Network-Based Analysis of The Genetic Effects of SARS-CoV-2 Infection To Patients With Exacerbation of Virus-Induced Asthma (VAE)

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Research

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Abstract

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel RNA virus that emerged in late 2019 and was responsible for coronavirus disease (COVID-19). The WHO has declared the COVID-19 in the world pandemic. The most exacerbations of asthma are triggered by viral infections. However, the genetic effects of COVID-19 on asthma need to be further studied.

Results

Eighty-eight common differentially expressed genes (cDEGs) were identified in datasets GSE147507 and GSE30326. Function analysis showed that cDEGs has antiviral activity, histone kinase activity, chemokine activity and viral protein interaction with cytokine activity. protein–protein interactions (PPIs) network revealed that the proteins encoded by cDEGs interact with each other at a high frequency. Hub genes and essential modules were detected based on the PPIs network. Transcription factors (TF) and miRNA interaction with cDEGs are identified. Drug molecules such as sulocidil HL60 UP and Yu Ping Feng San were recommended for the treatment of novel coronavirus-induced exacerbation of asthma.

Conclusions

COVID-19 has a genetic effect on virus-induced exacerbation of asthma, and the hub genes we screened may be a potential therapeutic target.

Background

Since the outbreak of COVID-19 in the end of 2019, the disease has rapidly spread to pandemic status [1]. The main pathological changes of COVID-19 are lung tissue consolidation and hyperemia, pulmonary embolism and microthrombus formation [2, 3]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the pathogen of COVID-19 and belongs to the coronavirus family. It has the characteristics of long incubation period, strong infectivity and widespread susceptibility among the population. At present, a mutant strain of this virus has emerged (Delta) [4–6]. As of August 2021, COVID-19 has spread to nearly 90 countries and territories, with more than 200 million confirmed cases, including more than 4 million deaths, and more than 400,000 new cases per day (https://covid19.who.int/). COVID-19 has seriously endangered the health of public around the world and caused a global health crisis. However, due to lack of effective clinical drugs to control the virus, people should be closely watched who are prone to inducing deterioration of underlying diseases by SARS-CoV-2.

Allergic asthma is a common and frequently-occurring disease in clinical practice. It belongs to type I hypersensitivity disease and is one of the important public health problems [7, 8]. The main pathogenesis of asthma is the production of specific IgE antibody, chronic airway inflammation, airway remodeling and airway hyperresponsiveness during the immune system responding to allergens in the environment [9, 10]. Studies have shown that most exacerbations of asthma are triggered by viral infections [11], which is called as exacerbations of virus-induce asthma (VAE). However, the biological pathways and relationships between the COVID-19 and VAE have not been reported; and the management of asthma patients becomes more complicated during the COVID-19 pandemic, given the impaired immune response to viral infection and the potential to trigger or exacerbate asthma symptoms.

In this study, bioinformatics methods were used to screen for common differentially expressed genes (cDEGs) between COVID-19 and VAE. Enrichment analysis understands the biological process (BP), cellular component (CC), molecular functions (MF) and metabolic pathways of cDEGs via Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway. The hub genes and essential modules were identified from protein-protein interactions (PPIs) network. Transfer factor (TF)-genes and miRNA interaction with cDEGs are also identified. The present study aims to provide a reference for the management of patients with asthma and the development of new therapeutic agents in the context of the COVID-19 pandemic.

Methods

Retrieval of datasets

Two datasets were involved in this study, GSE147507 and GSE30326, which both were from GEO database (https://www.ncbi.nlm.nih.gov/geo/). GSE147507 performed a comprehensive analysis of gene expression in terms of human lung epithelial cells responding to SARS-CoV-2 and airway of COVID-19 patients [36]. GSE30326 illustrated global patterns of gene expression was profiled in nasal lavage samples obtained from asthmatic children during an acute picornavirus-induced exacerbation [11]. Since SARS-CoV-2 is RNA virus, we chose the dataset GSE30326 to match with GSE147507.

Identification of COVID-19 and VAE common differentially expressed genes (cDEGs)

To identify DEGs for GSE147507, the limma package of R programming language is implemented. Data that is produced from microarray analysis is retrieved through DESeq2 and limma package [37, 38]. DEGs for the GSE30326 dataset were analyzed through GEO2Rweb tool (https://www.ncbi.nlm.nih.gov/geo/geo2r/) and limma package. Cut-off criteria was obtained for GSE147507 using adjusted $P$ value $< 0.05$ and log2-fold change (absolute) $> 1.0$. The cDEGs of GSE147507 and GSE35145 were identified by the R programming language.

Enrichment analysis of the Gene ontology and KEGG signaling pathway
The Gene Ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis were performed with the module gene. ClusterProfiler package (v.3.14.3) was used for enrichment analysis while Org.Hs.eg.db package (v.3.10.0) was for ID conversion.

**Module genes network construction**

The edge file, including source node and target node genes, was generated by WGCNA for protein-protein interaction (PPI) analysis in STRING (v11.5, https://www.string-db.org/). Parameter setting: organism selects Homo sapiens, required score selects medium confidence (0.400), and false discovery rate (FDR) stringency chooses medium (5 percent).

**Identification of hub genes and module analysis**

PPIs were analyzed via Cytoscape software, and the hub genes for the current research were revealed by the degree topological algorithm. The nodes that have the most interactions were considered to be a hub gene. Molecular Complex Detection (MCODE) plugin of Cytoscape software was used to detect the most profound modules from the PPIs network.

**Evaluation of interaction between transcription factors (TF) and hub genes and construction of TF-miRNA co-regulatory network**

NetworkAnalyst database (https://www.networkanalyst.ca/) was used to identify TF-gene interaction with identified cDEGs and TF-miRNA co-regulatory network. The common network topology measures were also computed based on well-established the igraph R package. TF and gene target data derived from the ENCODE ChiP-seq data. Only peak intensity signal < 500 and the predicted regulatory potential score < 1 were used.

**Screening of potential therapeutic drugs**

Drugs that modulate 88 cDEGs were screened using Enrichr platform. The access of the DSigDB database was acquired through Enrichr (https://amp.pharm.mssm.edu/Enrichr/). Potential therapeutic agents were determined by the adj. P values and the abundance of acting on cDEGs. Target genes of traditional Chinese medicine (TCM) were retrieved in Pubmed database (https://pubmed.ncbi.nlm.nih.gov/). If the target genes were consistent with hub genes in this study, they would be identified as potential therapeutic TCM formula.

**Results**

**Identification of common differentially expressed genes (cDEGs) between COVID-19 and VAE**

As regards the COVID-19, 814 differentially expressed genes were identified from GSE147507 dataset, including 419 down-regulated genes and 395 up-regulated genes. As for the VAE, 477 differentially expressed genes were identified from GSE30326, including 474 down-regulated genes and 3 up-regulated genes. Eighty-eight cDEGs were identified in both datasets (Fig. 1).

**Enrichment analysis of the GO and KEGG**

The current study analyzes GO terms including biological process (BP), cellular component (CC) and molecular functions (MF) for 88 cDEGs, as well as KEGG pathway. Gene ontology revealed that in terms of BP, these cDEGs were mainly involved in mitotic nuclear division, defense response to virus and organelle fission. From the perspective of CC, it mainly involves in spindle and condensed chromosome. As for MF, cDEGs were involved in binding and motor activity, histone kinase activity and chemokine activity. KEGG Enrichment analysis on the 88 cDEGs showed that the top 5 signal pathways which were significantly enriched were in Influenza A, NOD-like receptor signaling pathway, Cell cycle, Viral protein interaction with cytokine and cytokine receptor and Oocyte meiosis (Tab. 1). Visualization of GO and KEGG enrichment analysis see Fig. 2

**Tab. 1** Top 5 GO-KEGG terms and their corresponding P values for cGEGs
| ONTOLOGY | ID     | Description                                   | P. adjust |
|----------|--------|-----------------------------------------------|-----------|
| BP       | GO:0140014 | mitotic nuclear division                      | 6.04e-18  |
|          | GO:0051607 | defense response to virus                     | 1.56e-17  |
|          | GO:0009615 | response to virus                             | 1.79e-17  |
|          | GO:0048285 | organelle fission                            | 7.76e-15  |
|          | GO:0000280 | nuclear division                              | 1.36e-14  |
| CC       | GO:0005819 | spindle                                       | 1.54e-09  |
|          | GO:0005876 | spindle microtubule                           | 4.22e-09  |
|          | GO:0072686 | mitotic spindle                               | 4.22e-09  |
|          | GO:0000779 | condensed chromosome, centromeric region      | 7.76e-15  |
|          | GO:0000775 | chromosome, centromeric region                | 7.76e-15  |
| MF       | GO:0008017 | microtubule binding                          | 9.70e-05  |
|          | GO:0035173 | histone kinase activity                       | 8.00e-04  |
|          | GO:0042379 | chemokine receptor binding                    | 8.00e-04  |
|          | GO:0003774 | motor activity                                | 8.00e-04  |
|          | GO:0000809 | chemokine activity                            | 8.00e-04  |
| KEGG     | hsa05164  | Influenza A                                   | 5.66e-05  |
|          | hsa04621  | NOD-like receptor signaling pathway           | 3.31e-04  |
|          | hsa04110  | Cell cycle                                    | 7.31e-04  |
|          | hsa04061  | Viral protein interaction with cytokine and cytokine receptor | 0.003 |
|          | hsa04114  | Oocyte meiosis                                | 0.003     |

**Construction of Protein-protein interactions (PPIs) network**

The analyzed network holds 87 nodes and 638 edges (Fig. 3). Average node degree: 14.7. Expected number of edges: 31. Avg. local clustering coefficient: 0.632. It is suggested that these proteins have more interactions among themselves than what would be expected for a random set of proteins of similar size, drawn from the genome.

**Detection of hub genes and module analysis**

According to topology analysis, 10 cDEGs degree values are the highest, and these genes are considered as Hub genes (Tab. 3). The proteins encoded by the hub genes have rich interactions with other proteins, including 52 nodes and 618 edges (Fig. 4). Module analysis showed that TRIM38, GBP3, STAT1, CASP5, C19orf66 and other genes were high-density modules, including 41 spots and 126 edges. In addition, except for STAT1, which is both hub gene and high-density module, other hub genes are closely related to high-density module (Fig. 5).

**Tab. 3 Topological result exploration for top ten hub genes**

| Hub gene | Degree | EPC | BottleNeck | EcCentricity | Closeness | Radiality | Betweenness | Stress | Clustering Coefficient |
|----------|--------|-----|------------|--------------|-----------|-----------|-------------|--------|------------------------|
| STAT1    | 43     | 24.3| 6          | 0.3          | 52.16     | 4.20      | 421.65      | 2256   | 0.58                  |
| MX1      | 42     | 25.3| 4          | 0.3          | 51.33     | 4.25      | 158.83      | 1406   | 0.63                  |
| IFIH1    | 42     | 24.3| 1          | 0.3          | 51.16     | 4.24      | 206.80      | 1576   | 0.62                  |
| ISG15    | 40     | 24.2| 3          | 0.3          | 50        | 4.19      | 124.12      | 1206   | 0.66                  |
| DDX58    | 40     | 23.9| 5          | 0.3          | 50.33     | 4.22      | 274.77      | 1708   | 0.65                  |
| RSAD2    | 40     | 24.4| 2          | 0.3          | 50.17     | 4.20      | 105.99      | 1110   | 0.67                  |
| IFIT3    | 39     | 25.0| 2          | 0.3          | 49.33     | 4.17      | 83.57       | 982    | 0.70                  |
| IRF7     | 38     | 24.3| 1          | 0.3          | 49.17     | 4.18      | 98.44       | 958    | 0.68                  |
| CXCL10   | 38     | 22.6| 6          | 0.3          | 50        | 4.25      | 639.64      | 2948   | 0.60                  |
| IFIT1    | 37     | 24.2| 4          | 0.3          | 48.33     | 4.14      | 47.54       | 748    | 0.76                  |
Transcriptional factor regulatory network analysis of hub genes

By NetworkAnalyst analysis, 123 TFs regulating eight hub genes expression were identified. The main hub genes regulated by TF have ISG15, RSAD2, IFIT3. NF-κb1, SP1 and RALA are the most widely acting transcription factors that regulate the ISG15, RSAD2, IFIT1, and IFIT3 genes (Fig. 6).

TF-miRNA co-regulatory network

By NetworkAnalyst analysis, 308 miRNAs that regulated the expression level of hub genes were identified, and the main co-regulated hub genes were STAT1, CXCL10, IDG15, DDX58, IFIH1, IFIT3 et al. (Fig. 7). The frequency of co-regulation of miR-186, miR-135a, miR-362-5p, miR-409-3p and miR-496 with TF was higher.

Screening of potential therapeutic drugs

Enrichr Platform analysis found that suloctidil HL60 UP, 3'-Azido-3'-Deoxythymidine CTD 00007047, estradiol CTD 00005920 and acetaminophen CTD 00005295 have been identified as potential therapeutic targets for both COVID-19 and VAE, which target genes contain hub genes (Tab. 4). According to hub Genes, TCM formulas with therapeutic effects were searched in Pubmed database, and the results showed that YuPingFengSan and QingFeiPaiDu Decoction had therapeutic effects (Tab. 5).

Tab. 4 Potential drug components for treatment of both COVID-19 and VAE

| Drug                        | Adj. P value | cDEGs                                                                 |
|-----------------------------|--------------|----------------------------------------------------------------------|
| suloctidil HL60 UP          | 6.85E-57     | SAMD9;IFIT5;IF6;UBE2L6;ZC3HAV1;IFIT1;JFI44L;                          |
|                             |              | IFIT3;JFIT2;OASL;IFIH1;HERC5;CCL8;TNFSF10;                          |
|                             |              | TRIM21;TRIM22;HERC6;RSAD2;GCH1;DDX58;STAT1;PHF11;MX1;JFI44;EIF2AK2;ISG15;CXCL10;CXCL11;AIM2;OAS2;OAS3;TFEC; |
| 3'-Azido-3'-deoxythymidine  | 2.15E-23     | SAMD9;IFIT5;IF6;DDX60L;JFIT1;JFI44L;JFIT2;IFIH1;CASPS;LAMP3;C3AR;EPST1;TNFSF10;LGALS9;TRIM22;GBP4;HERC6;RSAD |
| CTD 00007047                |              |                                                                      |
| estradiol CTD 00005920      | 6.29E-08     | IF6;TMEM51;UBE2L6;DDX60L;JFIT1;JFIT3;JFIT2;OASL;IFIH1;HERC5;CASPS;LAMP3;TNFSF10;STAT4;SL |
| acetaminophen CTD 00005295  | 1.74E-07     | IF6;TARP;JFIT3;JFIT1;IFIH1;PSTPIP2;LAMP3;C3AR;TNFSF10;NBN;TRIM21;TRIM22;GBP4;TNS1;GBP3 |
| Tetradoxin CTD 00006848     | 1.70E-06     | IF6;TMEM51;UBE2L6;DDX60L;JFIT1;JFIT3;JFIT2;OASL;IFIH1;HERC5;CASPS;LAMP3;TNFSF10;STAT4;SL |
| cyclosporin A CTD 00007121  | 6.70E-04     | IF6;TMEM51;UBE2L6;DDX60L;JFIT1;JFIT3;JFIT2;OASL;IFIH1;HERC5;CASPS;LAMP3;TNFSF10;STAT4;SL |

Tab. 5 Potential TCM formulas for treatment of both COVID-19 and VAE

| TCM Formula       | Composition                                                                 | TCM Theory                                      | Hub gene |
|-------------------|----------------------------------------------------------------------------|-------------------------------------------------|----------|
| Yu Ping Feng San  | Fructus Forsythiae, Flos Lonicerae, Radix Platycodonis, Herba Mentheae, Herba Lophatheri, Radix Glycyrrhizae, Herba Schizonepetae, Fermented soybean, Fructus arctii, and Rhizoma Phragmitis | Disperses wind-heat, clears heat, and relieves toxicity | ISG15    |
| Qing Fei Pai Du decoction | Herba Ephedrae, Radix Glycyrrhizae, Semen Armeniacae Amaranum, Gypsum Fibrosom, Ramulus Cinnamomi, Rhizoma Alismatis, Polyoporus Umbellatus, Rhizoma Atractylodis Macrocephalae, Poria, Radix Bupleuri, Radix Scutellariae, Rhizome Pinelliae Preparata, Rhizoma Zingiberis Recens, Radix Asters, Flos Farfarae, Rhizoma elamcandae, Herba Asari, Rhizoma Dioscoreae, Fructus Aurantii Immaturus, Pericarpium Citri Reticulatae, Herba ogostemonis | Dispelling cold, clears damp and heat | IFIT1    |
|                   |                                                                            |                                                 | IFIT3    |

Discussion

As a respiratory disease, COVID-19 has a subtle relationship with asthma. On the one hand, WHO guidelines emphasize that people with asthma are at high risk for COVID-19 [12]. On the other hand, viral infection is an important cause of asthma deterioration, manifested by increased airway inflammation, increased mucus secretion and lower respiratory symptoms [13, 14]. Analysis of the possible causes of virus-induced exacerbation of asthma: (1) Asthma shows imbalance of Th1/Th2 cells in cytology, and Th2 cells increase[15], which reduces the generation of Th1 cytokine interferon, causing asthma patients to be deficient in antiviral and increase viral load [16]; (2) IgE antibodies eliminate the biological activity of IFN-α and reduce its concentration and antiviral ability [17]; (3) The dephosphorylation and deubiquitination ability of SARS-CoV is able to inhibit IFN signaling [18]. Worse, it is controversial in treatment
between virus-induced asthma aggravation and COVID-19, particularly with uncertainty regarding the object and timing of glucocorticoid therapy [12, 19]. Therefore, in the context of the COVID-19 pandemic and the lack of effective drugs, understanding the genetic effects of the two diseases is not only conducive to the research of vaccines for COVID-19 and development of gene-targeted therapeutics, but also important for the treatment of severe asthma.

In this study, bioinformatics methods were used to analyze datasets GSE147507 and GSE30326, and 88 cDEGs were identified. The biological process, cellular components, molecular functions and KEGG enrichment of these cDEGs were comprehensively analyzed. Through analysis, we speculated the molecular activity, cellular role, executive function location and metabolic pathway of cDEGs. Tasnimul et al. analyzed data sets GSE147507 and GSE35145, identified 11 common differentially expressed genes, and analyzed them for GO and KEGG enrichment [20]. More cDEGs were identified in this study than the above studies, and in both GO and KEGG enrichment analysis, mainly suggesting BP enrichment of cDEGs in antiviral and nuclear division; and MF, cDEGs in protein kinase activity and chemokine activity; coincidentally, KEGG signaling suggested significant enrichment of viral protein-cytokines. It is speculated that antiviral and chemokine management are the key to the treatment of these two diseases, which is consistent with the current treatment strategy advocated [21, 22].

Protein-protein interaction (PPI) is necessary for most of the biological processes and requisite for host-pathogen communication. Mapping protein interactions is to understand the interaction of proteins highly associated with the disease during development, and raising awareness of its function [23]. As can be seen from Figure 3, there are highly dense regions of interaction between proteins encoded by cDEGs, suggesting that these genes are involved in important disease processes. Ten hub genes were identified according to the frequency and degree of action of cDEGs (such as STAT1, MX1, IFIH1, et al.). Studies have shown that ISG15/ IRF7/ IFIT1 is considered as a potential drug target for the treatment of COVID-19 [24]; STAT1 is considered to be an important gene in mediating COVID-19 and asthma [25, 26]; CXCL10 encodes viral infection-related proteins and is considered to be an important signaling pathway that induces asthma exacerbation [27]. The results of this study support the above reports. Module analysis found that TRIM38, GBP3, STAT1, CASP5, et al. are high-density modules. Besides STAT1, other hub genes interact with high-density modules at a high frequency. Therefore, it is speculated that the above hub genes are potential therapeutic target for asthma exacerbation induced by SARS-CoV-2.

Transcription factors are the regulatory factors of gene expression and are closely related to the occurrence and development of human diseases. In this study, NF-κB1, SP1 and RALA were identified as the most widely active transcription factors. NF-κB1, a member of the Rel protein family, plays a key role in the inflammation of lung tissues by mediating asthma and COVID-19, which is activated by many stimulating factors and mediates the production of many inflammatory cytokines [28]. Sp1 belongs to Sp/KLF family of transcription factors. It is a paradigm for a ubiquitously expressed transcription factor and is involved in regulating the expression of genes associated with cancer, Huntington’s disease, and Alzheimer’s disease[29]. RALA participates in the regulation of NLRP3 inflammasome and has anti-inflammatory effects [30]. TF-miRNA co-regulation revealed that miR-186, miR-135a, miR-362-5p and miR-409-3p had the highest frequency, and miR-409-3p and miR-496 were highly expressed in patients with COVID-19 [31]. Therefore, we believe that targeting transcription factors and Mir-as therapeutic targets can provide a novel therapeutic strategy for SARS-CoV-2-induced asthma exacerbations.

Common differentially expressed genes were used to predict potential therapeutic agents in DSigDB database. Drugs such as Suloc tile, 3’-Azido-3 deoxythymidine et al. were screened for pharmacological effects such as anti-inflammatory, antiviral, and inhibition of inflammatory cytokine storms. This result was consistent with the results of GO-KEGG analysis. It is worth noting that TCM has unique advantages in the treatment of COVID-19 and asthma [32, 33]. Search the pubmed for TCMs that can act on hub genes. It was found that Yu Ping Feng San could act on ISG15[34], Qing Fei Pai Du decoction could act on IFIT1/3, IFIH1 [35]. Both genes such as ISG15 and IFIT1/3 affect interferon expression, which are key drugs for treatment.

Conclusions

In conclusion, cDEGs from two datasets of GSE147507 and GSE30326 were identified. On this basis, we constructed the differentially expressed gene PPIs, screened hub genes, and used module analysis to confirm the high-frequency interaction between hub genes and other cDEGs in the course of these two diseases. We further confirmed the critical role of hub genes in diseases through TFs and its co-regulatory network with miRNA. Finally, we screened out potential therapeutic agents (including TCMs). However, due to the sample size limitation, we also need to further experimentally confirm the expression and function of the identified hub genes in disease progression, aiming to provide new strategies for the prevention of COVID-19 and its induction of aggravated asthma.

Declarations

Authors’ contributions

Wei Guo and Yilong Xi conceived the idea and wrote the manuscript. Yi CAO, Ziyun JIANG and Hui LUO depicted figures and analyzed data. Hui LIU contributed for revision. Yilong Xi contributed for overall editing and supervision. All authors approved its submission.

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Ethics approval and consent to participate

Not applicable

Consent to publish
The authors declare that they have no competing interests.

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**Figures**

**COVID19**

**VAE**

| 726 (60.3%) | 88 (7.3%) | 389 (32.3%) |

**Figure 1**

Venn diagram of 88 cDEGs from the microarray datasets of GSE147507 and GSE30326. Eighty-eight genes were found common from the 814 differentially expressed genes of SARS-CoV-2 infection and 477 differentially expressed genes of VAE patients.
Figure 2

GO-KEGG enrichment analysis of cDEGs
Figure 3

Protein-protein interactions (PPIs) network for identified cDEGs that are shared by COVID-19 and VAE. Node indicate cDEGs and edge represents their interactions of two genes. PPI enrichment P-value < 1.0e-16.
Figure 4

Detection of hub genes from the PPIs network of cDEGs. Yellow, orange, and red represent hub genes, and the degree value increases gradually.

Figure 5

Module analysis network obtained from PPIs network. The network represents highly interconnected regions of the PPIs network. Yellow, orange and red represent high-density modules, and blue represents hub genes that are highly associated with them.
Figure 6

Network for TFs interaction with hub genes. The highlighted red color nodes represent the hub genes, and the blue color nodes represent TFs.
TF-miRNA co-regulatory network. The network consists of 1679 nodes and 1732 edges. The nodes in red color are the hub genes, the blue nodes represent miRNA, the pink nodes represent TFs, the yellow nodes represent protein.