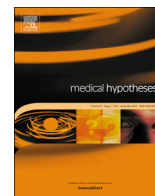




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Can COVID-19 induce glioma tumorigenesis through binding cell receptors?



ARTICLE INFO

Keywords:

COVID-19
ACE2 receptor
Spike protein
Glioma and Molecular Docking

ABSTRACT

The outbreak of Novel Coronavirus 2019 (COVID-19) represents a global threat to the public healthcare. The viral spike (S) glycoprotein is the key molecule for viral entry through interaction with angiotensin converting enzyme 2 (ACE2) receptor molecules present on the cell membranes. Moreover, it has been established that COVID-19 interacts and infects brain cells in humans via ACE2. Therefore in the light of these known facts we hypothesized that viral S protein molecule may bind to the other overexpressed receptor molecules in glioma cells and may play some role in glioma tumorigenesis. Thus we leverage docking analysis (HEX and Z-DOCK) between viral S protein and epidermal growth factor receptors (EGFR), vascular endothelial growth factor receptors (VEGFR) and hepatocyte growth factor receptors (HGFR/c-MET) to investigate the oncogenic potential of COVID-19. Our findings suggested higher affinity of Viral S protein towards EGFR and VEGFR. Although, the data presented is preliminary and need to be validated further via molecular dynamics studies, however it paves platform to instigate further investigations on this aspect considering the aftermath of COVID-19 pandemic in oncogenic perspective.

Novel Coronavirus 2019 (COVID-19) has caused an outbreak and is still spreading very rapidly across the world. COVID-19 infects the host respiratory cells and initiates complex immune responses, resulting in devastating clinical outcomes. The surface spike (S) glycoprotein (S protein) of COVID-19 has been shown to bind the host cell receptor angiotensin converting enzyme 2 (ACE2) and enter the target cells [1]. This is the critical step to initiate the disease and to produce clinical symptoms.

The role of COVID-19 in tumorigenesis of solid cancer is poorly understood and its role in glioma pathophysiology has not been reported. It is known that glial and neuronal cells express ACE2 on their surface, which makes the neuronal cells a potential target for COVID-19 infection [2]. We therefore hypothesize that the COVID-19 S protein may have binding affinity to the surface receptors of glioma cells and may induce molecular changes, with multiple influences on tumorigenesis, such as induction of tumor related signaling pathways. To understand this, we investigated the binding affinity between receptor binding domain (RBD) of S protein and a few known cell surface receptors documented in glioma pathogenesis.

Glioma cells have epidermal growth factor receptors (EGFR), vascular endothelial growth factor receptors (VEGFR) and hepatocyte growth factor receptors (HGFR/c-MET) on their surface, all of which are responsible for tumor growth and invasion [3]. The functional ability of these receptors to activate the downstream signaling pathways that take part in tumorigenesis make them stand out as potent targets for molecular therapeutics.

Considering the importance of these surface receptors on glioma cells, we studied the interaction between EGFR, VEGFR and c-MET receptor proteins with S protein of COVID-19. Since Wan et al. [4] already analyzed the binding of the human ACE2 protein with RBD of COVID-19 S protein, we used this binding as reference for protein-protein interaction in our analysis. The 3D structures of EGFR, VEGFR, c-MET, ACE2 and S protein were extracted from Uniprot, protein data

bank (PDB) id numbers – 1 m14, 1vpf, 2uzx, 2ajf and 2ghv, respectively. In order to test our hypothesis, we utilized two different molecular protein-protein docking platforms: Hex 5.1 and Z DOCK server [5,6]. Z-DOCK was performed on the protein-protein docking server using fast fourier transform algorithm.

Our results from Hex docking showed that COVID-19 S protein has binding affinity towards EGFR, VEGFR and c-MET receptor proteins, which was comparable to the binding affinity between ACE2 and S protein (Fig. 1). These findings were further substantiated by Z DOCK binding scores of S – EGFR, S - c-MET, S – VEGFR and S - ACE2 interacting protein complexes which were found to be 1697.528 for S – EGFR, 1958.115 for S - c-MET, 1690.053 for S – VEGFR and 1843.070 for S - ACE2.

The mechanism through which viruses exploit the presence of selective receptors on cells to interact with and infect the cells is well known [7,8]. For instance, complement receptor 2 (CR2), which is found on astrocytes, facilitates the entry of Epstein Bar virus (EBV) through interaction between EBV surface protein gp350 and CR2 [7,8]. Similarly, Cytomegalovirus (CMV) immediate-early (IE) proteins bind to retinoblastoma (Rb), p53 and p21, which subsequently leads to alteration in telomerase activity and cell cycle regulation [9]. Overall, there are several known receptor mediated entry and oncogenesis of different viruses.

Our preliminary findings suggested that COVID-19 S protein might have a binding affinity to EGFR, c-MET and VEGFR on glioma cells. Therefore, we speculate that COVID-19 can induce glioma tumorigenesis through the S protein, this may increase the risk of developing glioma in COVID-19 infected individuals, and may amplify tumor growth in COVID-19 infected glioma patients. Finally, our findings do not provide a definitive model for establishing the oncogenic potential of S protein and warrant further investigation. This could be accomplished via molecular dynamic simulation methods in the future.

<https://doi.org/10.1016/j.mehy.2020.110009>

Received 23 May 2020; Accepted 16 June 2020

Available online 19 June 2020

0306-9877/ © 2020 Elsevier Ltd. All rights reserved.

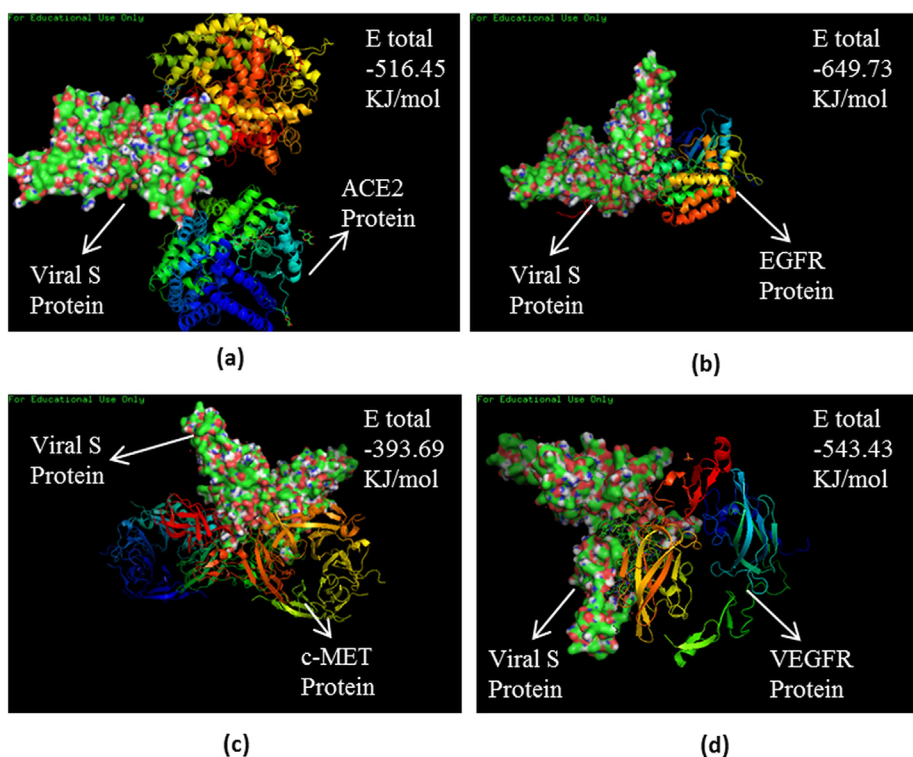


Fig. 1. Hex 5.0 generated protein-protein docked complexes with representative E-total energy values presented as KJ/mol (a) S-ACE2 protein-protein complex, (b) S-EGFR protein-protein complex, (c) S - c-MET protein-protein complex and (d) S-VEGFR protein-protein complex. Parameters opted for the Hex software were; (1) Grid Dimension – 0.6, (2) Twist Range – 360 and Distance Range – 40, (3) Receptor Range – 180, (4) Ligand Range – 180, (5) Post Processing – MM Energies, (6) FFT Mode – 3D and (7) Correlation type- Shape + Electrostatics.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors are grateful to Dr. A. Matteen Rafiqi for language editing of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2020.110009>.

References

- [1] Paules CI, Marston HD, Fauci AS. Coronavirus infections—More than just the common cold. *JAMA* 2020;323(8):707–8.
- [2] Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic

- mechanisms. *ACS Chem Neurosci* 2020;11(7):995–8.
- [3] Pearson JRD, Regad T. Targeting cellular pathways in glioblastoma multiforme. *Signal Trans Targeted Therapy* 2017;2(1):17040.
- [4] Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *J Virol* 2020;94(7):e00127–0.
- [5] Ritchie DW, Kemp GJ. Protein docking using spherical polar Fourier correlations. *Proteins* 2000;39(2):178–94.
- [6] Chen R, Weng Z. Docking unbound proteins using shape complementarity, desolvation, and electrostatics. *Proteins* 2002;47(3):281–94.
- [7] Menet A, Speth C, Larcher C, et al. Epstein-Barr virus infection of human astrocyte cell lines. *J Virol* 1999;73(9):7722–33.
- [8] Odumade OA, Hogquist KA, Balfour Jr. HH. Progress and problems in understanding and managing primary Epstein-Barr virus infections. *Clin Microbiol Rev* 2011;24(1):193–209.
- [9] Alibek K, Kakpenova A, Baiken Y. Role of infectious agents in the carcinogenesis of brain and head and neck cancers. *Infectious agents and cancer*. 2013;8(1):7.

Imran Khan^a, Mustafa Aziz Hatiboglu^{a,b,*1}

^a Department of Molecular Biology, Beykoz Institute of Life Sciences and Biotechnology, Bezmialem Vakif University, Yaliköy St., Beykoz, Istanbul, Turkey

^b Department of Neurosurgery, Bezmialem Vakif University Medical School, Vatan Street, Fatih, Istanbul, Turkey
E-mail address: mhatiboglu@bezmialem.edu.tr (M.A. Hatiboglu).

* Corresponding author.

¹ ORCID ID: 0000-0002-4409-6337.