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In silico analysis highlighting the prevalence of *BCL2L1* gene and its correlation to miRNA in human coronavirus (HCoV) genetic makeup

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ABSTRACT

The ongoing pandemic that resulted from coronavirus disease (COVID-19), which is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), had been spiraling out of control with no known antiviral drugs or vaccines. Due to the extremely serious nature of the disease, it has claimed many lives, with a mortality rate of 3.4% declared by the World Health Organization (WHO) on March 3, 2020. The aim of this study is to gain an understanding of the regulatory nature of the proteins involved in COVID-19 and to explore the possibility that microRNA (miRNA) could become a major component in the decoding of the virus. In the study, we were able to correlate the host protein gene *BCL2L1* with miRNA miR-23b via network analysis. MiRNAs have previously been associated with the antiviral properties of various viral diseases, such as enterovirus 71 and hepatitis. They have been reported to act as antiviral regulators, since they are an integral component in the direct regulation of viral genes. MiRNAs are also capable of enabling the virus to avoid the host immune response by suppressing the IFN-α/β signaling pathway or increasing the production of IFN-α/β and as a result, inhibiting the viral infection. Here, we explain and shed light on the various correlations in the miRNA-gene-disease association that are seen in the host proteins of COVID-19.

1. Introduction

Over the past couple of decades, a number of viral epidemics that have seriously affected human society have been well documented. The severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 to 2003 is an example, along with the H1N1 influenza in 2009. In 2019, the Chinese Center for Disease Control and Prevention (CDC) and the country's local CDCs organized an intensive outbreak investigation program and deemed Coronavirus disease 2019 (COVID-19) a global pandemic. COVID-19, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is a novel virus belonging to the coronavirus (CoV) family. Genomic study about the virus has revealed that the corona viral genome of the spike (S) protein (a major viral membrane protein responsible for cell entry), the nucleocapsid (N) protein (a protein and genome coat of the virus), the membrane (M) protein (forming the external layer of the virus), and the envelope (E) protein (a small membrane protein that plays a part in the virion assembly). Each of these proteins has an integral functionality in the structural composition and influences the biological processes of the virus.

A proteomics-based approach used in this study can be an important step for SARS-CoV-2 treatment. This method has been deemed to be helpful in the discovery of a variety of biomarkers that play important roles in the disease. Proteins mainly perform their functions with the help of interactions with different proteins and perform various functions such as signal transduction and metabolic processes (Gonzalez and Kann, 2012). Therefore, studies that are based on protein-protein interaction (PPI) play an essential role in the understanding and identification of the molecular basis of treatment for the disease. This type of interaction is also considered in research on potential drug targets and hub proteins (Singh et al., 2007), which can be useful for the development of effective diagnostic, therapeutic, and preventive strategies (Atan et al., 2014; Safari-Alighiarloo et al., 2014).

The analysis of the gene ontology base provides information about the cellular component, biological function, and molecular function of

Abbreviation: HCoV, Human Coronavirus; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; COVID-19, Coronavirus disease; MiRNA, MicroRNA; WHO, World Health Organization; IFN, Interferon; CDC, Control and Prevention; DNA, Deoxyribonucleic Acid; ncRNA, Non-coding RNA; PPI, Protein-Protein Interaction; TRRUST, Transcriptional regulatory relationships unraveled by sentence-based text-mining; TF, Transcription factor; SFN, Steiner Forest Network.

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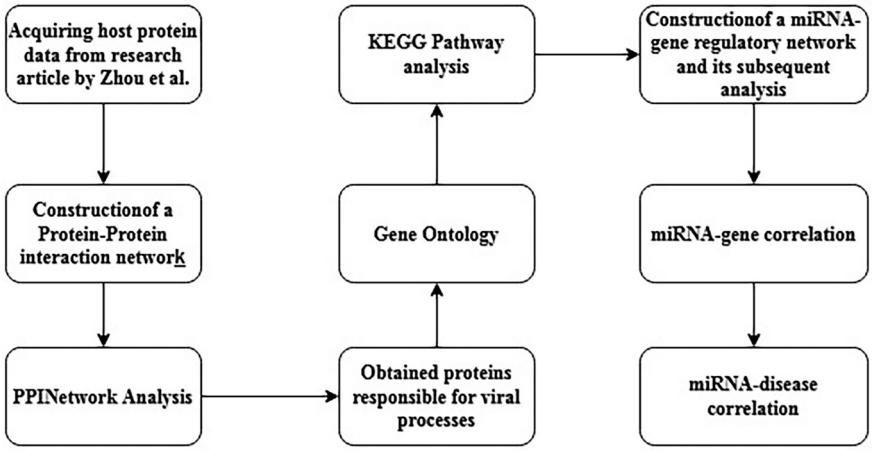

Fig. 1. Workflow of the study.

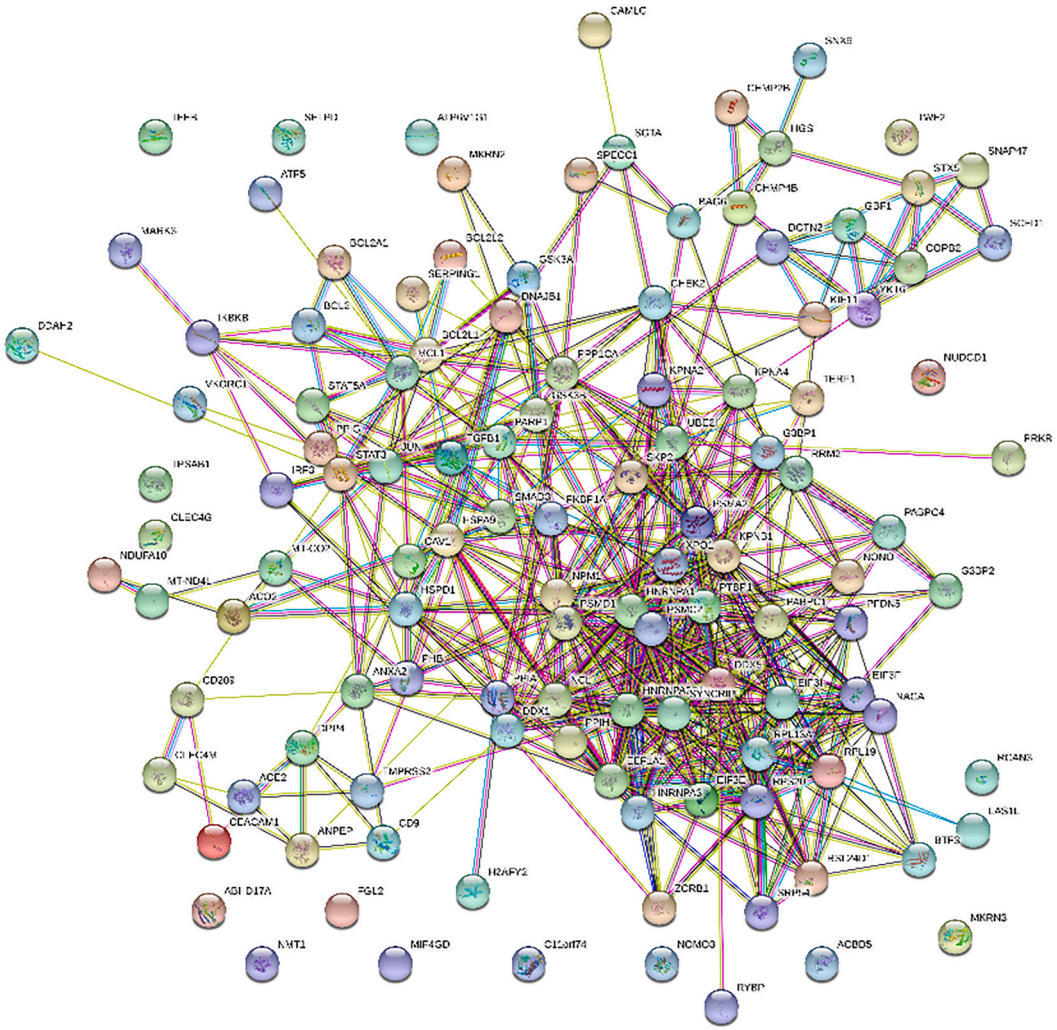

Fig. 2. In this network, the viral process proteins are shown in the red circles. In this network 29 proteins which are responsible for the viral process are obtained. These proteins are responsible for the viral processes therefore they are used for the protein-protein interaction analysis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the network proteins that are involved. Therefore, the study of the levels of the pathways and functions can be effective for the prevention and treatment of the SARS-CoV-2.

Over the last 2 decades, there has been a sudden surge of keen interest in non-coding RNA (ncRNA) as being a priority in helping to gain a better understanding of their involvement in various diseases, in the research community. NcRNA are RNA molecules that are transcribed from DNA but do not code (translate) for proteins. MiRNA is one such

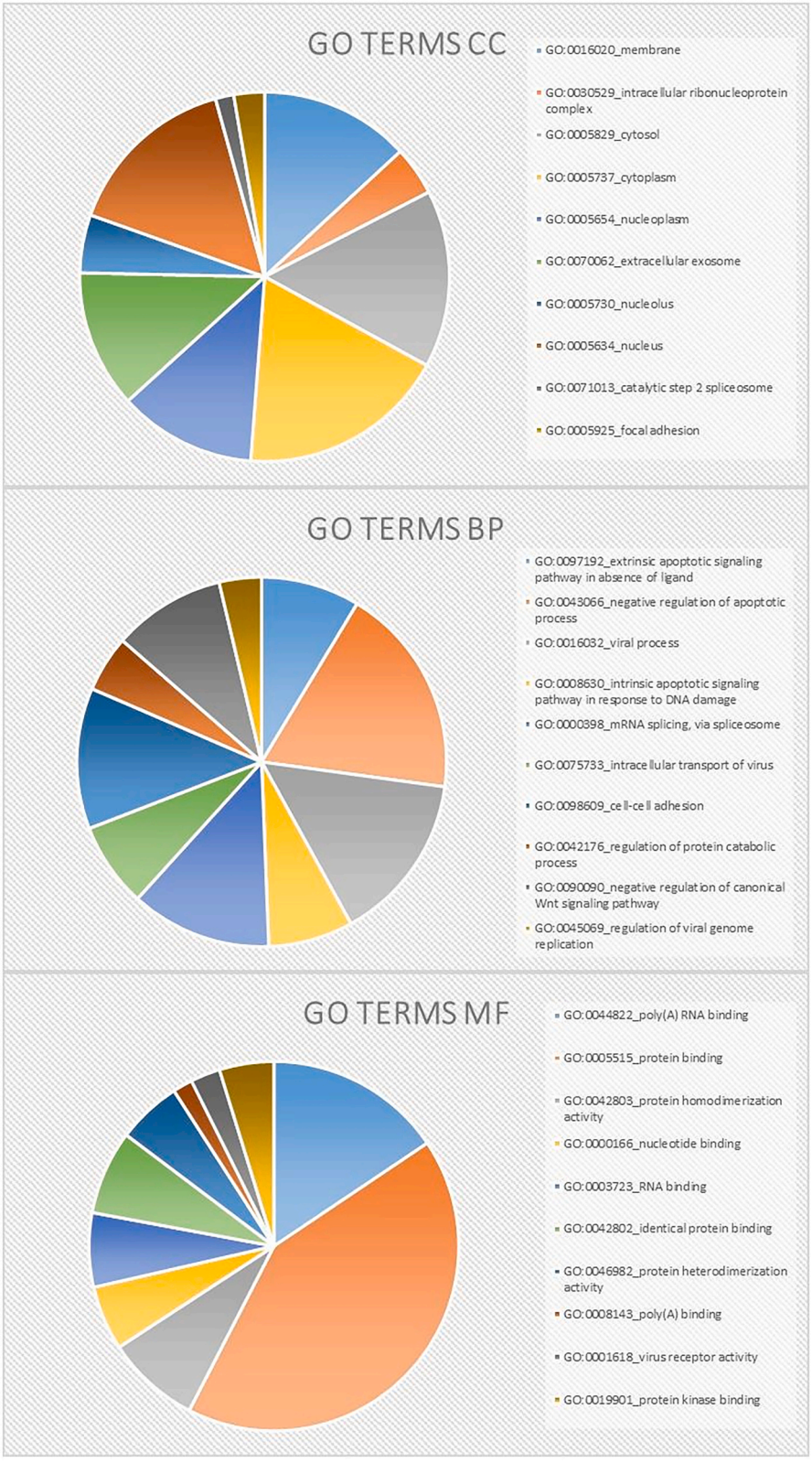

Fig. 3. GO terms related to the biological processes (BP), cellular components (CC) and molecular functions (MF) of the target genes.

ncRNA that has been seen prevalent in several diseases throughout its history. MiRNA, which generally measures 20-to-23 nucleotides in length, has been identified as single stranded, non-coding, intragenic RNA molecules and plays a role in controlling the gene expression. There have been several studies that emphasize the importance of the pathogenesis of these molecules in various human diseases (Brest et al., 2011; Lu et al., 2005). Over the past decade, miRNAs possesing viral origins have also been discovered and seen to act as transcriptional gene regulators to hosts as well as to viral genes (Grundhoff and Sullivan, 2011; Kincaid and Sullivan, 2012).

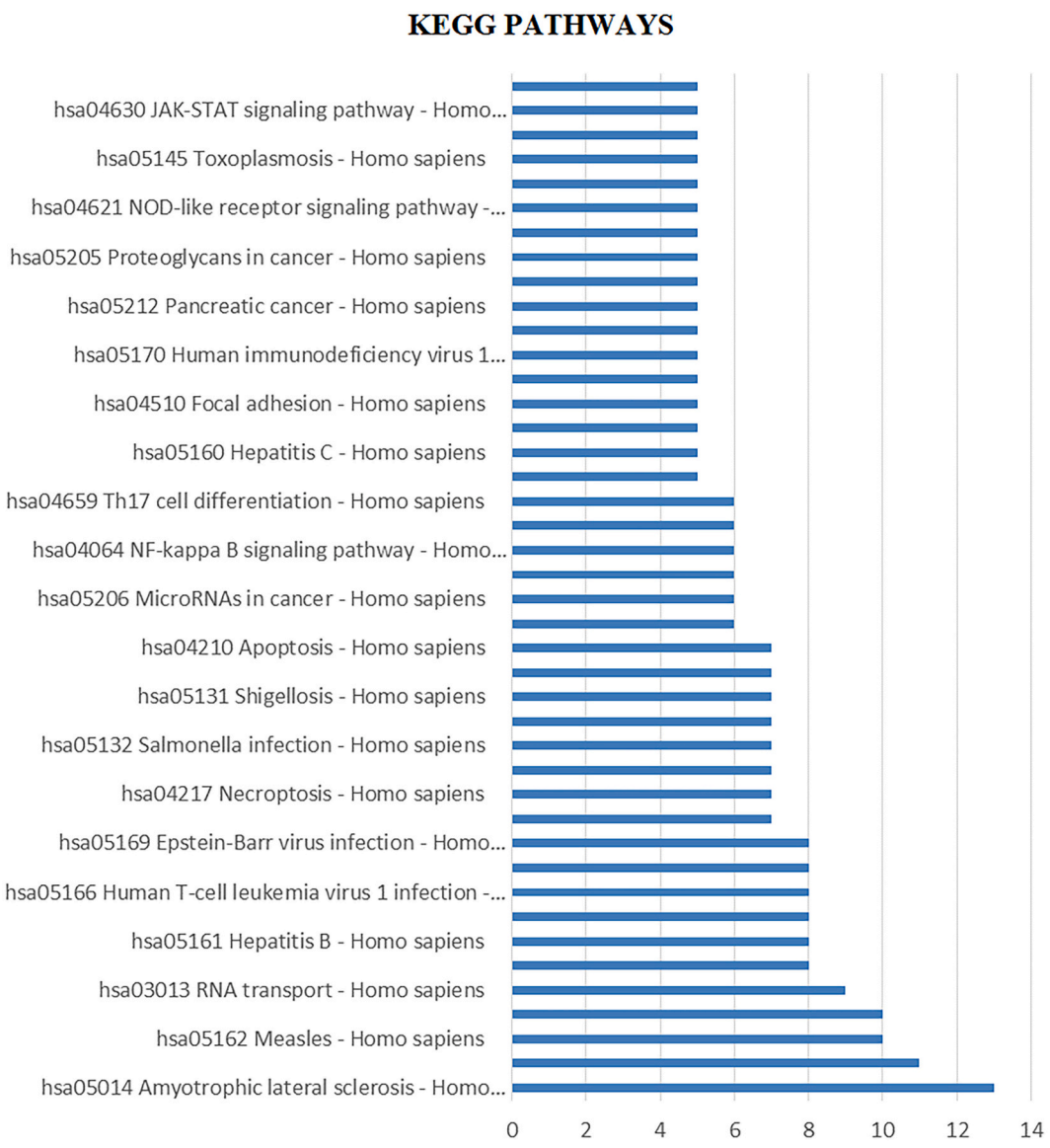

Fig. 4. KEGG analysis of the target genes showing various pathways involved where we have taken a threshold of 5 gene hits for a pathway to be considered.

2. Materials and methods

After extensive research we first decided to outline a potential workflow, which would suitably highlight the precedence of the viral proteins and miRNAs on the various biological processes and the genetic study. An outline for the workflow of the entire experiment is displayed in Fig. 1.

2.1. Data acquisition

A total of 130 human coronavirus (HCoV)-associated host protein data were obtained from a research article by Zhou et al., published in 2020. The article reported that these host proteins are from the various types of HCoVs, namely Middle East Respiratory Syndrome Coronavirus (MERS-CoV), SARS-CoV, and the coronavirus series HCoV-NL63 and HCoV-229E. The host proteins are also from other virus hosts such a mouse hepatitis virus (MHV) and an avian infectious bronchitis virus (IBV) (N protein). They were confirmed to be involved in important pathways of HCoV infection, as well as to be direct targets of HCoV proteins.

2.2. Construction of a protein-protein interaction network

The STRING database (Szklarczyk et al., 2019) was used to construct the PPI network using the enriched genes that had been previously selected. The STRING database is a hub of information regarding PPIs that are both known and prediction-based. The PPI network generation was accomplished after the selected genes had been provided to the database in the form of a list. The organism selected for our interactive study was *Homo sapiens.* In the table for the biological function processes, we select the "viral process" option to highlight the pathways involved in those proteins that adhere to functions of a viral nature, to use this data for further analysis of the network.

2.3. PPI network analysis

For the analysis of the PPI network we used the NetworkAnalyst tool for constructing the network. NetworkAnalyst (Zhou et al., 2019) is a powerful web-based visual analytics platform for comprehensive profiling, meta-analysis, and systems-level interpretation of gene expression data. This tool provides high quality, molecular interaction data to allow the user to develop gene regulatory networks, tissue

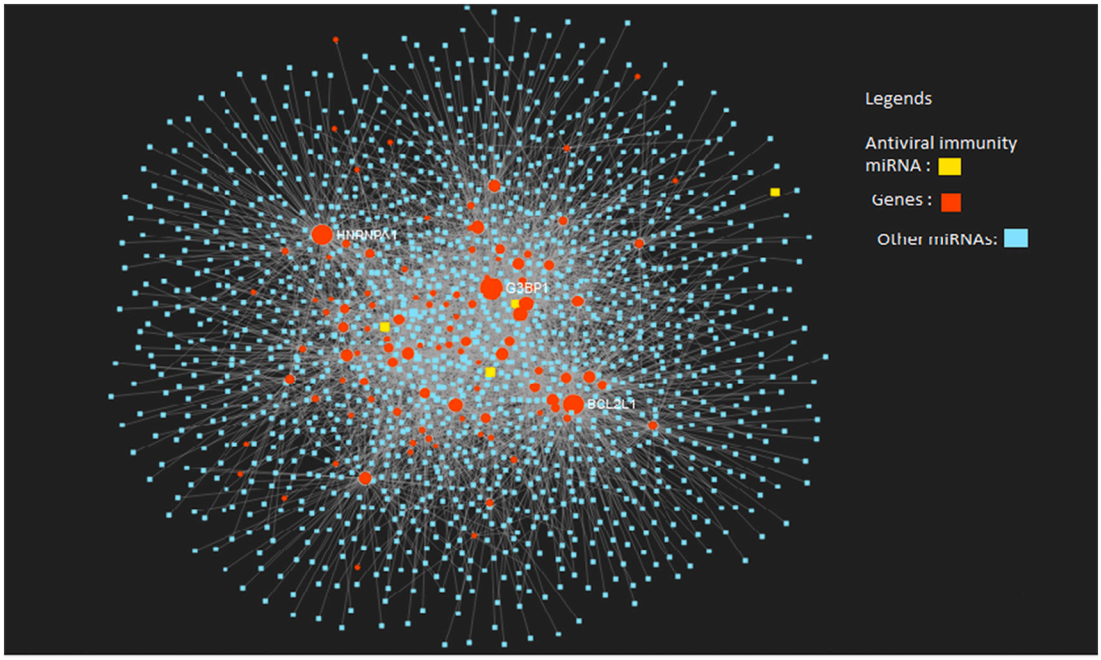

Fig. 5. Antiviral immunity miRNA network.

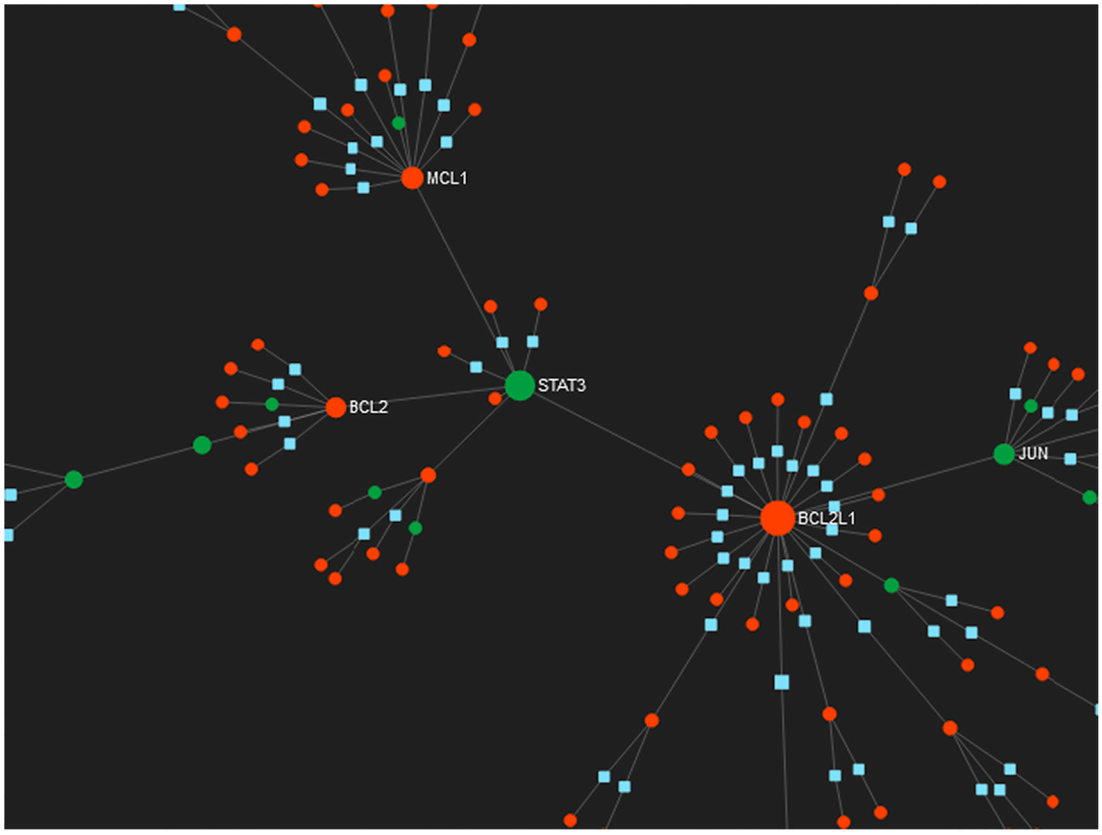

Fig. 6. miRNA regulatory network after application of Steiner Forest Network algorithm.

specific gene networks, and gene co-expression networks, which will subsequently be helpful for meaningful biological analysis.

In the NetworkAnalyst tool, the organism was specified as *H.sapiens* (human), the identification (ID) type was set as "official gene symbol," and the protein names obtained from the research paper were uploaded to the server. From the various options presented to us while we performed the network analysis, we selected "generic PPI" from the list for further analysis. We also opted for STRING INTERACTOME database for PPI study with a highest confidence score threshold of 0.900. We downloaded the subnetwork-1 which had a higher number of 1337 nodes, 2333 edges and 73 number of seed proteins and was used for further analysis. This subnetwork-1 is then analyzed in the Cytoscape

Table 1
miRNA association with SARS-CoV-2 host protein genes.

MiRNA	Genes
hsa-mir-23a-5p	SERPING1
hsa-mir-485-5p	CAMLG
hsa-mir-485-5p	XPO1
hsa-mir-485-5p	GBF1
hsa-mir-485-5p	PABPC1
hsa-mir-485-5p	CD209
hsa-mir-485-5p	SNX9
hsa-mir-485-5p	ZCRB1
hsa-mir-485-3p	KPNA2
hsa-mir-485-3p	GBF1
hsa-mir-485-3p	C11orf74
hsa-mir-23a-3p	DDX5
hsa-mir-23a-3p	SMAD3

Table 2
miRNAs and their functions.

Antiviral Immunity	Function	Reference
hsa-mir-23a-3p	Up-regulated during HSV-1 infection, and down-regulates interferon regulatory factor 1 (IRF1) gene expression, impairing the interferon pathway and leading to innate immune evasion.	(Bernier and Sagan, 2018)
hsa-mir-485-5p	Infection of various human and mouse cells with RNA viruses, resulted in the increased production of the microRNA miR-485, which targeted RIG-I mRNA for degradation.	(Ingle et al., 2015)
hsa-mir-485-3p	Infection of various human and mouse cells with RNA viruses, resulted in the increased production of the microRNA miR-485, which targeted RIG-I mRNA for degradation.	(Ingle et al., 2015)
hsa-mir-23a-5p	AAV expressing Human pre-miRNA hsa-mir-23a under an EF1a promoter, where mir-23a is overexpressed	(Zhang et al., 2018)

tool (Shannon et al., 2003).

2.4. Gene ontology and KEGG pathway analysis

To further validate our correlation we performed GO functional annotation using the DAVID database (Huang et al., 2009a, 2009b). The GO ontology features three major categories namely biological process (BP), cellular component (CC) and molecular function (MF). In this study, we employed the usage of DAVID and KEGG mapper to perform Gene Ontology (GO) functional annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis for predicted target genes of potential DE-miRNAs.

2.5. Constructing a miRNA-gene regulatory network

The genes which were earlier selected from the article by Zhou et al., (2020), were again used to construct a miRNA gene regulatory network, in order to find correlation between the genes and the respective antiviral miRNAs involved with those host protein genes. For this purpose we employed the help of miRNet (Fan et al., 2016), a collection of tools tailored specifically for statistical analysis of miRNA data.

The host protein genes were provided into the database along with specifying the organism as *H. sapiens*, ID type as "Official Gene Symbol". For the transcription factor TF we also specified the usage of transcriptional regulatory relationships unraveled by sentence-based text-mining (TRRUST) database (Han et al., 2015) which is a manually curated database of human and mouse transcriptional regulatory networks. Current version of TRRUST contains 8444 and 6552 TF-target regulatory relationships of 800 human TFs and 828 mouse TFs, respectively. They have been derived from 11,237 PubMed articles, which describe small-scale experimental studies of transcriptional regulations.

3. Results and discussion

3.1. PPI network analysis

When two or more proteins form a complex with the help of non-covalent bonds, it is called protein-protein interaction (PPI). After a comprehensive study, we sorted out a large number of coronavirus proteins that were reported in research articles. These proteins are responsible for many metabolic and biological processes along with their involvement in the viral process of SARS-CoV-2. With the help of protein-protein interaction study and gene ontology analysis, we identified the molecular and functional properties of the protein. Based on protein-protein interaction analysis, 29 proteins were found involved in the viral process (Fig. 2). Host cellular factors play an important role in the replication of viruses. The virus-host protein-protein interaction provides us with a deep understanding of the mechanism at play in disease infections. The targeting of cellular antiviral targets like the virus-host interactome is important for the development of the more effective treatment of viral infection like SARS-CoV17, MERS-CoV17, Ebola virus18, and Zika virus, etc.

The NetworkAnalyst tool was also used for the construction of the protein-protein interaction network. With the help of STRING Interactome, a protein-protein interaction network was constructed which had 75 Seed proteins, 1337 Nodes, and 2333 Edges. For the development of a protein-protein interaction network, we incorporated the HcoV protein from four human HCoVs (SARS-CoV, MERS-CoV, HCoV-229E, and HCoV-NL63), one mouse MHV, and one avian IBV (N protein).

In this study, we were able to obtain 119 host proteins associated with CoVs which are either the direct targets of SARS-CoV-2 proteins or are involved in pathways of SARS-CoV-2 infection.

3.2. Gene ontology and KEGG pathway analysis

We first performed GO functional annotation in a bid to identify and understand the biological features of the involved genes that we obtained from the 119 host proteins. We achieved that with the help of the DAVID database. As we know there are three major categories of GO annotation: cellular component (CC), biological process (BP), and molecular function (MF). Here we outline the top 10 GO terms regarding the biological processes, cellular components, and molecular functions. These included viral processes, regulation of viral genome replication, and intracellular transport of virus in the BP category. The presence of the target genes in the nucleus, cytoplasm, and intracellular ribonucleoprotein complex is seen in the CC category. Finally, in the MF category, we can highlight their enriched functions in viral receptor activity and various protein binding (Fig. 3).

KEGG pathway analysis of these target genes revealed their association in the PI3K-Akt signaling pathway, MAPK signaling pathway, ErbB signaling pathway, Ras signaling pathway, Hedgehog signaling pathway, TGF-beta signaling pathway, NF-kappa B signaling pathway, and JAK-STAT signaling pathway. The genes highlighted in these pathways further helped us validate their involvement in the analysis of an miRNA-gene regulatory network construction (Fig. 4).

3.3. miRNA regulatory network analysis

Using the miRNet database (Fan et al., 2016), we generated an miRNA-gene regulatory network as seen in Fig. 3, which helped us

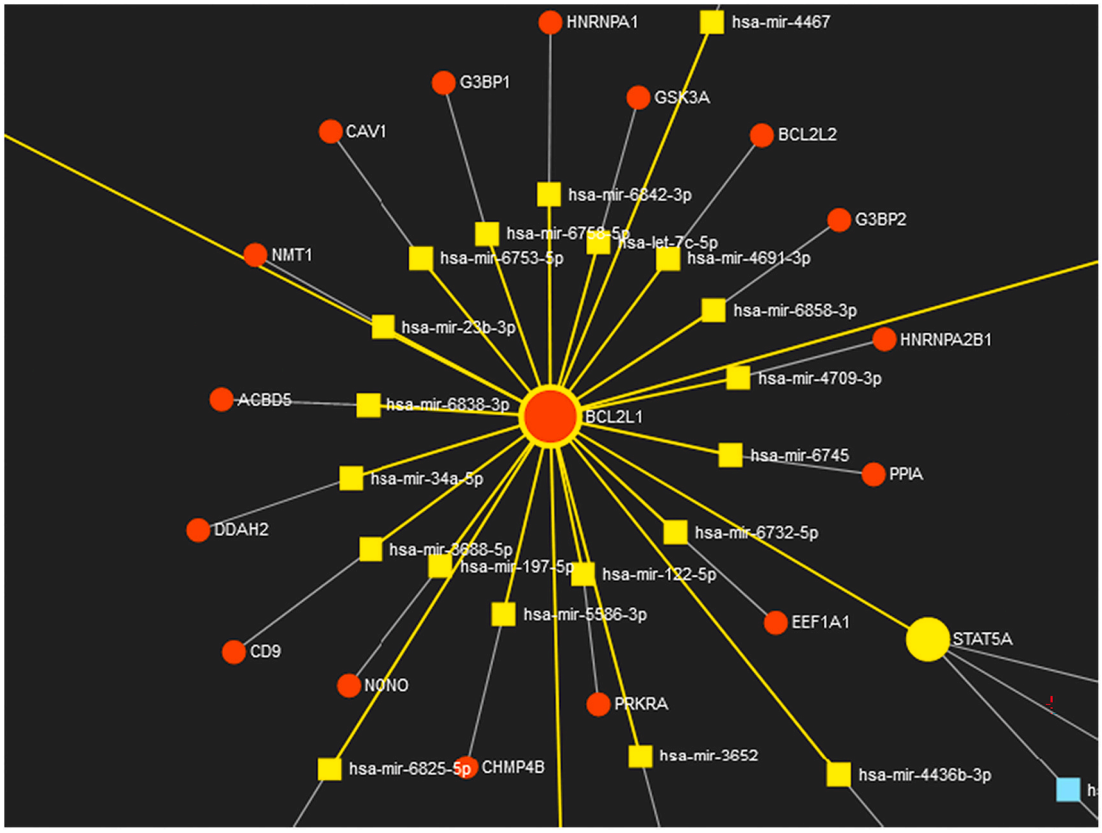

Fig. 7. *BCL2L1* gene and miRNA correlation.

Table 3
miRNA-disease correlation obtained through network analysis. The miRNAs denoted in bold are exclusive to the said disease.

Hepatitis B Virus Infection	Hepatitis C Virus Infection	Human Papilloma Virus Infection	Human Immunodeficiency Virus Infection	Hepatitis [unspecific]	Chronic Hepatitis B
hsa-let-7c-5p	**hsa-let-7f-1-3p**	hsa-mir-146a-5p	hsa-let-7c-5p	hsa-mir-122-5p	**hsa-mir-10a-5p**
hsa-mir-122-5p	hsa-mir-122-5p	hsa-mir-155-5p	hsa-mir-122-5p	hsa-mir-146a-5p	hsa-mir-122-5p
hsa-mir-124-3p	hsa-mir-124-3p	hsa-mir-15a-3p	hsa-mir-124-3p	**hsa-mir-197-5p**	hsa-mir-124-3p
hsa-mir-125a-3p	hsa-mir-125a-3p	hsa-mir-205-3p	hsa-mir-126-3p	hsa-mir-34a-5p	hsa-mir-125a-3p
hsa-mir-126-3p	hsa-mir-126-3p	**hsa-mir-23b-3p**	hsa-mir-146a-5p		hsa-mir-146a-5p
hsa-mir-141-5p	**hsa-mir-134-5p**	**hsa-mir-23b-5p**	hsa-mir-155-5p		hsa-mir-15a-3p
hsa-mir-146a-5p	hsa-mir-146a-5p	hsa-mir-24-3p	hsa-mir-29a-3p		**hsa-mir-98-5p**
hsa-mir-15a-3p	hsa-mir-155-5p	hsa-mir-34a-5p	**hsa-mir-331-3p**		
hsa-mir-186-5p	hsa-mir-22-3p	**hsa-mir-3653-3p**	hsa-mir-34a-5p		
hsa-mir-18a-5p	**hsa-mir-23a-3p**	hsa-mir-96-3p	**hsa-mir-382-3p**		
hsa-mir-205-3p	hsa-mir-24-3p		**hsa-mir-7-5p**		
hsa-mir-22-3p	hsa-mir-26b-5p				
hsa-mir-24-3p	hsa-mir-34a-5p				
hsa-mir-26b-5p	hsa-mir-96-3p				
hsa-mir-29a-3p	hsa-mir-99a-5p				
hsa-mir-99a-5p					

correlate the host protein genes with the miRNA they influence. We generated regulatory networks for gene-miRNA-transcription factor correlation. The network consisted of 113 gene and 7 TF queries which were possible to be mapped on the database out of the 130 provided, 1789 miRNA nodes, 133 TF nodes, 113 gene nodes, and overall 4825 interactions (edges). The resulting network was treated by applying Steiner Forest Network (SFN) algorithm (Fig. 5). SFN is based on a fast heuristic Prize-collecting Steiner Forest algorithm which works on the principle of minimizing the total edge cost, the total node prizes, and the number of trees (Akhmedov et al., 2017). Therefore after SFN application the nodes and edges were reduced to 90 miRNA and 13 TF nodes along with 208 interactions (edges) (Fig. 6).

MiRNAs have been reported to act as antiviral regulators as they are an integral component in the direct regulation of viral genes. They are also capable of enabling the virus to avoid the host immune response by suppressing the IFN-α/β signaling pathway or increasing the production of IFN-α/β and as a result, inhibit the viral infection. To further analyze the miRNAs found to be correlated with the host protein genes, we implemented the use of enrichment analysis to identify and group the miRNAs in gene ontology. Through which we aimed to highlight the biological processes of the host protein genes involved along with the miRNAs. Upon comparing the correlated miRNAs in the database we found a correlation of 4 miRNAs namely the hsa-mir-23a-3p and hsa-mir-23a-5p along with hsa-mir-485-3p and hsa-mir-485-5p and whose associations with their respective genes are shown in Table 1 and a description of their functions is briefed in Table 2.

3.4. miRNA-gene correlation

After performing the Steiner Forest Network (SFN) algorithm, we analyzed the network, and the top host genes which showed greater correlation with the miRNAs were sorted out. The other genes were sorted out and not included in this study because they showed a poor correlation with the miRNAs and were not deemed feasible enough for further analysis and coupled with the fact that these genes also showed enrichment in the KEGG pathway analysis. Those genes being, *BCL2L1*, *MCL1*, *BCL2*, *SYNCRIP,* and *TGFB1*. The *BCL2L1* is a protein-coding gene that has been found prevalent in the genetic makeup of SARS-CoV-2 as evidenced by Zhou Y. et al., 2020 in their research article. Further, it is also reported to be involved in the host-pathogen interaction of the human coronavirus pathway (Fung and Liu, 2019). KEGG analysis revealed that the *BCL2L1* gene was also prevalent in the PI3K-Akt signaling pathway, JAK-STAT signaling pathway, and NF-kappa B signaling pathway. All three pathways were reported to be involved in SAR-CoV2. The PI3K/AKT signaling pathway is seen to be involved in the inflammatory response of cells and they also regulate transmitters which cause inflammatory reactions and cause a chronic inflammatory response in the lungs and airways (Jiang et al., 2010). NF-kappa B signaling pathway has recently been seen as a positive target for SARS-CoV-2 due to its involvement in the activation of the pathway and thus suppresses the ability of the lungs to build its immune system to fight off the virus (Huang et al., 2020). The effect of SARS-CoV-2 also has an impact on the JAK-STAT signaling pathway, as it is responsible for creating a cytokine storm, which is triggered due to irregular immune responses. The pathway is mainly composed of cytokines, as a result, the elevated cytokines cause severe inflammation in the lungs and respiratory organs is directly related to the disease (Goker Bagca and Biray Avci, 2020). Network analysis revealed a direct and significant correlation between the *BCL2L1* gene and the miRNA hsa-miR23b-3p (Fig. 7). hsa-miR23b was also found to specifically target SARS-CoV2 genes in the research article by Sardar et al. (2020). Here we are able to report that the miRNA hsa-miR23b-3p targets the *BCL2L1* gene, which is a confirmed host protein gene of the SARS-CoV2. The *BCL2L1* gene is primarily responsible for the inhibition of cell death which we confirmed in the PANTHER (Mi et al., 2019) database along with a literature study (Fung and Liu, 2019; Li et al., 1998; Makkoch et al., 2016). hsa-miR-23b has also been reported to significantly down-regulate cell-infected viruses as seen in the case of Enterovirus 71 where it targets the Spike glycoprotein (Dai et al., 2013).

3.5. miRNA-disease correlation

The host proteins generated their correlated miRNAs which also were seen to be prevalent in other viral diseases like, Hepatitis B Virus Infection, Hepatitis C Virus Infection, Human Papilloma Virus Infection, Human Immunodeficiency Virus Infection, Hepatitis [unspecific], and Chronic Hepatitis B. In Table 3 the miRNAs found to be related or play a role in the regulatory function of these diseases have been listed.

4. Conclusion

We used gene–miRNA–disease association study to correlate the SARS-CoV-2 genes with their miRNA counterparts in a bid to shed some light on the regulatory nature of the virus and its correlation with other viruses. Using network-based methodology, we were able to identify that these proteins are responsible for many metabolic and biological processes. These proteins are also involved in the viral process of SARS-CoV-2. Employing protein–protein interaction study and gene ontology analysis, we discerned the molecular and functional properties of the proteins. Protein–protein interaction analysis revealed that 29 proteins are involved in the viral process. Furthermore, we generated an miRNA–gene regulatory network with which we were able to isolate the *BCL2L1* gene and fathom its correlation with miRNAs in the regulatory network. The *BCL2L1* gene is primarily responsible for the inhibition of cell death and has been reported to significantly down-regulate cell-infected viruses, as seen in the case of Enterovirus 71, where it targets the spike glycoprotein. KEGG analysis showed that the *BCL2L1* gene is also involved in the PI3K-Akt signaling pathway, JAK-STAT signaling pathway, and NF-kappa B signaling pathway. Moreover, hsa-miR-23b, an miRNA known to target the SARS-CoV-2 genes, was also found to play a key role in the regulation of the *BCL2L1* gene. These results were validated using literature data, therefore the absence of randomized clinical trials and experimental assays pose limitations. However, our findings are nonetheless expected to help in identifying and understanding the miRNA network activity of SARS-CoV-2 infection.

CRediT authorship contribution statement

Agnik Haldar: Conceptualization, Data curation, Formal analysis, Writing - original draft, Investigation, Methodology, Software, Visualization, Validation. **Keerti K. Yadav:** Data curation, Software. **Suchitra Singh:** Data curation. **Piyush K. Yadav:** Data curation. **Ajay K. Singh:** Supervision, Writing – review & editing.

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.

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