Integrated bioinformatics analysis for the screening of hub genes and therapeutic drugs in severe acute respiratory syndrome corona virus 2 infection/COVID 19

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Research Article

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Abstract

Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) infections (COVID 19) is a progressive viral infection that has been investigated extensively. However, genetic features and molecular pathogenesis underlying SARS-CoV-2 infection remain unclear. Here we used bioinformatics to investigate the candidate genes associated in the molecular pathogenesis of SARS-CoV-2 infection. Expression profiling by high throughput sequencing (GSE149273) was downloaded from the Gene Expression Omnibus (GEO), and the differentially expressed genes (DEGs) in remdesivir treated SARS-CoV-2 infection samples and non treated SARS-CoV-2 infection samples with an adjusted P-value < 0.05 and a $|\log \text{fold change (FC)}| > 1.3$ were first identified by limma in R software package. Next, Pathway and Gene Ontology (GO) enrichment analysis of these DEGs was performed. Then, the hub genes were identified by the Network Analyzer plugin and the other bioinformatics approaches including protein-protein interaction (PPI) network analysis, module analysis, target gene - miRNA regulatory network, and target gene - TF regulatory network construction was also performed. Finally, receiver-operating characteristic (ROC) analyses were for diagnostic values associated with hub genes. A total of 909 DEGs were identified, including 453 up regulated genes and 457 down regulated genes. As for the pathway and GO enrichment analysis, the up regulated genes were mainly linked with influenza A and defense response, whereas down regulated genes were mainly linked with Drug metabolism - cytochrome P450 and reproductive process. Additionally, 10 hub genes (VCAM1, IKBKE, STAT1, IL7R, ISG15, E2F1, ZBTB16, TFAP4, ATP6V1B1 and APBB1) were identified. ROC analysis showed that hub genes (CIITA, HSPA6, MYD88, SOCS3, TNFRSF10A, ADH1A, CACNA2D2, DUSP9, FMO5 and PDE1A) had good diagnostic values. In summary, the data may produce new insights regarding pathogenesis of SARS-CoV-2 infection and treatment. Hub genes and candidate drugs may improve individualized diagnosis and therapy for SARS-CoV-2 infection in future.

Introduction

At the December of 2019, a novel corona virus, called severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) or novel corona virus 2019 (2019-nCoV) is a single-stranded RNA, nonsegmented, enveloped viruses, resulted fast spreading from its origin in China to the rest of the globe [1]. Symptoms of this viral infection ranging in severity from the common cold to severe illness, and finally lead to death. Despite the fact that great progress has been made in antivirals and vaccination for this SARS-CoV-2 infection, survival rates is less. Since the precise molecular pathogenesis of SARS-CoV-2 infection (virus replication and dissemination) remains unknown, it is extremely essential to examine molecular pathogenesis and to develop effective therapeutic strategies in SARS-CoV-2 infection and to control the disease [2].

Expression profiling by high throughput sequencing is very essential to understand the molecular pathogenesis of viral infection and also to the advancement of novel antivirals drugs and vaccines for

the novel viral infections [3]. With the rapid advancement of bioinformatics such as microarray technology, some high throughput platforms for analysis of gene expression are commonly used to find the differentially expressed genes (DEGs) during viral infections [4]. We rationally presume that differentially expressed genes (DEGs) can affect the promotion of a various viral infections. Now, through Expression profiling by high throughput sequencing investigation using microarray technology, more and more DEGs were linked with SARS-CoV-2 infection and understanding its biological characteristics is essential in improving clinical treatment outcomes.

In the current investigation, we downloaded the RNA-seq data GSE149273 from the Gene Expression Omnibus database and conducted a bioinformatics analysis to study the differentially expressed genes (DEGs) between remdesivir traded SARS-CoV-2 infection samples and non treated SARS-CoV-2 infection samples. We performed function and pathways analyses, as well as protein–protein interaction (PPI) network analysis, modules analysis, target gene - miRNA regulatory network, and target gene - TF regulatory network and diagnostic values associated with hub genes was also assessed with the receiver-operating characteristic (ROC) analyses. []

Material And Methods

Microarray data and preprocessing

Expression profiling by high throughput sequencing GSE149273 based on GPL21290 Illumina HiSeq 3000 (Homo sapiens) Array was downloaded from the NCBI GEO [National Center for Biotechnology Information, Gene Expression Omnibus database] (<http://www.ncbi.nlm.nih.gov/geo/>) a public depository database of gene expression data [5]. GSE149273 contains 60 samples, including 30 remdesivir traded SARS-CoV-2 infection samples and 30 non treated SARS-CoV-2 infection samples. The downloaded raw data were preprocessed, including background adjustment and normalization using limma package of R software (version 3.10.3, <https://bioconductor.org/packages/release/bioc/html/limma.html>) [6]. []

Screening of the DEGs

For the expression profiling by high throughput sequencing dataset, the R package limma was applied for performing the differential analysis between 30 remdesivir traded SARS-CoV-2 infection samples and non treated SARS-CoV-2 infection samples. The p-values were adjusted by Benjamini & Hochberg method [7]. Based on the $|\log \text{fold change (FC)}|$ values and the p-values, the differentially expressed genes (DEGs; thresholds: $|\log \text{FC}| > 1.3$ for up regulated genes and $|\log \text{FC}| < -1.3$ for down regulated genes, adjusted $p < 0.05$).

Pathway enrichment analysis for DEGs

To analyze the functions of DEGs, BIOCYC (<https://biocyc.org/>) [8], Kyoto Encyclopedia of Genes and Genomes (KEGG) (<http://www.genome.jp/kegg/pathway.html>) [9], Pathway Interaction Database (PID) (<https://wiki.nci.nih.gov/pages/viewpage.action?pagelId=315491760>) [10], REACTOME

(<https://reactome.org/>) [11], GenMAPP (<http://www.genmapp.org/>) [12], MSigDB C2 BIOCARTEA (<http://software.broadinstitute.org/gsea/msigdb/collections.jsp>) [13], PantherDB (<http://www.pantherdb.org/>) [14], Pathway Ontology (<http://www.obofoundry.org/ontology/pw.html>) [15] and Small Molecule Pathway Database (SMPDB) (<http://smpdb.ca/>) [16] pathway analysis were carried out by using the ToppGene (ToppFun) (<https://toppgene.cchmc.org/enrichment.jsp>) [17] online tool. $P < 0.05$ was set as the cut-off point.

Gene ontology (GO) enrichment analysis for DEGs

The ToppGene (ToppFun) (<https://toppgene.cchmc.org/enrichment.jsp>) [17] was used to study GO enrichment analyses of DEGs. The ToppGene online tool for GO analysis (<http://www.geneontology.org>) [18] was used to complete the function of DEGs. Data from biological processes (BP), cellular components (CC) and molecular functions (MF) were documented from each set of genes. A $p < 0.05$ was considered statistically significant for all analyses.

PPI network construction and module analysis

The IMEX: The International Molecular Exchange Consortium (<https://www.imexconsortium.org/>) [19] is a biological database designed for predicting PPI networks and integrated with PPI data bases such as Database of Interacting Proteins (DIP) (<http://dip.doe-mbi.ucla.edu/dip/Main.cgi>) [20], IntAct Molecular Interaction Database (<https://www.ebi.ac.uk/intact/>) [21], the Molecular INTERaction database (MINT) (<https://mint.bio.uniroma2.it/>) [22], InnateDB (<https://www.innatedb.com/>) [23], Human Protein Reference Database (HPRD) (<http://www.hprd.org/>)²⁴, (BioGRID) (<https://thebiogrid.org/>) [25], IID (Integrated Interactions Database) from a well-known online server (<http://iid.ophid.utoronto.ca>) [26] and MatrixDB (<http://matrixdb.univ-lyon1.fr/>) [27]. Cytoscape (<http://www.cytoscape.org/>, version 3.8.0) [28], an open software, was used to visualize the PPI networks. The top genes with the highest node degree [29], betweenness centrality [30], stress centrality [31], closeness centrality [32] and lowest clustering coefficient [33] were considered as hub genes based on the analysis using Network Analyzer from Cytoscape. PEWCC1 (<http://apps.cytoscape.org/apps/PEWCC1>) [34], a plug-in of Cytoscape, can screen a significant module from the PPI network.

Construction of target genes - miRNA regulatory network

The miRNet database (<https://www.mirnet.ca/>) [35] is the biggest collection of predicted and experimentally verified target gene - miRNA interactions using 10 algorithms such as TarBase (<http://diana.imis.athena-innovation.gr/DianaTools/index.php?r=tarbase/index>) [36], miRTarBase (<http://mirtarbase.mbc.nctu.edu.tw/php/download.php>) [37], miRecords (<http://miRecords.umn.edu/miRecords>) [38], miR2Disease (<http://www.mir2disease.org/>) [39], HMDD (<http://www.cuilab.cn/hmdd>) [40], PhenomiR (<http://mips.helmholtz-muenchen.de/phenomir/>) [41], SM2miR (<http://bioinfo.hrbmu.edu.cn/SM2miR/>) [42], PharmacomiR (<http://www.pharmaco-mir.org/>) [43], EpimiR (<http://bioinfo.hrbmu.edu.cn/EpimiR/>) [44] and starBase (<http://starbase.sysu.edu.cn/>) [45].

Target genes - miRNA regulatory network among up and down regulated genes was constructed by Cytoscape (<http://cytoscape.org/>) [28].

Construction of target genes - TF regulatory network

The NetworkAnalyst database (<https://www.networkanalyst.ca/>) [46] is the biggest collection of predicted and experimentally verified target gene - TF interactions using JASPAR (<http://jaspar.genereg.net/>)⁴⁷ database. Target genes - TF regulatory network among up and down regulated genes was constructed by Cytoscape (<http://cytoscape.org/>) [28].

Validation of hub genes

In order to identify the diagnostic value of up and down regulated hub genes in SARS-CoV-2 infection, pROC package [48] in R language for illustrate receiver operating characteristic (ROC) curves was used in this investigation and area under the curve (AUC) of ROC curves was determined to check the act of each up and down regulated hub genes. When AUC value was greater than 0.6, the up and down regulated hub genes was treated able of distinguishing remdesivir traded SARS-CoV-2 infection samples and non treated SARS-CoV-2 infection samples. The diagnostic value of up and down regulated hub genes in GSE149273 dataset was estimated in our research work.

Results

Preprocessing and Screening of the DEGs

After preprocessing (Fig. 1A and Fig. 1B), a total of 909 DEGs (453 up regulated genes and 457 down regulated genes) were identified between remdesivir traded SARS-CoV-2 infection and non treated SARS-CoV-2 infection ($|\log FC| > 1.3$ for up regulated genes and $|\log FC| < -1.3$ for down regulated genes, adjusted $p < 0.05$) and volcano plots showing the results of differential analysis is given in Fig 2. The up regulated genes and down regulated genes are listed in Table 1. Heatmaps as shown in Fig. 3 and Fig. 4, respectively, indicated that these up and down regulated genes were good in distinguishing remdesivir traded SARS-CoV-2 infection samples and non treated SARS-CoV-2 infection samples.

Pathway enrichment analysis for DEGs

To further understand the function and mechanism of the identified up and down regulated genes, pathway enrichment analyses were performed using the ToppGene web tool. The main pathways that were particularly enriched by up regulated genes were pyrimidine deoxyribonucleosides degradation, tryptophan degradation to 2-amino-3-carboxymuconate semialdehyde, influenza A, cytokine-cytokine receptor interaction, IL23-mediated signaling events, direct p53 effectors, cytokine signaling in immune system, interferon signaling, C21 steroid hormone metabolism, purine metabolism, genes encoding secreted soluble factors, ensemble of genes encoding ECM-associated proteins including ECM-affiliated proteins, ECM regulators and secreted factors, toll receptor signaling pathway, inflammation mediated by

chemokine and cytokine signaling pathway, JAK-STAT signaling, purine metabolic, steroidogenesis and pyrimidine metabolism and are listed in Table 2. Similarly, down regulated genes were notably enriched in pyridoxal 5'-phosphate salvage, glutamine degradation/glutamate biosynthesis, Drug metabolism - cytochrome P450, chemical carcinogenesis, signaling events mediated by the hedgehog family, glypican 2 network, GPCR ligand binding, phase 2 - plateau phase, glycolysis, gluconeogenesis, type III secretion system, genes encoding secreted soluble factors, ensemble of genes encoding ECM-associated proteins including ECM-affiliated proteins, ECM regulators and secreted factors, notch signaling pathway, TGF-beta signaling pathway, notch signaling, wnt signaling, sulfate/sulfite metabolism and leukotriene C4 synthesis deficiency and are listed in Table 3.

Gene ontology (GO) enrichment analysis for DEGs

GO term enrichment analyses were performed using web tool ToppGene. Table 4 and Table 5 show the functions of the identified up and down regulated genes. Up regulated genes of BP were associated in defense response and response to external biotic stimulus. Down regulated genes of BP were associated in reproductive process and positive regulation of transcription by RNA polymerase II. Up regulated genes of CC were associated in cell surface and external side of plasma membrane. Down regulated genes of CC were associated in intrinsic component of plasma membrane and nuclear chromatin. Up regulated genes of MF were associated in cytokine activity and receptor ligand activity. Down regulated genes of MF were associated in transporter activity and cation transmembrane transporter activity.

PPI network construction and module analysis

The PPI network of up regulated genes consisting of 206 nodes and 412 edges was constructed in the IMEX database (Fig. 5). A top hub genes were selected by the Network Analyzer (Table 6), including VCAM1, IKBKE, STAT1, IL7R, ISG15, PML, NOS2, FBXO6, IRF1, IRF7, ADAM8, SBK1, ARL14 and TGM2, and statistical results in scatter plot for node degree distribution, betweenness centrality, stress centrality, closeness centrality and clustering coefficient are displayed in Fig. 6A - 6E. Enrichment analyses revealed that hub genes in this PPI network were mainly associated with malaria, influenza A, defense response, cytokine-cytokine receptor interaction, cytokine signaling in immune system, direct p53 effectors, ATF-2 transcription factor network, adaptive immune system, IL6-mediated signaling events, measles, innate immune system and ensemble of genes encoding ECM-associated proteins including ECM-affiliated proteins, ECM regulators and secreted factors. Similarly, PPI network of down regulated genes consisting of 206 nodes and 412 edges was constructed in the IMEX database (Fig. 7). A top hub genes were selected by the Network Analyzer (Table 6), including E2F1, ZBTB16, TFAP4, ATP6V1B1, APBB1, ELF5, CBX2, USP2, ERP27, DSCAML1, KCNF1, DLX3, EGFL6 and AMIGO1, and statistical results in scatter plot for node degree distribution, betweenness centrality, stress centrality, closeness centrality and clustering coefficient are displayed in Fig. 8A - 8E. Enrichment analyses revealed that hub genes in this PPI network were mainly associated with notch-mediated HES/HEY network, map kinase inactivation of SMRT corepressor, positive regulation of transcription by RNA polymerase II, iron uptake and transport, positive regulation of RNA metabolic process, nuclear chromatin, reproductive process, positive regulation of

developmental process, de novo pyrimidine ribonucleotides biosynthesis, neuronal system, transcription regulatory region sequence-specific DNA binding, signaling receptor binding and molecular function regulator.

Analysis using the PEWCC1 Cytoscape software plugin was used to create modules for the PPI networks. A total of 423 modules were created from PPI network of up regulated genes. Four significant modules were identified, including module 1 (nodes 44 and edges 173), module 6 (nodes 24 and edges 69), module 12 (nodes 20 and edges 38) and module 16 (nodes 18 and edges 33) are shown in Fig. 9. Enrichment analyses revealed that hub genes in these modules were mainly associated with influenza A, measles, chemokine signaling pathway, cytokine signaling in immune system, defense response, response to external biotic stimulus and innate immune response. A total of 219 modules were created from PPI network of down regulated genes. Four significant modules were identified, including module 4 (nodes 87 and edges 86), module 5 (nodes 77 and edges 76), module 13 (nodes 41 and edges 41) and module 16 (nodes 29 and edges 28) are shown in Fig. 10. Enrichment analyses revealed that hub genes in these modules were mainly associated with multi-organism reproductive process, iron uptake and transport, neuroactive ligand-receptor interaction and cell-cell signaling.

Construction of target genes - miRNA regulatory network

The up and down regulated genes were analyzed using the miRNet database. Target genes - miRNA regulatory network for up regulated genes consisting of 2182 nodes (1862 miRNAs and 320 up regulated genes) and 5899 edges (Fig. 11). The results of the topological property analysis demonstrated that SOD2 (degree = 257; ex, hsa-mir-4298), PMAIP1 (degree = 147; ex, hsa-mir-5697), APOL6 (degree = 127; ex, hsa-mir-4478), ICOSLG (degree = 119; ex, hsa-mir-4739) and NPR1 (degree = 118; ex, hsa-mir-6131) and are listed in Table 7. Enrichment analyses revealed that target genes in this network were mainly associated with cytokine-mediated signaling pathway, viral carcinogenesis, adaptive immune system and purine metabolism. Target genes - miRNA regulatory network for down regulated genes consisting of 2345 nodes (1783 miRNAs and 262 down regulated genes) and 4885 edges (Fig. 12). The results of the topological property analysis demonstrated that VAV3 (degree = 165; ex, hsa-mir-4315), ZNF703 (degree = 115; ex, hsa-mir-5787), FAXC (degree = 112; ex, hsa-mir-4279), GPR137C (degree = 97; ex, hsa-mir-3914) and ZNF704 (degree = 86; ex, hsa-mir-1538) and are listed in Table 7. Enrichment analyses revealed that target genes in this network were mainly associated with regulation of actin cytoskeleton, positive regulation of developmental process and transcription regulatory region sequence-specific DNA binding.

Construction of target genes - TF regulatory network

The up and down regulated genes were analyzed using the NetworkAnalyst database. Target genes - TF regulatory network for up regulated genes consisting of 516 nodes (92 TFs and 424 up regulated genes) and 3459 edges (Fig. 13). The results of the topological property analysis demonstrated that CD7 (degree = 265; ex, FOXC1), ELOVL7 (degree = 195; ex, GATA2), NTNG2 (degree = 136; ex, YY1), CXCL2 (degree = 125; ex, FOXL1) and (degree = 102; ex, NFKB1) and are listed in Table 8. Enrichment analyses revealed that target genes in this network were mainly associated with fas signaling pathway, ensemble

of genes encoding extracellular matrix and extracellular matrix-associated proteins , ensemble of genes encoding extracellular matrix and extracellular matrix-associated proteins and influenza A. Target genes - TF regulatory network for down regulated genes consisting of 516 nodes (80 TFs and 458 down regulated genes) and 2424 edges (Fig. 14). The results of the topological property analysis demonstrated that ABCA17P (degree = 217; ex, FOXC1), TACR1 (degree = 182; ex, GATA2), REEP1 (degree = 97; ex, YY1), TRAM1L1 (degree = 97; ex, FOXL1) and FGF9 (degree = 74; ex, TFAP2A) and are listed in Table 8. Enrichment analyses revealed that target genes in this network were mainly associated with calcium signaling pathway, signaling receptor binding, transmembrane transport and cell-cell signaling.

Validation of hub gene

The prediction achievement by ROC analysis showed that as single classifiers, CIITA, HSPA6, MYD88, SOCS3, TNFRSF10A, ADH1A, CACNA2D2, DUSP9, FMO5 and PDE1A had significant predictive values with AUCs of 0.956, 0.752, 0.992, 0.914, 0.837, 0.759, 0.781, 0.788, 0.833 and 0.788, and p-values of 0.00022, 0.00714, 0.00152, 0.00038, 0.00054, 0.00275, 0.00093, 0.00092, 0.00294 and 0.00252, respectively (Fig. 15).

Discussion

Outbreaks of appearing and reappearing of SARS-CoV-2 infection are frequent threats to human health across globe. When a novel virus was detection and linked with human disease, it is necessary to understand molecular pathogenesis of SARS-CoV-2 infection as soon as possible to progress treatment to the disease such as vaccines and antiviral drugs [49]. In this investigation, we performed a series of bioinformatics analysis to screen hub genes and pathways associated with SARS-CoV-2 infection. The expression profiling by high throughput RNA sequencing found that 49 up regulated genes and 72 down regulated genes were identified in remdesivir traded SARS-CoV-2 infection compared to non treated SARS-CoV-2 infection. Genes such as IRF7 [50], MX2 [51], TRIM25 [52], TRIM14 [53], IFIT5 [54] and IFIT1 [55] were liable for progression of influenza virus infection, but these genes may be responsible for advancement of SARS-CoV-2 infection. Genes such as OAS3 [56], OASL (2'-5'-oligoadenylate synthetase like) [57] and USP18 [58] were linked with progression of various viral infections, but these genes may be key for progression of SARS-CoV-2 infection. RSAD2 was involved in pathogenesis of measles virus infection [59], but this gene may be associated with progression of SARS-CoV-2 infection.

The ToppGene online tool was used to perform a pathway enrichment analysis. DDX58 was involved in the progression of measles virus infection [60], but this gene may be linked with advancement of SARS-CoV-2 infection. Enriched genes such as CIITA (class II major histocompatibility complex transactivator) [61], CCL2 [62], PML (promyelocytic leukemia) [63], ICAM1 [64], IL1A [65], MX1 [66], CXCL8 [67], MYD88 [68], CXCL10 [69], STAT1 [70], STAT2 [71], SOCS3 [72], CASP1 [73], TLR3 [74], TNF (tumor necrosis factor) [75], IL32 [76], TRIM22 [77], IFITM3 [78], FGF2 [79], IFITM1 [80], IFITM2 [81], IFI27 [82], ISG15 [83], SOCS1 [84], IRF1 [85], ISG20 [86], IL22RA1 [87], SOCS2 [88], GBP5 [89], BST2 [90], HERC5 [91], IL27 [92], CXCL13 [93], CXCL3 [94], TLR2 [95] and TNFAIP3 [96] were liable for development of influenza virus

infection, but these genes may be essential for progression of SARS-CoV-2 infection. Enriched genes such as CCL5 [97], IL19 [98], CCL3 [97], CCL4 [99], CCL20 [100], IFIT3 [101], CSF3 [102] and IL7R [103] were important for development of respiratory syncytial virus infection, but these genes may be liable for advancement of SARS-CoV-2 infection. Enriched genes such as IL6 [104] and JAK2 [105] were responsible for progression of SARS-CoV-2 infection. Enriched genes such as TICAM1 [106], OAS1 [107], OAS2 [108], CXCL9 [109], EREG (epiregulin) [110], CCL22 [111], VCAM1 [112], IFI35 [113], IFIT2 [114], TRIM5 [115], XAF1 [116], IFI6 [117], IL7 [118], SP100 [119], GBP1 [120], GBP2 [121], IRF4 [122], MIR5193 [123], IFNL3 [124], CYP21A2 [125], CXCL5 [126], CX3CL1 [127], CCL4L1 [128], WNT16 [129], GNB3 [130], FLG (filaggrin) [131] and HEY1 [132] were responsible for progression of various viral infections, but these genes may be involved in the development of SARS-CoV-2 infection. Expression of NOS2 was associated with development of rhinovirus infection [133], but this gene may be involved in progression of SARS-CoV-2 infection. Expression of CCR1 was liable for progression of pneumovirus infection [134], but this gene may be linked with advancement of SARS-CoV-2 infection. Expression of IRAK2 was important for progression of bronchitis virus infection [135], but this gene may be involved in development of SARS-CoV-2 infection. In general, the our findings suggested that novel biomarkers such as SCO2, TYMP (thymidine phosphorylase), HSPA6, IFNB1, IKBKE (inhibitor of nuclear factor kappa B kinase subunit epsilon), EIF2AK2, TNFSF10, TNFRSF10A, IFIH1, IL23A, UBE2L6, HLA-F, RASGRP3, TRIM38, BATF (basic leucine zipper ATF-like transcription factor), NRG2, BIRC3, MT2A, CSF1, TNFSF13B, IL15RA, GBP7, IL36A, IL17C, PSMB9, TNFRSF6B, GBP3, TRIM21, PTGS2, GBP4, BTC (betacellulin), TNFSF18, HBEGF (heparin binding EGF like growth factor), DUSP5, TRIM31, RET (ret proto-oncogene), CXCL2, TRIM10, LGALS9, LIF (LIF interleukin 6 family cytokine), LIFR (LIF receptor subunit alpha), EBI3, IL36G, HCK (HCK proto-oncogene, Src family tyrosine kinase), IFNL2, IFNL1, HSD11B1, CXCL11, S100A7A, ANGPTL1, KLHL23, PDXP (pyridoxal phosphatase), ADH1A, ADH1C, ADH6, GSTA5, ALDH3B1, FMO5, GSTT2, PTCH2, IHH (Indian hedgehog signaling molecule), CDON (cell adhesion associated, oncogene regulated), F2R, TAS2R50, WNT8B, WNT9A, OXGR1, PTGFR (prostaglandin F receptor), TACR1, GPER1, GRM4, CCKBR (cholecystokinin B receptor), OPRL1, RLN2, TAS1R1, ALDH3A2, GDF5, FGF9, EGFL6, FGF22, INHA (inhibin subunit alpha), INHBC (inhibin subunit beta C), GDF7, FGFBP3, BMP15, HES5, LFNG (LFNG O-fucosylpeptide 3-beta-N-acetylglucosaminyltransferase), HEYL (hes related family bHLH transcription factor with YRPW motif like), SULT1E1 and SULT2B1 may play key roles in the action mechanism of SARS-CoV-2 infection.

The functions of the up and down regulated genes were identified by GO enrichment analysis. Enriched genes such as TREX1 [136], IFNL4 [137], MICB (MHC class I polypeptide-related sequence B) [138], RAB43 [139], APOL1 [140], IFI16 [141], APOBEC3B [142], SLAMF7 [143], HDAC9 [144], APOBEC3A [145], SERPING1 [146], TAP2 [147], LAG3 [148], OPTN (optineurin) [149], CD68 [150], SP140 [151], PDCD1 [152], PLVAP (plasmalemma vesicle associated protein) [153], CD34 [154], CD38 [155], CD69 [156], SLC30A8 [157] and ATP6V1G2 [158] were liable for progression of various viral infections, but these genes may be involved in the progression of SARS-CoV-2 infection. Enriched genes such as APOBEC3G [159], ADAM8 [160], ZBP1 [161], NLRC5 [162], AIM2 [163], DUOX2 [164], NOX1 [165], IDO1 [166], CEACAM1 [167], PTX3 [168], TAP1 [169], FFAR2 [170] and E2F1 [171] were linked with progression of influenza virus infection,

but these genes may be associated with progression of SARS-CoV-2 infection. CD83 was responsible for advancement of respiratory syndrome virus [172], but this gene may be essential for development of SARS-CoV-2 infection. ACE2 was linked with progression of SARS-CoV-2 infection [173]. NMI (N-myc and STAT interactor) was liable for progression of severe acute respiratory syndrome corona virus [174], but this gene may be important for development of SARS-CoV-2 infection. CD274 was associated with progression of rhino virus infection [175], but this gene may be essential for progression of SARS-CoV-2 infection. In general, our findings suggested that novel biomarkers such as PIK3AP1, NT5C3A, NCF1, TNIP3, CLEC1A, CLEC7A, DTX3L, MEF2C, MEP1B, ADM (adrenomedullin), SAA2, SAA4, SERPINB9, MUC17, ABCD1, APOL2, PLSCR1, PMAIP1, FOXF1, DUOXA2, THEMIS2, ZC3H12A, DHX58, DDX60, C2CD4A, MUC13, PARP14, BATF2, PLA2G4C, NUB1, STX11, ZC3HAV1, TAGAP (T cell activation RhoGTPase activating protein), RNF19B, GCH1, PTGIR (prostaglandin I2 receptor), RTP4, ARID5A, TMEM106A, PRDM1, DEFB4A, IFIT1B, C1R, C1S, C3AR1, PARP9, IFI44L, HERC6, ICOSLG (inducible T cell costimulator ligand), TRIM15, NUPR1, TGM2, APOL3, TNFAIP6, MAPK8IP2, ACHE (acetylcholinesterase (Cartwright blood group)), CHRNA1, FZD9, PLAUR (plasminogen activator, urokinase receptor), SELL (selectin L), ACKR4, PDCD1LG2, KCNA1, SECTM1, WIPF3, APELA (apelin receptor early endogenous ligand), THEG (theg spermatid protein), PKDREJ (polycystin family receptor for egg jelly), TFCP2L1, TDRD6, TXNDC8, ZFP37, RIMBP3, NLRP14, FMN2, RIMBP3B, MYBL1, ZBTB16, INHBB (inhibin subunit beta B), NDP (norrincystine knot growth factor NDP), GGT3P, STOX2, GJB1, SOHLH2, BUB1B, DLX3, RAB3A, CBX2, GPR3, SPATA31A3, DPY19L2, BCL2L10, SOX30, E2F8, RLN1, VASH2, SLC29A3, CACNA2D2, PKD1L2, TMC3, AMIGO1, TRPM3, HPX (hemopexin), AKAP6, KCTD7, NLGN1, SLC47A2, SLC32A1, SLC9A2, TMEM37, CACNG4, ATP6V1B1, SLC46A1, SLC30A2, GPD1L, PPARGC1A, KCNF1, TMEM150C, CACNA1D, AQP10, CACNG1, SLC52A1, SLC16A9, HCN4, NGB (neuroglobin), TMEM63C, ABCC5, P2RX6, SLC16A14, SLC25A19 and SLC29A1 may play key roles in the action mechanism of SARS-CoV-2 infection.

The construction of protein-protein interaction network and module analysis for up and down regulated genes, has been proven to be useful in the analysis of hub genes involved in SARS-CoV-2 infection. HELZ2 was associated with development of dengue virus infection [176], but this gene may be liable for progression of SARS-CoV-2 infection. BATF3 was involved in advancement of respiratory poxvirus infection [177], but this gene may essential for development of SARS-CoV-2 infection. In general, our findings suggested that novel biomarkers such as FBXO6, SBK1, ARL14, LMO2, LAP3, TFAP4, APBB1, ELF5, USP2, ERP27, DSCAML1, NGEF (neuronal guanine nucleotide exchange factor), MARC1, GPRASP1, RAB26, DEPTOR (DEP domain containing MTOR interacting protein), HMGCS2, EEPD1, CAMKK1, PDE1A, PPP1R3C, WDR88, SERF1A, KLHL32, SMTNL2, RASL11B, ABLIM1, TOX2, LMCD1, TMCC2 and CERK (ceramide kinase) may play key roles in the action mechanism of SARS-CoV-2 infection.

The construction of target genes - miRNA regulatory network and target genes - TF regulatory network analysis for up and down regulated genes, has been proven to be useful in the analysis of target genes involved in SARS-CoV-2 infection. Target genes such as CD7 [178] and ELOVL7 [179] were liable for advancement of HIV infection, but these genes may be associated with progression of SARS-CoV-2 infection. In general, our findings suggested that novel biomarkers such as SOD2, APOL6, NPR1, NTNG2,

VAV3, ZNF703, FAXC (failed axon connections homolog, metaxin like GST domain), GPR137C, ZNF704, ABCA17P, REEP1 and TRAM1L1 may play key roles in the action mechanism of SARS-CoV-2 infection.

In conclusion, we conducted a comprehensive bioinformatics analysis on microarray data of SARS-CoV-2 infection. Pivotal DEGs (up and down regulated genes) and pathways were diagnosed and screened to provide a theoretical basis for potential drug target discovery and the molecular pathogenesis of SARS-CoV-2 infection. 10 hub genes, especially CIITA, HSPA6, MYD88, SOCS3, TNFRSF10A, ADH1A, CACNA2D2, DUSP9, FMO5 and PDE1A, were found to differentiate remdesivir treated SARS-CoV-2 infection from non treated SARS-CoV-2 infection. Nevertheless, additional relevant investigation are needed to further confirm the identified up and down regulated genes, and pathways in SARS-CoV-2 infection.

Declarations

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

No informed consent because this study does not contain human or animals participants.

Availability of data and materials

The datasets supporting the conclusions of this article are available in the GEO (Gene Expression Omnibus) (<https://www.ncbi.nlm.nih.gov/geo/>) repository. [(GSE149273) (<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE149273>)]

Consent for publication

Not applicable.

Competing interests

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Author Contributions

B. V. - Writing original draft, and review and editing

C. V. - Software and investigation

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Tables

Due to technical limitations, Tables 1-8 are only available as a download in the supplementary files section.

Figures

Figure 1

Box plots of the normalized data. (A) 30 non traded SARS-CoV-2 infection samples (B) 30 remdesivir traded SARS-CoV-2 infection samples. Horizontal axis represents the sample symbol and the vertical axis represents the gene expression values. The black line in the box plot represents the median value of gene expression. (A1 – A30 = non traded SARS-CoV-2 infection samples (blue color box); B1 – B30 = remdesivir traded SARS-CoV-2 infection samples (green color box))

Figure 2

Volcano plot of differentially expressed genes. Genes with a significant change of more than two-fold were selected. Green dot represented up regulated significant genes and red dot represented down regulated significant genes

Figure 3

Heat map of up regulated differentially expressed genes. Legend on the top left indicate log fold change of genes. (A1 – A30 = non traded SARS-CoV-2 infection samples (blue color box); B1 – B30 = remdesivir traded SARS-CoV-2 infection samples (green color box))

Figure 4

Heat map of down regulated differentially expressed genes. Legend on the top left indicate log fold change of genes. (A1 – A30 = non traded SARS-CoV-2 infection samples (blue color box); B1 – B30 = remdesivir traded SARS-CoV-2 infection samples (green color box))

Figure 5

Protein-protein interaction network of up regulated genes. Green nodes denotes up regulated genes.

Figure 6

Scatter plot for up regulated genes. (A- Node degree; B- Betweenness centrality; C- Stress centrality ; D- Closeness centrality; E- Clustering coefficient)

Figure 7

Protein–protein interaction network of down regulated genes. Red nodes denotes down regulated genes

Figure 8

Scatter plot for down regulated genes. (A- Node degree; B- Betweenness centrality; C- Stress centrality ; D- Closeness centrality; E- Clustering coefficient)

Module 1

Module 6

Module 12

Module 16

Figure 9

Modules in PPI network. The green nodes denote the up regulated genes

Module 4

Module 5

Module 13

Module 16

Figure 10

Modules in PPI network. The red nodes denote the down regulated genes

Figure 11

The network of up regulated genes and their related miRNAs. The green circles nodes are the up regulated genes, and yellow diamond nodes are the miRNAs

Figure 12

The network of down regulated genes and their related miRNAs. The red circles nodes are the down regulated genes, and blue diamond nodes are the miRNAs

Figure 13

The network of up regulated genes and their related TFs. The green circles nodes are the up regulated genes, and purple triangle nodes are the TFs

Figure 14

The network of down regulated genes and their related TFs. The green circles nodes are the down regulated genes, and blue triangle nodes are the TFs.

Figure 15

ROC curve validated the sensitivity, specificity of hub genes as a predictive biomarker for SARS-CoV-2 infection. A) CIITA B) HSPA6 C) MYD88 D) SOCS3 E) TNFRSF10A F) ADH1A G) CACNA2D2 H) DUSP9 I) FMO5 J) PDE1A

Supplementary Files

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