Deciphering the molecular pathogenesis behind neurological manifestations of SARS-CoV-2 and drug repurposing, a systems biology approach

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Research Article

Keywords: SARS-CoV-2, HCoV-OC43, gene regulatory network, protein-protein interaction network, neurological manifestations

DOI: https://doi.org/10.21203/rs.3.rs-351801/v1

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Abstract

**Introduction:** As the COVID-19 pandemic spreads worldwide, reports about the neurological complications of SARS-CoV-2 are excessively increasing. However, there is still insufficient high-throughput data on neuronal cells infected with SARS-CoV-2 to help predict its neural pathogenesis. HCoV-OC43 is another member of the beta coronavirus family that has confirmed neuro-invasive effects and has available neural omics data. This study predicts the critical genes, biological processes, and pathways mediating in SARS-CoV-2 neurological manifestations using a systems biology approach.

**Method:** We retrieved raw data related to SARS-CoV-2 and HCoV-OC43 infections from gene expression omnibus datasets (GSE147507 and GSE13879 respectively). We constructed gene regulatory networks for both infections, detected significant regulatory motifs by FANMOD software, and created their subnetworks. We also constructed PPI networks and identified the MCODE clusters. In the intersection of merged subnetworks of two viruses, the most critical genes were verified in GRN & PPI networks. We drug-repurposed for the selected target genes and performed the functional enrichment analysis using DAVID and String databases.

**Results:** Some of the top KEGG pathway results included NF-kappa B, Toll-like receptor, NOD-like receptor, MAPK, and Neurotrophin signaling pathways. The most essential identified genes included IL6, TNF, H0XA5, POU2F2, ITGB3, STAT1, YY1, E2F6, ESR1, FOXO3, FOXO1, MEF2A, ATF3, ATF4, DDIT3, TCF4, BCL2L2, and BMP4. These genes were also involved in mechanisms of other viral infections of the nervous system. This study repurposes nine medicines with effects on COVID-19 neurological complications. Some of the repurposed drugs were previously registered in clinical trials for COVID-19 treatment.

**Conclusion:** We recommended some identified crucial genes and medications to investigate further their potential role in treating COVID-19 neurological complications.

**Introduction:**

Human coronavirus OC43 (HCoV-OC43) is a member of the **Coronaviridae** family, **Nidovirales** order, and **Coronavirus** genus (Kasmi, Khataby et al. 2020). CoVs are enveloped, positive-sense, single-stranded RNA viruses with the largest genome among RNA viruses (~ 32 kb) (Perlman and Netland 2009). Various viruses belong to the beta-coronavirus genus, including Human coronavirus OC43, human coronavirus HKU1, Middle East Respiratory Syndrome (MERS), and severe acute respiratory syndrome (SARS).

HCoV-OC43 generally causes the common cold, mild upper and lower respiratory tract infections, although it also can show neuroinvasive and neurotropism properties (Beidas and Chehadeh 2018). In vivo studies in mice have demonstrated that HCoV-OC43 can infect neurons and cause encephalitis (Pierre J. Talbot 2011). HCoV-OC43 has been reported in the cerebrospinal fluid of patients with multiple sclerosis. It has also been reported in acute disseminated Encephalomyelitis cases (Arbour, Day et al. 2000, Yeh, Collins et al. 2004). Cases of fatal encephalitis associated with HCoV-OC43 infections are
reported even in children (Morfopoulou, Brown et al. 2016). Until recently, our knowledge about the process and dynamics of HCoV-OC43 infection in the CNS is limited, and no effective drug is available to treat the disease (Zumla, Chan et al. 2016, Niu, Shen et al. 2020).

In December 2019, a new coronavirus (SARS-CoV-2) was found in Wuhan, China, which led to a deadly infectious disease called COVID-19. Near forty million cases and over one million deaths have been confirmed for the SARS-CoV-2 pandemic worldwide Until 2020 October. SARS-CoV-2 primarily targets the human respiratory system, and its common symptoms include fever, cough, fatigue, headache, hemoptysis, and dyspnea. In severe COVID-19 cases, patients may develop pneumonia, acute respiratory distress syndrome (ARDS), acute cardiac injury, and multi-organ failure (Rothan and Byrareddy 2020).

Similar to HCoV-OC43, the SARS-CoV-2 has also shown neurotropic and neuroinvasive properties. Some new hypothesis has been proposed about the possible routes of SARS-CoV-2 neuroinvasion, including neuronal retrograde, hematogenous, and glymphatic routs (Desforges, Le Coupanec et al. 2019, Battagello, Dragunas et al. 2020). Several neurological manifestations are reported for SARS-CoV-2 infection so far, including headache, dizziness, confusion, ataxia, seizures, acute ischemic stroke, and acute cerebrovascular problems (cerebral venous sinus thrombosis and cerebral hemorrhage) (Chen, Zhou et al. 2020, Huang, Wang et al. 2020, Li, Li et al. 2020, Mao, Jin et al. 2020, Wang, Hu et al. 2020, Yang, Yu et al. 2020). Besides, it seems that choosing suitable drugs for the neural conditions of COVID-19 still requires a more in-depth insight from its molecular pathogenesis. Drug repurposing is an effective drug discovery strategy, which significantly shortens the time and reduces the cost, compared to de novo drug discovery and randomized clinical trials (Zhou, Hou et al. 2020). However, it needs further experimental and population-based validations (Cheng, Desai et al. 2018).

This study first investigated the essential biological processes, biochemical pathways, and crucial genes mediating in the molecular pathogenesis of SARS-CoV-2 infections. We used bioinformatics analysis of gene regulatory elements, including transcription factors and microRNAs, the most essential and well-characterized gene regulators. We also analyzed the host response protein-protein interaction networks (PPINs) to predict the underlying molecular mechanisms associated with HCoV-OC43 and SARS-CoV-2 infections, particularly their neurological manifestations (Yang, Fu et al. 2019, Blanco-Melo, Nilsson-Payant et al. 2020). Besides, we aimed to identify the critical genes responsible for neuronal complications in these patients. However, high-output data for analyzing the HCoV-OC43 infection impacts on neural cells were accessible in array databases; still not sufficient high-output data was available for neuronal cells infected with SARS-CoV-2. Considering the partial phylogenic proximity between the two viruses (both are beta coronavirus) and regarding their similar neuro-invasive effects, we investigated their possible shared molecular mechanisms to predict the molecular mechanisms of the new SARS-CoV-2 responsible for COVID-19 neural manifestations. We compared the host response's gene regulatory networks to the two infections to predict crucial genes accountable for their neural manifestation. The crucial shared genes were then selected as target genes to repurpose new drug candidates, and the new repurposed drug candidates were then validated using the experimental literature.
Material And Methods:

Gene expression analysis related to HCoV-OC43 & SARS-CoV-2 infections

The microarray datasets of neural cells infected by HCoV-OC43 were searched and retrieved from the European Array-Express database and the gene expression omnibus (GEO) database (Barrett, Wilhite et al. 2013). Using the GSE13879 dataset (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE13879), Dominique J. Favreau et al. (Favreau DJ et al., 2009) had studied the association of HCoV-OC43 with some human neurological diseases. Transcriptional profiling of N-Tera2 differentiated mock-infected human neural cell vs. N-Tera2 differentiated human neural cell infected by HCoV-OC43 at 24, 48, and 72 hours post-infection had been performed using Agilent-012097 Human 1A Microarray (Favreau, Desforges et al. 2009). We used the processed data registered in the ArrayExpress databank (https://www.ebi.ac.uk/arrayexpress/experiments/E-GEOD-13879/?query=GSE13879) for the gene dataset (ID: E-GEDD-13879= GSE13879). We then filtered the DEGs based on log\textsubscript{2}FC>0.5 or <-0.5fold and false discovery rate p-value <0.05. We first extracted the DEGs related to 24h post-infection and then the shared DEGs between 48&72h post-infection.

We obtained the SARS-CoV-2 related data from the GSE147507 dataset (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE147507) (Blanco-Melo, Nilsson-Payant et al. 2020). Daniel Blanco-Melo et al. investigated the impact of the SARS-CoV-2 on the lung epithelial cell lines (NHBE & A549) as an in vitro study model. The study has investigated the effect of the SARS-CoV-2 on the lung epithelial cell lines only after 24 hours post-infection. After 24 hours of infection by SARS-CoV-2, the total RNA of the infected and mock cells were extracted and sequenced using an Illumina NextSeq 500 platform. We selected the differentially expressed genes (DEG) of the two cell lines based on log\textsubscript{2}FC>0.5 or <-0.5fold and false discovery rate p-value <0.05.

Protein-protein interaction (PPI) network construction and module detection:

Up-regulated and down-regulated genes were fed into the STRING database and HIPPIE (Human Integrated Protein-Protein Interaction rEference) (http://cbdm-01.zdv.uni-mainz.de/) separately to retrieve the protein interaction maps. We selected the protein-protein interactions with a confidence score threshold of 0.7 for each gene set. We then imported the interaction tables to Cytoscape software (version 3.7.1) (https://cytoscape.org/) to visualize them and perform topological network analysis (Shannon, Markiel et al. 2003). To map the third PPI network for each gene set, we also used the Bisogenet app to retrieve the HPRD database's interactions. We merged the three PPI networks in Cytoscape and analyzed it, and nominated the top 10% of the nodes having the highest degree and betweenness centrality as the hub and bottleneck nodes, respectively. Hub genes are defined as highly connected nodes in the PPI network, and networks are usually sensitive to delete the hub genes. Both hub and bottleneck nodes are generally necessary for fundamental cellular processes. (Liu, Yi et al. 2019).

We used the Molecular Complex Detection (MCODE) app to screen the clusters and finding their seed genes. The clusters are highly interconnected regions in a PPI network, and seed genes have the highest
degree value in a cluster (Bader and Hogue 2003). The clusters with an MCODE-score bigger than five were then merged to perform functional enrichment analysis.

**Gene regulatory networks (GRNs)**

**Identification of transcription factors regulating DEGs**

We obtained manually curated TF-target gene interactions from TRANSFAC database (http://genexplain.com/transfac/), which is the gold standard in transcriptional regulation (Wingender 2008), and the TRRUST v2 database, which contains 8444 TF-target regulatory relationships for 800 human TFs (www.grnpedia.org/trrust/).

**Identification of microRNAs suppressing DEGs**

We extracted experimentally validated miRNA-target gene interactions from miRecords (http://c1.accurascience.com/miRecords/) and miRTarBase release 8.0 (http://miRTarBase.mbc.nctu.edu.tw/). The miRTarBase was developed to present comprehensive information on experimentally validated miRNA–target gene interactions. In this version, the database has collected more than 13,404 validated interactions from 11,021 articles manually curated (Huang, Lin et al. 2020).

**Identification of TFs regulating miRs**

We collected literature-curated TF-miRNA regulation from TransmiR v2.0. It contains the TF-miRNA interaction data of 623 TFs and 785 miRNAs for 19 organisms from 1,349 publications (http://www.cuilab.cn/transmir).

**Identification of miRs suppressing TFs**

MicroRNAs post-transcriptionally suppress transcription factors. We considered TFs as target genes and retrieved experimentally validated miR-TF interactions from miRTarBase release 8.0.

**GRN construction and motif detection**

We integrated the four types of regulations (TF-gene, miR-gene, TF-miR, and miR-TF) to construct the transcription factor-microRNA-gene regulatory network visualized by Cytoscape software (version 3.7.1). We then merged and exported them to FANMOD software to identify the network's significant 3-node regulatory motifs. FANMOD is a tool for network motif detection that uses a novel algorithm called RAND-ESU (Wernicke and Rasche 2006). We evaluated each of the possible 3-node motif types for their significance using random network generation and built the random networks 1000 times to compare them with the original input network. The 3-node motif types having Z-score >2.0 and p-value < 0.05 were considered significant. (The other FANMOD parameters were the same as our previous work with DOI: 10.1080/17435390.2018.1513090). We then created the motif-related specific subnetworks for each of
the significantly scored motifs separately. The motifs with the same FANMOD ID were merged and considered as a unique motif subnetwork.

**Functional enrichment analysis**

We performed functional enrichment analysis for Gene Ontology (GO, [www.geneontology.org](http://www.geneontology.org)) and Kyoto Encyclopedia of Genes and Genomes (KEGG, [https://www.genome.jp/kegg/](https://www.genome.jp/kegg/)) on the nodes of the merged PPI clusters and genes of the merged GRN motifs separately using the STRING ([string-db.org](http://string-db.org)) and DAVID databases ([https://david.ncifcrf.gov](https://david.ncifcrf.gov)) (Huang da, Sherman et al. 2009) ([The Gene Ontology Consortium 2019](http://www.geneontology.org)). Biological processes and biochemical pathways with p-value < 0.05 were considered statistically significant. We selected biological processes and KEGG pathways, which were shared between the enrichment results of both databases.

**Identification of critical genes and drug repurposing**

HCoV-OC43 showed neuroinvasive effects in mice and humans; besides, neurological manifestations in patients with SARS-CoV-2 are recently reported (Asadi-Pooya and Simani 2020). Therefore, we used GSE13879, in which the human neuronal cell line was infected with HCoV-OC43 and compared its gene regulatory network with the SARS-CoV-2 network to predict genes responsible for the central nervous system (CNS) involvement in SARS-CoV-2 patients. Therefore, the shared genes between the intersections of the motif-related subnetworks of HCoV-OC43 & SARS-CoV-2 were selected as target genes to repurpose new drug candidates. The genes that played the role of the hubs/bottlenecks of the GRN/PPINs and the genes participating in PPI MCODE clusters were considered the most critical target genes for drug repurposing. We enriched these target genes using the STRING and DAVID databases and reported biological processes and KEGG pathways with p-value <0.05 enriched in both databases. We retrieved the drug-gene interactions among the medications from three drug databases, including Drug Gene Interaction Database (DGI)db version 3.0.2 ([http://dgidb.org/](http://dgidb.org/)), PharmGKB ([https://www.pharmgkb.org/](https://www.pharmgkb.org/)) and DrugBank database version 5.1.6 ([https://www.drugbank.ca/](https://www.drugbank.ca/)) ([Wishart, Feunang et al. 2018](http://www.geneontology.org)). We then constructed and visualized the interaction network between the selected genes (available in GRN and PPI networks) and their related drugs using the Cytoscape software. (The medications targeting all the shared target genes were also identified and represented in online Supplementary table S14 & S15) We validated our repurposed drug candidates for possible treatment of neural manifestations of COVID-19 by comparing them with the medications registered in clinical trial platforms for COVID-19 treatment, extracted from the DrugBank database ([Wishart, Feunang et al. 2018](http://www.geneontology.org)). The repurposed drugs were also discussed and verified by other experimental reports available in the literature review. The study design and the scheme of the workflow are summarized in fig.1.

**Results:**

**Gene expression changes related to HCoV-OC43 & SARS-CoV-2**
In this study, we first investigated how DEGs and their related TF/miRs are involved in biological processes and pathways related to the host response to HCoV-OC43 & SARS-CoV-2 infections using gene regulatory network and protein-protein interaction network. We extracted the DEGs based on p-value<0.05 and log2 fold change (FC) <-0.5 or >0.5. The DEGs identified for the only microarray dataset available for HCoV-OC43 and RNA sequencing results of two lung epithelial cell lines (NHBE & A549) infected with SARS-CoV-2 are available in table 1 and online supplementary table S1. We first elicited the DEGs related to HCoV-OC43 24h post-infection, and the shared DEGs between 48&72h. The DEGs related to SARS-CoV-2 were identified for the two cell lines separately and merged to produce the SARS-CoV-2 up and down-regulated gene sets separately for further analysis.

**Protein-protein interaction network (PPIN) construction:**

We retrieved the protein-protein interaction maps among the DEGs using the HPRD (by BIOSOGENET app), STRING, and HIPPIE databases. We then merged them to create a PPIN for up and down-regulated genes of each infection, separately. The PPI networks were visualized and topologically analyzed using the Cytoscape software. The number of nodes and edges of each network are represented in table 2, and the topological network analysis results are available in online supplementary table S2. We selected the top 10% of the PPI network nodes having the highest degree and betweenness centrality as the hub and bottleneck nodes, respectively (available in online supplementary table S3).

We investigated the shared DEGs between the HCoV-OC43 (up and down-regulated) networks related to 24h post-infection with the SARS-CoV-2 PPI networks. The few numbers of DEGs shared between the two infections are represented in online supplementary fig.S1 and fig.S2. The number of the shared genes was not sufficient (six down-regulated and 20 up-regulated shared genes) to construct an intersectional network for further analysis. The shared DEGs between the PPI networks related to HCoV-OC43 48&72h post-infection and SARS-CoV-2 were then investigated and used for further analysis.

**MCODE cluster detection and functional enrichment analysis**

The identified clusters of each PPI network and their seed genes using the MCODE plugin are represented in fig.2. The number of PPI clusters for HCoV-OC43 up and down-regulated genes were eighteen and twenty-six subnetworks, respectively. Based on the MCODE-score of more than five, we selected eight clusters of up-regulated and seven clusters of down-regulated genes.

We performed the Gene Ontology and Biochemical KEGG pathway enrichment analysis on the selected PPI clusters’ union, using the STRING and DAVID database (based on p-value<0.05). We have described the results that were shared between the two databases in online supplementary tables S4 and S5. The Seed genes of the eight up-regulated clusters were RPLP2, NDUFA3, LSM8, ACKR3, FGA, CBX3, HOXC9, and SYT1. Seed genes of the seven down-regulated clusters included UFL1, APLN, TRA2B, DHX58, COG2, IARS, and HTR4.
The SARS-CoV-2 PPI up and down-regulated networks had nineteen and nine clusters, respectively. We selected the nine up-regulated clusters based on MCODE-score > 5 and the nine down-regulated clusters based on MCODE-score > 3 (no down-regulated cluster score was higher than five). We performed gene ontology and KEGG pathway enrichment analysis on the clusters’ merged union, using the STRING database and the DAVID database (based on p-value < 0.05). We described the shared biological processes and KEGG pathways in online supplementary tables S6 and S7. The Seed genes of the top nine up-regulated clusters included HLA-F, B2M, UBE2W, IFI44, FGA, TGM1, DDX28, IL1A, and HAUS3. The down-regulated clusters' Seed genes were RAB26, PDE5A, COL20A1, FBXW9, CEP44, TSC22D3, METTL7A, PPARGC1A, and CENPA.

**Gene Regulatory Network construction and motif detection**

We extracted four types of regulatory relationships (TF-gene, miR-gene, TF-miR, and miR-TF) for each gene set. The results are available in table 3 and online supplementary table S8. We then imported the four regulatory relationships to Cytoscape software (version 3.7.1) and constructed the GRN for each gene set separately. We selected the top 10% of the GRN nodes having the highest degree and betweenness centrality as the hub and bottleneck nodes, respectively (available in online supplementary table S9).

The four types of regulations were then fed into the FANMOD software as an incorporated list for each gene set. The significant 3-node motifs of the GRNS were identified and represented in online supplementary fig.S3- fig.S6 (p-value < 0.05, K-score > 2). We selected the motifs with at least two different color edges (represented in fig.3 and fig.4). The selected motif-related subnetworks were created and visualized using the Cytoscape software (version 3.7.1). We merged the motif-related subnetworks with the same FANMOD ID and reported the subnetworks' intersection in fig.5. Our motif detection results showed that all the four gene sets (up and down-regulated genes of HCoV-OC43, and SARS-CoV-2) had the same type of significant motifs with FANMOD IDs 78, 14, and 164.

**Biological process and Biochemical pathway enrichment analysis:**

We performed enrichment analysis on the DEGs and also on the TFs included in the related DEGs of the merged union of each gene set's motif-related subnetworks, using the STRING and DAVID databases (p-value < 0.05). The biological processes and KEGG pathways enriched in both databases are available in online supplementary table S10-S13.

The sub-networks’ total union related to the HCoV-OC43 up and down-regulated subnetworks had 325 and 560 genes/TFs. The union of SARS-CoV-2 up and down-regulated genes had 23 and 5 genes/TFs, respectively.

**The shared functional enrichment results between the PPINs & GRNs**

We performed gene ontology and KEGG pathway enrichment analysis on the nodes of merged MCODE clusters of each PPIN and merged motif-related subnetworks of each GRN separately. The shared
biological processes and KEGG pathways between enrichment results of PPIN & GRN of each gene set are available in tables 4 and 5.

Some of the top biological processes for HCoV-OC43 DEGs included translation, mRNA metabolic process, protein localization, protein modification, and response to virus and stress. Besides, the top ten biological process terms of SARS-CoV-2 up-regulated genes were mostly about immune response, cytokine-mediated, and interferon signaling pathways. Some of the top KEGG pathways of HCoV-OC43 DEGs included Parkinson's disease, Alzheimer's disease, Huntington's disease, NOD-like receptor signaling pathway, Measles, TNF, and NF-kappa B signaling pathway. Some of the top KEGG pathways of SARS-CoV-2 up-regulated genes were Influenza A, Herpes simplex infection, NOD-like receptor signaling pathway, Rheumatoid arthritis, Measles, TNF signaling pathway, Hepatitis C, and Cytokine-cytokine receptor interaction. The number of shared down-regulated DEGs between PPI and GRNs was insufficient to perform the enrichment analysis for SARS-CoV-2 down-regulated genes (online supplementary table S7 and S13).

**Construction of target gene-drug interaction network and drug repurposing**

To predict the genes possibly mediating in neural manifestations of SARS-CoV-2, we identified the intersection between the unions of the motif-related subnetworks of HCoV-OC43 and SARS-CoV-2 GRNs (up and down-regulated DEGs, separately). These intersections contained the shared TFs, miRs, and target genes. The number of shared genes between the up-regulated GRN networks was 31, and the number was 35 for the downregulated GRN networks, depicted in fig.6 and fig.7.

We also enriched the target genes using the STRING and DAVID databases and described the shared biological processes and KEGG pathway results (p-value <0.05) between the databases in online supplementary table S14 and S15. The top related KEGG pathways were NF-kappa B, Toll-like receptor, NOD-like receptor, Influenza A, Herpes simplex infection, Measles, HTLV-I infection, Hepatitis B, MAPK, and Neurotrophin signaling pathways.

We searched for the medications interacting with the 31 up-regulated and 35 down-regulated target genes in Drug Gene Interaction Database (DGIdb), PharmGKB, and DrugBank databases. In DrugBank, we retrieved interactions of the target genes with previously FDA-approved and pharmacologically active drugs. For the up-regulated shared target genes, we found 20 interactions in DrugBank, 184 interactions in DGIdb, and 68 interactions in PharmGKB and the overall number of the repurposed drug/compounds were 251 (online supplementary table S16). The numbers were 37, 150, and 42 interactions for the down-regulated shared target genes, respectively, and the overall number was 182 (online supplementary table S17).

Among the shared target genes, the GRN and PPIN hubs/bottlenecks and MCODE clusters' nodes were the essential target genes (table 6 and 7). Eleven of the selected essential target genes were among the HCoV-OC43 DEGs of the 24h post-infection, including TNF, HOXA5, E2F6, ESR1, BCL2L2, DDIT3, PRDM1, RBMX, FOSL1, CRTC3, and KLF13.
From the 31 shared up-regulated target genes, six genes (HOXA5, POU2F2, TNF, ITGB3, STAT1, and IL6) were among the critical genes of both GRN and PPI networks. Therefore, they were nominated as the most crucial target genes. Among the thirty-five shared down-regulated target genes, twelve genes were shared between GRN and PPI networks’ essential genes. Therefore, they were considered the most crucial target genes, including YY1, E2F6, ESR1, FOXO3, MEF2A, TCF4, FOXO1, ATF3, BCL2L2, ATF4, DDIT3, and BMP4.

We extracted the drug-gene interactions for the six and twelve critical up and down-regulated target genes, respectively. Among the six up-regulated genes, four of them had drug interactions, and we visualized their 144 drug-gene interactions (129 unique drugs) using Cytoscape (fig.8). Among the twelve down-regulated genes, six had drug interactions. The number of drug interactions visualized for the six down-regulated genes was also 136. (133 unique drugs) (fig.8).

We then investigated our candidate drugs among the 563 medications currently available in clinical trials for their possible effect against SARS-CoV-2, extracted from the DrugBank database (https://go.drugbank.com/covid-19 ). The number of medications repurposed for the up-regulated critical target genes currently registered for SARS-CoV-2 treatment clinical trials was 35, and the number was 20 for the down-regulated (table 8).

**Discussion:**

This study analyzed and compared the DEGs related to lung epithelial cell lines (NHBE and A549) treated with SARS-CoV-2 and N-Tera2 differentiated human neuronal cells treated with HCoV-OC43 to investigate the possible molecular mechanisms behind the neurological manifestations of SARS-CoV-2 infection. We constructed TF-miR-gene regulatory and protein-protein interaction networks to identify the critical nodes (hubs, bottlenecks, motif members, and MCODE cluster members), biological processes, and pathways mediating in the two infections’ pathogenesis. The shared critical genes between the HCoV-OC43 effect on neural cells and SARS-CoV-2 could shed light on the molecular mechanisms of brain conditions in COVID-19 patients (Fig. 9). Herein, we discuss and validate some of the predicted genes and pathways probably mediating in neural manifestations of COVID-19 using other experimental literature.

This study investigated the genes mediating in the central nerve system (CNS) involvement of SARS-CoV-2 using the shared genes between both OC43 and SARS-CoV-2 GRN and PPI networks. The most critical genes included six up-regulated shared genes (IL6, TNF, HOXA5, POU2F2, ITGB3, and STAT1) and 12 down-regulated shared genes (YY1, E2F6, ESR1, FOXO3, FOXO1, MEF2A, ATF3, ATF4, DDIT3, TCF4, BCL2L2, and BMP4). Several other studies have previously reported the mentioned critical genes to be involved in neural proliferation and differentiation (neurodevelopment), neurotransmission, synaptic plasticity, and myelination (Each molecule is separately described and referred to in Table 9) (Yang, Lindholm et al. 2002, Nakanishi, Niidome et al. 2007, Ragel, Couldwell et al. 2007, He and Casaccia-Bonnefil 2008, Imamura, Satoh et al. 2008, Lange, Chavez et al. 2008, Islam, Gong et al. 2009, Renault, Rafalski et al. 2009, Leung and Cahill 2010, Oh, McCloskey et al. 2010, Zolova and Wight 2011, Hunt,
Raivich et al. 2012, Pozo, Cingolani et al. 2012, Cosker, Pazyra-Murphy et al. 2013, Wang, Choi et al. 2013, Ma, Tang et al. 2014, Mazalouskas, Jessen et al. 2015, Varney, Polston et al. 2015, Doan, Kinyua et al. 2016, Kennedy, Rahn et al. 2016, Chen, Gao et al. 2017, Lizen, Moens et al. 2017, Higashi, Tanaka et al. 2018, Li, Jin et al. 2018, Liu, Amar et al. 2018, Zhu, Carmichael et al. 2018, Liu, Yu et al. 2019, Majidi, Reddy et al. 2019, Masgutova, Harris et al. 2019, Wu and Donohoe 2019, Hartman and Czyz 2020, Pennycook, Vesela et al. 2020). Below, we have hypothesized how some of these in-silico identified critical genes can play roles in neural manifestations of COVID-19 pathogenesis.

The SARS-CoV-2 RNA acts as a viral pathogen-associated molecular pattern (PAMPs) that can be identified by pattern-recognition receptors (PRRs) like toll-like receptors (TLRs) and NOD (nucleotide-binding oligomerization domain)-like receptors (NLRs) (Kopitar-Jerala 2015). The surface receptors were among the top enrichment results of KEGG pathways of the shared DEGs between the two infections and are the first molecules activated in the innate immune system against the CNS pathogens. An inflammatory cascade initiates after triggering TLRs 3, 7, 8, and 9 by activating the NF-κB signaling pathway and IFN α/β/γ gene expression (Sabroe, Parker et al. 2008, Totura, Whitmore et al. 2015). The NF-κB pathway was also another pathway enriched for the shared DEGs. It regulates gene expression by kB sites present in promoter and enhancer regions of various essential genes such as chemokines, cytokines, adhesion molecules, and pro-inflammatory transcription factors. Therefore, it regulates neuronal survival and neuronal inflammatory reactions. The NF-κB also induces pro-IL-1β, pro-IL-18, TNF, and IL-6 (Tergaonkar, Correa et al. 2005, Tergaonkar 2006, Wong and Tergaonkar 2009). The TNF and IL-6 were identified as hub/bottlenecks in the GRN/PPI networks of our in-silico analysis.

SARS-CoV-2 can also be recognized by NLRP3 (a kind of NLRs). NLRP3 forms an inflammasome complex with caspase-1 and cleaves IL-1β and IL-18 to mature forms (Zhao and Zhao 2020). These cytokines (IL-1β, IL-18, TNF, and IL-6) induce further NF-κB nuclear translocation, activation of the JAK/STAT pathway, and phosphorylation of p38 MAPK (Battagello, Dragunas et al. 2020). The pathways were also included among our top ten enrichment results of the shared genes. Activation of p38s regulates immune response and inflammatory processes in SARS-CoV-2 infection (Feng, Fang et al. 2019, Grimes and Grimes 2020). In CNS, elevated activity of MAPK signaling can modulate neuronal survival and homeostasis (Feng, Fang et al. 2019, Grimes and Grimes 2020). Besides, in the JAK/STAT pathway, cytokines like INF and IL-6 bind to their receptors, induce JAK proteins cross-phosphorylation and then recruit STAT proteins. The phosphorylated STAT proteins then dimerize and translocate into the nucleus and regulate gene expression as transcription factors and (O'Shea, Schwartz et al. 2015). STAT1 and STAT3 were also identified as two crucial genes in our GRN/PPI networks. STAT1 has an essential role in the IFN signaling type I and type II and the JAK/STAT pathway (Pasieka, Cilloniz et al. 2011, Kulkarni, Scully et al. 2017). The role of STAT-1 has been previously elucidated in the innate immune response to other neurotropic viruses such as the severe acute respiratory syndrome coronavirus (SARS), Herpes simplex virus type 1 (HSV-1), and West Nile virus (WNV) (Pasieka, Cilloniz et al. 2011, Mahlakōiv, Ritz et al. 2012, Winkelmann, Luo et al. 2016).
The neurotrophin signaling pathway was another enriched result between the shared genes of our in-silico study. The pathway makes crosslinks with various intracellular signaling cascades, including NF-κB and MAPK pathways. Neurotrophins, such as nerve growth and brain-derived neurotrophic factors, induce neurons’ survival, development, and function (Reichardt 2006).

In the nervous system, IL-6 and TNF-α are typically expressed at relatively low levels. However, their expression is up-regulated under different pathological conditions like inflammation and viral infections (Yang, Lindholm et al. 2002, Oh, McCloskey et al. 2010). SARS-CoV-2 can activate glial cells in the CNS and induce a pro-inflammatory state. IL-6 and TNF-α play essential roles in the Systemic Inflammatory Response Syndrome (SIRS), leading to brain damage (Li, Fu et al. 2004, Liguori, Pierantozzi et al. 2020, Serrano-Castro, Estivill-Torrús et al. 2020, Wan, Yi et al. 2020). The IL-6 level also increases in other viral respiratory infections with neurological complications such as a human respiratory syncytial virus (RSV) and Influenza. It can be considered as an indicator of their neurologic prognosis (Aiba, Mochizuki et al. 2001, Kawashima, Kashiwagi et al. 2012, Morichi, Morishita et al. 2017).

HOXA5 was identified as another critical gene in our in-silico analysis. It is a member of the HOX family of transcription factors expressed throughout adulthood, especially in glutamatergic and GABAergic neurons. It regulates many genes associated with neuronal survival and synaptic function (Lizen, Moens et al. 2017). HoxA5 is reported to regulate the viral immediate-early (IE) gene expression in herpes simplex virus (HSV). Besides, the IE gene has an essential role in acute viral replication and its latency in neurons (Mitchell, De Santo et al. 1993, Mitchell 1995). HOXA5 expression is also reported to change significantly in some other neurotrophic viral infections like Cytomegalovirus, Coxsackievirus B3 (CVB3), and lymphocytic choriomeningitis virus (LCMV). The viruses can infect neurons and cause meningitis and encephalitis (Ester 2011, Puccini, Ruller et al. 2014).

POU2F2 (Oct-2) was another identified crucial gene. It has an essential role in virus replication and is a member of the POU family. It is predominantly expressed in B cells, activated T cells, and the nervous system (Luchina, Krivega et al. 2003). Some POU family members, such as POU2F1, are reported to be necessary for viral DNA replication and gene expression in other viruses such as herpes simplex virus (HSV) (Ryan and Rosenfeld 1997). It can be hypothesized that SARS-CoV-2 elevates the expression of HOXA5 and POU2F1 to increase its viral proliferation possibly.

The ITGB3 gene, coding for the integrin β3 subunit, is expressed and enriched at cortical, hippocampal, and midbrain synapses in the brain (Varney, Polston et al. 2015). The integrin β3 mediates in HSV-1 cell entry by relocating HSV receptor nectin1, and thus HSV to cholesterol-rich microdomains of the membrane where TLR2 presents. Therefore, integrin β3 plays a vital role in endocytosis of the virus and initiation of the innate immune response (NF-κB activation and production of IFNα, IFNβ, IL2, and IL10) (Gianni, Leoni et al. 2012, Gianni, Leoni et al. 2013). The ITGB3 was up-regulated in our in-silico results. Therefore, we suggest that SARS-CoV-2 is probably utilizing this upregulation to increase its entry. However, further experimental studies are required to confirm the prediction.
The antiviral response is also activated by Yin Yang 1 (YY1). It is a multi-functional transcription factor that can activate or repress gene expression in various cell types, including neurons (He and Casaccia-Bonnefil 2008, Chen and Chan 2019). Some viral infections down-regulate the expression of YY1 since it can mediate the antiviral innate immune response and regulate the production of interferon-beta (IFN-β) (Zan, Zhang et al. 2017). YY1-1 can also repress the transcription of many retroviruses such as human immunodeficiency virus type I (HIV-1). It also contributes to a neurological disorder caused by the human T lymphotropic virus type 1 (HTLV-1) (Coull, Romerio et al. 2000, Wang and Goff 2020). We also identified the YY1 as a downregulated gene in SARS-CoV-2 and OC-43 infections. Therefore, it can be postulated that the virus is probably benefiting from the YY1-1 downregulation in its neural pathogenesis in COVID-19. E2F6 expression is a known mechanism that slows down or exits the cells from S-phase. Some viral proteins can inactivate E2F6 to extend the S-phase in virus-infected cells, such as human papillomavirus (HPV) E7 proteins, simian virus 40 T antigen, and adenovirus E1A (McLaughlin-Drubin, Huh et al. 2008). Our results showed that SARS-CoV-2 infection down-regulates the expression of E2F6. The E2F6 downregulation presumably contributes to the replication of the virus.

The Forkhead box O transcription factors (FOXO1 and 3) were the next identified critical genes. They mediate the regulation of the cell cycle, apoptosis, autophagy, and DNA repair. They also are reported to regulate neural cell survival, neuronal signaling, and stress responses in the nervous system (Santo and Paik 2018, Schäffner, Minakaki et al. 2018). Our results showed that SARS-CoV-2 down-regulated the FOXO proteins similar to other viruses such as the Japanese encephalitis virus (JEV). JEV induces cell apoptosis in neurons by inhibiting the FOXO-signaling pathway. Therefore, it can lead to severe viral encephalitis in humans and other animals (Guo, Yu et al. 2018). Furthermore, FOXO proteins have a validated role in the pathogenesis of HIV-I-infection and its associated neurological complications (Cui, Huang et al. 2009).

ESR1 (Estrogen receptor α) is present in the hypothalamus and amygdala regions related to human emotion and cognitive functions (Ma, Tang et al. 2014). It is also involved in the pathogenesis of hepatitis viruses (HBV & HCV) and their complications (Deng, Zhou et al. 2004, Zhai, Zhou et al. 2006, Watashi, Inoue et al. 2007). Neurological complications of these viruses range from peripheral neuropathy to cognitive impairment (Mathew, Faheem et al. 2016). SARS-CoV-2 is also a positive-sense RNA virus similar to HCV. Therefore, we predict that the molecular mechanisms behind the two viruses’ similar neurological complications are probably the same, and we recommend the prediction for further experimental investigations.

Myocyte enhancer factor 2 (MEF2, isoform A) is also highly expressed in the brain. MEF2A is a downstream protein of NMDA receptor-mediated excitotoxicity in which excessive stimulation of the NMDA receptor contributes to the death of neurons. It is also reported to mediate in the neuropathogenesis of some other single-strand RNA-viruses such as HIV-1 (Kaul and Lipton 2004, Yndart, Kaushik et al. 2015). The MEF2A was identified as a critical gene and is recommended for further studies in the neuropathogenesis of SARS-CoV-2, similar to HIV-1.
Activating transcription factors (ATFs) are members of the ATF/cAMP response element-binding protein (CREB) family. ATF3 and ATF4 usually are low in neural cells, but their expression increases rapidly in response to pathological stress (Lange, Chavez et al. 2008, Hunt, Raivich et al. 2012). Activation of innate and adaptive immune systems can induce the expression of ATF3. However, ATF3 acts as a negative regulator of the immune response (Hunt, Raivich et al. 2012). Our analysis showed that SARS-CoV-2 down-regulated the ATF3. Therefore, it can be suggested that down-regulation of ATF3 possibly mediates in hyper-activation of the immune system and neural manifestations of some patients with severe COVID-19. ATF4 is a downstream protein of a cellular protective signaling pathway called the Unfolded Protein Response (UPR). UPR and Autophagy pathways are tightly interconnected and are reported to play a vital role in some viral infections such as hepatitis C virus, herpes simplex virus type 1 (HSV-1), Influenza virus, and severe acute respiratory syndrome (SARS) (Tardif, Mori et al. 2004, Versteeg, van de Nes et al. 2007, Burnett, Audas et al. 2012, Sen, Balakrishnan et al. 2014, Sims and Meares 2019). We hypothesize that SARS-CoV-2 probably modulates the UPR/Autophagy signaling pathways to produce large quantities of viral proteins. Besides, ATF4 (CERB-2) interacts with Human T-cell leukemia virus type 1 (HTLV-1) tax protein to regulate its transcription. The virus causes a severe neurologic disorder called HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP) (Ahuja, Kampani et al. 2006, Barbeau and Mesnard 2011).

DDIT3 (DNA damage-inducible transcript 3) was another down-regulated critical gene in our in-silico results. It is a downstream protein of ATF4 in unfolded protein response (UPR), which can activate the autophagy pathway (Bello-Perez, Sola et al. 2020). DDIT3 also downregulates BCL2, which is involved in the apoptosis pathway and autophagy flux (Nabirotchkin 2020). Therefore, SARS-CoV-2, similar to other previously known coronaviruses, dysregulates these three genes (ATF4, DDIT3, BCL2) to possibly exploit the autophagy molecular machinery and replicate more rapidly (Bello-Perez, Sola et al. 2020, Mamoor 2020, Nabirotchkin 2020). DDIT3 is also dysregulated in other viral infections such as the Zika virus (ZIKV), Tick-borne encephalitis virus (TBEV), and West Nile virus (WNV). The three viral infections can progress to the CNS and cause encephalitis or meningitis in severe cases (Selinger, Wilkie et al. 2017, Huang, West et al. 2019, Ojha, Rodriguez et al. 2019, Bonenfant, Meng et al. 2020).

Bcl2l2 (Bcl-w) is an Anti-apoptotic member of The B-cell lymphoma-2 (BCL-2) family (Hartman and Czyz 2020). Various viruses are reported to interact with the Bcl-2 family to regulate the cellular apoptosis, including Influenza A virus, hepatitis B virus, hepatitis C virus, Epstein–Barr virus, vesicular stomatitis virus, human immunodeficiency virus, and SARS-CoV. (Tan, Tan et al. 2007, Nencioni, De Chiara et al. 2009, Pearce and Lyles 2009, Busca, Saxena et al. 2012, Geng, Huang et al. 2012, Park, Kang et al. 2012, Ghigna, Reineke et al. 2013). Some of the viruses have previously been reported with neural complications. The Influenza A virus and SARS-CoV are reported to suppress BCL-W and Bcl-XL (another anti-apoptotic member of the family) to induce cellular apoptosis and subsequent tissue damage (Tan, Tan et al. 2007, Nencioni, De Chiara et al. 2009, Guan, Shi et al. 2012). Our results showed that SARS-CoV-2 also down-regulates Bcl-w, Similar to SARS-CoV. The Bcl-w probably also mediates in SARS-CoV-2 subsequent tissue damage in a similar way.
BMP4 is one of the Bone morphogenetic proteins (BMPs), which are members of the transforming growth factor-beta (TGF-b) superfamily (Higashi, Tanaka et al. 2018). TGF-beta and BMP signaling pathways are activated following some neurotropic viral infections, such as reovirus. The signaling pathways are part of the host immune response and have a neuroprotective effect (Beckham, Tuttle et al. 2009). Besides, the synergistic activation of BMP and alpha-interferon signaling pathways is also reported to reduce the hepatitis C virus [136]. Based on our results, the SARS-CoV-2 down-regulated the BMP4. Therefore, we suggest that the virus probably is benefitted from the BMP4 down-regulation in infected neurons.

In this study, we investigated our 259 repurposed medicines indications and mechanisms using the DrugBank database. Our emphasis was on drugs that affect the nervous system; since SARS-CoV-2 is a neurotropic virus, and the immune system's hyperactivation has a vital role in its complications (Table 8). We also reported the drug candidates that were categorized as inflammatory drugs or antiviral drugs. We have reported forty-four drugs with immunomodulatory or immunosuppressive functions that have validated effects in treating inflammatory or autoimmune diseases such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Chron's disease, ulcerative colitis, systemic lupus erythematosus, and Behcet's disease (Suzuki Kurokawa and Suzuki 2004, Allison 2005, Potthast, Dressman et al. 2005, Klotz, Teml et al. 2007, Mease 2007, Lucas 2016, Corbett, Chehadah et al. 2017, Laurence L. Brunton 2018, Yang, Wu et al. 2018, Afra, Razmi et al. 2019). Ten antiviral medications (mostly anti-HIV-1 and hepatitis) were also among our repurposed drugs. For example, Hydroxychloroquine and chloroquine were two drugs reported to inhibit the viral entry by changing the endosomal PH and disrupting glycosylation of ACE2 (Vincent, Bergeron et al. 2005, Plantone and Koudriavtseva 2018, Devaux, Rolain et al. 2020, Wang, Cao et al. 2020).

Our repurposed medications that have validated effects in the nervous system included 1-Risperidone (schizophrenia and bipolar disorders), 2-Ibudilast (neuroprotective in multiple sclerosis), 3-Carbamazepine (control seizures, trigeminal neuralgia, and Bipolar disease), 4-Midazolam (hypnotic-sedative, muscle relaxant and anticonvulsant ), 5-pyridoxine (synthesis of the neurotransmitters), 6-Duloxetine (neuropathic pain and Generalized Anxiety disorder), 7-melatonin (sleep-wake cycle disturbances), 8-Rizatriptan (migraine), and 9-selective serotonin receptor inhibitors (antidepressant) (Tambasco-Studart, Titiz et al. 2005, Chen and Lin 2012, Tolou-Ghamari, Zare et al. 2013, Kennedy, Lam et al. 2016). We have also discussed Ibudilast's neuroprotective properties, Melatonin, Pyridoxine, and SSRIs, to validate the repurposed drugs.

Ibudilast suppresses the excess production of pro-inflammatory cytokines such as interleukin IL-1β, IL-6, and TNF-α in the CNS. This anti-inflammatory property can help treat other viral-related neurocognitive disorders, such as HIV-associated neurocognitive disorders (HAND) and other neuro-inflammatory diseases [155–157]. Our SARS-CoV-2 treated cells in-silico results also showed the up-regulation of IL-1β, IL-6, and TNF-α. Therefore, it can be recommended as a possibly suitable repurposed drug for COVID-19 neural manifestations' investigations (in vitro and in vivo).
Melatonin seems a suitable candidate in treating COVID-19 since it shows excellent anti-oxidative properties by directly scavenging free radicals and stimulating antioxidant enzymes. Furthermore, Melatonin has anti-inflammatory effects by reducing pro-inflammatory cytokines and balancing innate immune response's over-activation while promoting adaptive immunity [158, 159]. The published reports related to Melatonin used in the animals with deadly viral infections such as Venezuelan equine encephalomyelitis virus (VEEV), Semliki Forest virus (SFV), and West Nile virus (WNV) showed that Melatonin is not viricidal. However, somewhat it reduces the severity of viral infections [158, 159]. Adequate Pyridoxine supplementation can prevent polyneuropathy, which is the most common neurological complication associated with HIV [160, 161]. Perhaps, Pyridoxine can be helpful in such kinds of pains in COVID-19 patients.

Serotonin shows immunomodulatory properties by downregulating central and peripheral inflammatory responses. So selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (with a clinical trial ID of NCT04377308) and Fluvoxamine (NCT04342663) could effectively dampen the excessive production of cytokines and prevent neurological complications in various neurocognitive disorders and COVID-19 [162].

We investigated the number of shared medicines between our list and the list of all registered drugs for COVID-19 clinical trials to verify our repurposed medications for their possible use in treating neural manifestations of COVID-19. Fifty-four of our repurposed medications were previously registered for investigations against COVID-19 (Table 8).

**Conclusion**

The current study revealed significant regulatory motifs and clusters of protein-protein interactions that play essential roles in the pathogenesis of HCoV-OC43 & SARS-CoV-2. With the accessible information on neuronal cells infected with HCoV-OC43, we predicted crucial genes, biological processes, and pathways in SARS-CoV-2 neurological manifestations that were mostly linked to activation of the innate immune system in CNS. This bioinformatics analysis can help shed light on molecular mechanisms and interactions involved in the neurological aspects of COVID-19. This study recommends some identified crucial genes and medications for further investigations in vitro and in vivo.

**Declarations**

**Funding**

No funding was received for conducting this study.

**Conflict of interest**

The authors have no conflicts of interest to declare that are relevant to the content of this article.
Availability of data and material

All authors confirm that all data and materials as well as software application or custom code support their published claims and comply with field standards.

Code availability

Not applicable

Authors' contributions

All authors contributed to the study design. Maryam Mozafar, Seyed Amir Mirmotalebisohi, and Hakimeh Zali performed Material preparation, data collection and analysis. Maryam Mozafar and Seyed Amir Mirmotalebisohi wrote the first draft of the manuscript. All authors supervising on completing this version of the manuscript. All authors read and approved the final manuscript.

Ethics approval

Not applicable

Consent to participate

Not applicable

Consent for publication

Not applicable

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### Tables

**Table1.** The number of differentially expressed genes related to the HCoV-OC43 microarray dataset and RNA-seq analysis of two cell lines infected with SARS-CoV-2.

|                      | Up-regulated genes (log2 FC>0.5) | Down-regulated genes (log2 FC <-0.5) |
|----------------------|----------------------------------|--------------------------------------|
| GSE13879 (24h)       | 2264                             | 833                                  |
| GSE13879 (shared between 48h&72h) | 537                             | 845                                  |
| NHBE cell line       | 250                              | 190                                  |
| A549 cell line       | 351                              | 101                                  |

**Table2.** Number of nodes and edges in each PPI network.

| PPI network of each input | Number of nodes | Number of edges |
|---------------------------|-----------------|-----------------|
| HCoV-OC43 (24h) Up-regulated genes | 2323            | 8438            |
| HCoV-OC43 (24h) Down-regulated genes | 855             | 2136            |
| HCoV-OC43 (48h&72h) Up-regulated genes | 551             | 1550            |
| HCoV-OC43 (48h&72h) Down-regulated genes | 882             | 1322            |
| SARS-CoV-2 Up-regulated genes | 578             | 1709            |
| SARS-CoV-2 Down-regulated genes | 290             | 163             |

**Table3.** Summary of the number of four regulatory relationship types among miRNAs, genes, and TFs.
| Input type                                      | Relationships | Number of pairs | Number of genes | Number of TFs | Number of miRs |
|------------------------------------------------|---------------|-----------------|-----------------|---------------|----------------|
| **Up-regulated genes of GSE related to HCoV-OC43** | TF gene       | 8471            | 516             | 263           | ___            |
|                                                 | miR gene      | 10280           | 404             | ___           | 1594           |
|                                                 | TF miR        | 2044            | ___             | 356           | 335            |
|                                                 | miR TF        | 9045            | ___             | 229           | 1556           |
| **Down-regulated genes of GSE related to HCoV-OC43** | TF gene       | 12672           | 798             | 298           | ___            |
|                                                 | miR gene      | 20184           | 657             | ___           | 1688           |
|                                                 | TF miR        | 2092            | ___             | 356           | 339            |
|                                                 | miR TF        | 10188           | ___             | 262           | 1584           |
| **Up-regulated genes of RNA sequencing results of SARS-CoV-2 infected cell lines** | TF gene       | 9051            | 529             | 313           | ___            |
|                                                 | miR gene      | 10018           | 437             | ___           | 1572           |
|                                                 | TF miR        | 2077            | ___             | 357           | 338            |
|                                                 | miR TF        | 20682           | ___             | 277           | 1599           |
| **Down-regulated genes of RNA sequencing results of SARS-CoV-2 infected cell lines** | TF gene       | 4267            | 256             | 237           | ___            |
|                                                 | miR gene      | 4721            | 190             | ___           | 1365           |
|                                                 | TF miR        | 2038            | ___             | 355           | 331            |
|                                                 | miR TF        | 8283            | ___             | 204           | 1534           |

Table 4. Top shared biological processes between enrichment results of GRN & PPI networks of each gene set.
| selected up-regulated genes of GSE related to HCoV-OC43 | selected down-regulated genes of GSE related to HCoV-OC43 | selected up-regulated genes of RNA sequencing results of SARS-CoV-2 infected cell lines |
|--------------------------------------------------------|----------------------------------------------------------|-----------------------------------------------------------------------------------|
| nuclear-transcribed mRNA catabolic process            | protein poly-ubiquitination                              | defense response                                                                  |
| nonsense-mediated decay                                | protein ubiquitination                                   | cytokine-mediated signaling pathway                                               |
| SRP-dependent cotranslational protein targeting to membrane | protein modification by small protein conjugation or removal | immune response                                                                   |
| nuclear-transcribed mRNA catabolic process             | tRNA aminoacylation for protein translation              | response to other organisms                                                        |
| translation                                            | cellular protein metabolic process                       | type I interferon signaling pathway                                               |
| mRNA metabolic process                                 | NIK/NF-kappaB signaling, cellular response to organic substance | innate immune response                                                            |
| establishment of protein localization to membrane      | cellular response to organic substance                   | response to cytokine                                                              |
| peptide metabolic process                              | response to virus                                         | cellular response to cytokine stimulus                                            |
| protein targeting                                      | response to organic substance                            | immune system process                                                             |
| establishment of protein localization to organelle     | response to stress                                        | response to stress                                                                |

Table 5. Top shared KEGG pathways between enrichment results of GRN & PPI networks of each gene set.
| selected up-regulated genes of GSE related to HCoV-OC43 | selected down-regulated genes of GSE related to HCoV-OC43 | selected up-regulated genes of RNA sequencing results of SARS-CoV-2 infected cell lines |
|--------------------------------------------------------|-----------------------------------------------------------|----------------------------------------------------------------------------------|
| Ribosome                                               | Aminoacyl-tRNA biosynthesis                               | Influenza A                                                                     |
| Oxidative phosphorylation                              | TNF signaling pathway                                     | Herpes simplex infection                                                        |
| Parkinson's disease                                    | NOD-like receptor signaling pathway                       | NOD-like receptor signaling pathway                                              |
| Non-alcoholic fatty liver disease (NAFLD)              | NF-kappa B signaling pathway                              | Rheumatoid arthritis                                                           |
| Alzheimer's disease                                    | Toxoplasmosis                                             | Measles                                                                         |
| mRNA metabolic process                                 | Measles                                                   | TNF signaling pathway                                                           |
| Huntington’s disease                                   |                                                           | Hepatitis C                                                                     |
| Spliceosome                                            |                                                           | Pertussis                                                                       |
| Pathogenic Escherichia coli infection                  |                                                           | Cytokine-cytokine receptor interaction                                          |
|                                                        |                                                           | Legionellosis                                                                   |

Table 6. The table represents the hub/bottleneck nodes available among the 31 crucial shared genes of the intersection of merged motifs in the two GRN networks of up-regulated genes. The most critical genes are bolded.
| Gene name | Hub genes in both GRN networks | Hub genes in one of GRN networks | Bottleneck genes in both GRN networks | Bottleneck genes in one of GRN networks | Hub genes in one of the PPI networks | Bottleneck genes in one of the PPI networks | MCODE cluster in one of PPI networks | Seed gene |
|-----------|-------------------------------|----------------------------------|--------------------------------------|----------------------------------------|--------------------------------------|----------------------------------------|----------------------------------------|----------|
| ZFHX3     | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| HOXA5     | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| POU2F2    | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| HIF1A     | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| MAZ       | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| POU3F1    | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| LIN28B    | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| TNF       | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| ITGB3     | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| FOSL1     | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| STAT1     | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| IL6       | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| PRDM1     | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| SAMD9L    | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| BMP2      | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| RELB      | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| USF1      | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| RBMX      | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| NFKB2     | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| IRF9      | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| IRF7      | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| IL1B      | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| PBX1      | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| PLAU      | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |
| SPRR2A    | +                             | +                                | +                                    | +                                      | +                                    | +                                      | +                                      |          |

Table 7. The table represents the hub/bottleneck nodes available among the 35 crucial shared genes of the intersection of merged motifs in the two GRN networks of down-regulated genes. The most critical genes are bolded.
| Gene name       | Hub genes in both GRN networks | Hub genes in one of GRN networks | Bottleneck genes in both GRN networks | Bottleneck genes in one of GRN networks | Hub genes in one of the PPI networks | Bottleneck genes in one of the PPI networks | MCODE cluster in one of PPI networks | Seed gene |
|-----------------|--------------------------------|----------------------------------|---------------------------------------|------------------------------------------|--------------------------------------|------------------------------------------|----------------------------------------|-----------|
| YY1             | +                              | +                                | +                                     | +                                       | +                                    |                                          |                                        | +         |
| LEF1            | +                              | +                                |                                        |                                         |                                      |                                          |                                        | +         |
| E2F6            | +                              | +                                |                                        |                                         | +                                    |                                          |                                        | +         |
| 3ATA6           | +                              | +                                |                                        |                                         | +                                    |                                          |                                        | +         |
| BTB7A           | +                              | +                                |                                        |                                         | +                                    |                                          |                                        | +         |
| ESR1            | +                              | +                                |                                        |                                         | +                                    | +                                        |                                        | +         |
| KLF13           | +                              | +                                |                                        |                                         | +                                    |                                          |                                        | +         |
| 3OXO3           | +                              | +                                |                                        |                                         | +                                    | +                                        |                                        | +         |
| 4EF2A           | +                              | +                                |                                        |                                         | +                                    |                                          |                                        | +         |
| ETS1            | +                              | +                                |                                        |                                         | +                                    |                                          |                                        | +         |
| TCF4            | +                              | +                                |                                        |                                         | +                                    |                                          |                                        | +         |
| 3OXO1           |                                | +                                |                                        |                                         | +                                    |                                          |                                        | +         |
| ATF3            | +                              | +                                |                                        |                                         | +                                    |                                          |                                        | +         |
| hCL2L2          |                                | +                                |                                        |                                         |                                      |                                          |                                        | +         |
| ATF4            | +                              | +                                |                                        |                                         | +                                    |                                          |                                        | +         |
| TP63            |                                | +                                |                                        |                                         |                                      |                                          |                                        | +         |
| BMP4            | +                              |                                  |                                        |                                         |                                      |                                          |                                        | +         |
| APEX1           | +                              |                                  |                                        |                                         |                                      |                                          |                                        | +         |
| MTF1            |                                | +                                |                                        |                                         |                                      |                                          |                                        | +         |
| BMP4            |                                | +                                |                                        |                                         |                                      |                                          |                                        | +         |
| DDIT3           |                                | +                                |                                        |                                         |                                      |                                          |                                        | +         |
| CBFB            |                                |                                  |                                        |                                         |                                      |                                          |                                        | +         |
| XBP1            |                                |                                  |                                        |                                         |                                      |                                          |                                        | +         |
| CRTC3           |                                |                                  |                                        |                                         |                                      |                                          |                                        | +         |
| AMD9L           |                                |                                  |                                        |                                         |                                      |                                          |                                        | +         |
Table 8. The categorization of the most crucial repurposed medications.

| Categorization                                  | drugs                                                                 | Target genes                      |
|------------------------------------------------|-----------------------------------------------------------------------|-----------------------------------|
| Drugs that affect the nervous system            | risperidone, ibudilast, carbamazepine, midazolam, pyridoxine, duloxetine, melatonin, rizatriptan, SSRI s | TNF-α, IL-6, ESR1, FOXO1, ATF3     |
| Immunosuppressive or immunomodulatory drugs     | etanercept, adalimumab, infliximab, golimumab, certolizumab, pomalidomide, talactoferrin alfa, placulumb, pirfenidine, pentoxifylline, oncept, afelimomab, oxoralizumab, pegsnercept, hydroxychloroquine, chloroquine, aremilast, talmapinod, ibudilast, cyclosporine, mycophenolate mofetil, siltuximab, ginseng, sirukumab, olokizumab, clazakizumab, peg) interferon alfa-2b, ifosfamide, peginterferon alfa-2a, rituximab, tacrolimus, antithymocyte immunoglobulin, aspirin, prasterone (DHEA), everolimus, lefunomide, cyclophosphamide, bortezomib, ibuprofen, penicillamine, indomethacin, Sirolimus, Diclofenac, Celecoxib | TNF-A, IL-6, ITGB3 ESR1, FOXO1, BCL2L2 |
| Anti-viral drugs                                 | hydroxychloroquine, chloroquine, abacavir, didanosine, stavudine, interferon alfa-2b, saquinavir, nelfinavir, peginterferon alfa-2a, ribavirin | TNF-α, IL-6                          |
| Shared drugs with clinical trials on SARS-CoV-2 | arsenic trioxide, clazakizumab, rabeprazole, pyridoxine, nelfinavir, thalidomide, pirfenidine, hydroxychloroquine, tirofibian, olokizumab, midazolam, etanercept, lenalidomide, cyclosporine, omeprazole, spirinactone, atorvastatin, ibudilast, peginterferon alfa-2a, infliximab, adalimumab, metronidazole, tacrolimus, siltuximab, aremilast, clopidogrel, sirukumab, interferon alfa-2b, levofloxacin, pentoxifylline, talactoferrin alfa, folic acid, ribavirin, nafamostat, chloroquine, estradiol, genistein, melatonin, iodine, doxycycline, tamoxifen, vitamin e, leflunomide, progesterone, curcumin, etoposide, fenretinide, suramin, hydrogen peroxide, ibuprofen, sirolimus, indomethacin, deferroxamine, celecoxib | TNF-α, IL-6                          |

Table 9. Role of the crucial genes available in the intersection of merged motifs of HCoV-OC43 and SARS-COV-2 in the nervous system
| NSPCs<sup>a</sup> proliferation / differentiation | Synaptic function | others | references |
|-----------------------------------------------|-------------------|--------|------------|
| Neurogenesis, gliogenesis | neuronal myelination, neurotrophin release | | Islam, Gong et al. 2009, Nakanishi, Niidome et al. 2007, Oh, McCloskey et al. 2010 |
| α | promote neuronal death or survival, depending on the types of target neurons and receptor subtypes (TNFRI or TNFRII) | | Leung and Cahill 2010, Yang, Lindholm et al. 2002 |
| A5 | synaptogenesis | synaptic transmission, synaptic plasticity of pre-cerebellar circuits | | Lizen, Moens et al. 2017 |
| F2 | dorsal interneurons (dINs) differentiation and distribution | regulates both structure and function of serotonergic and glutamatergic synapses in the CNS | | Masgutova, Harris et al. 2019 |
| 3 | increase the proliferation of NSCs but decrease their differentiation into neurons and glia cells | synaptic transmission and plasticity | | Mazalouskas, Jessen et al. 2015, Pozo, Cingolani et al. 2012, Varney, Polston et al. 2015 |
| T1 | neural development | myelination | | Liu, Yu et al. 2019 |

<sup>a</sup> NSPCs: Neural Stem/Progenitor Cells
|   | decrease the proliferation of NSCs but increase their differentiation | synaptic plasticity and neurotransmission | improve cerebral blood flow and neuronal repair |
|---|---|---|---|
| 1 |  | synapse and development and neural plasticity |  |
| 2 | long-term maintenance of the NSPC pool to protect cognition function during aging | controls energy balance and glucose homoeostasis |  |
| 3 | neurogenesis, pre and postsynaptic dendritogenesis, synaptogenesis | modulator of neurogenesis, modulator of neuronal plasticity | involved in neuron-immune cell interactions |
| 4 | modulator of neurogenesis, modulator of neuronal plasticity | contributes with neurotrophin neuroprotection |  |
| 4 | Synaptic Plasticity | associated with Memory Function and language development |  |
| L2 | neuronal development | involves in neurotrophin survival responses | Hartman and Czyz 2020, Cosker, Pazzyra-Murphy et al. 2013 |
| 4 | neurogenesis, synaptogenesis | regulation of appropriate synaptic density |  |
| 3 | ERKb-regulated antiproliferative | induce neuronal apoptosis in response | Imamura, Satoh et al. 2008,
| gene that switch from proliferative to differentiative phase | to neurotrophin deprivation and ischemia | Ragel, Couldwell et al. 2007 |
|-------------------------------------------------------------|----------------------------------------|-----------------------------|

a Neural stem/progenitor cells, b Extracellular signal-regulated kinase

**Figures**
Figure 1

The workflow of the study

Searching for high-throughput data related to HCoV-OC43 & SARS-CoV-2 in GEO database, Array Express, and published works:
HCoV-OC43: GSE13879
SARS-CoV-2: RNA-seq results from the study of Daniel Blanco-Melo et al.

Prediction of regulatory relationships:
TRRUST & TRANSFAC databases: TF → gene
miRTarBase & miRecords databases: miR → gene
miRTarBase database: miR → TF
TransmiR database: TF → miR

GRN Network construction
Detection of significant 3-node regulatory motifs
Creation of sub-networks

Functional enrichment analysis
(Gene ontology and KEGG pathway)

Identifying crucial genes
(Hub, bottleneck, intersection of motifs)

In the intersection of merged motifs of two viruses, both GRN & PPI networks verify the most critical genes

Drug repurposing
(DGIdb, PharmGKB, and DrugBank)

Enrichment analysis
(Gene ontology and KEGG pathway)

PPI Network construction
Detection of MCODE clusters
Creation of sub-networks

Identifying crucial genes
(Hub, bottleneck, Mcode clusters)

Extraction of protein-protein interactions:
STRING database
HIPPIE database
HPRD data source
Figure 2

Merge of selected clusters of PPI network of up & down-regulated genes of OC-43 treated cells (a) Merge of selected clusters of PPI network of up & down-regulated genes of SARS-CoV-2 treated cells (b) Seed genes are shown in yellow octagons. Up and down-regulated genes are pink and green rectangles, respectively.
| ID.count | Motifs of SARS-CoV-2 treated cells up-regulated network | Motifs of SARS-CoV-2 treated cells down-regulated network |
|----------|---------------------------------------------------------|---------------------------------------------------------|
| 78.1     | ![Diagram of 78.1](image)                               | ![Diagram of 78.1](image)                               |
| 78.2     | ![Diagram of 78.2](image)                               | ![Diagram of 78.2](image)                               |
| 14.1     | ![Diagram of 14.1](image)                               | ![Diagram of 14.1](image)                               |
| 14.2     | ![Diagram of 14.2](image)                               | ![Diagram of 14.2](image)                               |
| 14.3     | ![Diagram of 14.3](image)                               | ![Diagram of 14.3](image)                               |
| 164      | ![Diagram of 164](image)                                | ![Diagram of 164](image)                                |

**Figure 3**

Selected GRN motifs of HCoV-OC43 DEGs network
| ID.count | Motifs of OC-43 up-regulated network | Motifs of OC-43 down-regulated network |
|----------|--------------------------------------|---------------------------------------|
| 78.1     | ![Diagram](image1.png)               | ![Diagram](image2.png)               |
| 78.2     | ![Diagram](image3.png)               | ![Diagram](image4.png)               |
| 14.1     | ![Diagram](image5.png)               | ![Diagram](image6.png)               |
| 14.2     | ![Diagram](image7.png)               | ![Diagram](image8.png)               |
| 164      | ![Diagram](image9.png)               | ![Diagram](image10.png)              |

**Figure 4**

Selected GRN motifs of SARS-CoV-2 DEGs network
Figure 5

The intersection of merged motifs with the same FANMOD ID of up-regulated DEGs (a) and down-regulated DEGs (b) network of HCoV-OC43 treated cells. The intersection of merged motifs with the same FANMOD ID for up-regulated DEGs (c) and for down-regulated DEGs (d) network of SARS-CoV-2 treated cells.
The intersection of the merged motifs between the HCoV-OC43 and SARS-CoV-2 treated cells up-regulated DEGs networks.

The intersection contains the shared TFs, miRs, and target genes. Thirty-one DEGs were shared between HCoV-OC43 and SARS-CoV-2 treated cells up-regulated DEGs networks.

```
PLAU  EHF  NR2F1  POU3F1  NFKB2  CDX2  PBX1  TNF
LIN28B  ETV4  POU2F2  IL6  SPRR2A  RBMX  ITGB3  IRF9
IRF7  HOXA5  STAT1  PRDM1  HIF1A  RELB  IL1B  FOSL1
SAMD9L  BMP2  MAZ  NKX3-1  USF1  ZFHX3  TAF15
```
Figure 7

The intersection of the merged motifs between the HCoV-OC43 and SARS-CoV-2 treated cells down-regulated DEGs networks
Figure 8

Drug-gene interactions of the most crucial shared up-regulated genes (a) and down-regulated genes (b) of the intersection of merged motifs in the two GRN networks, involved in neurological processes.
Figure 9

The picture depicts the molecular mechanisms of the identified enriched pathways (JACK-STAT, NF-κβ, p38 MAPK, TLR, NLR), probably mediating in the COVID-19 pathogenesis

Supplementary Files

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