spike protein of the virus are bind with STRA6 receptor in a good binding affinity and RMSD to declare the mechanism of the interaction in in most COVID-19 symptoms with unknown etiology.

Protein-Protein Interaction Network

The STRA6 receptor protein were submitted to the server for functional interaction associated network between partners for the STRING (Research Online of Interacting Genes/Proteins Data Basis version 10.0)13 (Szklarczyk et al. 2007), with interactions examined at medium confidence.

Results

In this study, the Spike and STRA6 receptor protein was investigated for declare the mechanism of the interacting of the viral protein with the deferent symptoms of the patients and see the properties of the reaction for the first time, which could be used as alternative for therapeutic purposes. Here, the proteins of the Spike and STRA6 receptor were prepared and docked using HDOCK sever where the reaction are made between the spike protien and the STRA6 receptor for detection and declare the mode of action of the the mechanism

Selection and preparation and Binding site determination of the receptor proteins and ligand proteins

For the proteins structure of the ACE2 – Spike protein are downloaded from pdb database and prepare the structure by remove all water molecule and ligands while hydrogen atoms were added to the target protein and RDB are defined of cholesterol and calmodulin in the STRA6 protein are determine to get the pocket for preparation for docking. In addition, the affinity minimization was performed using MOE software and also 3DREFINE server and then we separate the two chain of the spike – Ace2 to get two separated structure to prepare for docking The docking system of the 3D structure binding models was built by using HDOCK server as described before

Redocking of spike – ACE2 protein complex molecules

After the preparation of the proteins by SAMSON software The docking of ACE2 target protein with spike viral protein which revealed the involvement of the spike protein into the extracellular and membrane part of the ACE2 receptor and amino acids residues of spike along with RDB of the ACE2 protein which make interactions and play an important role in formation of complexes. ACE2- Spike protein complex with PDB ID (7DMU),the chain B for spike ,A for ACE2 with Align – length (196, 597) representatively then the quarry coverage of proteins 1.000 and 1.000 because of the structure is crystal structure with sequence identity 100,0 %. The surface view of complex reveals that the binding pocket of Spike – ACE2 protein complexes with RMSD (1.00 Å) and docking score (-354.68) kcal/mol the quality of the receptor and the ligand are dependent upon LGscore and MaxSub which the score are (5.056 ,0.217) where the result are indicate the structure are very good and correct representatively for the Spike ligand protein see (Table 1) .

Docking of spike and STRA6 proteins molecules

The docking of STRA6 target protein with spike viral protein which revealed the involvement of the spike protein into the extracellular and membrane part of the STRA6 receptor and amino acids residues of STRA6 along with spike protein which make interactions and play an important role in formation of complexes. STRA6- Spike protein complex with PDB ID (5SY1, 6LZG) representatively ,the chain A ,B with Align – length (582 ,194) then the quarry coverage of proteins 0.793 and 1.000 with sequence identity 96.2 % and 100,0 % representatively. The surface view of complex reveals that the binding pocket of STRA6- Spike protein and Spike ACE 2 complexes with RMSD (189.44 Å, 1.00 Å) representatively and docking score (-341.21 ,-354.68) kcal/mol the quality of the receptor and the ligand are LGscore and MaxSub (2.416, 0.147) where the structure are correct representatively for the STRA6 receptor protein, and LGscore and MaxSub ,(5.056 ,0.217) where the structure are very good and correct representatively for the Spike ligand protein see (Table 1) .

Table 1

Complex Template Information between and Docking scores (spike protein, human STRA6 receptor protein) and (spike protein, ACE 2) where the PDB ID, chain ID of the protein, Aline length, coverage and seq ID, Docking scores, RMSD, LGscore and MaxSub which resulted from HDock

Complex Template Information between (STRA6 – SPIKE)									
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	-359.45	229.41	2.416	0.147
Ligand (SPIKE)	6LZG	B	194	1.000	100.0			5.056	0.217
Complex Template Information between (STRA6 – SPIKE)									
Molecule	PDB ID	Chain ID	Align_length	Coverage	Seq_ID (%)	Docking Score	Ligand rmsd (Å)	LGscore:	MaxSub:
Receptor (SPIKE)	7DMU	B	196	1.000	100.0	-354.68	1.00	4.504	0.201
Ligand (ACE 2)	7DMU	A	597	1.000	100.0			6.618	0.396

Analysis of binding energy in complexes

The interactive residues of target protein STRA 6 and ligand spike protein that will help the researchers to design and develop the drugs that are more efficient and specific for their target protein. The docking of STRA6 target protein with spike viral protein which revealed the involvement of the spike protein into the extracellular and membrane part of the STRA6 receptor and amino acids residues of STRA6 along with spike protein which make interactions and play an important role in formation of complexes the corresponding distances about the residue contacts between proteins STRA6- Spike protein complex are in Table 2 where the STRA6- Spike protein complexes binding site are the RDB of the **CHOLESTEROL to** STRA6 receptor which is bind with interface residue(ARG 511A, VAL 512A THR 515A ALA 516A ASN 519A with interface residue degree (2.965, 3.595, 3.286, 4.592, and 4.235) representatively also the ability of the spike to bing to RDB of the STRA 6 protein in the ILE 131C, MET 145C, HIS 86A with interface residue(4.961, 4.953 and 3.271) representatively

Table 2

contain the full details about the binding pocket of the RDB of the STRA 6 protein Receptor interface residue with the spike viral protein Ligand interface residue with their amino acid number and the RMSD of the interface residues

Receptor interface residue(s) STRA 6 protein		Ligand interface residue(s): spike viral protein		Receptor-ligand interface residue pair(s) STRA 6 - spike	
PHE 98A	4.825	THR 345	3.385	98A - 446	4.825
LEU 101A	2.600	ARG 403	3.484	101A - 445	2.600
GLU 121A	3.385	ASP 405	2.898	101A - 446	3.688
PHE 122A	3.261	ARG 408	3.542	121A - 345	3.385
ILE 125A	1.963	LYS 417	2.815	122A - 440	3.806
LEU 128A	3.081	ASN 440	1.963	122A - 441	3.261
LEU 129A	4.782	LEU 441	3.261	125A - 440	1.963
ARG 393A	2.898	SER 443	3.229	125A - 441	3.276
PRO 394A	2.945	LYS 444	3.081	128A - 443	3.229
ALA 395A	4.958	VAL 445	2.600	128A - 444	3.081
VAL 397A	2.104	GLY 446	2.397	128A - 445	3.690
CYS 398A	2.971	GLY 447	4.521	128A - 499	4.986
MET 400A	3.268	TYR 449	2.841	129A - 499	4.782
GLY 401A	3.923	TYR 453	4.496	393A - 405	2.898
SER 404A	2.828	LEU 455	3.064	393A - 408	3.542
TYR 405A	2.076	PHE 456	3.345	393A - 504	4.869
ALA 407A	4.932	THR 478	2.965	394A - 403	4.451
ALA 408A	2.397	CYS 480	4.585	394A - 405	4.088
PHE 409A	3.185	ASN 481	4.31	394A - 505	2.945
LEU 412A	4.520	VAL 483	3.595	395A - 505	4.958
ARG 511A	2.965	GLU 484	2.855	397A - 501	4.170
VAL 512A	3.595	GLY 485	3.286	397A - 502	3.186
THR 515A	3.286	PHE 486	3.152	397A - 503	4.476
ALA 516A	4.592	ASN 487	3.408	397A - 504	4.045
ASN 519A	4.235	TYR 489	1.928	397A - 505	2.104
LEU 530A	4.709	GLN 493	3.539	398A - 505	2.971
LEU 531A	1.928	SER 494	4.607	400A - 500	3.268
ASN 532A	2.782	GLY 496	3.025	400A - 501	3.411

Receptor interface residue(s) STRA 6 protein		Ligand interface residue(s): spike viral protein		Receptor-ligand interface residue pair(s) STRA 6 - spike	
VAL 535A	3.116	GLN 498	2.076	400A - 502	3.860
PHE 538A	2.815	PRO 499	4.782	401A - 498	4.759
ASP 539A	4.610	THR 500	3.268	401A - 500	3.923
PRO 540A	3.539	ASN 501	3.038	401A - 501	4.401
ARG 543A	2.466	GLY 502	3.186	404A - 446	3.954
CYS 544A	4.859	VAL 503	4.476	404A - 498	2.828
CLR 701A	2.855	GLY 504	4.045	404A - 500	4.395
		TYR 505	2.104	404A - 501	4.772
				405A - 449	4.362
				405A - 496	3.025
				405A - 498	2.076
				405A - 501	3.038
				405A - 505	4.742
				407A - 446	4.932
				408A - 446	2.397
				408A - 447	4.521
				408A - 449	2.841
				408A - 498	4.101
				409A - 449	3.185
				412A - 449	4.520
				511A - 478	2.965
				511A - 486	3.152
				512A - 480	4.585
				512A - 481	4.318
				512A - 483	3.595
				512A - 484	4.812
				515A - 484	3.589
				515A - 485	3.286
				515A - 486	3.288
				516A - 484	4.592

Receptor interface residue(s) STRA 6 protein	Ligand interface residue(s): spike viral protein	Receptor-ligand interface residue pair(s) STRA 6 - spike	
		519A - 484	4.235
		530A - 489	4.709
		531A - 455	4.937
		531A - 456	3.806
		531A - 489	1.928
		532A - 486	3.480
		532A - 487	3.408
		532A - 489	2.782
		535A - 489	3.116
		538A - 417	2.815
		538A - 453	4.823
		538A - 455	3.064
		538A - 456	3.345
		538A - 493	4.770
		539A - 455	4.610
		540A - 453	4.496
		540A - 493	3.539
		540A - 494	4.607
		543A - 403	3.484
		543A - 505	2.466
		544A - 505	4.859
		701A - 483	4.559
		701A - 484	2.855
		405A - 449	4.362
		405A - 496	3.025
		405A - 498	2.076
		405A - 501	3.038
		405A - 505	4.742
		407A - 446	4.932
		408A - 446	2.397

Receptor interface residue(s) STRA 6 protein	Ligand interface residue(s): spike viral protein	Receptor-ligand interface residue pair(s) STRA 6 - spike	
		408A - 447	4.521
		408A - 449	2.841
		408A - 498	4.101
		409A - 449	3.185
		412A - 449	4.520
		511A - 478	2.965
		511A - 486	3.152
		512A - 480	4.585
		512A - 481	4.318
		512A - 483	3.595
		512A - 484	4.812
		515A - 484	3.589
		515A - 485	3.286
		515A - 486	3.288
		516A - 484	4.592
		519A - 484	4.235
		530A - 489	4.709
		531A - 455	4.937
		531A - 456	3.806
		531A - 489	1.928
		532A - 486	3.480
		532A - 487	3.408
		532A - 489	2.782
		535A - 489	3.116
		538A - 417	2.815
		538A - 453	4.823
		538A - 455	3.064
		538A - 456	3.345
		538A - 493	4.770
		539A - 455	4.610

Receptor interface residue(s) STRA 6 protein	Ligand interface residue(s): spike viral protein	Receptor-ligand interface residue pair(s) STRA 6 - spike	
		540A - 453	4.496
		540A - 493	3.539
		540A - 494	4.607
		543A - 403	3.484
		543A - 505	2.466
		544A - 505	4.859
		701A - 483	4.559
		701A - 484	2.855
		519A - 484	4.235
		530A - 489	4.709
		531A - 455	4.937
		531A - 456	3.806
		531A - 489	1.928
		532A - 486	3.480
		532A - 487	3.408
		532A - 489	2.782
		535A - 489	3.116
		538A - 417	2.815
		538A - 453	4.823
		538A - 455	3.064
		538A - 456	3.345
		538A - 493	4.770
		539A - 455	4.610
		540A - 453	4.496
		540A - 493	3.539
		540A - 494	4.607
		543A - 403	3.484
		543A - 505	2.466
		544A - 505	4.859
		701A - 483	4.559

Receptor interface residue(s) STRA 6 protein	Ligand interface residue(s): spike viral protein	Receptor-ligand interface residue pair(s) STRA 6 - spike	
		701A - 484	2.855

Protein-Protein Interaction Network

The protein-protein interaction associative network for the STRA6 receptor through STRING server. The active interaction sources were set based on the seven parameters including experiments, co-expression, gene fusion, co-occurrence, databases, text mining, and neighborhood. with a maximum of five interacting partners from both shells of interactions. The color nodes describe query proteins and the first shell of interactions, whereas white nodes are the second shell of interactors. The large node size represents characterized proteins and smaller nodes for characterized proteins which the number of nodes: 7, number of edges 10, average node degree 2.86, avg. local clustering coefficient 0.895, expected number of edges 6 and also PPI enrichment p-value 0.0973. The functional interactive network formed by STRA6 receptor protein was analyzed at the medium confidence level (0.40) has been shown in Figure. The protein was shown to have an interaction with

RBP4 Retinol-binding protein 4; Retinol-binding protein that mediates retinol transport in blood plasma, TTR ransthyretin; Thyroid hormone-binding protein. Probably transports thyroxine from the bloodstream to the brain, RBP1 Retinol-binding protein 1; Cytoplasmic retinol-binding protein. Accepts retinol from the transport protein STRA6, CALM3 Calmodulin 3 (phosphorylase kinase, delta); Calmodulin mediates the control of a large number of enzymes, ion channels,, CALM2 Calmodulin 2 (phosphorylase kinase, delta); EF-hand domain containing and CALM1 Calmodulin-1; Calmodulin mediates the control of a large number of enzymes, ion channels, aquaporins and other proteins with score (0.983, 0.881, 0.733, 0.551, 0.421 and 0.421) representatively. also its interact with deferent processes biological processes ,molecular function, cellular compounds, reactome pathways, disease gen associations Tissue expression and also the subcellular localization

Fig. represents the protein-protein interaction network of STRA6 receptor The color nodes describe query proteins and the first shell of interactors, whereas white nodes are the second shell of interactors. The large node size represents characterized proteins and smaller nodes for uncharacterized proteins.

Discussion

Surprisingly, our molecular docking based analysis showed that spike protein Receptor Binding Domain(RDB) of COVID-19 strongly and efficiently binds to STRA6 receptor, definitely to the RDB vital residues of RBP-binding motif located in STRA6 receptor. STRA6 receptor is a membrane receptor responsible for signaling and transporting of Vitamin A(Retinol) from plasma retinol binding protein (RBP) to our cells. In an outstanding manner, COVID-19 Spike protein exhibited high docking score with human STRA6 with low binding energy. The docking score of COVID-19 spike protein was stronger than the docking score of spike protein with ACE2. The docking score (-341.21 ,-354.68) kcal/mol) representatively. Based on these findings STRA6 may play a key role in COVID-19 pathogenesis and may explain the common pre- and post-COVID-19 symptoms of unknown etiology. Here we explained different mechanisms that could be associated with hijacking and invading STRA6 by COVID-19

COVID-19, JAK/STAT pathway, IFN-stimulated genes (ISGs) and Stra6

The main signaling pathway activated and initiated by Interferons (IFNs) is the pathway of Janus kinase/signal transducer and activator of transcription (JAK/STAT), which results in the expression of IFN-stimulated genes (ISGs), including numerous antiviral agents. Various strategies have developed by Viruses to antagonize the pathway of JAK/STAT to influence viral virulence and pathogenesis (35) .

Binding of holo-retinol/retinol binding protein complex (holo-RBP) to STRA6 enhances phosphorylation of STRA6, resulting in the activation and recruitment of STAT5 and JAK2, Stat5 full activation is essentials for Type I interferon-dependent gene transcription(36). The activation of JAK/STAT pathway leads to expression of STAT target genes, including IFN-stimulated genes (ISGs), numerous antiviral agents and suppressor of SOCS3, which inhibits cytokine signaling mediated by the JAK/STAT pathway, and PPARγ, which maintains homeostasis Of adipocyte lipid (9). Berry and colleagues showed that the STRA6 mutations would disrupt the above signaling cascade(37)(2)

Therefore, we suggest that COVID-19 block the action of stra6 leading to suppression of IFN-stimulated genes (ISGs) via deactivation of JAK/STAT signaling pathway.

COVID-19, STRA6 and IL-6

1- SOCS3 inhibition

Phosphorylation of STRA6 by JAK2 also triggers the recruitment and activation of STAT3 or STAT5 and their corresponding signaling cascades. Upon activation, STAT3 dimerizes and translocates to the nucleus to function as a transcription factor driving oncogenesis (22). STAT5 activation induces the expression of its target genes including suppressor of cytokine signaling 3 (SOCS3), a known inhibitor of insulin signaling, leading to insulin resistance and reduced responses to inflammatory cytokines (23,24). A study found that SOCS3 inhibit IL6 signalling with high potency and specificity(25).SOCS3 negatively regulates signaling of IL-6 in vivo preventing IFN-gamma-like responses in cells stimulated by IL-6(26).A cytokine storm linked to interferon-gamma was induced post SARS coronavirus infection, and this cytokine storm could be contributing to the immunopathological damage seen in SARS patients. (27).knockout of SOCS1 in mice model results in neonatal death due to inflammatory disease induced by interferon gamma (IFNγ), and knockout of SOCS3 leads to lethality of embryo (28). Therefore, according to our study we think that COVID-19 after binding to STRA6 receptors, It blocks this receptor and hinder its function leading to JAK/STAT signaling pathway deactivation and SOCS3 downregulation. As a result the action of IL-6 is stimulated without control leading to cytokine storm and more inflammatory complication .

2- Reducing plasma retinol and inducing circulating RBP4

The systemic cytokine profiles found in severe COVID-19 patients show similarities to those observed in cytokine release syndromes, such as macrophage activation syndrome, with increased production of cytokines such as IL-6 and tumour necrosis factor (TNF) and also of inflammatory chemokines including CXC-chemokine ligand 10 (CXCL10) and CC-chemokine ligand 2 (CCL2), CCL3 , as well as of the soluble form of the α-chain of the IL-2 receptor(29). The concentration of plasma retinol-free RBP4 may be increased after hijacking STRA6 signaling pathway by COVID-19 spike protein

STRA6 connects circulating RBP4 to retinoid metabolism within the cell. [10]. Retinol is converted into retinal and retinoic acid (RA) once it is delivered into target cells.30)

By hindering the function of stra6 , the concentration of plasma retinol will be declined , a study showed thatreduced vitamin A plasma levels were found to be associated with higher levels of inflammatory markers (CRP, ferritin) and

signs of acute SARS-CoV-2 infection. (31). Therefore, we think that retinol-free RBP4 will be increased leading to activation of inflammatory cytokine signaling , Surprisingly, retinol-free RBP4 (apo-RBP4) is just as effective in generating proinflammatory cytokines in macrophages as retinol-bound RBP4 (holo-RBP4). (32)

Retinoic acid , Stra6 , COVID-19 and lymphopenia

Lympopenia is a disorder in which the number of lymphocytes in the blood is abnormally low(33). Despite the fact that T cells were originally raised at the outset of COVID19, these patients had a low lymphocyte count, which is linked to higher COVID19 severity(33). It was demonstrated that COVID-19 infects and kills lymphocyte thorough its ACE2 receptor. But numerous studies found that lymphocytes did not express ACE2 receptors or express it with low insufficient amount. Interestingly, lymphocytes in alveoli, pancreas, oesophagus, and spleen did not express ACE2 gene. but a small fraction of T-cells in kidney , colon , heart and lung expressed ACE2 gene (34). It was found that the fraction of ACE2 expressing immune cells is very small(34). Another study investigated the expression of TMPRSS2 and ACE2 across databases of multiple single-cell sequencing including 9 independent studies. However, it found no evidence of expression of ACE2 in these cells(lymphocytes and macrophages). (35)

According to our study we found that COVID-19 spike protein binds potentially with STRA6 receptor of retinol and this receptors are expressed in lymphocytes and regulates its activation. Plasma retinol-binding protein (RBP) carries absorbed retinol through the circulatory system. (1,4,5). Blood retinol is taken up by cells in both retinoic acid 6 (STRA6)-dependent and retinoic acid 6 (STRA6)-independent ways. STRA6 is a membrane receptor that binds to retinol and takes it over from RBP (2). A recent study showed that all T cell, monocyte, natural killer cell and dendritic cell subsets expressed the retinol binding receptor (STRA6)(3). STRA6 initiates cellular retinol uptake , in immune cells for improving homeostasis of the immune system in various populations(3).

STRA6's involvement in vitamin A transport and the STAT5 signalling pathway are unquestionably important for T-cell activation and function. Retinoids are known to modulate Th2, Th17, Th1 (T helper 1) and reglulatory T (Treg) cell function and development (36,37) . Induction phosphorylation of STRA6 trigger activation and recruitment of STAT5 and JAK2 (38) At the molecular level, it has been reported that RA opens up the FoxP3 promoter tertiary structure for transcription of activated FoxP3 (39) . RAR has the ability to interact with STAT5 b and a (40), which are important factors in the signaling pathway of a key T activation cytokine IL-2 (41). Therefore, We suggest that COVID-19 may hijack STRA6 and STAT5a pathways resulting in formation of vitamin A/ retinoic acid deficient lymphocytes.

vitamin A/ retinoic acid deficient lymphocytes cannot counter the infection as in condition of COVID-19 because Vitamin A controls CD4+ T lymphocyte and dendritic cell maturation and its insufficiency alters the balance between T helper 2 lymphocytes and T helper 1 (42).The vitamin A metabolite 9-cis retinoic acid appears to boost T helper 1 responses in experimental model systems.. T cells are drawn to the gut-associated lymphoid tissue by retinoic acid, which stimulates their migration (homing). (42). Interestingly, Retinoic acid can be synthesized by some gut-associated immune cells(43).. Retinoic acid is necessary for CD8+ T cell survival and proliferation, as well as appropriate B lymphocyte function, including antibody production. Thus, deficiency of vitamin A can impair the response of T cells to vaccination.(42,43) Moreover, it can infect lymphocytes thorough STRA6 receptor of retinol, leading to deactivation and killing of these cells.

Retinoic acid, Stra6, COVID-19, Cholesterol Efflux and Primary Human CD4+ T Cells

Drastic reduction of CD4+ T cell counts in COVID-19 patients have been linked with poor clinical outcome. As CD4+ T cells play a critical role in orchestrating responses against viral infections(44). Researchers from Wenzhou, China

looked at clinical laboratory investigations including lipid levels in patients with COVID-19. They showed a marked reduction in the cholesterol levels of COVID-19 infected patients compared with healthy controls (45). Also, during the early stages of infection, it was found that cholesterol levels decline rapidly and increase as the patient starts to recover. Therefore, indicating that cholesterol may play an important role in defending the body against such infections (46).. Intracellular cholesterol level is regulated by two competing pathways, cholesterol uptake and efflux, and ATP-binding cassette transporter (ABCA1) plays a major role in the cholesterol efflux pathway(47). Retinoic Acid Induces Macrophage Cholesterol Efflux and Inhibits Atherosclerotic Plaque Formation in apoE-deficient Mice, was reported in a study (48) The ATRA induces ABCA1 expression and ABCA1-dependent cholesterol efflux is activated primary human CD4+ T cells implying that RA could affect T cell functions by regulating the cellular cholesterol levels (49). All trans-retinoic acid (ATRA) and 13-cis-retinoic Acid upregulates ABCA1 expression only in activated CD4+ T cells, indicating that induction of ABCA1 by ATRA and 13-cis-RA may play an important role in immune response (50). Retinoic acid and liver X receptor agonist act synergistically to inhibit HIV infection in CD4+ T cells by up-regulating ABCA1-mediated cholesterol efflux (17). 13-cis-retinoic acid increased CD4 cells and markedly inhibited viremia in HIV (highly mutated virus) positive patients suffering from acne vulgaris(51). Stemming from previous studies, our review demonstrates that there is a strong relation between immune response and cholesterol levels. The immune response is compromised and antiviral immune cells are reduced and suppressed when cholesterol levels are inhibited in the case of viral infection such as COVID-2019 infection. Confocal microscopy was used to determine cellular location and lipid raft association of STRA6 on cell lines and isolated PBMC. All T cell, natural killer cell, monocyte, and dendritic cell subsets analyzed expressed STRA6(3,52)

As a result, we suggest that COVID-19 binds to Vitamin A STRA6 receptors, resulting in vitamin A/retinoic acid deficiency, reduced cholesterol efflux, and suppressed CD4 cells.

Retinoic acid, Stra6, COVID-19, Hypothalamus and Mental retardation

. In fact, many findings suggest damage of brain during infection and persistent neurological symptoms after infection of COVID-19 .The most common symptoms appearing after infection of COVID-19 are headache , anosmia, , muscle, dysgeusia, or ageusia and joint pain and mental fog, Symptoms that can continue for weeks, or even months(53). In epithelial barriers with tight junctions, STRA6 is extremely expressed including the choroid plexus/(CP) and the retinal pigment epithelium(RPE) the blood–brain barrier, and Sertoli cells of the testes, The CP is found to be a gateway from the peripheral blood to the CSF and central nervous system (54,55,56,57)

The RA cellular signalling system has been found to be controlled in the hypothalamus of rodents.. The retinol transport protein Stra6 and retinoid synthetic enzymes were found in the cells lining the third ventricle permitting synthesis of RA from retinol present in the CNS to act via retinoid X receptors and RA receptors in the hypothalamus(58). The hypothalamic neuroendocrine peptide adrenocorticotrophic hormone can be regulated by RA. in vitro (58).STRA6 plays a pivotal function for retinoil/Vitamin A transport across blood–tissue barriers of the testis, eyes and brain, in particular, under conditions of vitamin A deprivation.(57). In peripheral tissues including the eye and the brain, A knockout mouse(KO mice) have much decreased levels of retinoids. (57)

Mutation of STRA6 leads to a broad spectrum of malformations including lung hypoplasia and mental retardation(59)

COVID-19, insulin resistance, Retinoic acid , Stra6 and holo-RBP.

COVID-19-infected patients, particularly those with severe illness, have a high level of insulin resistance GT (60).What is certain is that SARS-CoV-2 infection, like many other diseases, can cause hyperglycemia in patients who have

never been diagnosed with diabetes(61,62) In case reports, diabetes development has been documented to occur simultaneously with acute SARS-CoV-2 infection or in the weeks to months after recovery from the viral infection(63). A study discovered that STAT target genes induced by holo-RBP in STRA6-expressing tissues such as adipose tissue and muscle include the gene that encodes suppressor of cytokine signaling 3 (SOCS3)(64,65) In adipose tissue, STRA6 is required for the diurnal rhythmicity of insulin action and JAK/STAT signalling. (66). STRA6 and holo-RBP are potent controllers of diurnal insulin responses (66). SNPs in STRA6 have been linked to type 2 diabetes in humans, according to a recent study (67). It's unclear whether the effect is due to changes in STRA6-mediated vitamin A absorption or signalling.. Therefore, blocking of stra6 by spike protein of COVID-19 may disrupt its diurnal insulin responses regulatory role leading to diabetes as in COVID-19

Retinoic acids, COVID-19, nervous and ocular system

Pinkeye (conjunctivitis), which is also associated with vitamin A deficiency, is prevalent symptom in patients with severe COVID-19 infection. (68,69).According to our findings, the binding of COVID-19 spike protein to STRA6, which is one of the main receptors for retinol cell entrance and retinoic acid production in the retina, strongly explains this symptoms .It was showed that genetic null mutation of STRA6 in mice model results in high retinoid reduction in the neurosensory retina and retinal pigment epithelium , diminished eye morphology and visual responses , despite the fact the last-mentioned problem is not as serious as in patients with mutant STRA6 (11).STRA6-mediated transport is especially significant in the eye and in the existence of vitamin A deficiency in the diet (Probable). Retinoic acid isn't transported. (70). A study strongly suggested that STRA6 works as a retinol channel/transporter(70). Analysis of function Loss- in embryos of zebrafishshowed that deficiency of Stra6 caused vitamin A deprivation of the developing eyes(70). RA signaling pathway promotes normal development of the optic nerve and ventral retina via its activities in the neural crest cell-derivedperiocular mesenchyme (71)and its deficiency may leads to retinitis. Although, several studies applied on COVID-19 patients have attempted to identify parameters linked to the olfactory disorders and taste with Angiotensin-Converting Enzyme 2 (ACE2)receptors it is clear that it takes place via receptors of vitamin A . (72)

It's worth noting that vitamin A shortage also causes olfactory and taste problems, In a study by Garrett-Laster et al., (73)the patients had vitamin A deficiency because of malnutrition and alcoholic liver cirrhosis; they lost their sense of smell after that disorder. LaMantia and Rawson reported that administration of retinoid acid after the damage of olfactory system motivates an immune response and produces a more quick recovery of olfactoryguided behavior(74).

13 cis retinoic acid improved the sense of smell and the performance of the olfactory test in acne patients (75) This also propose that insufficiency of vitamin A also rises in COVID-19.

Therefore, we strongly suggest that loss of stra6 function thorough blocking it by COVID-19 spike protein which binds to it with high affinity as a result it may hijack its signaling pathway leading to retinoic acid synthesis disruption and vitamin A deficiency . The symptoms and outcomes that arise in the eyes and nervous system of patients with COVID-19 are with unknown etiology but the results of retinoic acid deficiency manifested through vitamin A receptors. Ataxia , Headache , acute cerebrovascular disorder, impaired and consciousness are observed in patients with COVID-19 as central nervous system involvement and hyposmia, hypogeusia, neuralgia and hypopsia are seen as involvement of the peripheral nervous system. Patients with muscle involvement were also observed(76,77). COVID-19-related acute hemorrhagic necrotizing encephalopathy instances have also been documented. The unenhanced cranial BT obtained in the patients revealed hypodensity in both medial thalamuses (78). Similarly, this

is a region with a lot of Stra6 receptors of Vitamin A (58). Zhao et al (79) reported the first case of Guillain-Barré syndrome linked to COVID-19.

Retinoic acids play a critical role in inducing neurogenesis and neuroplasticity. RA are important for hypothalamus and the hippocampus that control alertness and mentality .All-trans retinoic acid (atRA) can be formed from the vitamin A/ retinol in the brain. This is important for long-term potentiation (LTP). Vitamin A insufficiency also leads to circadian dysfunction. Cognitive dysfunction is also commonly showed(80,81).Pasutto et al.(7) reported that STRA6 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.

For the adult brain, components of the retinoid metabolic pathways have been thoroughly characterized(81). In some parts of the brain, all-trans-retinoic acid is synthesized.. Certain neuronal-specific genes contain recognition sequences for retinoid receptors and can be arranged directly by retinoids. receptors of retinoid have a widespread distribution in the human nervous system. This distribution differs significantly from that seen during embryonic development, implying that retinoid signalling may have a physiological role in the adult hypothalamus , cortex, striatum , amygdala, hippocampus, and other brain regions (81,82).

Retinoid signal pathways disruption in models of rodent caused in disturbance in synaptic plasticity, memory behaviors and learning . Signal pathways of retinoid also play a critical role in the pathophysiology of schizophrenia , Alzheimer's disease, and depression(81).

Retinoic acid regulates gonadotropin-releasing hormone (GnRH) and its receptor G-protein coupled receptor (GnRH) an important action in smelling process .

The olfactory bulb (OB) is a conserved region found in brain that its main function is receiving sensory neurons direct synaptic input in the nasal epithelium part and conveys that instructions to the rest of the brain. (81). It gets instructions from the brain regarding odours recognized by cells in the nasal cavity. Axons of the olfactory sensory neurons extends to the region of the olfactory bulb, which is dedicated to process odour-related instructions (82).The nervusterminalis, or zeroeth cranial nerve, contains specific neurons that produce gonadotropin-releasing hormone (GnRH). All vertebrate animals without sharks have a nervusterminalis, a chain of neurons implanted within vomeronasal or olfactory nerves in the region of the nasal canal, where it is considered a distinct nerve. The main role of the gonadotropin-releasing hormone (GnRH) constituent of the nervusterminalis is supposed to have neuromodulatory properties . (83). Numerous studies suggested that the role of the intranasal gonadotropin-releasing hormone (GnRH) system is to adapt and modify olfactory information, maybe at opportune times for reproduction(83). Gonadotropin-releasing hormone (GnRH), was showed to be expressed on 30 to 40 percent of neurons located in the region of the nervusterminalis and also, a small dozen of these neurons may produce gonadotropin-releasing hormone (GnRH) directly into blood veins underlying the olfactory epithelium (OE). (84). During prenatal GnRH neurons emerge from the nasal placode until reach the brain(1). These neurons become critical ingredients of the hypothalamic-pituitary-gonadal axis, which is required for activity of reproduction, after they enter the brain. Hypogonadotropichypogonadism (HH) is caused when this mechanism is disrupted (HH).

The primary modulator of mammalian function of reproduction in both men and women is gonadotropin-releasing. hormone (GnRH). It acts via distinct receptors, G-protein coupled receptor (GnRH) found in gonadotropes to (LH)(85). a,induce production of the gonadotropin hormones, follicle and luteinizing -stimulating hormones (FSH) study found that congenital anosmia (loss of smell) is frequently linked with GnRH deficiency in human patients,

leading to the widely held belief that GnRH neurons rely on olfactory structures to reach the brain, but this suggestion has yet to be proven(86).

Retinoic acid regulates both GnRH neurons and G-protein coupled receptor (GnRH-R).

Furthermore, retinoic acid plays critical physiological roles in synaptic plasticity, learning and memory(27), hormone production(27,28) and adult neurogenesis(27) (15).They also control a variety of processes in adults, including vision, cellular differentiation, fertilization, and tissue homeostasis(87). Retinoids are therefore essential for optimal physiology during both the early stages of development and throughout maturity(87). The mammalian type I gonadotropin releasing hormone receptor (GnRH-R) is a structurally unique G protein-coupled receptor (GPCR)(88). The majority of hormones stimulates and mediates their signal transduction via G protein-coupled receptors (GPCRs).(90) Retinoic acid induce expression of G protein-coupled receptor called

Retinoic Acid - Inducible G Protein-Coupled Receptors(89) . Studies show general agreement that all-*trans* retinoic acid (atRA) has been linked to the regulation of G protein-coupled receptor (GPCRs) signaling,(91,92,93). Retinoic acid induces expression of G protein-coupled receptors that are used by Gonadotropin-releasing hormone (GnRH). Retinoic acid (RA) appears to be a significant regulator of GnRH neurons in GT1-1 of rat neuronal cells and hypothalamic fragments in vitro, according to a study. (93). In this study during a short period (2hours), Retinoic acid raised gonadotropin-releasing hormone (GnRH) production in a dose-dependent manner in addition, time-course tests revealed that Retinoic acid speedily induced gonadotropin-releasing hormone (GnR0H release by thirty min in both types of used cells. Furthermore, significant increase in mRNA levels of gonadotropin-releasing hormone by Retinoic acid was observed within 12hours. (94). In another study showed that that all-trans-RA controls gene expression and release of gonadotropin-releasing hormone (GnRH) in neuronal cells and hypothalamic fragments of rat. All-trans-RA increased GnRH transcription by activating functional retinoic acid response elements (RARE) in the promoter's distal region of GnRH. (95).

Conclusion

Even though, ACE2 has been identified as the principal host cell receptor of 2019-nCoV, and it is thought to play a many cells can be infected by COVID-critical role in the virus's entrance into the cell and subsequent infection, Furthermore, COVID-19 may case a variety of pre and post symptoms with while also expressing little or no ACE219 unknown etiology . It was documented that COVID-19 infection leads to a loss of smell (anosmia) but The COVID-19 entry receptor, angiotensin-converting enzyme 2 (ACE2), is not expressed in receptor of olfactory neurons, or its generation is limited to a minor fraction of these neurons. Moreover It was demonstrated that COVID-19 infects and kills lymphocyte thorough its ACE2 receptor. But numerous studies found that lymphocytes did not express ACE2 receptors or express it with a little, insufficient amount. it is obvious that COVID-19 not only binds to ACE2, but also to additional receptors, leading to existence of pre- and post-covid-19 symptoms which remain unexplained. As a receptors could lead to the development of new treatments that couldresult, discovering and identifying these Fortunately, our findings has revealed STRA6 as asuppress COVID-19 and reduce its severity and pathogenicity. STRA6 was found to be expressed in many organs and immune cells,novel COVID-19 binding receptor . upregulated by retinoic acid jm6 (STRA6) 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 Therefore, STRA6 may play a key role inthat binds to retinol binding protein facilitating cellular uptake of retinol. COVID-19 pathogenesis and may explain the common pre- and post-COVID-19 symptoms of unknown Consequently, reconstitution of the signaling of retinoid may prove to be a valid strategy for COVID-19. etiology management. We suggest that Vitamin A supplements and retinoic acid will be promising and effective treatments

for COVID-91 infection and its unknown aetiology symptoms. It worth mentioning that aerosolized all- trans retinoic acid and 13 cis retinoic acid is currently under clinical investigation by the authors (ClinicalTrials.gov Identifier: NCT05002530, NCT04353180)

Declarations

Conflicts of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article

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Figures

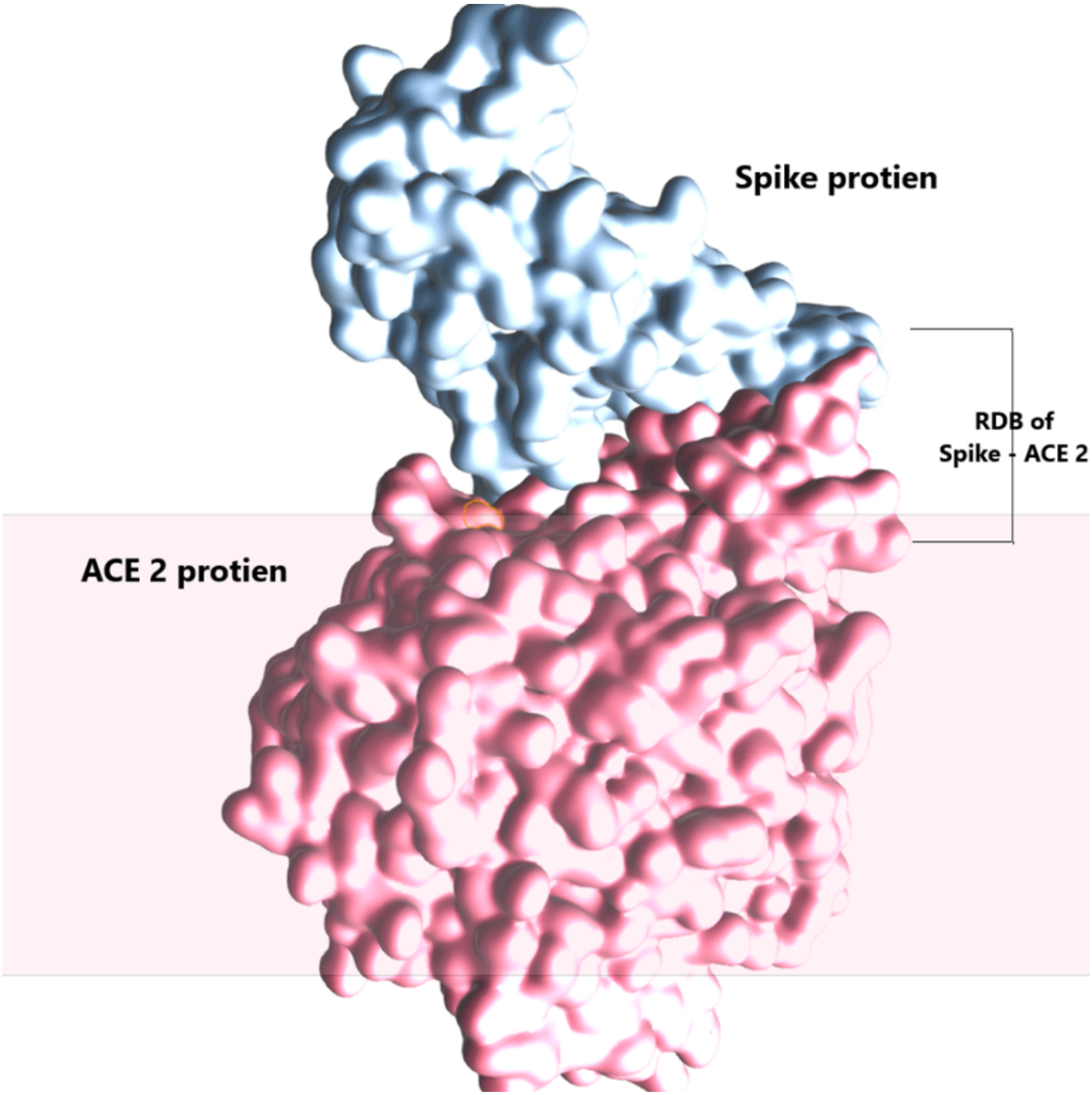

Figure 1

Spike - ACE2 receptor with the extracellular , membrane position with the binding spike

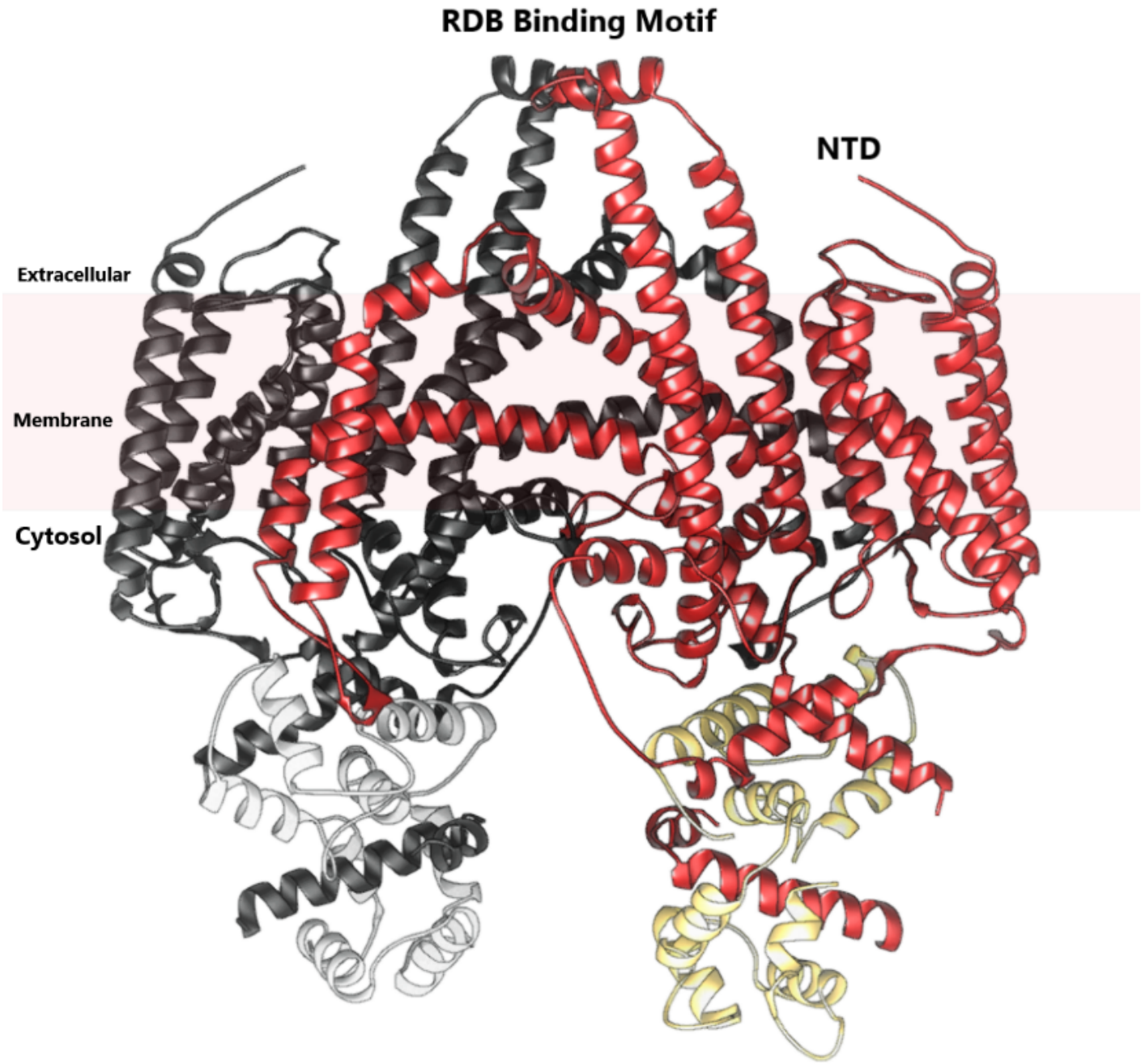

Figure 2

star6 receptor with the extracellular , membrane and the third part in cytosol where star6 A, B, C , D

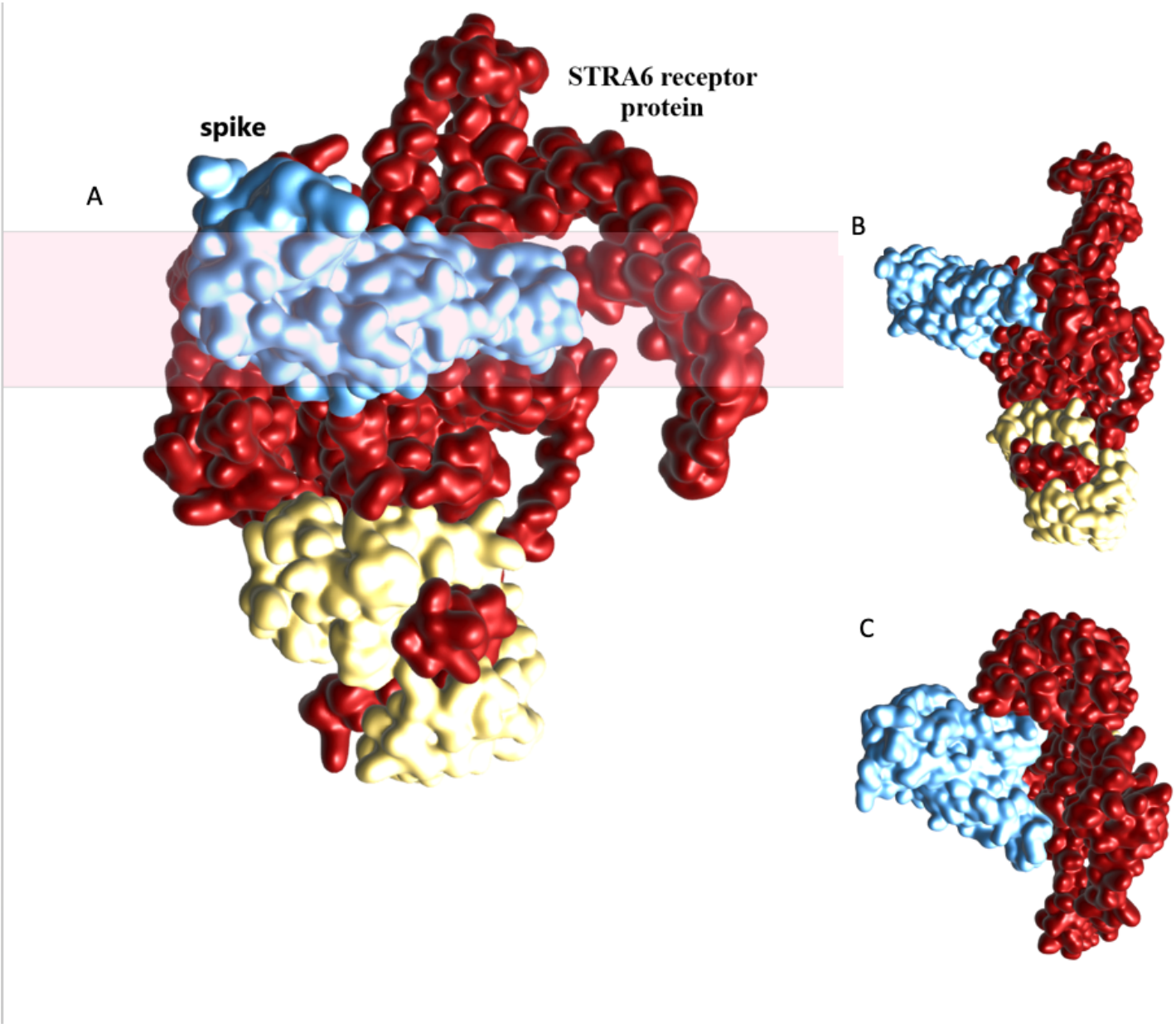

Figure 3

The spike – STRA6 protein complex structure from deferent orientation the Space fill representation of the STRA6-spike complex (A) in two views along (B) which the left part of the STRA 6 with Spike protein which spike are bind with vital residues of the cholesterol binding site and from above (C) the plane of the membrane with the spike interacting with the STRA 6, colored as in

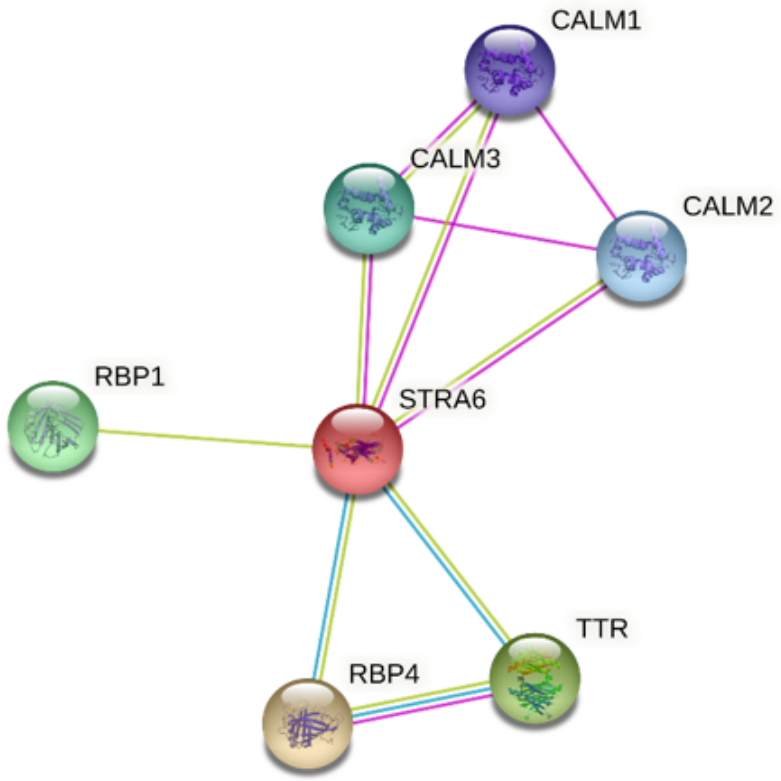

Figure 4

represents the protein-protein interaction network of STRA6 receptor The color nodes describe query proteins and the first shell of interactors, whereas white nodes are the second shell of interactors. The large node size represents characterized proteins and smaller nodes for uncharacterized proteins.

Supplementary Files

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