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The structure of the membrane protein of SARS-CoV-2 resembles the sugar transporter semiSWEET

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the disease COVID-19 that has decimated the health and economy of our planet. The virus causes the disease not only in people but also in companion and wild animals. People with diabetes are at risk of the disease. As yet we do not know why the virus is highly successful in causing the pandemic within 3 months of its first report. The structural proteins of SARS include, membrane glycoprotein (M), envelope protein (E), nucleocapsid protein (N) and the spike protein (S). The structure and function of the most abundant structural protein of SARS-CoV-2, the membrane (M) glycoprotein is not fully understood. Using *in silico* analyses we determined the structure and potential function of the M protein. *In silico* analyses showed that the M protein of SARS-CoV-2 has a triple helix bundle, form a single 3-transmembrane domain (TM), and are homologous to the prokaryotic sugar transport protein semiSWEET. SemiSWEETs are related to the PQ-loop family that function as cargo receptors in vesicle transport, mediates movement of basic amino acids across lysosomal membranes, and is also involved in phospholipase flippase function. The advantage and role of sugar transporter-like structure in viruses is unknown. Endocytosis is critical for the internalization and maturation of RNA viruses, including SARS-CoV-2. Sucrose is involved in endosome and lysosome maturation and may also induce autophagy, pathways that help in the entry of the virus. It could be hypothesized that the semiSWEET sugar transporters could be used in multiple pathways that may aid in the rapid proliferation and replication of the virus. Biological experiments would validate the presence and function of the semiSWEET sugar transporter.

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Key words

SARS-CoV-2, COVID-19, Virus, sugar transporter, SemiSWEET, Membrane glycoprotein.

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Introduction

The Covid-19 disease is currently responsible for the pandemic that has decimated the health and economy of every country. COVID-19 is regarded as a respiratory disease that manifests with fever, cough, shortness of breath or difficulty breathing, chills, muscle pain, headache, sore throat, loss of taste and smell. Other symptoms include diarrhea, nausea and vomiting (Yang et al. 2020; Effenberger et al. 2020). The prolonged pandemic has resulted in social distancing, travel restrictions, decreased trade, high unemployment, commodity price decline, and financial stress that has impacted the global economy. COVID-19 disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a member of the betacoronavirus genus (Wang et al. 2020). Currently, the disease has resulted in a mortality of around 5-7 percent. As yet, there are no effective drugs available for treatment of the disease nor vaccines available commercially to protect against the virus.

The major structural proteins of SARS-CoV-2 are spike (S), membrane (M), envelop (E), and the nucleocapsid (N) proteins (Shereen et al. 2020; Chan et al. 2020). The spike protein of SARS-CoV-2 uses the host angiotensin-converting enzyme 2 (ACE2) as the entry receptor (Wrapp et al. 2020). Hence, the research community has an interest in studying the spike protein for drug and vaccine development.

The most abundant structural protein of coronaviruses is the M glycoprotein; it spans the membrane bilayer, leaving a short NH2-terminal domain outside the virus and a long COOH terminus (cytoplasmic domain) inside the virion (Mousavizadeh and Ghasemi, 2020). As the M proteins cooperates with the S protein, mutations may influence host cell attachment and entry of the viruses (Bianchi et al. 2020). The function of the M protein is also not fully understood. It is also not clearly understood how SARS-CoV-2 mediates sugar uptake and also the sugar transporters involved in the process.

Sugars will eventually be exported transporters (SWEETs) and SemiSWEETs are sugar transporters in eukaryotes and prokaryotes, respectively. SWEET proteins were first identified in plants as the novel family of sugar transporters that mediates the

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translocation of sugars across cell membranes (Chen et al. 2010, Feng and Frommer, 2015; Jia et al. 2018; Jeena et al. 2019). Sugar transporters are essential for the maintenance of blood glucose levels in animals, nectar production, phloem loading, seed and pollen development in plants, and also in pathogen nutrition (Chen et al. 2010; Jeena et al. 2019). Engineering of SWEET mutants using genomic editing tools mediated resistance to pathogens (Chen, 2014).

In eukaryotes, SWEET can discriminate and transport the uptake of mono and disaccharides across the plasma membrane by allowing solutes to permeate across biological membranes following a concentration gradient (Chen et al. 2010; Chen, 2014; Han et al. 2017). Eukaryotic SWEETs are composed of seven transmembrane helices (TMHs) that contain a pair of three transmembrane repeats, which are connected by an additional helix, while SemiSWEETs, the homologs of SWEETs in prokaryotes, contain three TMHs (Xuan et al. 2013; Feng and Frommer, 2015). The human genome contains only one *SWEET* gene and may be involved in glucose transport (Chen et al. 2010).

The prokaryotic semiSWEETs may be involved in the metabolism and transport of sugar synthesis. The semiSWEETs of prokaryotes are more diverse than SWEETs in plants; they seldom have homologs sharing >50% identity (Jia et al. 2018). The limited number of semiSWEET homologs suggest that they are not as important as the SWEETs in eukaryotes (Jia et al. 2018).

It is clearly not understood the function and role of the M proteins of the SARS-CoV-2 during host infection. Here, we report that the M proteins of SARS-CoV-2 are structurally similar to semiSWEET sugar transport proteins of prokaryotes based on *in silico* analyses.

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Materials and Methods

SARS-CoV-2 protein structure

The structural protein sequences of the SARS-CoV-2 were downloaded from Pubmed (https://www.ncbi.nlm.nih.gov/pubmed), protein database. The structural proteins include Membrane protein (Accession No. QJA17755), Envelope protein (Accession No. QJA17754), Spike protein (Accession No. QHR63290), Nucleocapsid protein (Accession No. QJC20758).

Protein modeling

Swiss model is a server that is used for 3D structure prediction. Homology modeling was constructed using Swiss model server (http//swissmodel.expasy.org/) with default settings. The M protein sequence of SARS-CoV-2 was entered in FASTA format.

Residue-based diagram of proteins, also called snake diagrams or protein plots, are 2D representations of a protein sequence that contains information about properties such as secondary structure (Skrabanek et al. 2003). To determine snake diagram model of protein we used Protter (http://wlab.ethz.ch/protter). Protter is an open-source tool that supports interactive protein data analysis and hypothesis generation by visualizing both annotated sequence features and experimental proteomic data in the context of protein topology.

Sequence alignment

Clustal W2 is a server for multiple sequence alignment which is also used for phylogenetic tree analysis. Multiple sequence alignment between M protein of SARS-CoV-2 and semiSWEET sequences from different microorganisms was performed using the clustalW2 server (http:/www.ebi.ac.uk/tools/msa/clustalW2/).

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Results

The S protein of SARS-CoV-2 binds to ACE2 receptors of the host for cell entry and may be a key target for drugs and vaccines. Hence the S protein of SARS-CoV-2 virus is well characterized. The SARS-CoV-2 is one of the most successful virus as it caused a pandemic within just two months of its first report in Wuhan, China. As yet, we do not yet know why the virus is successful in inducing a pandemic leading to millions of infection and thousands of death.

Three-dimensional (3D) protein structures provide valuable insights into the molecular basis of protein function (Schweede et al. 2003). Using *in silico* techniques the structure and potential function of the M protein of the SARS-CoV-2 virus is elucidated.

The structural protein sequence of the membrane protein (M) of SARS-CoV-2 was downloaded from NCBI protein database (Fig. 1). The FASTA sequence of the M protein was entered into the Swiss model server. Based on the sequence, the structure of the molecule was predicted as bidirectional sugar transporter SWEET2b. The ribbon representation, spacefill and surface models of the M protein is shown in Fig. 2.

The sugar transporter SWEET of eukaryotes are generally composed of seven transmembrane helices. Modeling proteins using residue-based diagram (snake diagrams) helps understand its function. Hence, we used Protter (http://wlab.ethz.ch/protter) to model the M protein.

The M glycoprotein is the most abundant envelope protein of SARS-CoV-2. *In silico* analyses of the M protein of SARS-CoV-2 using Protter demonstrated that it has a triple helix bundle, and formed a single 3-transmembrane domain (TM). In addition, the M glycoprotein has a short amino terminal outside the membrane and a long carboxy-terminal domain inside the membrane (Fig. 3A). The SWISS-MODEL predicted the M glycoprotein as SWEET2b. However, the M protein only has three transmembrane helices, not six or seven transmembrane helices observed in the SWEET sugar

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transporters of eukaryotes. Hence, the M glycoprotein structure of SARS-CoV-2 may be considered as semiSWEET. To confirm accuracy of the study, we also modeled the E, N and S proteins of SARS-CoV-2. The modeling showed that the E protein has long outer amino terminal, a single helix and a short inner carboxy-terminal (Fig. 3B). The N protein had its entire structure inside the membrane (Fig. 3C). Whereas, the S protein had the majority of its structure outside the membrane with only a short carboxy-terminal inside the membrane (Fig. 3D).

The SemiSWEET sugar transporter of prokaryotes are more diverse than SWEET counterpart in plants. In the prokaryotes the semiSWEET seldom share identity. We used Clustal W2 to determine sequence homology of the sugar transporters of multiple microorganisms. The sequence of semiSWEET of the M glycoprotein of SARS had an identity of 26% with the semiSWEET of *Rhizobiales* and 20% with *Streptococcus pneumoniae* demonstrating that the semiSWEET of the SARS-CoV-2 may be highly conserved (Fig. 4A, B).

Discussion

The COVID-19 pandemic caused by the coronavirus SARS-CoV-2 is spreading at an alarming rate and has resulted in an unprecedented health emergency all over the world (Ghosh et al. 2020). The rapid spread of SARS-CoV-2 justifies the global effort to identify effective preventive strategies and optimal medical management (Castagnoli et al. 2020). As yet there are no effective vaccine to protect against COVID-19 nor effective approved drugs to treat patients with the disease. The development of antivirals is an urgent priority to combat the disease (Ghosh et al. 2020). Understanding the biochemical events of the coronavirus replication cycle may provide a number of attractive targets for drug development (Ghosh et al. 2020). Current strategies involve developing drug and vaccine candidates against spike (S) protein of the virus. The rationale being that neutralizing antibodies against the S protein prevent uptake of the virus via the human ACE2 receptor

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(Le et al. 2020). Identifying drug targets that blunt the activity of the virus may lead to effective treatments for COVID-19.

Viruses are non-living entities, without any organelles devoid of their own metabolism, though they have the capability to dramatically modify the host cellular metabolism upon entry. Viruses upregulate consumption of glucose and converge on similar metabolic pathways for anabolism (Thaker et al. 2019). Virus-induced metabolism may provide free nucleotides for rapid viral genome replication, increased amino acid production for rapid virion assembly, and high amounts of ATP for the high energy costs of genome replication and packaging. The mechanism for increased glucose uptake by the virus is still not clearly understood.

Glucose is the energy source of cells and tissues. Cellular uptake of glucose is a fundamental process for metabolism, growth, and homeostasis. Glucose is a polar molecule that does not readily diffuse across the hydrophobic plasma membrane of the cells. Glucose molecules are transported through the glucose transporters that include, GLUTs, the sodium-driven glucose symporters SGLTs, STP, and SWEETs (Deng and Yan, 2016). SWEETs are seen in plants and animals. SWEET induction by plant pathogens leads to secretion of sucrose that is used by these microorganisms for nutrition/reproduction (Bezrutczyk et al. 2017).

The bacterial ancestors of SWEET, known as semiSWEET are the smallest of the sugar transporters and assemble into dimers (Xuan et al. 2013; Chen et al. 2015; Lee et al. 2015). In fact, eukaryotic SWEETs consist of two SemiSWEET-like units fused via an inversion linker transmembrane helix (Jia et al. 2018). The diverse gene neighbors of semiSWEETs suggest that semiSWEETs may transport diverse substrates and play several physiological roles in different organisms (Jia et al. 2018). The SWEETs and their bacterial homologues, SemiSWEETs, are related to the PQ-loop family, characterized by highly conserved proline and glutamine residues (PQ-loop motif) (Lee et al. 2015). The PQ-loop family exhibits diverse activities; they function as cargo receptors in vesicle

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transport, mediates movement of basic amino acids across lysosomal membranes, and is also involved in phospholipase flippase function (Saudek, 2012; Yamamoto et al. 2017; Kawano-Kawada et al. 2019). As yet there are no reports of sugar transporters in viruses.

It is not known how SARS-CoV-2 has been successful to spread all over the world within three months of its first report in Wuhan, China. Identifying the mechanisms of how viruses alter cellular metabolism and where in the virus life cycle these metabolic changes are necessary will provide an understanding of virus replication needs and potentially provide cellular targets for inhibition of these viruses. In this paper using *in silico* data analysis we demonstrate that the structure of the membrane (M) glycoprotein of SARS-CoV-2 resemble the semiSWEET sugar transporter of the prokaryotes.

Clues to the viral metabolism can be understood from the patient population at risk of infection. It is known that people with diabetes are more prone to COVID-19 disease (Bornstein et al. 2020). It has been demonstrated that SARS coronavirus enters islets and damages islets causing acute diabetes (Yang et al. 2010). As people with diabetes have high glucose, the environment may favor proliferation of viruses.

Virus uses multiple mechanisms for the uptake of glucose. *Human cytomegalovirus* (HCMV), a herpesvirus, induces the sugar transporter, GLUT4 to increase glucose uptake during infection (Yu et al. 2011). Whereas, transmissible gastroenteritis virus (TGEV), a coronavirus induces multiple sugar transporters EGFR, SGLT1 and GLUT2 for glucose uptake (Dai et al. 2016). Rhinoviruses (RVs) are responsible for the majority of upper airway infections and they enhance the expression of the PI3K-regulated glucose transporter GLUT1; glucose deprivation from medium and via glycolysis inhibition by 2-deoxyglucose (2-DG) impairs viral replication (Gualdoni et al. 2018).

Sucrose is used for energy metabolism by cells. In addition, sucrose is also used for endosome and lysosome maturation, autophagosomes and also to induce autophagy (Hu et al. 2015; Higuchi et al. 2015; Yang and Shen, 2020). Coronaviruses, including SARS,

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SARS-CoV-2 use endosome for cellular entry, and they are known to manipulate autophagosome and autolysosome for viral dissemination in the cell (Burkard et al. 2014; Yang and Shen, 2020).

The membrane (M) glycoprotein is the most abundant envelope protein of coronaviruses (deHaan et al. 1999). *In silico* analysis showed that the M protein of SARS-CoV-2 resembles the sugar transporter, SWEET. Further analysis by residue-based structure demonstrated that the protein has the characteristic structure of semiSWEET, the sugar transporter of prokaryotes. To our knowledge this is the first report of the presence of a sugar transporter in a virus membrane. It is known that the prokaryotes have diverse sugar transporters. In our analysis, the SARS-CoV-2 sequence of semiSWEET has no homology to other prokaryotes.

An advantage of the virus having a sugar transporter in its membrane is that it may influence energy metabolism. How, the virus utilizes sugar molecules is unknown. In addition, it could be hypothesized that the sucrose transporters of the virus membrane may influence sucrose entry into the endosome, lysosome or autophagosome that are manipulated by the virus, thereby aiding the virus release into cells. Thus, the presence of a semiSWEET glucose transporter in the M protein of the virus may be an efficient mechanism that may induce its rapid proliferation.

Generally, the enveloped viruses, including SARS-CoV-2, use a two-step procedure to release their genetic material into the cell – 1) they bind to specific surface receptors of the target cell membrane and 2) they fuse the viral and cell membranes. This second step may occur at the cell surface or after internalization of the virus particle by endocytosis. Currently, it is not known how the M proteins of the virus is fused to the host cell membrane. If the M proteins are fused to host cell membrane, it could theoretically function as a sugar transporter.

People with diabetes are at risk of COVID-19 infection may be due to the high proliferation of the virus due to unmetabolized glucose. A characteristic of some COVID-19 patients

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is coagulopathy (Tang et al. 2020a). Anticoagulant therapy with low molecular weight heparin had better prognosis in severe COVID-19 patients that were associated with high mortality (Tang et al. 2020b). Platelets, produced by the megakaryocytes of the bone marrow is responsible for blood clotting. Glucose is taken up through the platelets mediated through the glucose transporters GLUT1 and GLUT3. Lack of glucose transporters in the platelets reduce its counts and increase clearance of platelets (Fidler et al. 2017). Normal glucose reduces platelet activation; whereas, hyperglycemia increases platelet glucose metabolism thereby contributing to increased platelet activation and thrombosis in animal models of diabetes (Fidler et al. 2019).

Some of the COVID -19 patients have lungs that are not effectively oxygenating the blood (hypoxia), but feel alert and healthy and hardly gasp for breath. Glucose transport is acutely stimulated by hypoxic conditions, and the response is mediated by enhanced function of the facilitative glucose transporters GLUT (Zhang et al. 1999; Wood et al. 2007). Prolonged exposure to hypoxia results in enhanced transcription of the GLUT1 glucose transporter gene, with little or no effect on transcription of other GLUT genes (Zhang et al. 1999).

Several pulmonary disorders are associated with a decrease in alveolar oxygen tension and Alveolar epithelial cells (AEC) exhibits different adaptive mechanisms to cope with oxygen deprivation. Under hypoxia, because of inhibition of oxidative phosphorylation, adenosine triphosphate supply is dependent on the ability of cells to increase anaerobic glycolysis. Hypoxia induces stimulation of Na-independent glucose transport and increase in 2-deoxy-D-glucose (DG) uptake; it also induces the glucose transporter, GLUT1 at both protein and mRNA levels (Ouiddir et al. 1999). HIF-1α regulates the activity of glucose transporters, GLUT, that are responsible for glucose uptake. Hypoxia-inducible factors (HIFs) are oxygen-sensitive transcription factors that allow adaptation to hypoxic environments (Sadlecki et al. 2014). HIF-1α reduces acute lung injury by optimizing carbohydrate metabolism in the alveolar epithelium (Eckle et al. 2013).

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An early characteristic of COVID-19 patients is loss of smell. The glucose receptors, GLUT is expressed in taste receptor cells (Merigo et al. 2011). Glucose receptors are expressed in the olfactory bulb and its changes may influence olfaction (Al Koborssy et al. 2014). Whereas, Villar et al. (2017) demonstrated that glucose removal and the inhibition of glycolysis or oxidative phosphorylation inhibits odor.

The current data described in this paper are based on *in silico* analyses. However, further biological experiments are required to validate the presence and function of the virus membrane sugar transporter.

Reference

Al Koborssy D, Palouzier-Paulignan B, Salem R, Thevenet M, Romestaing C, Julliard AK. Cellular and molecular cues of glucose sensing in the rat olfactory bulb. Front Neurosci. 2014; 8:333.

Bezrutczyk M, Yang J, Eom JS, Prior M, Sosso D, Hartwig T, Szurek B, Oliva R, Vera-Cruz C, White FF, Yang B, Frommer WB. Sugar flux and signaling in plant-microbe interactions. Plant J. 2018; 93:675-685.

Bianchi M, Benvenuto D, Giovanetti M, Angeletti S, Ciccozzi M, Pascarella S. Sars-CoV-2 envelope and membrane proteins: Differences from closely related proteins linked to cross-species transmission? Preprints 2020; 2020040089 (doi: 10.20944/preprints202004.0089.v1).

Bornstein SR, Rubino F. et al. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol. 2020; DOI:https://doi.org/10.1016/S2213-8587(20)30152-2

Burkard C, Verheije MH, Wicht O, van Kasteren SI, van Kuppeveld FJ, Haagmans BL, Pelkmans L, Rottier PJ, Bosch BJ, de Haan CA. Coronavirus cell entry occurs through the endo-/lysosomal pathway in a proteolysis-dependent manner. PLoS Pathog. 2014; 10(11):e1004502.

Chan JF, Kok KH, Zhu Z, Chu H, To KK, Yuan S, Yuen KY. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microbes Infect. 2020; 9:221-236.

Chen LQ, Cheung LS, Feng L, Tanner W, Frommer WB. Transport of sugars. Annu. Rev. Biochem. 2015; 84: 865–894.

Chen LQ, Hou BH, Lalonde S, Takanaga H, Hartung ML, Qu XQ, Guo WJ, Kim JG, Underwood W, Chaudhuri B, Chermak D, Antony G, White FF, Somerville SC, Mudgett MB, Frommer WB. Sugar transporters for intercellular exchange and nutrition of pathogens. Nature 2010; 468:527-532.

Chen LQ. SWEET sugar transporters for phloem transport and pathogen nutrition. New Phytol. 2014; 201:1150-1155.

Dai L, Hu WW, Xia L, Xia M, Yang Q. Transmissible gastroentitis virus infection enhances SGLT1 and GLUT2 expression to increase glucose uptake. PLoS One. 2016; 11(11):e0165585.

de Haan CA, Smeets M, Vernooij F, Vennema H, Rottier PJ. Mapping of the coronavirus membrane protein domains involved in interaction with the spike protein. J Virol. 1999; 73: 7441-7452.

Deng D, Yan N. GLUT, SGLT, and SWEET: Structural and mechanistic investigations of the glucose transporters. Protein Sci. 2016; 25: 546-558.

Eckle T, Brodsky K, Bonney M, Packard T, Han J, Borchers CH, et al. (2013) HIF1A Reduces Acute Lung Injury by Optimizing Carbohydrate Metabolism in the Alveolar Epithelium. PLoS Biol 11(9): e1001665.

Effenberger M, Grabherr F, Mayr L, Schwaerzler J, Nairz M, Seifert M, Hilbe R, Seiwald S, Scholl-Buergi S, Fritsche G, Bellmann-Weiler R, Weiss G, Müller T, Adolph TE, Tilg H. Faecal calprotectin indicates intestinal inflammation in COVID-19. Gut 2020; pii: gutjnl-2020-321388.

Feng L, Frommer WB. Structure and function of semiSWEET and SWEET sugar transporters. Trends Biochem Sci. 2015; 40: 480-486.

Fidler TP, Campbell RA, Funari T, Dunne N, Balderas Angeles E, Middleton EA, Chaudhuri D, Weyrich AS, Abel ED. Deletion of GLUT1 and GLUT3 reveals multiple roles for glucose metabolism in platelet and megakaryocyte function. Cell Rep. 2017; 21:1705.

Fidler TP, Marti A, Gerth K, Middleton EA, Campbell RA, Rondina MT, Weyrich AS, Abel ED. Glucose metabolism is required for platelet hyperactivation in a murine model of type 1 diabetes. Diabetes 2019; 68: 932-938.

Ghosh AK, Brindisi M, Shahabi D, Chapman ME, Mesecar AD. Drug development and medicinal chemistry efforts toward SARS-Coronavirus and Covid-19 therapeutics. Chem. Med. Chem. 2020, doi: 10.1002/cmdc.202000223.

Gualdoni GA, Mayer KA, Kapsch AM, Kreuzberg K, Puck A, Kienzl P, Oberndorfer F, Frühwirth K, Winkler S, Blaas D, Zlabinger GJ, Stöckl J. Rhinovirus induces an anabolic reprogramming in host cell metabolism essential for viral replication. Proc Natl Acad Sci U S A. 2018; 115: E7158-E7165.

Han L, Zhu Y, Liu M, Zhou Y, Lu G, Lan L, Wang X, Zhao Y, Zhang XC. Molecular mechanisms of substrate recognition and transport by the AtSWEET 13 sugar transporter. Proc Natl Acad Sci U S A. 2017; 114:10089-10094.

Higuchi T, Nishikawa J, Inoue H. Sucrose induces vesicle accumulation and autophagy. J Cell Biochem. 2015; 116: 609-617.

Jeena GS, Kumar S, Shukla RK. Structure, evolution and diverse physiological roles of SWEET sugar transporters in plants. Plant Mol Biol. 2019; 100:351-365.

Jia B, Hao L, Xuan YH, Jeon CO. New Insight into the Diversity of SemiSWEET Sugar Transporters and the Homologs in Prokaryotes. Front Genet. 2018; 9:180.

Kawano-Kawada M, Manabe K, Ichimura H, Kimura T, Harada Y, Ikeda K, Tanaka S, Kakinuma Y, Sekito T. A PQ-loop protein Ypq2 is involved in the exchange of arginine

and histidine across the vacuolar membrane of Saccharomyces cerevisiae. Sci Rep. 2019; 9:15018.

Le T, Andreadakis Z, Kumar A, Gómez Román R, Tollefsen S, Saville M, Mayhew S. The COVID-19 vaccine development landscape. Nat Rev Drug Discov. 2020 Apr 9. doi: 10.1038/d41573-020-00073-5.

Lee Y, Nishizawa T, Yamashita K, Ishitani R, Nureki O. Structural basis for the facilitative diffusion mechanism by SemiSWEET transporter. Nat Commun. 2015; 6:6112.

Merigo F, Benati D, Cristofoletti M, Osculati F, Sbarbati A. Glucose transporters are expressed in taste receptor cells. J. Anat. 2011; 219:243-252.

Mousavizadeh L, Ghasemi S. Genotype and phenotype of COVID-19: Their roles in pathogenesis. J Microbiol Immunol Infect. 2020; pii: S1684-1182(20)30082-7.

Ouiddir A, Planès C, Fernandes I, VanHesse A, Clerici C. Hypoxia upregulates activity and expression of the glucose transporter GLUT1 in alveolar epithelial cells. Am. J. Respir. Cell Mol. Biol. 1999; 21: 710-718.

Sadlecki P, Bodnar M, Grabiec M, Marszalek A, Walentowicz P, Sokup A, Zegarska J, Walentowicz-Sadlecka M. The role of Hypoxia-inducible factor-1 α, glucose transporter-1, (GLUT-1) and carbon anhydrase IX in endometrial cancer patients. Biomed Res Int. 2014; 2014:616850.

Saudek V. Cystinosin, MPDU1, SWEETs and KDELR belong to a well-defined protein family with putative function of cargo receptors involved in vesicle trafficking. PLoS One. 2012; 7(2):e30876.

Schwede T, Kopp J, Guex N, Peitsch MC. SWISS-MODEL: An automated protein homology-modeling server. Nucleic Acids Res. 2003; 31: 3381-3385.

Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J Adv Res. 2020; 24:91-98.

Skrabanek L, Campagne F, Weinstein H. Building protein diagrams on the web with the residue-based diagram editor RbDe. Nucleic Acids Res. 2003; 31: 3856-3858.

Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J. Thromb. Haemost. 2020b; 18: 1094-1099.

Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J. Thromb. Haemost. 2020a; 18: 844-847.

Thaker SK, Ch'ng J, Christofk HR. Viral hijacking of cellular metabolism. BMC Biol. 2019; 17:59.

Villar PS, Delgado R, Vergara C, Reyes JG, Bacigalupo J. Energy requirements of odor transduction in the chemosensory cilia of olfactory sensory neurons rely on oxidative phosphorylation and glycolytic processing of extracellular glucose. J. Neurosci. 2017; 37: 5736-5743.

Wang X, Xu W, Hu G, Xia S, Sun Z, Liu Z, Xie Y, Zhang R, Jiang S, Lu L. SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion. Cell Mol Immunol. 2020 Apr 7. doi: 10.1038/s41423-020-0424-9.

Wood IS, Wang B, Lorente-Cebrián S, Trayhurn P. Hypoxia increases expression of selective facilitative glucose transporters (GLUT) and 2-deoxy-D-glucose uptake in human adipocytes. Biochem Biophys Res Commun. 2007; 361: 468-73.

Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh C-L, Abiona O, Graham BS, McLellan JS. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020; 367): 1260–1263.

Xuan YH, Hu YB, Chen LQ, Sosso D, Ducat DC, Hou BH, Frommer WB. Functional role of oligomerization for bacterial and plant SWEET sugar transporter family. Proc Natl Acad Sci U S A. 2013; 110: E3685-94.

Yamamoto T, Fujimura-Kamada, K, Shioji E, Suzuki R, Tanaka K. Cfs1p, a novel membrane protein in the PQ-loop family, is involved in phospholipid flippase functions in Yeast. G3 2017; 7: 179–192.

Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol. 2010; 47:193-199.

Yang N, Shen HM. Targeting the endocytic pathway and autophagy process as a novel therapeutic strategy in COVID-19. Int J Biol Sci. 2020; 16:1724-1731.

Yang X, Zhao J, Yan Q, Zhang S, Wang Y, Li Y. A case of COVID-19 patient with the diarrhea as initial symptom and literature review. Clin Res Hepatol Gastroenterol. 2020; pii: S2210-7401(20)30085-1.

Yu Y, Clippinger AJ, Pierciey FJ Jr, Alwine JC. Viruses and metabolism: alterations of glucose and glutamine metabolism mediated by human cytomegalovirus. Adv Virus Res. 2011; 80:49-67.

 doi:10.20944/preprints202004.0512.v3

Zhang JZ, Behrooz A, Ismail-Beigi F. Regulation of glucose transport by hypoxia. Am. J. Kidney Dis. 1999; 34: 189-202

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Conflict of interest

The author declares no conflict of interest.

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Fig.1. The protein sequence of the M glycoprotein of SARS-CoV-2. The sequence was downloaded from NCBI protein database.

QJA17755.1 membrane glycoprotein
[Severe acute respiratory syndrome coronavirus 2]

1 madsngtitv eelkklleqw nlvigflflt wicllqfaya nrnrflyiik liflwllwpv
61 tlacfvlaav yrinwitggi aiamaclvgl mwlsyfiasf rlfartrsmw sfnpetnill
121 nvplhgtilt rplleselvi gavilrghlr iaghhlgrcd ikdlpkeitv atsrtlsyyk
181 lgasqrvagd sgfaaysryr ignyklntdh ssssdniall vq

Fig. 2. Predicted M protein structure using the software SWISS-MODEL. The (A) ribbon representation, (B) spacefill and (C) surface models of the M protein of SARS-CoV-2.

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Fig. 3A. Membrane topology of proteins (snake diagrams) determined using Protter. (A) The membrane (M) glycoprotein of SARS-CoV-2 has a triple helix bundle, and formed a single 3-transmembrane domain. (B) Snake diagram of envelope (E) protein, (C) nucleocapsid (N) protein, and (D) spike protein (S).

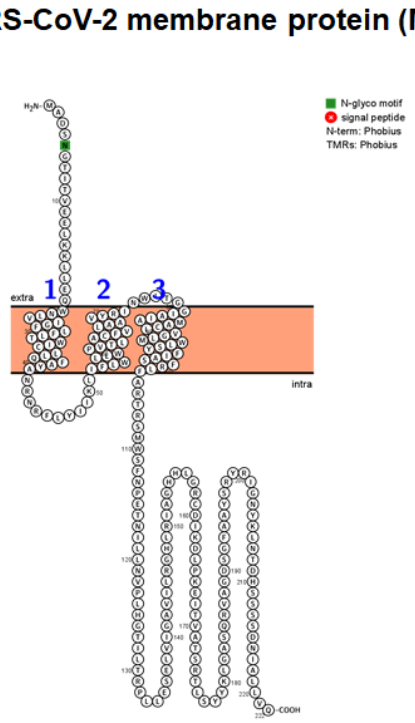

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Fig. 3B

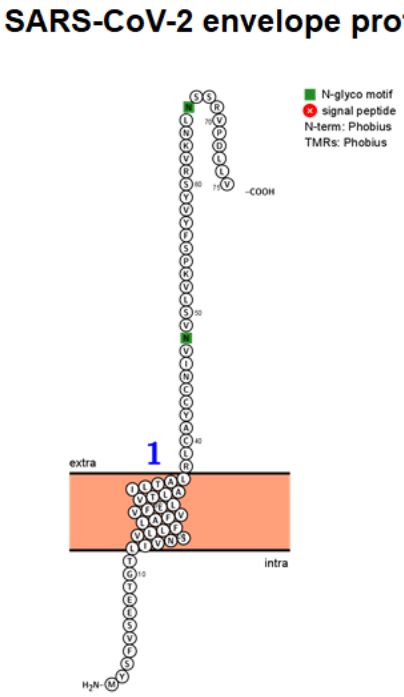

Fig. 3C

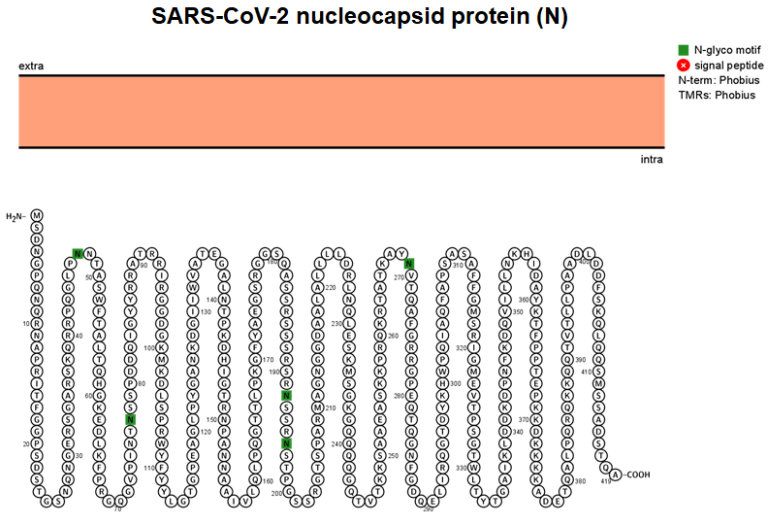

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Fig. 3D

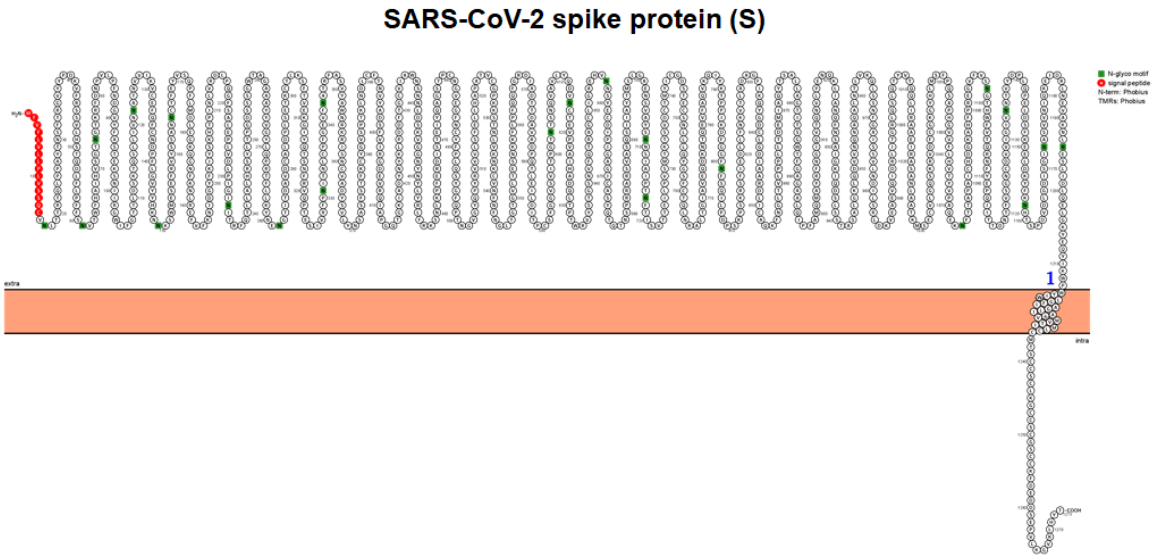

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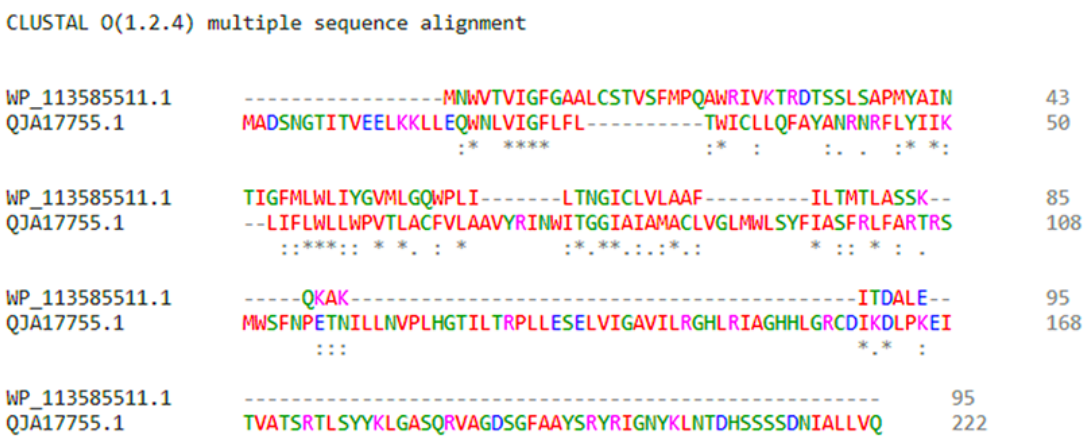
Fig. 4A. Protein sequences were aligned using ClustalW. (A) Comparison of protein sequence of the M protein of SARS-COV-2 with semiSWEET sugar transporter of Rhizobiales. (B) Comparison of protein sequence of the M protein of SARS-COV-2 with semiSWEET sugar transporter of *Streptococcus pneumoniae.*



WP_113585511.1: semiSWEET Rhizhobiales
QJA17755.1: Membrane protein SARS-CoV-2
Percent identity: 26.51

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Fig. 4B

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CLUSTAL O(1.2.4) multiple sequence alignment

WP_000580383.1      --------MIGSIAAILT------TFAFLPQVFR------------VVK---TKDTGSI        30
QJA17755.1          MADSNGTITVEELKKLLEQWNLVIGFLFLTWICLLQFAYANRNRFLYIIKLIFLWLLWPV        60
                             : .:  :*       * **  :               ::*        :

WP_000580383.1      ALGMYVMQVIGIALWLDHGIRIGDLPLILANSVSFLLSGI--------------------        70
QJA17755.1          TLACFVLAAVYRINWITGGIAIAMACLVGLMWLSYFIASFRLFARTRSMWSFNPETNILL        120
                    :*. :*: .:    *:  ** *.   *:    :*:::::.:

WP_000580383.1      ------------------------------------------------------ILFYK        75
QJA17755.1          NVPLHGTILTRPLLESELVIGAVILRGHLRIAGHHLGRCDIKDLPKEITVATSRTLSYYK        180
                                                                         : :**

WP_000580383.1      LKYK-----------------------------------  79
QJA17755.1          LGASQRVAGDSGFAAYSRYRIGNYKLNTDHSSSSDNIALLVQ  222
                    *  .
```

WP_000580383.1: semiSWEET *Streptococcus pneumoniae*
QJA17755.1: Membrane protein SARS-CoV-2
Percent identity: 20.25